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AVALIAÇÃO DO RISCO E INTENSIDADE DA DOR UTILIZANDO ANESTESIA TÓPICA EM DIFERENTES PROCEDIMENTOS ODONTOLÓGICOS

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Tese apresentada como pré-requisito para obtenção do título de Doutor na Universidade Estadual de Ponta Grossa, no curso de Doutorado em Odontologia – Área de Concentração Clínica Integrada. Linha de Pesquisa: Propriedades Físico-Químicas e Biológicas de Materiais.

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LETICIA MAIRA WAMBIER

Avaliação do risco e intensidade da dor utilizando anestesia tópica em diferentes procedimentos odontológicos.

Tese apresentada ao Programa de Pós-graduação Stricto sensu em Odontologia da Universidade Estadual de Ponta Grossa, como requisito parcial à obtenção do título de Doutora em Odontologia, área de concentração em Clínica Integrada, linha de pesquisa de Propriedades Físico-Químicas e Biológicas dos Materiais.

Ponta Grossa, 30 de Junho de 2017.

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Todas as minhas conquistas devo a vocês!

Amo vocês!

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DADOS CURRICULARES

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RESUMO

Wambier, L.M. **Avaliação do risco e intensidade da dor utilizando anestesia tópica em diferentes procedimentos odontológicos.** [Tese] Doutorado em Clínica Integrada. Ponta Grossa: Universidade Estadual de Ponta Grossa; 2017.

O objetivo deste trabalho foi realizar revisões sistemáticas e estudos clínicos randomizados para avaliar a efetividade dos anestésicos tópicos, para reduzir o risco e a intensidade de dor durante procedimentos odontológicos em crianças e adultos. Nos experimentos 1 e 2, revisões sistemáticas foram conduzidas para responder as perguntas PICO: “A anestesia tópica exerce influência na dor durante a raspagem radicular (RAP) em pacientes adultos?” e “A anestesia infiltrativa exerce influência na dor durante a raspagem radicular (RAP) em pacientes adultos?” A patente foi obtida com o gel anestésico fotoativado. Nos estudos 3 e 4, um dos géis anestésicos (lipossomal termossensível ou fotoativado versus placebo) foi aplicado ao redor da gengiva de primeiros molares permanentes inferiores para adaptação do grampo # 26, colocação do dique de borracha e aplicação de selante resinoso. No estudo 5, participaram adultos com lesões cervicais não cariosas, cujo tratamento foi realizado com o gel anestésico fotoativado versus placebo para a adaptação do grampo # 212. Os dados do estudo 1 evidenciaram que a anestesia tópica diminuiu o risco (p= 0,002), a intensidade da dor (VAS e Heft Parker, p= 0,002; VRS, p= 0,023) e a necessidade de anestesia resgate (p= 0,005) durante a sondagem e RAP comparada ao uso de um placebo. O estudo 2 mostrou que a anestesia infiltrativa foi melhor somente na avaliação da intensidade de dor (p = 0,03) comparada a anestesia tópica, sem diferença estatística para o risco de dor (p = 0,58), necessidade de anestesia de resgate (p < 0,0001) e preferência dos pacientes (p = 0,09). No estudo 3 não foram detectadas diferenças estatísticas para o risco de dor (p = 0,52) entre o gel anestésico lipossomal termossensível e o gel placebo em crianças, havendo diferenças para a intensidade de dor com resultados positivos para o gel anestésico (p= 0,023 para escala numérica e p= 0,013 para escala facial). O estudo 4 mostrou resultados positivos para o gel anestésico fotoativado versus placebo, com diferenças significativas para o risco de dor (p= 0,0002) e intensidade da dor nas diferentes escalas (P<0,001). Dados semelhantes foram observados no estudo 5, com resultados também favoráveis para o gel anestésico fotoativado versus placebo aplicado em adultos, sendo detectadas diferenças estatísticas para o risco de dor (p= 0,0339) e intensidade da dor nas diferentes escalas empregadas (VAS, p=0,005 e VRS, p=0,015). As revisões sistemáticas demonstraram que a anestesia tópica pode ser uma alternativa para substituir a infiltrativa na RAP, enquanto que os ensaios clínicos randomizados demonstraram que os anestésicos tópicos lipossomal termossensível e fotoativado são efetivos para diminuir a intensidade de dor em crianças e adultos, e são uma alternativa de trabalho para procedimentos odontológicos menos invasivos.

Palavras-chave: Anestesia dental; Anestésicos; Dor; Ansiedade ao tratamento odontológico; Materiais dentários.

ABSTRACT

Wambier, L.M. **Risk and pain assessment using topical anesthesia in different dental procedures.** [Tese] Doutorado em Clínica Integrada. Ponta Grossa: Universidade Estadual de Ponta Grossa; 2017.

The objective of these researche was to conduct systematic reviews and randomized clinical trials to evaluate the effectiveness of topical anesthetics to reduce the risk and intensity of pain during dental procedures in children and adults. In the experiments, 1 and 2, systematic reviews were conducted to answer the PICO questions: "Does topical anesthesia influence pain during scaling and root planing (SRP) in adult patients?" and "Does infiltrative anesthesia influence pain during scaling and root planing (SRP) in adult patients?" The patent was obtained with the light-curred anesthetic gel. In the studies 3 and 4, one of the anesthetic gels (thermosensitive liposomal or light-curred gel versus placebo) was applied around the lower permanent first molars gingiva to adapted the clamp # 26, placement of the rubber dam and application of resin sealant. In the study 5, adults with non-carious cervical lesions, whose treatment was performed with the light-curred anesthetic gel versus placebo for the clamp # 212 adaptation,were enrolled.The data from study 1 showed that topical anesthesia reduced risk ($p = 0.002$), pain intensity (VAS and Heft Parker, $p = 0.002$; VRS, $p = 0.023$) and need for rescue anesthesia ($p = 0.005$) during the probing and RAP compared to the placebo. Study 2 showed that infiltrative anesthesia was better only in the assessment of pain intensity ($p = 0.03$) compared to topical anesthesia, with no statistical difference for pain risk ($p = 0.58$), need for rescue anesthesia ($p<0.0001$) and patients' preference ($p = 0.09$). In the study 3, no statistical differences were detected for the risk of pain ($p = 0.52$) between thermosensitive liposomal anesthetic and placebo gel in children, with differences for pain intensity with positive results for the anesthetic gel ($p = 0.023$ for numerical scale and = 0.013 for facial scale). Study 4 showed positive results for the light-curred anesthetic gel versus placebo, with significant differences for the risk of pain ($p = 0.0002$) and pain intensity at the different scales ($p<0.001$). Similar data were observed in study 5, with favorable results for light-curred anesthetic gel versus placebo applied in adults. Statistical differences were found for the risk of pain ($p = 0.0339$) and pain intensity in the different scales used (VAS, $p = 0.005$ and VRS, $p = 0.015$). Systematic reviews have demonstrated that topical anesthesia may be an alternative to replace infiltrative anesthesia in SRP, where as randomized clinical trials have demonstrated that thermosensitive liposomal and light-curred anesthetics gels are effective in reducing pain intensity in children and adults, and are an alternative for less invasive dental procedures.

Key-words: Anesthesia, dental; Anesthetics; Pain; Dental anxiety; Dental materials.

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LISTA DE ABREVIATURAS E SIGLAS

BBO	Bibliografia Brasileira de Odontologia
CAIC	Centro de Atenção Integral à Criança e ao Adolescente
COEP	Comissão de Ética em Pesquisa
ECRs	Ensaios Clínicos Randomizados
FDI	Federação Dentária Internacional
LCNC	Lesões cervicais não cariosas
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
Min	Minuto (s)
Mm	Milímetro (s)
n	Número amostral
NRS	Escala de Escolha Numérica
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RAP	Raspagem alisamento e polimento
REBEC	Registro Brasileiro de Ensaios Clínicos
S	Segundo (s)
TCLE	Termo de Consentimento Livre e Esclarecido
UEPG	Universidade Estadual de Ponta Grossa
VAS	Escala Analógica Visual
VRS	Escala de Avaliação Verbal

SUMÁRIO

1 INTRODUÇÃO

A percepção da dor é um fenômeno sensorial que pode ser somatizado por influências psicológicas e culturais, gerando ansiedade, medo e até fobias (medo extremo) com rejeição ao tratamento odontológico (Hurter et al.[1] 2014, Renton[2] 2015). Um estímulo visual, como o da agulha na seringa já é fator desencadeante de insegurança, pois mesmo sem experiência negativa anterior com anestesias infiltrativas, pode ocorrer o medo subjetivo (Kudo[3] 2005). Como a dor e o medo influenciam no comportamento dos pacientes, seu controle representa um desafio aos profissionais que precisam de alternativas para minimizar o desconforto com os procedimentos adotados (Milgrom et al.[4] 1997). Alguns pacientes argumentam contra o uso da agulha (Gunsolley[5] 2005) e, outros consideram a injeção indolor como um critério importante para a escolha do dentista (de St Georges[6] 2004). Aproximadamente 18% dos pacientes apresentam "muito" medo da agulha e 31% sentem medo "moderado" (Armfield e Heaton[7] 2013).

Outros fatores a serem considerados são o efeito longo do anestésico injetado e a sensação de formigamento ou inchaço (Kudo[3] 2005, Armfield e Heaton[7] 2013), que podem desencadear ansiedade, fazendo com que os indivíduos evitem o tratamento odontológico ou a freqüência regular ao dentista (Milgrom et al.[4] 1997, Armfield e Heaton[7] 2013, van Steenberghe et al.[8] 2004).

Sempre que possível, e principalmente para procedimentos minimamente invasivos ou não invasivos, deve-se optar pelos anestésicos tópicos para evitar esses desconfortos e o risco de lesões por mordedura nos lábios e língua (Milgrom et al.[4] 1997). A anestesia tópica é uma estratégia que minimiza a dor dos pacientes provocada pela punção da agulha (Wambier et al.[9] 2016), e em alguns procedimentos dentários (raspagem e alisamento radicular, adaptação do grampo para o isolamento absoluto), já foi testada com o objetivo de substituir a anestesia infiltrativa (Perry et al.[10] 2005, Lim e Julliard[11] 2004).

Cerca de 30 a 40% dos pacientes com doença periodontal que necessitam de raspagem e alisamento radicular (RAP), solicitam anestesia infiltrativa para o controle da dor (Gunsolley[5] 2005, Cobb[12] 1996). A prevalência de dor durante a sondagem varia de 15 a 77% em pacientes com doença periodontal ativa (Magnusson et al.[13] 2004, Al-Ajmix et al.[14] 2005, van Steenberghe et al.[15] 2004).

Em torno de 64 a 80% das crianças que tiveram seus primeiros molares permanentes tratados com selantes resinosos sob isolamento absoluto, receberam anestesia infiltrativa para a adaptação do grampo (Lim e Julliard[11] 2004). E para a realização de restaurações de lesões cervicais não cariosas foi relatado que 70% dos pacientes necessitaram de anestesia infiltrativa (Loguercio et al.[16] 2015).

Os anestésicos tópicos são disponibilizados em forma de géis, soluções, pomadas, adesivos e aerossóis, com efetividade superficial nos tecidos, em torno de 2 a 3 mm de profundidade (AAPD[17] 2016). A concentração do agente ativo é mais alta nas formulações tópicas para permitir rápida absorção na mucosa e seu efeito depende de uma técnica adequada que envolve um local seco (AAPD[17] 2016).

Os produtos comercializados demonstraram resultados positivos, mas ainda incluem algumas desvantagens, tais como efeito anestésico curto (10-15 min) e insuficiente para alguns procedimentos (Daneshkazemi et al.[18] 2016, Nayak e Sudha[19] 2006), escoam do local aplicado para as áreas vizinhas, podem ser facilmente removidos pela saliva (Friskopp et al.[20] 2001, Franz-Montan et al.[21] 2007, Stecker et al.[22] 2002) e deixam um sabor residual desagradável (Lim e Julliard[11] 2004, Meechan[23] 2000). Encontrar um meio eficiente e mais confortável para se conseguir anestesia local em procedimentos odontológicos faz parte de uma busca constante dos pesquisadores para minimizar a forma invasiva e muitas vezes dolorosa da injeção, método mais frequentemente utilizado na Odontologia (Peedikayil e Vijayan[24] 2013).

Com base no exposto, foram desenvolvidas revisões sistemáticas para avaliar o potencial da anestesia tópica versus placebo / infiltrativa no controle da dor em adultos submetidos a procedimentos periodontais. Foram elaborados géis anestésicos tópico com propriedades diferenciadas, sendo o anestésico fotoativado patenteado e submetido aos testes descritos nesta tese. Foram desenvolvidos ensaios clínicos randomizados triplo-cegos para analisar o risco e a intensidade da dor em crianças e adultos.

2 OBJETIVOS

2.1.1 OBJETIVO GERAL

- Avaliar a efetividade de anestésicos tópicos no controle da dor, analisando o risco e a intensidade, em diferentes procedimentos odontológicos, realizados em crianças e adultos, por meio de revisões sistemáticas da literatura e estudos clínicos randomizados triplo-cegos.
- Elaborar um novo gel anestésico com um sal anestésico mais potente que não possua escoamento do sítio aplicado.

2.1.2 OBJETIVOS ESPECÍFICOS

- Avaliar se a anestesia tópica versus placebo exerce influência na dor durante a raspagem radicular (RAP) em pacientes adultos, por meio de revisão sistemática e meta análise.

- Avaliar se a anestesia infiltrativa versus anestesia tópica exerce influência na dor durante a raspagem radicular (RAP) em pacientes adultos, por meio de revisão sistemática e meta análise.

- Elaborar um novo anestésico tópico fotoativado que não escoe para áreas vizinhas e apresente em sua composição um sal anestésico mais potente.

- Realizar um anestésico tópico lipossomal termossensível com capacidade de liberar o sal anestésico lentamente.

- Verificar a efetividade de um gel anestésico tópico formulado lipossomal termossensível versus placebo na redução do risco e intensidade de dor em crianças de 8 a 12 anos, na adaptação do grampo # 26 para isolamento absoluto e colocação de selantes.

- Verificar a efetividade de um gel anestésico tópico formulado fotoativado versus placebo na redução do risco e intensidade de dor em crianças de 8 a 12 anos, na adaptação do grampo # 26 para isolamento absoluto e colocação de selantes.

- Comparar o gel anestésico fotoativado com um gel placebo fotoativado no controle do risco e na intensidade da dor em adultos, portadores de lesões cervicais não cariosas, na adaptação do grampo # 212 para isolamento absoluto e restauração.

3 MATERIAL E MÉTODOS

Nesta sessão a metodologia de cada estudo será descrita de forma resumida. As informações detalhadas deste item podem ser encontradas nos artigos referentes a cada estudo.

3.1 ESTUDOS 1 e 2

Os protocolos das revisões sistemáticas e meta-análises foram registrados no banco de dados PROSPERO (Estudo 1- CRD42015017081, ANEXO A) e (Estudo 2- CRD42016032380, ANEXO B). Foram seguidas as recomendações do PRISMA para a realização destas revisões sistemáticas (Moher et al.[25] 2009). As metodologias desses estudos estão descritas no ARTIGO 1 (pág. 32) e ARTIGO 2 (pág. 65).

3.1.1 Fontes de informação e estratégia de busca

O vocabulário controlado (termos no MeSH) e palavras-chave livres na estratégia de busca foram definidos com base no acrônimo PICOS que norteia a pergunta de pesquisa clínica:

1. População (P): pacientes adultos com necessidade de realizar raspagem e alisamento radicular.
2. Intervenção (I): anestesia tópica.
3. Comparação (C): placebo (Estudo 1) / anestesia infiltrativa (Estudo 2)
4. Resultado primário (O): risco e intensidade de dor durante a raspagem e alisamento radicular.
5. Desenho do estudo (S): ensaios clínicos randomizados.

A busca da pesquisa incluiu as bases de dados eletrônicas MEDLINE via PubMed, Scopus, Web of Science, a base de dados da Literatura Latino-Americana em Ciências da Saúde (LILACS), a Biblioteca Brasileira em Odontologia (BBO) e a Cochrane Library. Também foi realizada uma busca na

Literatura Cinzenta e nos Registros de Estudos Clínicos. Não foram aplicadas restrições quanto à data de publicação ou idiomas.

3.1.2 Critério de Elegibilidade

Foram incluídos ensaios clínicos randomizados (ECRs) com desenhos paralelos ou de boca dividida em humanos que compararam o risco e a intensidade de dor durante a RAP com anestesia tópica versus placebo (Estudo 1) e anestesia tópica versus anestesia infiltrativa (Estudo 2) em pacientes adultos sem restrição de faixa etária.

Os artigos e textos que atendiam aos critérios de inclusão foram recuperados para posterior avaliação e extração de dados.

Estudos (ECRs) foram excluídos se: 1) outros tipos de procedimentos periodontais além de RAP fossem realizados; 2) géis anestésicos não fossem comparados com um placebo (Estudo 1) ou com anestesia infiltrativa (Estudo 2); 3) os participantes fizessem uso de analgésicos ou antiinflamatórios antes da RAP.

3.1.3 Seleção dos estudos e Processo de Coleta de Dados

Os artigos foram selecionados por título e resumos de acordo com os critérios de elegibilidade descritos. Foram obtidos os textos completos dos artigos quando as informações apresentadas nos resumos eram insuficientes para uma tomada de decisão. Posteriormente, dois revisores classificaram aqueles que preenchiam os critérios de inclusão. Detalhes sobre o estudo, os métodos, os participantes e os resultados foram extraídos utilizando formas de extração personalizadas.

3.1.4 Risco de viés dos estudos individuais

As avaliações da qualidade dos ensaios incluídos foram realizadas por dois revisores (LMW e JLG), utilizando a ferramenta Cochrane Collaboration para verificação do risco de viés dos ensaios randomizados (Higgins et al.[26] 2011). Os critérios aplicados continham seis itens: geração de seqüências (randomização), ocultação da alocação, cegamento dos operadores ou pacientes, dados dos resultados incompletos, relato seletivo dos desfechos, e

outras possíveis fontes de viés. Durante a extração dos dados para avaliação da qualidade, os desacordos entre os revisores eram resolvidos por meio de discussão e, quando necessário, consultando um terceiro revisor (A.R).

Para cada dado na avaliação da qualidade, o risco de viés foi pontuado seguindo as recomendações descritas no Manual Cochrane de Avaliações Sistemáticas de Intervenções 5.1.0 (http://handbook.cochrane.org). O julgamento para cada dado consistia em registrar "sim" (baixo risco de viés), "não" (alto risco de viés) ou "indefinido" (falta de informação ou incerteza sobre o potencial de viés).

Foram considerados para o estudo 1- três dos seis itens como domínios-chaves na ferramenta Cochrane de risco de viés (randomização, alocação e cegamento), e, para o estudo 2- dois (randomização e alocação) dos seis itens como domínios-chaves (Higgins et al.[26] 2011). O estudo foi definido como de "baixo" risco de viés quando os autores explicavam como foi realizado o método de randomização, havia ocultação da alocação e ainda cegamento dos pacientes ou operadores. Quando um ou mais domínios-chaves não eram explicados no estudo, o artigo era classificado como "indefinido" para o risco de viés e, se não fosse realizado um ou mais domínios-chaves o artigo era julgado como de “alto” risco de viés.

3.1.5 Resumo das Medidas e Síntese dos Resultados

Os dados dos estudos elegíveis foram dicotômicos (risco absoluto de dor) e contínuos (intensidade da dor). Somente os estudos classificados como de "baixo" risco de viés (Estudo 1) ou risco de viés "indefinido" nos domínios-chave entraram na meta-análise (Estudo 2).

Os resultados foram resumidos pelo cálculo da diferença de médias padronizadas para os dados contínuos e a razão de chances para os dados dicotômicos. Para ambas as medidas, o intervalo de confiança (IC) de 95% foi calculado. Os modelos de efeitos aleatórios foram empregados. A heterogeneidade foi avaliada utilizando o teste Cochran Q e estatísticas I^2. Todas as análises foram realizadas utilizando o software CMA (versão 3, Biostat Englewood, EUA). Nenhuma análise de subgrupos foi realizada.

3.2 DESENVOLVIMENTO DA PATENTE

A presente invenção refere-se à descrição do processo de obtenção de barreira gengival fotoativada contendo um sal anestésico (pág. 94), para o uso em várias áreas da odontologia e medicina (Patente –BR 10 2016 007724 9), (Wambier et al.[27] 2016). A formulação proposta é inovadora, já que é o primeiro anestésico tópico fotoativado, apresentando vantagens como: longo tempo de duração, fácil aplicação, por ser fotoativado, não há escoamento do produto para áreas vizinhas e nem a deglutição o que diminui a ocorrência de efeitos colaterais, além disso, como fica restrito a área onde é aplicado não apresenta gosto desagradável.

A obtenção da formulação foi feita a partir do uso de reagentes da matriz orgânica e inorgânica, empregando-se os seguintes componentes: inibidor da fotoativação nas concentrações de 0,1 a 2%; monômero metacrílico de 10 a 60%; monômero metacrílico-uretânico entre 20 a 80%; sal anestésico entre 1 a 10%; fotoiniciador de 0,1 a 2%; co-iniciador de 0,1 a 2%; pigmento de 0,1 a 2%; e carga inerte entre 5 a 30%.

Tento em vista todas as dificuldades e limitações dos anestésicos existentes, essa formulação tende a suprir os comercializados atualmente, sendo de fácil uso, longa duração, fácil remoção que o torna seguro, evita a ingestão do produto devido sua viscosidade e capacidade de ser fotoativado, permanece apenas na região aplicada, dispensa uso da agulha, não apresenta sabor desagradável.

3.3 ELABORAÇÃO DO GEL LIPOSSOMAL TERMOSSENSÍVEL

O preparo do gel anestésico está detalhado na tabela 1, o qual foi manipulado por um pesquisador (LMW). O gel anestésico lipossomal termossensível foi manipulado em duas fases. Primeiro realizou a manipulação dos reagentes da fase aquosa composta por: poloxamer 407 (6,78 g) (BASF®, Guarulhos, SP, Brazil); polaxamer 188 (2,40 g) (BASF®, São Bernando do Campo, SP, Brazil); benzoato de sódio (0,1 g) (BIOXtra, Sigma-Aldrich, SP, Brazil); água purificada (30 mL), que eram misturados com um bastão de vidro em um Becker, em seguida, armazenados por 12 h em geladeira (4ºC). No

mesmo dia, manipulava-se os reagentes da fase oleosa, composta por: lecitina granulada (6,6 g) (European Pharmacopoeia Reference Standard, Sigma-Aldrich, SP, Brazil);, palmitato de isopropila (7,6 g) (European Pharmacopoeia Reference Standard, Sigma-Aldrich, SP, Brazil); ácido benzoico (0,12 g) (BIOXtra, Sigma-Aldrich, SP, Brazil); que depois de misturados manualmente em um Becker com auxilio de um bastão de vidro, ficaram armazenados por 12 h em temperatura ambiente.

Após 12 h, realizou-se a manipulação dos agentes anestésicos composto por: lidocaína base (1,5 g) (Nortec Química, Rio de Janeiro, Brasil); prilocaína base (1,5 g) (Nortec Química, Rio de Janeiro, Brasil); etanol (2,5 mL) (BIOXtra, Sigma-Aldrich, SP, Brazil); ácido clorídrico (0,1 mL) (ACS reagent, Sigma-Aldrich, SP, Brazil); e água purificada (10 mL) que foram misturados em um Becker com auxilio de um bastão de vidro. Os agentes anestésicos foram transferidos para uma seringa e em outra seringa foram transferidos os reagentes da fase aquosa, essas duas fases foram misturados com um auxilio de um adaptador, realizando a homogeneização por quatro vezes com uma seringa. Depois disso, em outra seringa, transferiu-se os produtos da fase oleosa, realizando a extrusão de todos os reagentes por 10 vezes até ficar na consistência de um gel.

O gel anestésico ficou armazenado na geladeira (4ºC) até ser usado, tendo validade de até 60 dias. O gel foi manipulado na Farmácia Escola da Universidade Estadual de Ponta Grossa, sempre pelo mesmo pesquisador.

Para manipulação do gel placebo, seguiu todos os passos da manipulação do gel anestésico, não incluindo apenas os agentes anestésicos.

Tabela 1. Reagentes utilizados para a fabricação do gel anestésico lipossomal termossensível.

Fases/Anestésicos	Composição	Quantidade	Proporção	Manipulação
Oleosa	Lecitina granulada Palmitato de isopropila Ácido benzóico	6,6 g 7,6 mL 0,12 g	22%	Os reagentes foram misturados em um Becker, lacrados com papel alumínio e armazenados em temperatura ambiente por 12 h.
Aquosa	Poloxamer 407 (Lutrol® 127) Poloxamer 188 (Lutrol® F68) Benzoato de sódio Água purificada GPS	6,78 g 2,40 g 0,1 g 1º dia: 30 mL	73%	Os reagentes foram misturados em um Becker, lacrados com papel alumínio e armazenados em geladeira a 4° C por 12 h.
Anestésicos	Lidocaína base Prilocaína base Etanol Ácido clorídrico Água purificada GPS	1,5 g 1,5 g 2,5 mL 0,1 mL 2º dia: 10 mL + 4 mL de tutti-frutti)	5%	Os reagentes anestésicos foram misturados em um Becker após 12 horas da manipulação das fases oleosa e aquosa.
Após a manipulação dos agentes anestésicos, todos os reagentes foram transferidos para seringas de 60 mL. Os agentes anestésicos foram homogenizados com os reagentes da fase aquosa, essa mistura foi homogenizada com os reagentes da fase oleosa realizando a extrusão por 10 vezes até ficar pronto o gel anestésico.				

3.4 ESTUDOS 3 e 4

Os projetos destes estudos clínicos foram aprovados pela Comissão de Ética em Pesquisa (COEP) da Universidade Estadual de Ponta Grossa (número: 974.470/2015- Estudo 3; número: 974.502/2015 - Estudo 4), (Anexos C e D). A metodologia detalhada destes experimentos está descrita nos ARTIGOS 3 (pág. 113) e 4 (pág. 132).

3.4.1 Registro do protocolo

Os estudos foram preparados usando o protocolo estabelecido pela declaração “Consolidated Standards of Reporting Trials” – CONSORT(Pandis et al.[28] 2017). Os protocolos foram registrados no Registro de Ensaios Clínicos Brasileiros (Rebec) com os números de identificações RBR-3WWQC3 (Estudo 3, ANEXO E) e RBR-6DYTYF (Estudo 4, ANEXO F).

3.4.2 Desenho do estudo e seleção dos pacientes

Foram realizados ensaios clínicos randomizados triplo-cegos de boca dividida. Os participantes incluídos no estudo tinham entre 8 à 12 anos, boa saúde geral e bucal. Também apresentavam os dentes 36 e 46 totalmente erupcionados e com indicação para aplicação de selantes resinosos (sulcos profundos e retentivos ou ICDAS 3). As crianças foram atendidas na Universidade Estadual de Ponta Grossa (UEPG) e no Centro de Atenção Integral à Criança e ao Adolescente (CAIC, Ponta Grossa, Paraná).

Já os critérios de exclusão foram: dentes que não estavam totalmente erupcionados ou com lesões de cárie que precisassem de restauração. Também foram excluídos pacientes com história de alergia; sensibilidade ou qualquer forma de reação alérgica aos anestésicos a base de amida (gel lipossomal termossensível) ou éster (gel fotoativado); portadores de doença sistêmica grave não controlada (problemas cardíacos, neurológicos, renais, hepáticos ou sanguíneos) e pacientes não colaboradores.

Todos os responsáveis receberam informações detalhadas sobre o estudo, incluindo informações que um placebo seria aplicado em um dos dentes da criança. Todos os pacientes incluídos os responsáveis assinaram um Termo de Concentimento Livre e Esclarecido.

Os cálculos para a determinação do tamanho amostral, alocação do gel experimental ou placebo que seria aplicado, foram realizados com um programa específico para esta finalidade (www.sealedenvelope.com).

3.4.3 Intervenção

O primeiro dente a ser tratado foi o dente # 36 (notação FDI de dois dígitos). O envelope contendo a descrição do grupo foi aberto apenas no momento da intervenção. Apenas um operador calibrado realizou todos os passos os tratamentos. Antes da colocação do grampo, os pacientes foram

instruídos em uma linguagem apropriada, explicando as sensações que eles provavelmente sentiriam: "Eu vou colocar um gel em seu dente e colocar um anel, você pode sentir uma pressão ao redor do seu dente. Essa sensação durará alguns segundos e você vai me dizer de 0 a 10 e apontar de acordo com uma figura que eu vou te mostrar como é esse desconforto. Se esse desconforto for demais para você suportar, você pode levantar sua mão que eu vou remover o grampo para acabar esse incomodo".

Após o explicado os passos do tratamento para as crianças, um envelope com registro de um dos tratamentos (gel ou placebo) era aberto imediatamente antes do início do procedimento. O protocolo consistiu de isolamento dos quadrantes com rolos de algodão, secagem do tecido gengival e colocação dos géis ao redor do dente a ser selado (Figura 1). No Estudo 3 foi empregado o gel anestésico lipossomal termossensível e no Estudo 4 o gel anestésico fotoativado, Patente –BR 10 2016 007724 9 (Wambier et al.[27] 2016), (Anexo G), os quais foram comparados a um gel placebo.

Aguardava-se a ação do anestésico (2 min – lipossomal termossensível; 15 s – gel fotoativado) e o grampo # 26 (Duflex-SS White, Rio de Janeiro, RJ, Brasil) era posicionado (Figura 2). Se neste momento, o paciente relatasse dor ou desconforto, o grampo era removido, e o procedimento poderia ser realizado sob isolamento relativo (Estudo 3) ou, uma anestesia infiltrativa (lidocaína 2% com epinefrina 1: 100.000 - Alphacaine, DFL, Rio de Janeiro, RJ, Brasileira) era aplicada como anestesia de resgate (Estudo 4). O dique de borracha era adaptado após a colocação do grampo naqueles pacientes que não relatassem dor ou desconforto.

Após profilaxia e isolamento absoluto, a superfície oclusal do dente 36 era condicionada com ácido fosfórico a 37% por 30 s (Condac 37- FGM Prod. Odont, Ltda, Joinville, SC), seguido de lavagem e secagem da superfície com jatos de água e ar (30 s). Selante resinoso Fluroshield (Dentsply, Petrópolis, RJ, Brasil) era aplicado e fotoativado por 40 s com dispositivo LED (Radii-cal, SDI, Bayswater, Victoria, Austrália) a 1200 mW/cm^2. Em seguida, o mesmo procedimento era realizado no dente 46.

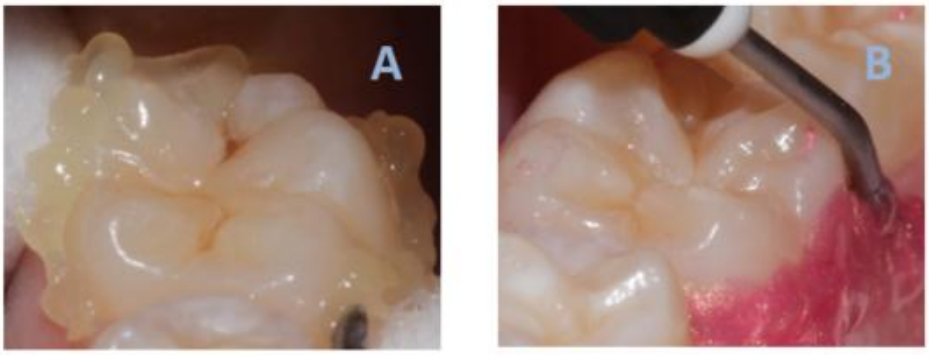


Figura 1: Aspecto do gel anestésico lipossomal termossensível (A) e do gel anestésico fotoativado (B), aplicados ao redor dos dentes.

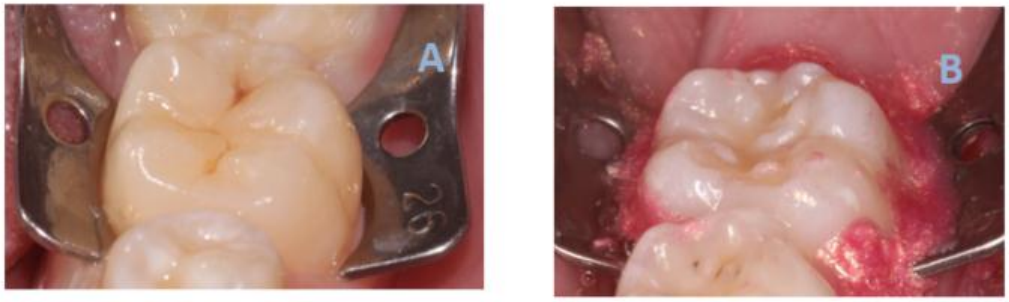


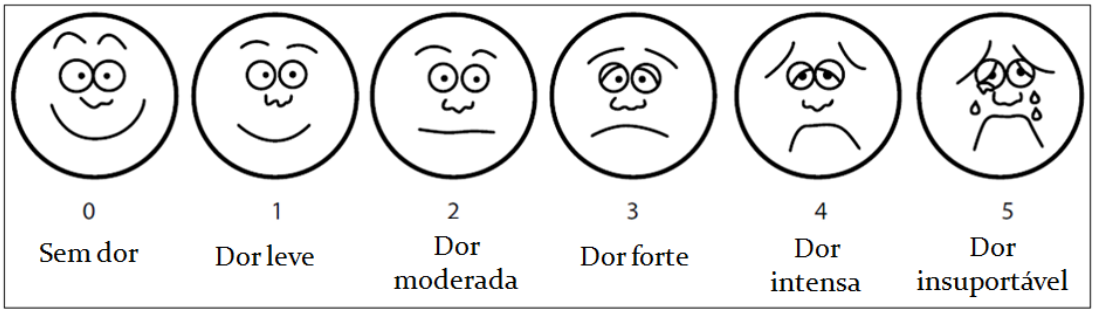
Figura 2: Grampo # 26 posicionado para avaliar a intensidade da dor utilizando anestésico lipossomal termossensível (A) e gel anestésico fotoativado (B).

3.4.4 Avaliação da dor

Todos os resultados foram coletados logo após a colocação do grampo para adaptação, pois é a fase mais crítica em termos de sensação dolorosa durante o procedimento. O risco absoluto de dor foi calculado contando o número de participantes que sentiram dor ou desconforto durante a colocação do grampo dividido pelo número total de participantes. A intensidade da dor foi ainda avaliada usando duas diferentes escalas de dor:

1. Escala de expressão facial de Wong-Baker (Figura 3). Os pacientes indicavam escores de 0 a 5 (0= sem dor; 1= dor leve; 2= dor moderada; 3= dor forte; 4= dor intensa; 5= dor insuportável) para expressar a intensidade da dor.

2. Escala numérica de 11 pontos (Escala de Escolha Numérica- NRS), nesta o paciente relatava a presença de dor de 0 (nenhuma dor) a 10 (dor insuportável).
3. Escala observacional de Flacc (Tabela 2) foi utilizada apenas no estudo 4. Essa escala possibilita a avaliação da dor usando linguagem corporal, mesmo sem verbalização, registrando os movimentos do paciente com escores de 0 a 10.



Classificação da dor: 0- sem dor; 1: dor leve; 2: dor moderada; 3: dor forte; 4: dor intensa; 5: dor insuportável

Figura 3: Escala de Faces de Wong-Baker.

Tabela 2. Escala observacional de Flacc para avaliação de dor em crianças.

	Pontuação		
Categorias	**0**	**1**	**2**
Face	Nenhuma expressão especial ou sorriso	Caretas ou sobrancelhas franzidas de vez em quando, introversão, desinteresse	Tremor freqüente do queixo, mandíbulas cerradas
Pernas	Normais ou relaxadas	Inquietas, agitadas, tensas	Chutando ou esticadas
Atividade	Quieta, na posição normal, movendo-se facilmente	Contorcendo-se, movendo-se para frente e para trás, tensa	Curvada, rígida ou com movimentos bruscos
Choro	Sem choro (acordada ou dormindo)	Gemidos ou choramingos; queixa ocasional	Choro continuado, grito ou soluço; queixa com freqüência
Consolabilidade	Satisfeita, relaxada	Tranqüilizada por toques, abraços ou conversas ocasionais; pode ser distraída	Difícil de consolar ou confortar

3.4.5 Análise estatística

Para a análise estatística, utilizou-se o teste de McNemar para calcular o risco de dor e necessidade de anestesia resgate (Estudo 4). Para verificar a intensidade da dor nas diferentes escalas, utilizou-se o teste de Wilcoxon Signed Rank. O nível de significância adotado foi de 5%. Todos os cálculos foram realizados com o programa estatístico Sigma Plot for Windows (Systat Software Inc., San Jose, CA, USA).

3.5 ESTUDO 5

Este estudo clínico foi aprovado pelo COEP da UEPG, protocolado sob o número 974.479/2015 (ANEXO H). A metodologia detalhada deste experimento está descrita no ARTIGO 5 (pág. 151).

3.5.1 Registro do protocolo

Esse estudo também seguiu as recomendações do CONSORT(Pandis et al.[28] 2017), com número RBR-6HXHX7 de identificação no Rebec (ANEXO I).

3.5.2 Desenho do estudo e seleção dos pacientes

Foi realizado um ensaio clínico randomizado triplo-cego de boca dividida na clínica odontológica da UEPG. Foram incluídos pacientes com no mínimo 18 anos de idade, que apresentassem um par de lesões cervicais não cariosas. Estas lesões (com tamanho, profundidade e localização semelhante na margem gengival) deveriam estar localizadas em dois dentes do mesmo paciente, no mesmo arco (superior ou inferior), mas em lados opostos.

Todos pacientes receberam informações detalhadas do estudo incluindo sobre o uso de um gel placebo em um dos seus dentes que poderia causar desconforto ao adaptar o grampo. Todos os participantes concordaram com o Termo de Concentimento Livre e Esclarecido.

3.4.3 Intervenção

Antes de iniciar o procedimento, os pacientes receberam explicações em uma linguagem acessível de todos os passos do tratamento. O procedimento era realizado sempre pelo mesmo pesquisador (LMW). Um envelope era aberto para determinar qual produto deveria ser aplicado (gel ou placebo), iniciando-se pelo dente localizado no quadrante com o menor sistema de numeração de dois dígitos (FDI-World Dental Federation), este recebia o produto registrado no envelope e o dente do lado oposto o outro.

Os quadrantes eram isolados com rolos de algodão para a aplicação do gel anestésico fotoativado (Patent –BR 10 2016 007724 9), (Wambier et al.[27] 2016) ou gel placebo fotoativado, os quais foram colocados ao redor do tecido gengival do dente a ser restaurado. O gel ficava em torno de 2 mm ao redor da margem gengival em ambos os lados (vestibular e lingual), (Figura 4). Aguardava-se 15 s para fazer a fotoativação com aparelho LED (Radii-cal, SDI, Bayswater, Victoria, Austrália) ajustada a 1.200mW / cm^2 do dente com tempo de 15 s. Em seguida, o grampo # 212 (Duflex-SS White, Rio de Janeiro, RJ, Brasil) era posicionado (Figura 4). Neste momento, se o paciente relatasse dor ou desconforto, o grampo era removido e uma anestesia infiltrativa (lidocaína a 2% com epinefrina 1: 100.000 - Alphacaine, DFL, Rio de Janeiro, RJ, Brasil) era aplicada como anestesia resgate. O dique de borracha só era instalado após a adaptação do grampo.

Após a colocação do dique de borracha, a superfície dentária era condicionada com ácido fosfórico à 37% durante 15 s (Condac 37- FGM, Joinville, SC, Brasil), seguida de lavagem com água (15 s) e secagem com jatos de ar (10 s). Aplicava-se duas camadas do adesivo Ambar (FGM, Joinville, SC, Brasil) com aplicação ativa, e eliminava-se o solvente com um jato de ar durante 5 s. O adesivo era fotoativado por 20 s com o mesmo dispositivo de fotopolimerização. A resina composta Opallis (FGM, Joinville, SC, Brasil) era colocada em incrementos na lesão, e cada incremento era fotopolimerizado por 40 s. Ambos os géis foram utilizados na mesma consulta clínica nos diferentes lados do mesmo arco.

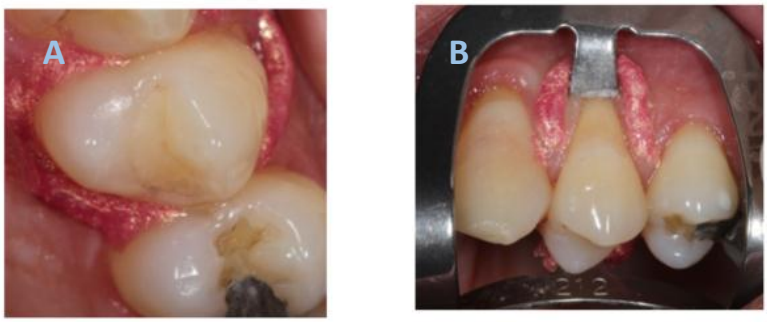


Figura 4: Gel com aproximadamente 2 mm ao redor da margem gengival em ambos os lados vestibular e lingual (A). Grampo # 212 posicionado para avaliar a intensidade da dor (B).

3.5.4 Avaliação da dor

Todos os resultados foram coletados logo após a colocação do grampo para adaptação, pois é a fase mais crítica em termos de sensação dolorosa durante o procedimento. O risco absoluto de dor foi calculado contando o número de participantes que sentiram dor ou desconforto durante a colocação do grampo dividido pelo número total de participantes. A intensidade da dor foi ainda avaliada usando duas diferentes escalas de dor:

1. Escala analógica visual (VAS). Esta escala é uma linha horizontal de 10 cm com pontuações de 0 e 10 nas suas extremidades, sendo 0 = sem dor e 10 = dor insuportável. O paciente deve marcar com uma linha vertical a sua intensidade da dor. Em seguida, a distância em mm da extremidade nula foi medida com a ajuda de uma régua milimétrica.

2. Escala de Avaliação Verbal (VRS). O paciente foi solicitado a indicar o valor numérico de 0 a 4 (0 = nenhum, 1 = leve, 2 = Moderado, 3 = considerável e 4 = grave) da intensidade da dor.

3.5.4 Análise estatística

Utilizou-se o teste de McNemar para calcular o risco de dor. A intensidade de dor medida com as escalas VAS e VRS, foi analisada com o teste de Wilcoxon Signed Rank. O nível de significância adotado foi de 5%. Todos os cálculos foram realizados com o programa estatístico Sigma Plot for Windows (Systat Software Inc., San Jose, CA, USA).

4 ARTIGOS

4.1 Intra-pocket anaesthesia and pain during probing, scaling and root planing: a systematic review and meta-analysis

4.2 Intra-pocket anesthesia X injected anesthesia for pain control during scaling and root planning in adult patients: Systematic review and meta-analysis

4.3 Processo de Obtenção de Barreira Gengival Anestésica Fotoativada

4.4 Efficacy of a thermo-sensitive liposomal anesthetic gel for clamp placement before rubber dam isolation for resin sealants: randomized clinical trial

4.5 Efficacy of a new light-cured anesthetic gel for clamp placement before rubber dam isolation in children: a triple-blinded randomized controlled clinical trial

4.6 Efficacy of a new anesthetic light-cured gel for clamp placement before rubber dam isolation for restorative treatment of non-carious lesions: a triple-blind randomized clinical trial

ARTIGO 1

TÍTULO: INTRA-POCKET ANESTHESIA AND PAIN DURING PROBING, SCALING AND ROOT PLANING: A SYSTEMATIC REVIEW AND META-ANALYSIS

STATUS: PUBLICADO

REVISTA: JOURNAL OF CLINICAL PERIODONTOLOGY

Intra-pocket anesthesia and pain during probing, scaling and root planing: a systematic review and meta-analysis

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Short title: Intra-pocket anesthesia: meta-analysis

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Abstract

Aim- A systematic review/meta-analysis was performed to evaluate pain during probing, scaling and root planing using intra-pocket anesthesia versus placebo in adult patients.

Methods- A search was performed in PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library and Grey literature. IADR abstracts, unpublished trials registries, dissertations and theses werealso searched for randomized clinical trials comparing the clinical effectiveness of intra-pocket anesthesia and placebo. Risk/intensity of pain was the primary outcome. The risk of bias tool from the Cochrane Collaboration was used for quality assessment. Meta-analysis was performed on studies considered at low risk of bias.

Results- 1740 articles were identified. Eleven remained in the qualitative synthesis, and 9 studies were considered at “low” risk of bias for meta-analysis. Standardized Hedge’s g mean difference for pain intensity using VAS and Heft Parker pain scales was - 0.576 (95% CI -0.94 to 0.22; p = 0.002) and for VRS pain scale it was - 1.814 (95% CI -3.38 to 0.245; p = 0.023). The odds ratio for the risk of pain was 0.025 (95% CI -0.003 to 0.25; p = 0.002) and for the need for rescue anesthesia it was 0.358 (95% CI -0.174 to 0.736; p = 0.005).

Conclusions: The anesthetic gel decreases the risk and intensity of pain during probing/SRP.

Key words: systematic review; meta-analysis, periodontal diseases, dental scaling, anesthetic.

1. Introduction

Periodontal disease is a major public health problem that contributes to the global burden of chronic diseases (Petersen and Ogawa, 2012), with high prevalence worldwide. About 20% of the adult population in the USA presents periodontal pockets and 9% presents some form of severe periodontitis (Eke et al., 2015). The prevalence of periodontal diseases has risen in Latin America (Oppermann et al., 2015), Asia (Corbet and Leung, 2011) and in some European regions (Konig et al., 2010).

The most effective measure to control the progress of periodontal disease is subgingival mechanical debridement by means of scaling and root planing (SRP) (Lang et al., 2008). This procedure can be painful and uncomfortable (Canakci and Canakci, 2007, van Steenberghe et al., 2004), requiring local anesthesia in approximately 40% of patients (Cobb, 1996). Altogether, these factors can trigger dental anxiety, which leads to treatment avoidance or irregular attendance (van Steenberghe et al., 2004, Milgrom et al., 1997, Armfield and Heaton, 2013).

Approximately 18% of patients are “very much” afraid of needles. If “moderate” fear is included, this percentage rises to 31% (Armfield and Heaton, 2013). Many patients argue against the use of the needle (Gunsolley, 2005), which is painful in it self (van Steenberghe et al., 2004). Another factor is the long-lasting effect of injectable local anesthetic and the tingling or numbing sensation. It reduces the acceptance of SRP carried out under conventional local anesthetics (Friskopp et al., 2001, Donaldson et al., 2003, Milgrom et al., 1997). Another common event is pain during probing, the prevalence of which varies from 15 to 77% in patients with active periodontal disease (Magnusson et al., 2004, van Steenberghe et al., 2004, Al-Ajmix et al., 2005, Heft et al., 1991).

Topical and sulcular anesthesia are alternatives that have been tested with the aim of replacing local anesthetic injection (Perry et al., 2005). However, these products are not commonly used in clinical practice yet. There are several commercial brands with different delivery methods, such as a trans-mucosal patch containing 10% or 20% lidocaine (DentiPatch™, Inc., Miami, FL, USA), a 5% lidocaine/prilocaine cream (EMLA, AstraZeneca, RεDSödertälje, Sweden)

and a 5% lidocaine/prilocaine gel that uses a reversible thermosetting system (Oraqix,Dentsply, York, PA, USA). The use of topical anesthesia for SRP has been shown to be superior to placebo (Magnusson et al., 2004, Mayor-Subirana et al., 2013). Even so, there are reports of the occurrence of pain with the need for infiltrative terminal anesthesia after topical anesthetic application (Jeffcoat et al., 2001, Donaldson et al., 2003, Magnusson et al., 2003).

Variations in the studies design, such as in the sample selection, patient randomization, operator experience, level of periodontal involvement, type of scales used to assess pain can influence the results (Donaldson et al., 2003). Different shaped hand and power-driven instruments may also be a factor that influences pain intensity (Braun et al., 2007).

In order to standardize the main research problem, systematic reviews tend to use a particular process when it comes to framing a research question. The question should be constructed by following the acronym PICOS (patient-P, intervention-I, comparison-C, outcome-O, study design-S). Therefore this study addressed the following PICO question: Does the intra-pocket anesthesia compared to a placebo influence the pain during probing, scaling and root planing in adult patients? The null hypothesis we considered that there is no difference in pain experience using intra-pocket anesthesia or placebo.

2. Materials and methods

2.1 Protocol and registration

This study protocol was registered in the PROSPERO database (CRD42015017081) and the recommendations of the PRISMA statement were followed (Moher et al., 2009). It was accomplished from February to December of 2015 at State University of Ponta Grossa, Paraná, Brazil.

2.2 Information sources and search strategy

The controlled vocabulary (MeSH terms) and free keywords in the search strategy were defined based on the PICOS question:

1. Population (P): adult patients in need of probing, scaling and root planing.
2. Intervention (I): intra-pocket anesthesia with an anesthetic gel.

3. Comparison (C): placebo
4. Primary outcome (O): intensity/risk of pain during probing and/or scaling and root planing. The secondary outcomes of pain and the need for rescue anesthesia were also evaluated.
5. Study design (S): randomized clinical trials.

To identify the trials to be included, we searched the electronic databases MEDLINE via PubMed, Scopus, Web of Science, the Latin American and Caribbean Health Sciences Literature database (LILACS), the Brazilian Library in Dentistry (BBO) and the Cochrane Library (Table 1). We also hand-searched the reference lists of all primary studies for additional relevant publications and investigated the related article links for each primary study in the PubMed database. No restrictions on publication date or languages were involved.

Abstracts of the annual conference of the International Association for Dental Research (IADR) and its regional divisions (1990–2015) were used; the authors of relevant abstracts were contacted for further information. The grey literature was explored using the database System for Information on Grey Literature in Europe (SIGLE). Dissertations and theses were searched using the ProQuest Dissertations and Theses Full Text data bases and the Periódicos Capes Theses database.

To locate unpublished and ongoing trials, the following clinical trials registries were searched: Current Controlled Trials (www.controlled-trials.com), International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), the ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu).

The search strategy and the date of search for all databases were included in Table 1. The search strategy developed for PubMed was modified for the other databases to identify eligible studies. Full-text versions of the papers that appeared to meet the inclusion criteria were retrieved for further assessment and data extraction.

2.3. Eligibility criteria

We included randomized clinical trials (RCTs) with parallel, crossover or split-mouth designs. We also included clinical trials in humans that compared pain

during probing and/or SRP with intra-pocket anesthesia versus placebo in adult patients of any age group.

RCT studies were excluded if: 1) other types of periodontal procedures besides probing and/or SRP were performed; 2) anesthetic gels were not compared with a placebo; 3) participants took analgesics or anti-inflammatory drugs before probing and/or SRP.

2.4. Study selection and data collection process

The articles were selected by title and abstracts according to the described search strategy. Articles appearing in more than one database were considered once. Full-text articles were obtained when there was insufficient information in the title and abstract to make a clear decision.

Subsequently, full-text articles were acquired, and two reviewers (L.M.W. and J.L.G.) classified those that met the inclusion criteria. To handle such a large number of studies, we created an ID for each eligible study, combining first author and year of publication. Relevant information about the study design, participants, interventions and outcomes were extracted using customized extraction forms by three authors (L.M.W., J.L.G. and A.R.) (Table 2).

When there were multiple reports of the same study (*i.e.,* reports with different follow-ups), data from all reports were extracted directly into a single data collection form to avoid overlapping data. The collection form was pilot tested using a sample of study reports to ensure that the criteria were consistent with the research question.

When more than two anesthetic gels were tested, data were combined to make a single entry. When the pain was reported in different time periods after a single clinical session of probing and/or SRP, we collected the data from the most immediate period. If data from multiple clinical sessions of probing and/or SRP were reported, we averaged the values.

2.5 Risk of bias in individual studies

Quality assessments of the included trials were evaluated by two independent reviewers (L.M.W. and J.L.G.), using the Cochrane Collaboration tool for assessing risk of bias in randomized trials (Higgins et al., 2011). The assessment criteria contained six items: sequence generation, allocation

concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. During data extraction and quality assessment, any disagreements between the reviewers were resolved through discussion, and if needed, by consulting a third reviewer (A.R.).

For each aspect of the quality assessment, the risk of bias was scored following the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org). The judgment for each entry consisted of recording “yes” (low risk of bias), “no” (high risk of bias) or “unclear” (either lack of information or uncertainty over the potential for bias).

We considered three out of the six domains in the Cochrane risk of bias tool as key domains (Higgins et al., 2011). At the study level, studies were judged to be at “low” risk of bias if there was adequate sequence generation, allocation concealment and blinding (operators and participants). If one or more criteria werenot met, the study would be considered at “high” risk of bias. When the study wasjudged as “unclear” in its key domains, we tried to contact the authors to obtain more information and allow a definitive judgment of “low” or “high” risk.

2.6 Summary measures and synthesis of the results

Data from eligible studies were either dichotomous (absolute risk of pain) or continuous (pain intensity). Only studies classified at “low” risk of bias in the key domains were entered into the meta-analysis. The outcomes were summarized by calculating the Hedge’s g standardized mean difference for the continuous data and the odds ratio for dichotomous data. For both summary measures, the 95% confidence interval (CI) was calculated.

The random-effects models were employed. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. All analyses were conducted using CMA software (version 3, Biostat Englewood, USA). No subgroup analysis was performed.

When matched data was available (split-mouth and cross-over designs), we imputed an external correlation of 0.5 for both groups, as this information was not available in any of the studies. Sensitivity analyses using lower (0.1) and

higher (0.9) external correlations were performed to check the impact of such an imputation in the all the meta-analyses. Additionally, whenever heterogeneity was detected, we performed sensitivity analysis to identify if the heterogeneity was caused by any of the included studies.

3. Results

Some studies did not contain all the information needed, and e-mails were sent to 10 authors for further information (Antoniazzi et al., 2015, Donaldson et al., 2003, Jeffcoat et al., 2001, Hodosh et al., 2007, Jacob and Nath, 2013, Magnusson et al., 2003, Mayor-Subirana et al., 2013, Perry et al., 2005, Svensson et al., 1994, Winning et al., 2012). Three of them did not answer (Svensson et al., 1994, Perry et al., 2005, Hodosh et al., 2007).

3.1. Study selection

After the database screening and removal of duplicates, 1740 studies were identified (Figure 1). After title screening, 105 studies remained. This number was reduced to 24 after examination of the abstracts and their full texts were assessed to check eligibility. Among them, 13 were excluded because: 1) they were not placebo-controlled studies (Chung et al., 2011, Donaldson and Meechan, 1995, Friskopp et al., 2001, Wambier et al., 2014, Termaat et al., 2007, Lowden et al., 2008), 2) they were not observational studies (Derman et al., 2013, Matthews et al., 2002, Magnusson et al., 2004), 3) the pain was not assessed (Jadhav et al., 2004, Graça, 1997), and 4) they did not use an active anesthetic gel (Kasaj et al., 2006, Paquette et al., 2013).

3.2 Characteristics of included articles

The characteristics of the 11 selected studies are listed in Table 2. The split-mouth study design prevailed (Svensson et al., 1994, Antoniazzi et al., 2015, Jacob and Nath, 2013, Mayor-Subirana et al., 2013, Varma et al., 2013, Winning et al., 2012); one study used the cross-over design (Perry et al., 2005) and the remaining employed the parallel study design (Donaldson et al., 2003, Jeffcoat et al., 2001, Magnusson et al., 2003, Hodosh et al., 2007).

Four out of the 11 studies used Oraqix® product (Winning et al., 2012, Jeffcoat et al., 2001, Magnusson et al., 2003, Donaldson et al., 2003), one used Emla cream® (Svensson et al., 1994), two used an experimental anesthetic gel (Hodosh et al., 2007, Varma et al., 2013), one employed DentiPatch™ (Perry et al., 2005), and another study used the Mucopain® product (Jacob and Nath, 2013). Two studies evaluated the analgesia effect of two anesthetic gels: one evaluated Oraqix® and Huricaine® (Mayor-Subirana et al., 2013) and the other evaluated Emla® and Benzotop® (Antoniazzi et al., 2015).

Most of the patients included in the primary studies had periodontal disease with a probing pockets depth (PPD) of ≥5 mm (Antoniazzi et al., 2015, Donaldson et al., 2003, Jacob and Nath, 2013, Jeffcoat et al., 2001, Magnusson et al., 2003, Mayor-Subirana et al., 2013, Svensson et al., 1994). Two studies included participants with a PPD of ≥5.5 mm (Winning et al., 2012, Perry et al., 2005). In two studies, the periodontal condition and PPD were not reported (Hodosh et al., 2007, Varma et al., 2013).

The period that the anesthetic gel was left in the pocket before starting the probing and SRP procedures varied from 30 s to 2 min in the majority of the studies (Donaldson et al., 2003, Jeffcoat et al., 2001, Magnusson et al., 2003, Hodosh et al., 2007, Antoniazzi et al., 2015, Jacob and Nath, 2013, Mayor-Subirana et al., 2013, Varma et al., 2013, Winning et al., 2012), with the exception of two that waited for at least 5 min (Svensson et al., 1994, Perry et al., 2005). The time used for probing and SRP varied (Table 2), and this information was not reported in seven studies (Winning et al., 2012, Varma et al., 2013, Perry et al., 2005, Mayor-Subirana et al., 2013, Jeffcoat et al., 2001, Hodosh et al., 2007, Donaldson et al., 2003).

The number of patients included in the primary studies ranged from 15 to 300. The mean age of all the participants included in the clinical trials was approximately 42 years. The percentage of males ranged from 40 to 76% (Table 2); however, this information was not reported in three studies (Donaldson et al., 2003, Hodosh et al., 2007, Antoniazzi et al., 2015).

Most of the studies used rescue anesthesia when the patients experienced pain during the treatment. In five studies, the authors employed the same anesthetic gel (Donaldson et al., 2003, Jacob and Nath, 2013, Magnusson

et al., 2003, Varma et al., 2013, Winning et al., 2012), in three studies, the same anesthetic gel plus injectable anesthesia were used (Antoniazzi et al., 2015, Jeffcoat et al., 2001, Mayor-Subirana et al., 2013) and in one study, the authors only used injectable anesthesia (Perry et al., 2005). This information was not reported in two studies (Hodosh et al., 2007, Svensson et al., 1994).

Eight studies employed both the 0-10 visual analog scale (VAS) and the 0-4 verbal rating scale (VRS) for pain evaluation (Jeffcoat et al., 2001, Svensson et al., 1994, Antoniazzi et al., 2015, Donaldson et al., 2003, Hodosh et al., 2007, Mayor-Subirana et al., 2013, Magnusson et al., 2003, Perry et al., 2005); two studies employed only the VAS scale (Varma et al., 2013, Winning et al., 2012). One used the Heft Parker0-170 scale (Jacob and Nath, 2013). The absolute risk and pain intensity were evaluated in nine studies (Antoniazzi et al., 2015, Hodosh et al., 2007, Jacob and Nath, 2013, Jeffcoat et al., 2001, Magnusson et al., 2003, Mayor-Subirana et al., 2013, Svensson et al., 1994, Varma et al., 2013, Winning et al., 2012) and two studies just evaluated the intensity of pain (Donaldson et al., 2003, Perry et al., 2005).

3.3 Assessment of the risk of bias

The assessment of the risk of bias of the selected studies is presented in Figure 2. Some full-text studies did not report the method of randomization and how the allocation concealment and blinding were performed. As these three items were the key domains of the current systematic review, authors were contacted for further information.

At the study level, from the 11 studies, two full-text studies (Jeffcoat et al., 2001, Svensson et al., 1994) were considered to be at “high” risk of bias, and nine (Antoniazzi et al., 2015, Donaldson et al., 2003, Hodosh et al., 2007, Jacob and Nath, 2013, Mayor-Subirana et al., 2013, Magnusson et al., 2003, Perry et al., 2005, Varma et al., 2013, Winning et al., 2012) were considered to be at “low” risk in the key domains of the Cochrane risk of bias tool, yielding nine studies (Antoniazzi et al., 2015, Donaldson et al., 2003, Hodosh et al., 2007, Jacob and Nath, 2013, Mayor-Subirana et al., 2013, Magnusson et al., 2003, Perry et al., 2005, Varma et al., 2013, Winning et al., 2012) that met the best requirement features (randomization, allocation concealment and blinding) for quantitative analysis.

3.4 Meta-analysis

All meta-analyses were performed on studies classified as being at “low” risk of bias in the key domains and from which the information could be extracted.

3.4.1 Intensity of pain using VAS and Heft Parker pain scales

This analysis was based on seven studies (Donaldson et al., 2003, Magnusson et al., 2003, Jacob and Nath, 2013, Perry et al., 2005, Winning et al., 2012, Mayor-Subirana et al., 2013, Antoniazzi et al., 2015). The Hedge’s g standardized difference in the means was – 0.576 (CI = – 0.94 to - 0.22; p = 0.002). This demonstrates that the anesthetic gel has an impact on reducing the intensity of pain when assessed with the VAS and Heft Parker scale (Figure 3). Data related to pain intensity based on the VAS and Heft Parker scales demonstrated heterogeneity (chi^2 test p < 0.001; I^2 = 81.49%; Figure 3), which means that all studies included in the analysis did not share a common effect size.

3.4.2 Intensity of pain using VRS pain scale

This analysis was based on five studies (Magnusson et al., 2003, Perry et al., 2005, Hodosh et al., 2007, Varma et al., 2013, Mayor-Subirana et al., 2013). The Hedge’s g standardized difference in means was – 1.814 (CI = – 3.38 to – 0.245; p = 0.023). This is evidence that the anesthetic gel has an impact on reducing pain intensity, when it is assessed using the VRS scale (Figure 4). Data on pain intensity using the VRS scale suggested that the data were heterogeneous (chi^2 test p < 0.001; I^2 = 98.84%; Figure 4), which means that all the studies included in the analysis did not share a common effect size.

3.4.3 Risk of pain

This analysis was based on five studies (Magnusson et al., 2003, Hodosh et al., 2007, Varma et al., 2013, Mayor-Subirana et al., 2013, Antoniazzi et al., 2015). The odds ratio was 0.025 with a 95% confidence interval of 0.003 to 0.25 (p = 0.002). This is evidence that the use of an anesthetic gel has a positive impact in reducing the risk of pain during probing and SRP (Figure 5). The data were heterogeneous (chi^2 test p = 0.002; I^2 = 89.2%; Figure 5), which means that all the studies included in the analysis did not share a common effect size.

3.4.4 Need for rescue anesthesia

This analysis was based on five studies (Donaldson et al., 2003, Magnusson et al., 2003, Mayor-Subirana et al., 2013, Antoniazzi et al., 2015, Winning et al., 2012). As no event was observed in one study (Winning et al., 2012), the effect size for this study could not be computed and therefore it was not used for the meta-analysis, this explains why the author was not added to the forest plot. The odds ratio was 0.358 with a 95% confidence interval of 0.174 to 0.736 ($p = 0.005$). This allowed us to reject the null hypothesis that the anesthetic gel has no impact on the need for rescue anesthesia (Figure 6). No evidence of heterogeneity was found (chi^2 test $p = 0.20$; $I^2 = 34.44\%$; Figure 6), which means that all the studies included in the analysis probably share a common effect size.

3.4.5 Sensitivity analysis

The change of the external correlation for extreme conditions (external correlations of 0.1 and 0.9) did not affect the results of any of the meta-analyses performed as part of this study. Through a sensitivity analysis, we could not identify any study responsible for the high heterogeneity detected by the Q-statistics in the meta-analyses. The low number of studies included in all the meta-analyses prevented us from running a meta-regression model to evaluate the impact of some independent variables, such as the composition of the anesthetic gel and the type of intervention (probing or SRP), on the summary estimates.

We also ran a sensitivity analysis to evaluate the impact of the study of Winning et al. (Winning et al., 2012) on the summary effects reported. This study was the only one that evaluated probing instead of SRP. Even when excluding this study, the pain intensity was still significant ($p = 0.001$), with an overall OR (95% CI) of – 0.399 (- 0.643 to – 0.155) (graphic not shown).

4. Discussion

Adequate management of domain randomization, allocation concealment and blinding minimizes selection and performance bias. The judgment of the risk of bias of these domains was not straightforward in the great majority of studies included in the qualitative synthesis (Table 2), which meant that contacting the authors. Although some investigators in their full-text articles mentioned that the

participants were randomly distributed, they rarely described the method of randomization. Description of the allocation concealment was even more infrequent in the studies. The single item described in sufficient detail in most of the studies was blinding.

In general, the present study showed that the use of an anesthetic gel in the periodontal pocket and/or gingival tissue, compared to a placebo, reduced the risk and intensity of pain and the need for rescue anesthesia during probing and/or SRP. These results were expected, as the placebo gels in the primary studies did not contain any anesthetic component and the procedure itself was already reported as being painful (van Steenberghe et al., 2004, Magnusson et al., 2004, Al-Ajmix et al., 2005).

An important aspect of the included studies is the clinical condition of the periodontal sites evaluated. Nine of the eleven included articles reported that these sites had a PPD ranging between 5 mm to 8 mm (Antoniazzi et al., 2015, Donaldson et al., 2003, Jacob and Nath, 2013, Jeffcoat et al., 2001, Magnusson et al., 2003, Mayor-Subirana et al., 2013, Perry et al., 2005, Svensson et al., 1994, Winning et al., 2012). Pain experience may be different if the procedure is performed supra or subgingivally (Guzeldemir et al., 2008, Canakci et al., 2002). The degree of periodontal pain reported by the patients is influenced by the location and depth of the pockets and the periodontal destruction. The periodontal destruction is proportional to the pain response from the patient (Canakci et al., 2002).

Additionally, the scaling procedure is carried out in repeated movements until the operator feels that the affected surfaces are smooth and hard, which can result in more pain. Another factor to consider is that the tips of the periodontal instruments may not be the appropriate size to insert into atresic periodontal pockets or multirooted teeth (Tunkel et al., 2002). Once operators try to perform the appropriate movement, they may exacerbate the pain experienced by the patient. Therefore, the treatment of patients in such periodontal conditions offers different degrees of difficulty, which periodontists or clinicians must overcome in their daily practice. Therefore, the results of the meta-analyses provide an alternative, since they show that the use of an anesthetic gel is capable of reducing the risk and intensity of pain in such conditions.

In the meta-analysis of the risk and intensity of pain, we observed a high statistical heterogeneity. This heterogeneity manifests itself in the fact that the observed treatment effects differ more widely than one would expect due to random error (chance) alone. Both clinical diversity (variability in interventions) and methodological diversity are responsible for the observed statistical heterogeneity. For instance, different local anesthetics, with variable efficacy, were employed in the primary studies of this investigation.

Usually, the amide group of local anesthetics has a better anesthetic potential than the ester group except for tetracaine (Sadove et al., 1951, Milam and Giovannitti, 1984). Oraqix® is a topical anesthetic gel that uses thermosetting agents (it is a low-viscosity fluid at room temperature and becomes an elastic gel at body temperature) and contains lidocaine and prilocaine as its active ingredients (Friskopp et al., 2001, Mayor-Subirana et al., 2013). Emla® is a eutectic mixture of local anesthetics with lidocaine and prilocaine as its active ingredients and presented as a cream (Svensson et al., 1994, Antoniazzi et al., 2015). Benzotop®, Hurricaine® and Mucopain® are presented in the form of a gel and contain benzocaine as the active ingredient (Antoniazzi et al., 2015, Mayor-Subirana et al., 2013, Jacob and Nath, 2013). DentiPatch™ is a trans-mucosal anesthetic patch that contains lidocaine (Perry et al., 2005). Two studies used an experimental topical anesthesia containing KNO3, benzocaine and tetracaine added to an aqueous hydroxyethyl cellulose gel (Varma et al., 2013, Hodosh et al., 2007). Despite the fact that Emla® and Oraqix® have similar active anesthetic components, Oraqix® has more advantages than Emla® such as the quick onset of action and the ability to stay in place after application. As Emla® is not delivered in a thermosetting agent, it tends to be diluted by saliva (Al-Melh and Andersson, 2007). Although benzocaine-based anesthetic gels are very common and widely used in dentistry (Paphangkorakit et al., 2012, Rosivack et al., 1990), this type of anesthetic salt has inferior analgesia potential compared to lidocaine and prilocaine (Antoniazzi et al., 2015, Al-Melh and Andersson, 2007). On the other hand, lidocaine and prilocaine are less efficient and less potent than tetracaine-based gels, which exhibits a longer duration due to the prolonged connection with the sodium channel of the nerve fibers (Eidelman et al., 2005, Romsing et al., 1999).

Although we were unable to run meta-regression analysis to assess the impact of the active component of the anesthetic gels on the summary outcomes due to the reduced number of included studies, one can clearly observe in the meta-analysis of the risk and intensity of pain (Figures 4 and 5) that the studies employing tetracaine-based gels (Hodosh et al., 2007, Varma et al., 2013) showed a higher effect size in favor of the anesthetic gel.

All studies included in this meta-analysis applied the anesthetic gel for the period of time suggested by the different manufacturers before starting probing and SRP (Table 2). According to previous studies, the Oraqix® products provide anesthesia 30 s after application, with a mean duration of action of about 17 to 20 min (Friskopp et al., 2001). Although Emla® can reduce pain perception after 2 min (Antoniazzi et al., 2015), this product showed a higher degree of analgesia after 5 min of application (Holst and Evers, 1985).

The primary studies evaluated the intensity and/or the absolute risk of pain using scales for this purpose (Jacob and Nath, 2013, Winning et al., 2012, Varma et al., 2013), which explains why these studies were included twice in the evaluation of the intensity of pain (Figure 2 and 3). Usually, studies use more than one scale to measure pain to confirm that the values are correlated and reliable (List et al., 2014, Antoniazzi et al., 2015). This care is based on the fact that pain is a very individual experience, which may be influenced by psychological and physical effects (Renton, 2015, Hurter et al., 2014). Additionally pain varies from individual to individual being more intense in females than in males (Chesterton et al., 2003, Derman et al., 2013, Renton, 2015).

One final aspect should be discussed. Although the meta-analyses were run with studies that performed probing and SRP, only one of the ten included studies in these meta-analyses performed probing. Concerns about the differences in the pain experience during SRP and probing can be raised. Each point/area is accessed only once during probing while repetitive movements at the same point are performed during SRP. However, no significant differences in the meta-analysis were observed after a sensitivity analysis, in which the study on probing had been removed (Winning et al., 2012). This shows the robustness of the results presented here.

This systematic review is the first to compare topical anesthetic gels to a placebo during probing and/or SRP, focusing on their ability to reduce the risk and intensity of pain and the need for rescue anesthesia. The topical anesthetics were shown to be efficient and therefore, they can be a friendly alternative to injectable anesthesia during probing and SRP in adult patients.

It can be argued that infiltrative anesthesia may be more effective than intra-pocket anesthesia in controlling pain in periodontal procedures. The literature is controversial on this specific issue. The intra-pocket anesthesia (EMLA) showed an equivalent effect on pain control compared to the injectable anesthesia, and it performed better than a placebo in SRP procedures (Antoniazzi et al., 2015). On the other hand, it has been shown that infiltrative local anesthesia controlled pain more effectively than an intra-pocket gel (Derman et al., 2014, Stoltenberg et al., 2007, van Steenberghe et al., 2004). Therefore, our research group is already preparing a systematic review (PROSPERO database CRD 42016032380) that will compare the risk and intensity of pain during probing and SRP using intra-pocket anesthetic gel and local injectable anesthesia.

6. Conclusions

Topical anesthesia was superior to placebo during probing, scaling and root planing as it reduced the risk and intensity of pain and the need for rescue anesthesia during periodontal diagnosis and treatment.

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Figure and Table legends:

Figure 1- Flow diagram of study identification.

Figure 2- Summary of the risk of bias assessment according to the Cochrane Collaboration tool. Underlined authors provided extra information by e-mail to allow assessment of the risk of bias.

Figure 3- Forest plots of the intensity of pain measured with the VAS and Heft-Parker pain scales and the VRS pain scales.

Figure 4- Forest plots of the risk of pain and the need for rescue anesthesia.

Table 1 – Electronic database and search strategy**.**

Table 2-Summary of the studies selected for this systematic review.

Table 1 – Electronic database and search strategy.

Pubmed= 476 (10/02/2015)		
#1 ((Periodontics[MeSH Terms]) OR Gingivitis[MeSH Terms]) OR Periodontitis[MeSH Terms]) OR Dental scaling[MeSH Terms]) OR Periodontal diseases[MeSH Terms]) OR Periodontitis[Title/Abstract]) OR "Periodontal maintenance"[Title/Abstract]) OR Periodontal[Title/Abstract]) OR Gingivitis[Title/Abstract]) OR "Gingival tissue"[Title/Abstract]) OR "Periodontal tissue"[Title/Abstract]) OR "Periodontal pocket"[Title/Abstract]) OR "Periodontal recall"[Title/Abstract]) OR "Periodontal therapy"[Title/Abstract]) OR "Scaling and root planing"[Title/Abstract])) OR SRP[Title/Abstract]) OR "Periodontal treatment"[Title/Abstract]) OR "Root planing"[Title/Abstract]) OR "Scaling root planing"[Title/Abstract]) OR "Ultrasonic scaler"[Title/Abstract]) OR "Ultrasonic scalers"[Title/Abstract]) OR "Non surgical periodontal"[Title/Abstract]) OR "Nonsurgical periodontal"[Title/Abstract]))	**#2** ((((Anesthetic[MeSH Terms]) OR Anesthesia[MeSH Terms]) OR Carticaine[MeSH Terms]) OR Emla[Supplementary concept]) OR Lidocaine[MeSH Terms]) OR Prilocaine[MeSH Terms]) OR Benzocaine[MeSH Terms]) OR Tetracaine[MeSH Terms]) OR Anesthetics[Title/Abstract]) OR Anesthetic[Title/Abstract]) OR "Gel anaesthetic"[Title/Abstract]) OR Anesthesia[Title/Abstract]) OR "Intrapocket anesthesia"[Title/Abstract]) OR "Intrapocket anesthetic"[Title/Abstract]) OR "Anesthesia local"[Title/Abstract]) OR "Anesthesia dental"[Title/Abstract]) OR "Dental anesthesia"[Title/Abstract]) OR "Local anaesthesia"[Title/Abstract]) OR "Local anesthetics"[Title/Abstract]) OR "Topical anesthetic"[Title/Abstract]) OR "Topical anaesthesia"[Title/Abstract]) OR "Anesthesia topical"[Title/Abstract]) OR "Anesthetics local"[Title/Abstract]) OR "Transmucosal drug"[Title/Abstract]) OR Articaine[Title/Abstract]) OR Emla[Title/Abstract]) OR Oraqix[Title/Abstract]) OR Hurricaine[Title/Abstract]) OR Ropivacaine[Title/Abstract]))))	**#3** (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])
#1 AND #2 AND #3		
Scopus= 758 (10/02/15)		
#1TITLE-ABS-KEY (**periodont***) OR TITLE-ABS-KEY (**gingivitis**) OR TITLE-ABS-KEY (**"dental scaling"**) OR TITLE-ABS-KEY (**"periodontal diseases"**) OR TITLE-ABS-KEY (**"periodontal maintenance"**) OR TITLE-ABS-KEY (**"gingival tissue"**) OR TITLE-ABS-KEY (**"periodontal tissue"**) OR TITLE-ABS-KEY (**"periodontal pocket"**) OR TITLE-ABS-KEY (**"periodontal recall"**) OR TITLE-ABS-KEY (**"periodontal therapy"**) OR TITLE-ABS-KEY (**srp**) OR TITLE-ABS-KEY (**"periodontal treatment"**) OR TITLE-ABS-KEY (**"ultrasonic scaler"**) OR TITLE-ABS-KEY (**"*root planing"**) OR TITLE-ABS-KEY (**"*surgical periodontal"**)	**#2**TITLE-ABS-KEY (**anesthe***) OR TITLE-ABS-KEY (**carticaine**) OR TITLE-ABS-KEY (**emla**) OR TITLE-ABS-KEY (**lidocaine**) OR TITLE-ABS-KEY (**prilocaine**) OR TITLE-ABS-KEY (**benzocaine**) OR TITLE-ABS-KEY (**tetracaine**) OR TITLE-ABS-KEY (**"gel anaesthetic"**) OR TITLE-ABS-KEY (**"intrapocketanesthe*"**) OR TITLE-ABS-KEY (**"anesthesia dental"**) OR TITLE-ABS-KEY (**"dental anesthesia"**) OR TITLE-ABS-KEY (**"local anesthe*"**) OR TITLE-ABS-KEY (**"local an*sthesia"**) OR TITLE-ABS-KEY (**"topical anesthe*"**) OR TITLE-ABS-KEY (**"anesthe* topical"**) OR TITLE-ABS-KEY (**"anesthe* local"**) OR TITLE-ABS-KEY (**"transmucosal drug"**) OR TITLE-ABS-KEY (**articaine**) OR TITLE-ABS-KEY (**oraqix**) OR TITLE-ABS-KEY (**hurricaine**) OR TITLE-ABS-KEY (**ropivacaine**))) AND LIMIT-TO (SUBJAREA , **"DENT"**)
#1 AND #2		

Web of Science- 713 (10/02/2015)	
#1 **TOPIC:** (periodont*) *OR***TOPIC:** (gingivitis) *OR***TOPIC:** ("dental scaling") *OR***TOPIC:** ("periodontal diseases") *OR***TOPIC:** ("periodontal maintenance") *OR***TOPIC:** ("gingival tissue") *OR***TOPIC:** ("periodontal tissue") *OR***TOPIC:** ("periodontal pocket") *OR***TOPIC:** ("periodontal recall") *OR***TOPIC:** ("periodontal therapy") *OR***TOPIC:** (SRP) *OR***TOPIC:** ("periodontal treatment") *OR***TOPIC:** ("ultrasonic scaler*") *OR***TOPIC:** ("*root planing") *OR***TOPIC:** ("*surgical periodontal")	**#2** **TOPIC:** (anesthe*) *OR***TOPIC:** (carticaine) *OR***TOPIC:** (EMLA) *OR***TOPIC:** (lidocaine) *OR***TOPIC:** (prilocaine) *OR***TOPIC:** (benzocaine) *OR***TOPIC:** (tetracaine) *OR***TOPIC:** ("gel anaesthetic") *OR***TOPIC:** ("intrapocketanesthe*") *OR***TOPIC:** ("anesthesia dental") *OR***TOPIC:** ("dental anesthesia") *OR***TOPIC:** ("local an*sthe*") *OR***TOPIC:** ("anesthe* topical") *OR***TOPIC:** ("anesthe* local") *OR***TOPIC:** ("transmucosal drug") *OR***TOPIC:** (articaine) *OR***TOPIC:** (oraqix) *OR***TOPIC:** (hurricaine) *OR***TOPIC:** (ropivacaine)
#1 AND #2	
Lilacs and BBO= 366 (02/03/15)	
#1 (MH:periodontics OR MH:gingivitis OR MH:periodontitis OR MH:dental scaling OR MH:periodontal diseases OR "Periodontal maintenance" OR "manutenção periodontal" OR "mantenimiento periodontal" OR periodontal OR periodonto OR "Gingival tissue" OR "tecidogengival" OR "tejido gingival" OR "Periodontal tissue" OR "tecido periodontal" OR "tejido periodontal" OR "Periodontal pocket" OR "bolsa periodontal" OR "bolsillo periodontal" OR "Periodontal recall" OR "revocatorio periodontal" OR "Periodontal therapy" OR "terapia periodontal" OR "Scaling and root planing" OR "Raspagem e alisamento radicular" OR "Raspado y alisado radicular" OR SRP OR RAP OR RAR OR "Periodontal treatment" OR "tratamento periodontal" OR "tratamiento periodontal" OR "Root planing" OR "alisamento radicular" OR "alisado radicular" OR "Ultrasonic scaler" OR "ultra som" OR "escaladorultrasónico" OR "Ultrasonic scalers" OR "ultra sônicos" OR "escaladoresultrasónicos" OR "Non surgical periodontal" OR "Periodontal nãocirúrgico" OR "Periodontal no quirúrgico")	**#2** (MH:anesthetic OR MH:anesthesia OR MH:Carticaine OR MH:emla OR MH:lidocaine OR MH:prilocaine OR MH:benzocaine OR MH:tetracaine OR anesthetics OR anestésicos OR "Gel anaesthetic" OR "gel anestésico" OR "anestésico Gel" OR "Intrapocket anesthesia" OR "anestesiaintrasulcular" OR "Intrapocket anesthetic" OR "anestésicointrasulcular" OR "Anesthesia local" OR "anestesia local" OR "Anesthesia dental" OR "anestesia dental" OR "Dental anesthesia" OR "Local anaesthesia" OR "Local anesthetics" OR "anestésicoslocais" OR "anestésicos locales" OR "Topical anesthetic" OR "anestésicotópico" OR "anestesiatópica" OR "Topical anaesthesia" OR "Anesthesia topical" OR "Anesthetics local" OR "Transmucosal drug" OR "drogatransmucosa" OR Articaine OR articaína OR Oraqix OR Hurricaine OR Hurricaína OR Ropivacaine OR ropivacaína)
#1 AND #2	
Cochrane Library = 165 (11/02/2015)	
#1 MeSH descriptor: [Periodontics] explode all trees **#2** MeSH descriptor: [Gingivitis] explode all trees **#3** MeSH descriptor: [Periodontitis] explode all trees **#4** MeSH descriptor: [Dental Scaling] explode all trees **#5** MeSH descriptor: [Periodontal Diseases] explode all trees **#6** #1 OR #2 OR #3 OR #4 OR #5 **#7** "periodontal maintenance":ti,ab,kw or periodontal:ti,ab,kw or "gingival tissue":ti,ab,kw or "periodontal tissue":ti,ab,kw or "periodontal pocket":ti,ab,kw (Word variations have been searched) **#8** "periodontal recall":ti,ab,kw or "periodontal therapy":ti,ab,kw or SRP:ab or "periodontal treatment":ti,ab,kw or *root near planing :ti,ab,kw (Word variations have been searched) **#9** ultrasonic near scaler* :ti,ab,kw or *surgical near periodontal :ti,ab,kw (Word variations have been searched) **#10** #6 OR #7 OR #8 OR #9	**#1** MeSH descriptor: [Anesthetics] explode all trees **#2** MeSH descriptor: [Anesthesia] explode all trees **#3** MeSH descriptor: [Carticaine] explode all trees **#4** MeSH descriptor: [Lidocaine] explode all trees **#5** MeSH descriptor: [Prilocaine] explode all trees **#6** MeSH descriptor: [Benzocaine] explode all trees **#7** MeSH descriptor: [Tetracaine] explode all trees **#8** #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 **#9** "gel anaesthetic":ti,ab,kw or intrapocket near anesthe* :ti,ab,kw or anesthe* near local :ti,ab,kw or local near an*sthesia :ti,ab,kw (Word variations have been searched) **#10** "anesthesia dental":ti,ab,kw or "dental anesthesia":ti,ab,kw or topical near anesthe* or topical near an*sthesia :ti,ab,kw or "transmucosal drug":ti,ab,kw (Word variations have been searched) **#11** articaine:ti,ab,kw or emla:ti,ab,kw or oraqix:ti,ab,kw or hurricaine:ti,ab,kw or ropivacaine:ti,ab,kw (Word variations have been searched) **#12** #8 OR #9 OR #10 OR #11
#10 AND #12	

Table 2 - Summary of the studies included in this systematic review.

Study ID	Study design	Subjects' age mean±SD [range] (years)	No. of male subjects [%]	Total No. patients [drop-outs]	Presence of periodontal disease? [Severity]	Peridontal pocket depth (mm)	Topical anesthetic used	Time gel was left before treatment	Time used for probing / SRP	Treatment phase	Outcomes evaluated	
											Was the need of rescue anesthesia evaluated? [type]	Pain
Antoniazzi et al 2015 (Antoniazzi et al.[29] 2015)	Split-mouth	49.4±9.4 [n.r.]	n.r. [n.r.]	41 [9]	Yes [gingivitis/ periodontitis]	≥5	Emla®: 5% [a] Benzotop®:2 % [b]	2 min	SRP: ± 60 min (2 teeth)	Non-surgical therapy	Yes [the same anesthetic gel/ injectable anesthesia]	Absolute risk and pain intensity in VAS and VRS scales
Donaldsonet al 2003(Donaldson et al.[30] 2003)	Parallel	Active: 47 ±n.r.[23-75] Placebo: 45 ±n.r. [23 - 80]	n.r. [n.r.]	130 [0]	Yes [n.r.]	≥5	Oraqix®:5% [c]	30 s – 2 min	SRP: n.r.	Non-surgical therapy	Yes [the same anesthetic gel]	Intensity in VAS and VRS scales
Hodosh et al 2007(Hodosh et al.[31] 2007)	Parallel	n.r. [18-85]	n.r. [n.r.]	200 [0]	Yes [periodontitis]	n.r.	Experimental gel based on KNO_3, tetracaine and benzocaine [d]	2 min	SRP: n.r.	maintenance treatment	n.r.	Absolute risk and pain intensity in VAS and VRS scales
Jacobet al 2013(Jacob e Nath[32] 2013)	Split-mouth	25.6 ± 6.6 [18-40]	16 [76]	21 [0]	Yes [periodontitis]	≥5	Mucopain®: 20 % [e]	1-2 min	SRP: Active: 23.9 ± 15.2 Placebo: 21.5 ± 10.2	Non-surgical therapy	Yes [the same anesthetic gel]	Absolute risk* and pain intensity in Heft Parkerscale
Jeffcoatet al 2001(Jeffcoat et al.[33] 2001)	Parallel	Active: 43± 11 [20 - 71] Placebo: 46± 12 [21 - 86]	56 [45]	122 [0]	Yes [severe periodontitis]	≥5	Oraqix®:5% [c]	30 s – 2 min	SRP: n.r.	Non-surgical therapy	Yes [the same anesthetic gel/ injectable anesthesia]	Absolute risk and pain intensity in VAS and VRS scales

Magnusson et al 2003(Magnusson et al.[34] 2003)	Parallel	Active:n.r ± n.r. [21-71] Placebo: n.r± n.r. [21-77]	34[40]	85 [0]	Yes [moderate/severe periodontitis]	≥5	Oraqix®:5% [c]	30 – 45 s	SRP: 1 – 19 (3 min per tooth)	Non-surgical therapy	Yes [the same anesthetic gel]	Absolute risk and pain intensity in VAS and VRS scales
Mayor-Subiranaet al 2013(Mayor-Subiranaet al.[35] 2013)	Split-mouth	51 ±n.r. [29-71]	10 [66]	15 [0]	Yes [periodontitis]	≥5	Oraqix®:5% [c] Hurricaine:20 % [f]	30 – 45 s	SRP: n.r.	Non-surgical therapy	Yes [the same anesthetic gel/ injectable anesthesia]	Absolute risk and pain intensity* in VAS and VRS scales
Perryet al 2005(Perry et al.[10] 2005)	Cross-over	39 ± 9.7 [25-63]	17 [42]	40 [0]	Yes [moderate periodontitis]	≥5 and ≤8	Denti Patch ™: 4.5%[g]	5 – 13 min	SRP: n.r.	Non-surgical therapy	Yes [injectable anesthesia]	Intensity in VAS and VRS scales.
Svensson et al1994(Svensson et al.[36] 1994)	Split-mouth	44 ± 14 [n.r.]	9 [45]	20 [n.r.]	Yes [mild chronic periodontitis]	≥5	Emla®: 5% [a]	5 min	SRP: 2 – 5 min per tooth	Non-surgical therapy	n.r.	Absolute risk and pain intensity in VAS and VRS scales
Varmaet al 2013 (Varma et al.[37] 2013)	Split-mouth	Males: 33.8 ± 6.8 [n.r.] Females: 35.1 ± 6.8 [n.r.]	186 [62]	300 [0]	n.r.	n.r.	Experimental gel based on KNO_3, tetracaine and benzocaine[d]	2 min	SRP: n.r.	Non-surgical therapy	Yes [the same anesthetic gel]	Absolute risk and pain intensity in VAS scale
Winning et al 2012(Winning et al.[38] 2012)	Split-mouth	46.2 ± 7.9 [33-66]	15 [50]	30 [0]	Yes [generalized chronic periodontitis]	≥5.5	Oraqix®:5% [c]	30 s	Probing: n.r.	diagnosis	Yes* [the same anesthetic gel]	Absolute risk* and pain intensity in VAS scale

ID – identification; SD – standard deviation; n.r. – not reported; SRP- scaling and root planing; VAS (Visual Analog Scale):0 a 100-cm horizontal line with words "no pain" at one end and "worst pain" at the opposite end; Heft-Parker scale:0- 170-cm horizontal line with words "no pain" at one end and "worst pain" at the opposite end; VRS (Verbal Rating Scale): 0-4 - no pain, mild pain, moderate pain, severe pain, extremely severe pain.* This information was obtained by email contact with the author.

[a] Emla® 5%, AstraZeneca, RεD Södertälje, Sweden.
[b] Benzotop® 2%, DFL, Rio de Janeiro, RJ.
[c] Oraqix® 5%,Dentsply, York, PA, USA.[d] KNO_3 (35%)/ Benzocaine (20%)/ Tetracaine (10%) added to an aqueous hydroxyethyl cellulose gel.
[e] Mucopain® 20%, ICPA, India.
[f] Hurricaine® 20%,Clarben, Madrid, Spain.
[g] Denti Patch®4,5%, lidocaine transmucosal delivery system (LTDS), Noven Pharmaceuticals, Inc., Miami, FL, USA.

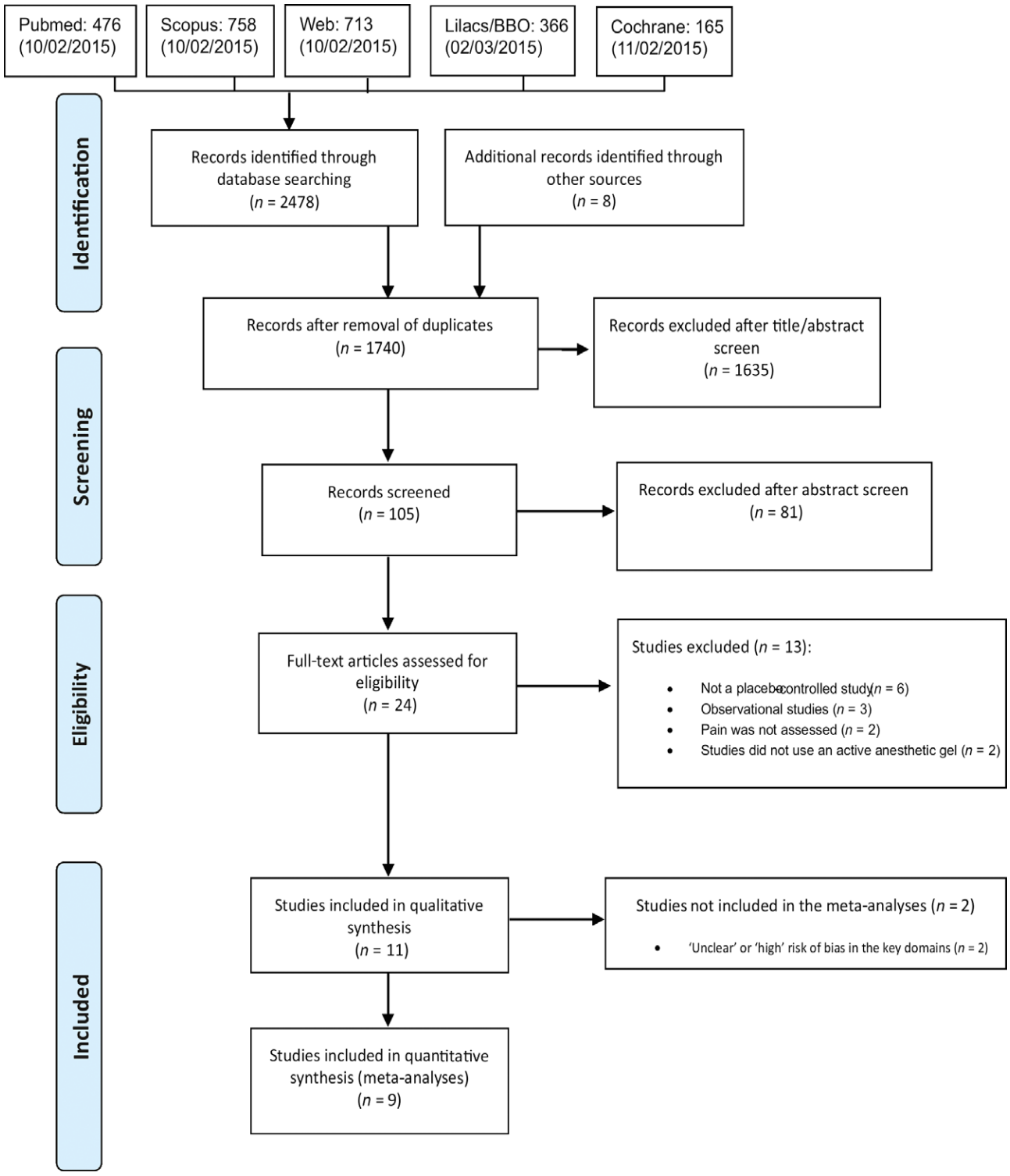

Fig 1 – Flow diagram of study identification.

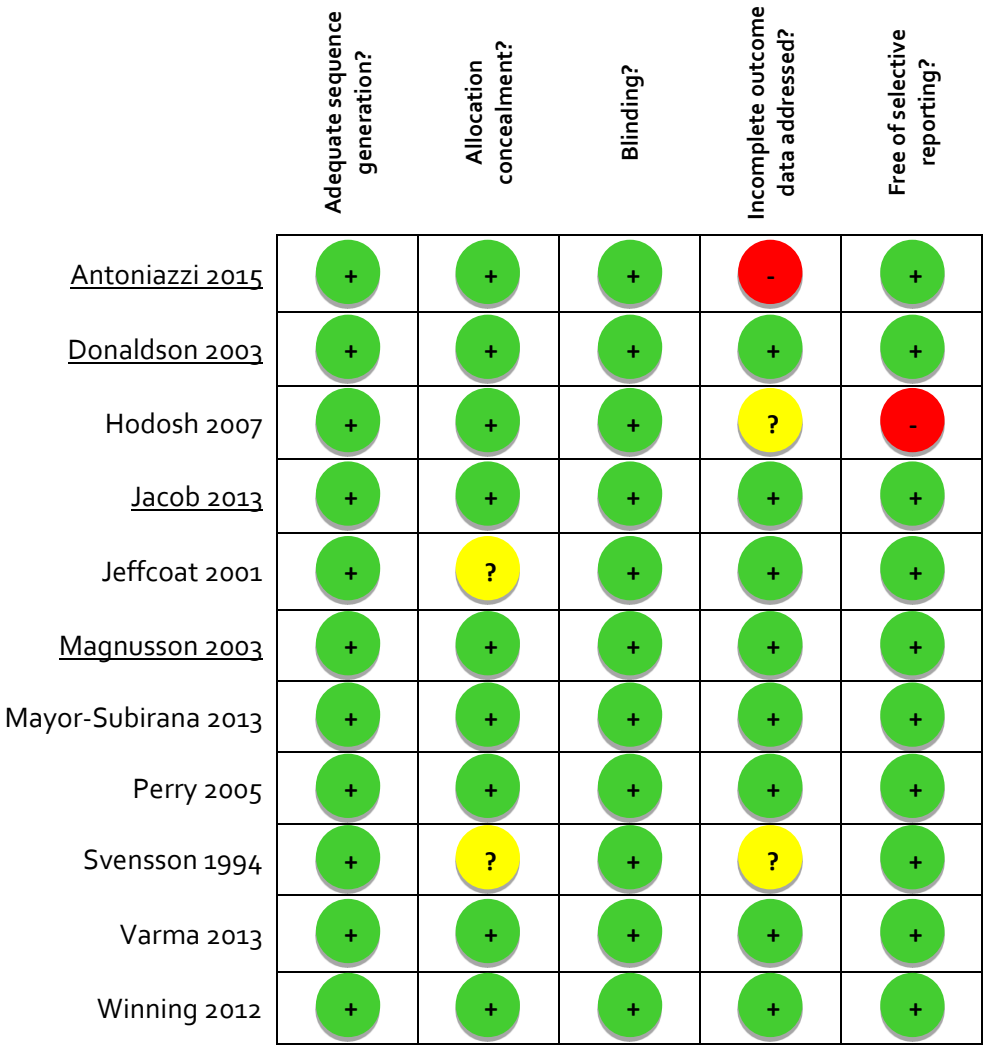

Fig 2 – Summary of the risk of bias assessment according to the Cochrane Collaboration tool. Underlined authors provided extra information by e-mail to allow assessment of the risk of bias.

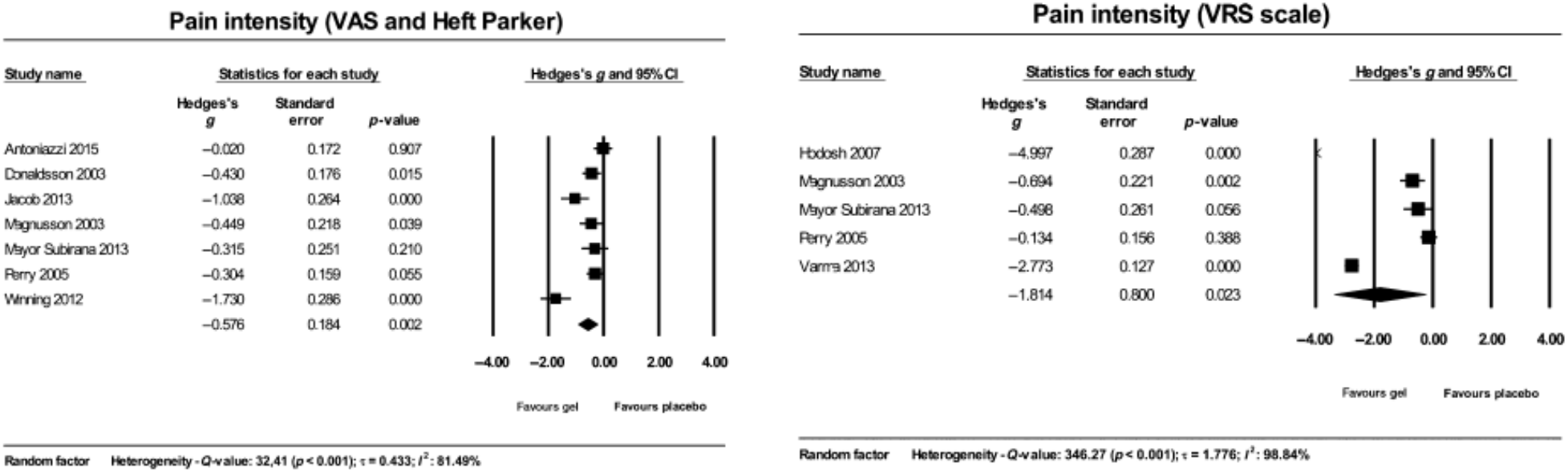

Fig. 3. Forest plots of the intensity of pain measured with the VAS and Heft–Parker pain scales and the VRS pain scales.

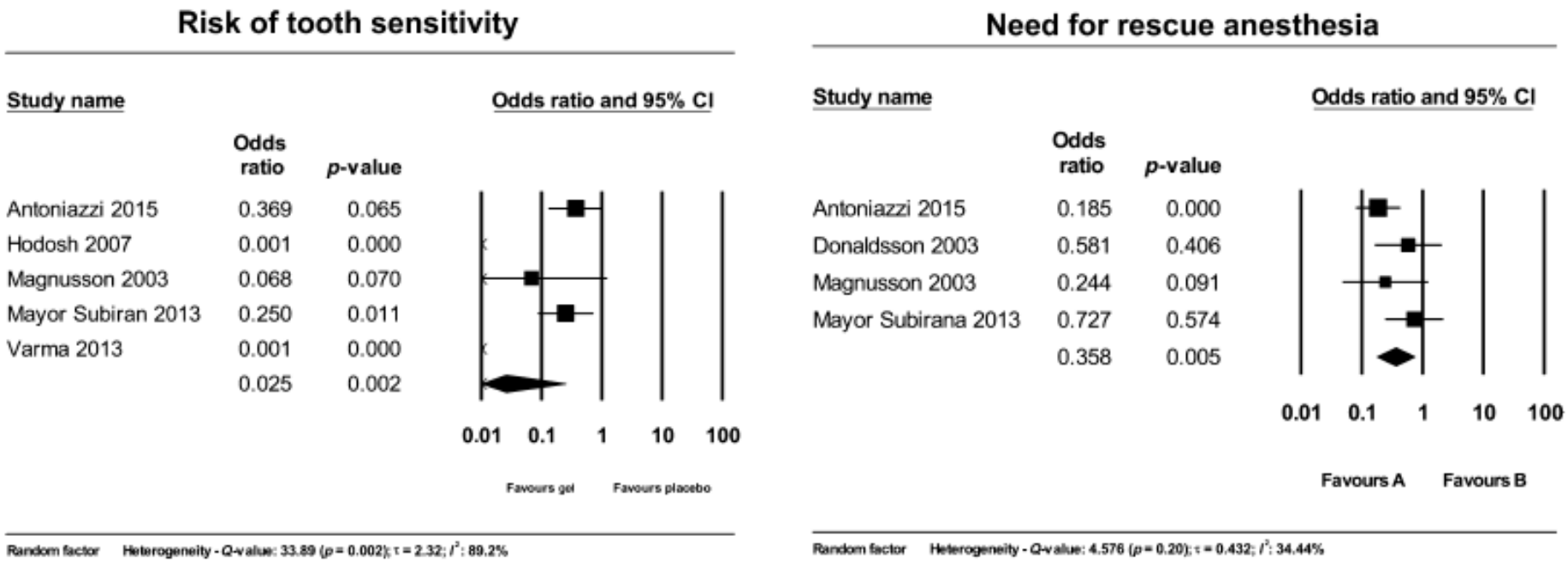

Fig. 4. Forest plots of the risk of pain and the need for rescue anaesthesia.

ARTIGO 2

TÍTULO: INTRA-POCKET ANESTHESIA X INJECTED ANESTHESIA FOR PAIN CONTROL DURING SCALING AND ROOT PLANNING IN ADULT PATIENTS: SYSTEMATIC REVIEW AND META-ANALYSIS

STATUS: ACEITO PARA PUBLICAÇÃO

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Intra-pocket anesthesia X injected anesthesia for pain control during scaling and root planning in adult patients: Systematic review and meta-analysis

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Abstract

Background: This systematic review/meta-analysis evaluated the pain during scaling and root planing (SRP) using topical anesthesia versus injected anesthesia in adult patients.

Methods: Seven databases were searched for randomized clinical trials comparing clinical effctiveness of intra-pocket and injectable anesthesia. The primary outcome was the risk/intensity of pain. Quality assessment followed the guidelines from the risk of bias tool from the Cochrane Collaboration. Meta-analysis was performed on studies considered at low risk of bias.

Results: From 976 articles identified, 6 remained in the qualitative synthesis (4 at “low”; 2 at “unclear” risk of bias). Difference for the risk of pain was 1.49 ($p = 0.58$) and for pain intensity was -0.45 ($p = 0.03$), favoring injected anesthesia. The OR for the need of rescue anesthesia was 14.35. Rescue anesthesia was less required with injected anesthesia ($p < 0.0001$). There was no difference in patients’ preference (OR =2.39; $p = 0.09$).

Conclusions/ Practical Implications: The injected anesthesia decreases the intensity of pain and the need for rescue anesthesia during SRP, but the risk of pain yielded similar results for injected and topical anesthesia.

Key words: periodontal diseases; anesthesia, dental; pain; anesthetics, local.

1. Introduction

Conventional treatment can be controled by scaling and root planing (SRP) [1]. This procedure can be painful and uncomfortable for some patients [2, 3], and about 30 to 40% of them ask for local anesthesia for pain control [4, 5].

The most common anesthesia during SRP is the infiltrative anesthesia [6], but it has been associated with anxiety and pain, fear of needle and discomfort due to the anesthetic effect in soft-tissues [5, 7, 8]. Furthermore, the use of local anesthesia reduces the acceptance of SRP [9-11]. An alternative to control pain during SRP could be the intra-pocket topical anesthesia [12-14].

Topical anesthetics have shown promising results for pain control during SRP and good acceptance by the patients[3, 12, 15]. They are presented in different delivery methods, such as ointment (Benzotop, DFL, Rio de Janeiro, RJ), cream (EMLA, AstraZeneca, RεDSödertälje, Sweden), gels (Oraqix,Dentsply, York, PA, USA) and adhesives (DentiPatch™, Inc., Miami, FL, USA) [16-18].

A recently systematic review and meta-analysis showed better results for intra-pocket anesthesia compared to placebo during SRP, as it reduced the risk, intensity of pain and the need for rescue anesthesia under periodontal diagnosis and treatment [19]. The next step in this research line would be the comparison between intra-pocket anesthesia and injected anesthesia, since the literature has not reached consensus: there are reports that intra-pocket anesthesia can be more effective [16], equivalent [3] or less effective than injectable anesthesia [6, 15, 20].

In order to synthesize the information about this subject, we performed a systematic review that addressed the following PICO question: Could an infiltrative anesthesia be replaced by topical anesthesia during SRP to control pain in adults? Our null hypothesis was that that there is no difference in pain levels when using intra-pocket anesthesia or injectable anesthesia.

2. Materials and methods

The methodology described here followed the sequence from a previous systematic review and meta-analysis published by our research group [19]. In both

reports, we followed the PRISMA statement [21]. The differences between the two research protocols are described bellow.

2.1 Protocol and registration

This study was accomplished from April to July of 2016 at the State University of Ponta Grossa, Paraná, Brazil and registered in the PROSPERO database (CRD42016032380).

2.2 Information sources and search strategy

The search strategy was developed based on the concepts of population (P), intervention (I) and comparison (C) from the PICO question. Within each concept, the controlled vocabulary (MeSH terms) and free keywords were combined with the boolean operators “OR” and “AND” (Table 1).

The electronic databases searched are described in Table 1. We also searched the reference lists of all primary studies and conference abstracts from the International Association for Dental Research (IADR) (1990–2015). Grey literature was inspected using the System for Information on Grey Literature in Europe (SIGLE). ProQuest Dissertations and Theses Full Text databases and the Periódicos Capes Theses database were also searched. Ongoing trials were searched in the same registries described in an earlier publication [19]. We placed no restrictions on publication date or languages.

2.3. Eligibility criteria

We included randomized clinical trials (RCTs) with parallel, crossover or split-mouth designs in humans. Similarly to an earlier publication [19], we excluded studies if: 1) other types of periodontal procedures besides SRP were employed; 2) the topical anesthetics were not compared with an infiltrative anesthesia or 3) the participants took analgesics or anti-inflammatory drugs before SRP.

2.5. Study selection and data collection process

After database screening, duplicates were removed and possible eligible articles were selected by title and abstracts. Full-text articles were obtained and classified according to the inclusion criteria by two reviewers (L.M.W. and J.L.G). Pilot tested customized extraction forms were used to register details about the

studies [19]. Papers reporting data from the same study with different follow-ups were extracted directly into a single data collection form to avoid overlapping data.

If more than two anesthetic gels or infiltrative anesthesia were tested, data were combined to make a single entry. We collected the pain from most immediate period and merged data from multiple clinical sessions of SRP when reported.

2.7 Risk of bias in individual studies

We used the Cochrane Collaboration tool for assessing risk of bias in RCTs [22] as performed previously [19]. Two independent reviewers performed this task (L.M.W. and J.L.G.). The domains evaluated are described in Figure 1. In case of any disagreement, a third reviewer were consulted (A.R.).

Each domain was judged to be at “low”, “unclear” and “high” risk of bias according to Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http://handbook.cochrane.org). Two out of the six domains were considered as the key domains in this systematic review: sequence generation and allocation concealment. At the study level, a study was considered to be at “low” risk of bias if the key domains were judged to be at “low” risk of bias. The study was considered to be at “unclear” risk if one domain was judged at “unclear” risk. And finally, the study was considered to be at “high” risk when at least one of the key domains were judged to be at “high” risk of bias. We contacted the authors to obtain more information for judgment the study.

2.8 Summary measures and synthesis of the results

The selected papers for meta-analysis were those classified as at “low” or at “unclear” risk of bias in the key domains. We calculated the Hedge’s g standardized mean difference for the continuous data (pain intensity) and the odds ratio (absolute risk of pain, need for rescue anesthesia and patient’s preference of the anesthesia) for dichotomous outcomes along with the 95% confidence interval (CI).

We applied the random effects models and assessed heterogeneity using the Cochran Q test and I^2 statistics. Subgroup analysis was performed based on the risk of bias of the included articles. The analyses were conducted using CMA software (version 3, Biostat Englewood, USA).

In case of paired data, observed in split-mouth or cross-over designs, we arbitrarily imputed an external correlation of 0.5, due to lack of availability this correlation in any of the studies. The use of lower (0.1) and higher (0.9) external correlations were evaluated in a sensitivity analysis. In case of heterogeneity sensitivity analysis was also used in an attempt to detect the reason.

3. Results

We send e-mails to five authors for additional information about the articles [3, 6, 16, 20, 23]; two of them didn't reply. [6, 23].

3.1. Study selection

The database screening resulted in 976 studies after the removal of the duplicates (Figure 2). Forty studies remained after the title screening; 17 after examination of the abstracts and their full texts. Eleven papers were excluded: 1) they did not use infiltrative anesthesia [14, 24-26], 2) they did not use an active anesthetic gel [27-29], 3) they used a patch to assess the healing after the SRP [30], 4) topical anesthetic was used to relieve the punch of needle [31], 5) literature review study [5] and 6) duplicate study [32].

3.2 Characteristics of included articles

Table 2 shows the characteristics of the six selected studies. The study designs were split-mouth [3, 15, 16, 20, 23] and cross-over [6]. The samples were composed of 21 to 170 patients (mean age of 48 years) and the percentage of males ranged from 20 to 71%.

The inclusion criteria in five studies was the pocket depth of at least 4 mm or 5 mm in different sites or quadrants. The evaluation of the descriptive data (mean, median and range) allowed us to arbitrarily infer that the majority of periodontal sites used for evaluation of pain were deep (four studies) or moderate pockets (two studies) [6, 15].

The topical anesthesia used in the RCTs was: Oraqix® [15], Emla cream® [6], and benzocaine gel [20] ; three studies evaluated the effect of Emla® and Benzotop® [3]; another study used the Emla® and Lidocaine Patch ® [16] ; the last one employed Precaine 8% with 0.8% dibucaine and Wocaine® gel [23].

The anesthetics used for infiltrative anesthesia varied among the studies: three used 2% lidocaine with epinephrine/adrenaline [3, 6, 20]; one used articaine with epinephrine [15]; one study used injectable anesthesia without vasoconstrictor [23] and one used electronic anesthesia [16].

The anesthetic gel was left in the periodontal pocket before starting the SRP for 30s to 2 min (Table 2) in most of the studies [3, 6, 20]. One of them reported a waiting protocol of 5 min to 13 min, depending on the anesthetic topic used [16] and two studies [15, 23] did not report this feature. The duration of the SRP procedure ranged from 41 min to 79 min [3, 6, 20], but this information was not reported in three studies [15, 16, 23].

The treatment protocol from all the six studies selected was nonsurgical. Two studies [3, 16] used hand instruments, three studies [6, 15, 20] used ultrasonic scaler and hand instruments and one [23] did not report the type of instrument used for SRP.

The type of rescue anesthesia was inconstant among studies. In two studies, the authors employed the same type of anesthesia previously employed [6, 16], in another study, the same anesthetic gel plus injectable anesthesia were used [3]. In another study, the authors used only injectable anesthesia [20]. This information was not reported in one study [23], and the authors excluded the patients who experienced pain during SRP in another one [15].

The absolute risk and pain intensity were evaluated in four studies [3, 15, 16, 23]. In one study [20], the authors just evaluated the pain intensity and in another one [6], the authors did not evaluated the absolute risk and pain intensity.

3.3 Assessment of the risk of bias

From the six studies, two were considered to have “unclear” risk of bias [6, 23], and four [3, 15, 16, 20] were considered to be at “low” risk in the key domains of the Cochrane risk of bias tool (Figure 1).

3.4 Meta-analysis

This procedure was performed on studies classified as being at “low” and “unclear” risk of bias and from which the information could be extracted. Subgroup analysis by risk of bias was also performed.

3.4.1 Intensity of pain using VAS and Heft Parker pain scales

The Intensity of pain with these scales was analyzed based on five studies [3, 15, 16, 20, 23]. The overall standardized difference in the means was -0.45 (95% CI = -0.62 to -0.27; p = 0.03) when all studies were included in the data synthesis. This demonstrates that infiltrative anesthesia was more effective in reducing the intensity of pain (Figure 3). When we observe only the data from studies at "low" risk of bias, no differences among groups were observed, probably due to the low number of studies in this subgroup. Data related to pain intensity based on the VAS and Heft Parker scales were heterogeneous (chi^2 test p < 0.0001; I^2 = 82.9%; Figure 3).

3.4.2 Risk of pain

Four studies [3, 15, 16, 23] were employed in this analysis. The odds ratio was 1.49 (CI= 0.44 - 5.10; p = 0.58), which shows that the anesthetic gel does not have a positive impact on reducing the risk of pain during SRP (Figure 3) compared to the infiltrative anesthesia. The overall meta-analysis, including studies at "low" and "unclear" risk of bias and the one run with the studies at "low" risk of bias yielded similar results. The data were heterogeneous (chi-square test p < 0.0001; I^2 = 93.7%; Figure 3).

3.4.3 Need for rescue anesthesia

Four studies at "low" risk of bias [3, 15, 20] were included in this analysis. As no event was observed in one study [16], the effect size for this study could not be computed, it was not used for the meta-analysis or added to the forest plot. The odds ratio was 14.355 (95% CI= 3.45 - 59.72; p < 0.0001). This allowed us to reject the null hypothesis that the anesthetic gel has no impact on the need for rescue anesthesia (Figure 4). No evidence of heterogeneity was found (chi-square test p = 0.97; I^2 = 0 %; Figure 4), which means that all the studies included in the analysis probably share a common effect size.

3.4.4 Patients' preference

This analysis was based on four studies [6, 15, 20, 23]. The overall odds ratio was 2.39 (95% CI= 0.85 to 6.72 ; p = 0.09). The null hypothesis that there isn't a significant difference in the patients' preference of either injection or anesthetic gel was not rejected. The overall meta-analysis, including studies at "low" and

"unclear" risk of bias and the one ran only with studies at "low" risk of bias yielded similar results. Evidence of heterogeneity was found (chi^2 test $p < 0.0001$; $I^2 = 85.4\%$; Figure 4), which means that all the studies included in the analysis probably share a common effect size.

3.4.6 Sensitivity analysis

For extreme conditions, the change of the external correlation (external correlations of 0.1 and 0.9) did not affect the results of any of the meta-analyses performed as part of this study. Through a sensitivity analysis, we could identify that the study of Pandit et al. [16] was responsible for the high heterogeneity detected by the Q-statistics in the meta-analysis of pain intensity.

The low number of studies included in the meta-analysis of risk of pain and patients' preference prevented us from identifying the reasons for the high heterogeneity in these meta-analyses.

3. Discussion

Systematic reviews and meta-analysis are the top of the pyramid of scientific evidence [33]. This modality of research is able to critically evaluate and summarize all the research available for a particular issue [34]. The confidence in the results obtained in this type of scientific research is based on a rigid methodology that selects and evaluates clinical trials [34, 35].

When performing a systematic review and meta-analysis, we opt to include only studies with good metrological quality, which guarantees the confidence in our final conclusion [34, 35]. Particularly in this paper, we considered the randomization and allocation concealment as critical domains, which assure us that there is no tendency of authors to use a more appropriate treatment for a given patient [22]. These criteria are part of the CONSORT Statement (Consolidated Standards of Reporting Trials), which is a list of all the steps that a clinical study should take to avoid bias in the results and misinterpretation of the data[36, 37].

Papers that didn't fulfilled the requirements of methodology described were removed from this systematic review. By doing so, we assured that the results evaluated were not biased. Therefore, the conclusions based on the remaining papers correspond to the clinical reality.

Randomization and allocation concealment were considered the key domains of the present systematic review. Correct randomization guarantees that the chances of a patient being allocated in either test or control group is the same for all participants, which means that both known and unknown prognostic factors are balanced between groups [22]. The allocation concealment is necessary to protect the randomization process, since the treatment to be allocated is not known before the patient is enrolled into the study [22]. Four [3, 15, 16, 20] out of the six studies included in the qualitative synthesis were classified as having “low” risk of bias in these two domains and this information could not be obtained for the other two studies [6, 23], making them classified as “unclear” in the key domains.

Blinding the study participants and personnel may avoid performance bias [22]. For the present systematic review, participants’ blinding in the primary studies was difficult to perform, as injectable anesthesia could be easily identified by the patients, which is the reason of why this was not considered a key domain for the present systematic review.

The exclusion of 99% of the papers are very common among readers. Searches for systematic reviews aim to be as extensive as possible to ensure that as many as possible of the necessary and relevant studies are included in the review. When we are preparing the search strategy we should seek high sensitivity (comprehensiveness) to not miss any possible article in the field. Increasing sensitivity (number of relevant reports divided by the total number of reports in existence) we reduce precision (number of relevant papers divided by the total number of articles retrieved).

Consequently, the search results will include a high number of non-relevant articles that are mostly removed by title reading and when in doubt by abstract and full-text reading. This is the reason of why we start we a high number of papers and end up with only few on the topic. In summary, we cannot say that we exclude 99% of the articles; what we may say is that the disadvantage of making a very comprehensive search is that a very high number of non-relevant articles will be retrieved.

For an evidence-based perspective, only systematic reviews and meta-analysis may solve the problem of controversies among different clinical trials.

Clinical recommendations performed by a panel of experts in different specialties rely on the results of systematic review and meta-analysis.

Recently, our research group conducted a systematic review comparing topical intra-pocket anesthetic gels to placebo on their ability to reduce the risk and intensity of pain and the need for rescue anesthesia during probing and/or SRP. We showed that intra-pocket anesthetics were more effective than placebo [19]. However, we noticed during this investigation that there were some studies that compared the intra-pocket anesthetic gel with infiltrative anesthesia, which motivated us to conduct the present systematic review.

Differently from the earlier systematic review [19], few primary studies in the present one were classified as being at “low” risk of bias. Most of them were judged as “unclear” in the key domains, even after attempts to contact their authors. Unfortunately, responses were obtained only from three sets of authors [3, 16, 20].

It was noted in this study that the injectable anesthesia in the periodontal pocket and/or gingival tissue, compared to intra-pocket anesthesia, reduced the intensity of pain and the need for rescue anesthesia during SRP in the overall meta-analysis (with studies at “low” and “unclear” risk of bias). These results were expected as the injectable anesthesia blocks the nerve fibers by binding to specific receptors on sodium channels, which results in blocked pain perception at the periphery of the nerve ending and also in the deeper tissue region [38, 39]. In addition, infiltrative anesthesia is able to block pain in the tooth and tissue around the site where the procedure is being performed.

Injectable anesthesia shows longer duration compared to topical anesthesia [15, 40], and also produces a vasoconstrictor effect that increases the length of anesthetic action [41, 42]. Intra-pocket anesthetics have a limited capacity of penetration, since they have to overpass the keratinized cells that protect the outer layer of the oral mucosa. They act by blocking the transmission of signals from the terminal fibers of the sensory nerves, but their effects are limited to control the painful stimuli occurring on or just beneath the mucosa [43], without anesthesia of the tooth.

Notwithstanding, intra-pocket anesthesia is effective in controlling risk of pain and pain during SRP [19], when compared to placebo. Patients describe this

procedure as a friendly one, that don't trigger anxiety and fear. There is also reports of patients that prefer this kind of anesthesia over the infiltrative trechnique[16].

Moreover, intra-pocket anesthesia has short duration of action [11], lasting around 15-20 min [9], while injection anesthesia lasts more than one hour [44]. This short period of analgesia may limit the usage of intra-pocket anesthetic gels [6], being necessary the rescue anesthesia (another application of topic anesthetic or infiltrative anesthesia).

The aimed to compare all the available anesthetics with infiltrative anesthesia for pain control during SRP. We asked a very broad question regardless of the brand and active component of the active gel. The decision to join them together is that they are all amide-based anesthetics with a similar mechanism of action which is the blockage of the calcium canals [38, 39]. The difference between them is the vehicle of application and the type of amide, but they all have to overcome the mucosa to reach the sensory fibers[43]. In this purpose, we considered these studies similar enough to be provide a summary estimate for the PICO question.

There is a variation in duration time, presentation form and effect of each anesthetic agent. Most topical anesthetics had amida group in their composition. Such was Oraqix® is a topical anesthetic gel with thermosetting agents (at room temperature, it is a low-viscosity fluid, whereas at body temperature, it becomes an elastic gel) and contains lidocaine and prilocaine as active ingredients [12, 15]. Emla® is a eutectic mixture of local anesthetics with lidocaine and prilocaine active ingredients presented as a cream [3, 16]. Patch is a trans-mucosal anesthetic that contains lidocaine [16]. Precaine and Wocaine presented in the form of gel and contain lidocaine as active ingredients [23]. Benzotop® are presented in the form of a gel and contain benzocaine as the active ingredient [3, 20]. Despite the fact that Emla® and Oraqix® have similar active anesthetic components, Oraqix® has more advantages than Emla® such as the quick onset of action and the ability to stay in place after application. As Emla® is not delivered in a thermosetting agent, it tends to be diluted by saliva [45]. Although benzocaine-based anesthetic gels are very common and

widely used in dentistry[3] , this type of anesthetic salt has inferior analgesia potential compared to lidocaine and prilocaine [3, 45].

A high heterogeneity of the pain intensity was observed probably due to different clinical inclusion criteria and probing depths evaluated, ranging from 3.6.mm [6] to equal or more than 5 mm [20]. From a clinical point of view, the inclusion criteria should be a mean probing depth of 5 mm [16]. Considering this, it is known that deep pockets are more sensitive to pain than shallow pockets [46]. The heterogeneity may have also occurred due to the study of Pandit et al. [16], as demonstrated in the sensitivity analysis. Contrary to the other included RCTs, this was the only study that employed electronic anesthesia and perhaps this is the reason for the trend being different from the other RCTs.

In terms of risk of pain, however, we did not observe any significant difference between the two analgesia methods. This means that, somewhere during treatment, patients feel pain regardless of the method of analgesia employed. Although injectable anesthesia produced lower intensity of pain during SRP than intra-pocket anesthesia, the pain caused by needle puncture is uncomfortable [47, 48]. In such situation, patients who received injectable anesthesia may have perceived lower pain during SRP, but felt pain during puncture. Instead, patients who received intra-pocket anesthesia did not felt pain during gel application but experienced more pain during SRP. Therefore, from a practical clinical endpoint, the patients can be advised about the advantages and disadvantages of each anesthesia method. For most of the patients who suffer from anxiety and fear of needle the second option would be more recommended.

By calculating the overall risk of pain for both groups by combining the data from all included studies, we have an additional evidence of the similar risk of pain in both groups. In the meta-analysis of the risk of pain, we summed the number of events in all studies and divided them by the total number of participants from the studies included in the meta-analysis. This allowed us to make the calculation of the overall risk of pain for both anesthetic methods. The risk of pain of the intra-pocket anesthesia was 69.6 (95% CI 61.1 to 77.0), which is quite similar to that of the injectable anesthesia (55.2 [95% CI 46.5 to 63.6]).

Due to the higher pain intensity in the intra-pocket anesthesia group, the higher need for rescue anesthesia in this group was somewhat expected. The more superficial analgesia effect, inflammation or bone loss generated by periodontal disease [46, 49] associated with the variations in the force exerted by the operators during the SRP [50, 51] and the dilution of the topical anesthetic by saliva, may require additional anesthesia during the procedure.

The SRP varies from 41 to 79 minutes, intra-pocket anesthesia has short duration of action [11], lasting around 15-20 min [9], usually when the effect of anesthesia passed, the authors reported the use of rescue anesthesia that varied between infiltrative anesthesia or reapplication of the topical anesthetic used in the study [3, 6, 16]. The variation of the time to perform the procedure reflect what occurs in the daily practices and this variation is reflected in the 6 studies [3, 6, 15, 16, 20, 23].

The meta-analysis of the patients' preference did not show differences between groups, however, one might see a trend towards patients' preference for intra-pocket anesthesia. In spite of the better analgesic effect produced by the infiltrative anesthesia, it is likely that the fear of needle puncture [5, 7, 8]can yield to a higher preference for topical anesthetics. Well-designed randomized clinical trials should be conducted to focus on patient-centered outcomes and perhaps to evaluate the use of repeated applications of intra-pocket anesthesia during the SRP.

Anesthetic methods impact the results of periodontal therapy because they reduce pain and discomfort in patients[19]. As a direct consequence, the patients accepted the periodontal maintenance appointments more often [3, 6]. The possibility of an anesthetic technique without needle and numbness after treatment may contribute to patient's adhesion to the treatment, which make topical anesthetics a good alternative for patients undergoing non-surgical periodontal procedures[3].

In general, we could observe that the injectable anesthesia was superior to topic anesthesia during SRP as it reduced the intensity of pain and the need for rescue anesthesia during SRP.

Conclusions

Injectable anesthesia was superior to topical anesthesia during SRP as it reduced the intensity of pain and the need for rescue anesthesia during periodontal treatment. There was no superiority on patients' preferences and the risk of pain yielded similar results for injected and topical anesthesia.

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Figure and Table legends:

Figure 1 – Summary of the risk of bias assessment according to the Cochrane Collaboration tool. Underlined authors provided extra information by e-mail to allow assessment of the risk of bias.

Figure 2 – Flow diagram of study identification.

Figure 3- Forest plots of the pain intensity measured with the VAS and Heft-Parker pain scales and the risk of pain.

Figure 4- Forest plots of the need for rescue anesthesia and the patient's preference.

Table 1 – Electronic database and search strategy**.**

Table 2-Summary of the studies selected for this systematic review.

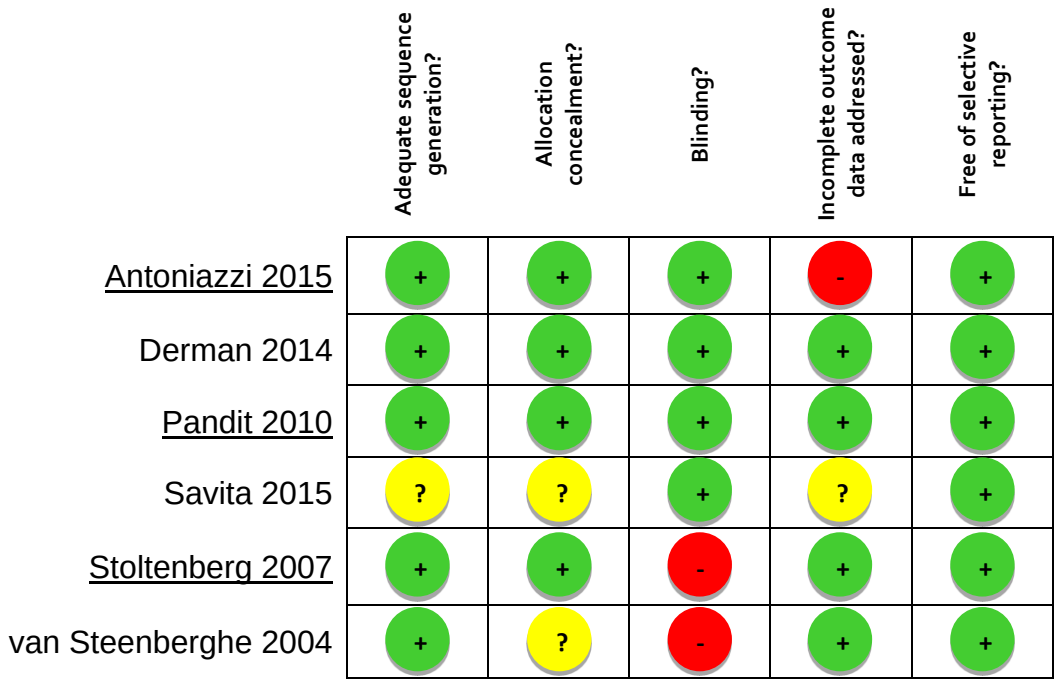


Figure 1 – Summary of the risk of bias assessment according to the Cochrane Collaboration tool. Underlined authors provided extra information by e-mail to allow assessment of the risk of bias.

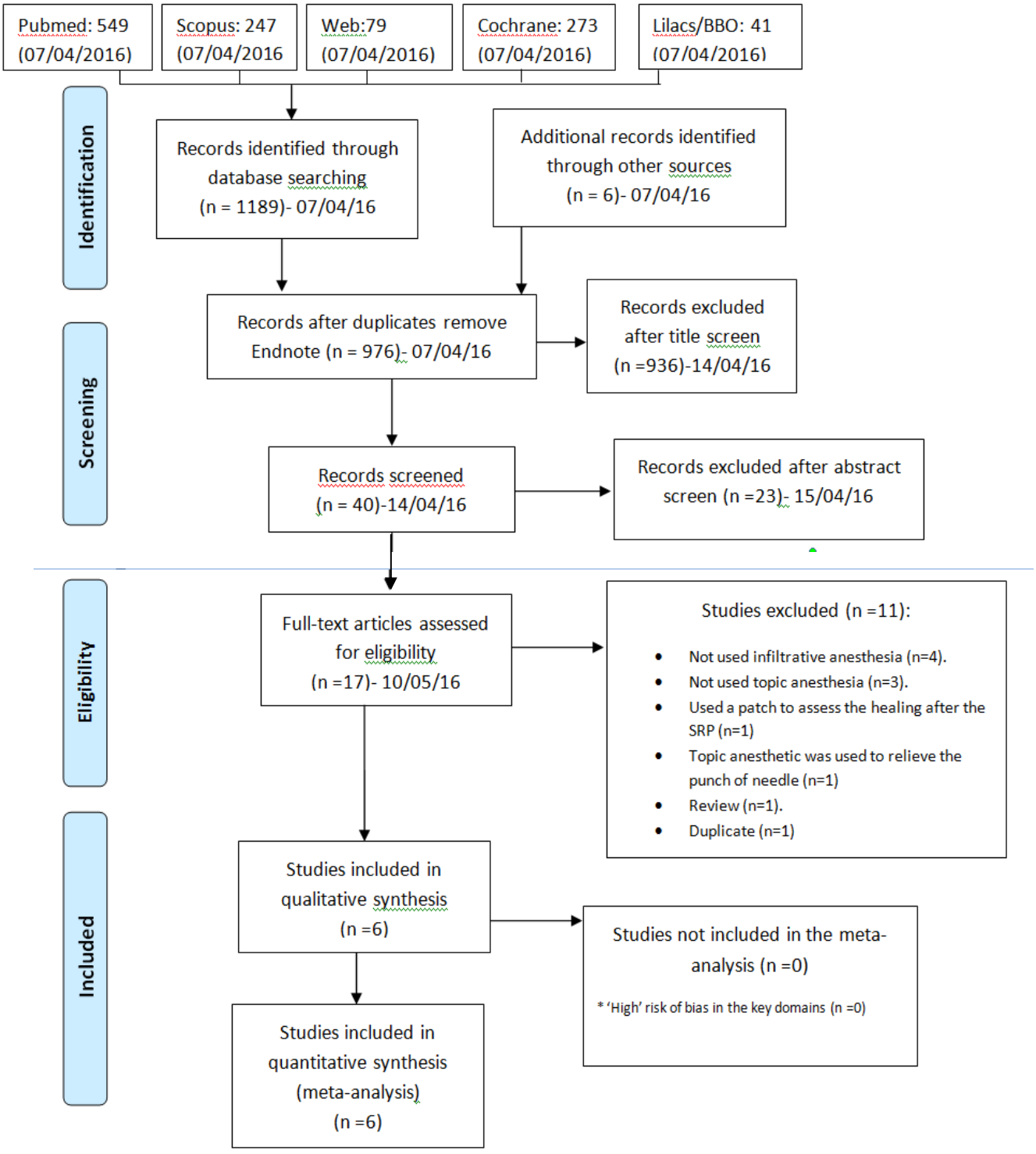


Figure 2 – Flow diagram of study identification.

Table 1 – Electronic database and search strategy.

Pubmed= 549 (07/04/2016)		
#1 Dental scaling[MeSH Terms]) OR Gingivitis[MeSH Terms]) OR Periodontitis[MeSH Terms]) OR Periodontal diseases[MeSH Terms]) OR "Periodontal maintenance"[Title/Abstract]) OR "Gingival tissue"[Title/Abstract]) OR "Periodontal tissue"[Title/Abstract]) OR "Periodontal pocket"[Title/Abstract]) OR "Periodontal recall"[Title/Abstract]) OR "Periodontal therapy"[Title/Abstract]) OR "Scaling and root planing"[Title/Abstract])) OR SRP[Title/Abstract]) OR "Periodontal treatment"[Title/Abstract]) OR "Root planing"[Title/Abstract]) OR "Scaling root planing"[Title/Abstract]) OR Ultrasonic scaler*[Title/Abstract]) OR "Non surgical periodontal"[Title/Abstract]) OR "Nonsurgical periodontal"[Title/Abstract]))	**#2** Anesthesia, dental[mh:noexp]) OR Carticaine[MeSH Terms]) OR Emla[Supplementary concept]) OR Lidocaine[MeSH Terms]) OR Prilocaine[MeSH Terms]) OR Benzocaine[MeSH Terms]) OR Tetracaine[MeSH Terms]) OR "Non injectable"[Title/Abstract]) OR "Gel anaesthetic"[Title/Abstract]) OR "Gel anesthetic"[Title/Abstract]) OR "Intrapocket anesthesia"[Title/Abstract]) OR "Intrapocket anaesthesia"[Title/Abstract]) OR "Intrapocket anesthetic"[Title/Abstract]) OR "Intrapocket anaesthetic"[Title/Abstract]) OR "Dental anesthesia"[Title/Abstract]) OR "Dental anaesthesia"[Title/Abstract]) OR "Local anesthetics"[Title/Abstract]) OR "Local anaesthetics"[Title/Abstract]) OR "Topical anesthetic"[Title/Abstract]) OR "Topical anaesthesia"[Title/Abstract]) OR "Topical administration"[Title/Abstract]) OR Articaine[Title/Abstract]) OR "Emla cream"[Title/Abstract]) OR Emla[Title/Abstract]) OR Oraqix[Title/Abstract]) OR Hurricaine[Title/Abstract]) OR Ropivacaine[Title/Abstract]) OR "Electronic anesthesia"[Title/Abstract]) OR "Injectable anesthesia"[Title/Abstract]) OR "Injectable anaesthetic"[Title/Abstract]) OR "Infiltration anesthesia"[Title/Abstract]) OR "Injectable anesthetic"[Title/Abstract]) OR "Infiltration anaesthesia"[Title/Abstract]) OR "Injectable anesthesia"[Title/Abstract]) OR "Computerized anesthesia"[Title/Abstract]) OR "Traditional anesthesia"[Title/Abstract]) OR "Conventional anesthesia"[Title/Abstract]) OR "Computerized anaesthesia"[Title/Abstract]) OR "Traditional anaesthesia"[Title/Abstract]) OR "Conventional anaesthesia"[Title/Abstract])	**#3** (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh]))
#1 AND #2 AND #3		
Scopus= 247 (07/04/16)		
#1TITLE-ABS-KEY ("dental scaling") OR TITLE-ABS-KEY (gingivitis) OR TITLE-ABS-KEY (periodontitis) OR TITLE-ABS-KEY ("periodontal diseases") OR TITLE-ABS-KEY ("periodontal maintenance") OR TITLE-ABS-KEY ("gingival tissue") OR TITLE-ABS-KEY ("periodontal tissue") OR TITLE-ABS-KEY ("periodontal pocket") OR TITLE-ABS-KEY ("periodontal recall") OR TITLE-ABS-KEY ("periodontal therapy") OR TITLE-ABS-KEY ("root planing") OR TITLE-ABS-KEY (srp) OR TITLE-ABS-KEY ("periodontal treatment") OR TITLE-ABS-KEY ("ultrasonic scaler*") OR TITLE-ABS-KEY ("nonsurgical periodontal"))	**#2** (TITLE-ABS-KEY ("dental anesthesia") OR TITLE-ABS-KEY (carticaine) OR TITLE-ABS-KEY (emla) OR TITLE-ABS-KEY (lidocaine) OR TITLE-ABS-KEY (prilocaine) OR TITLE-ABS-KEY (benzocaine) OR TITLE-ABS-KEY (tetracaine)OR TITLE-ABS-KEY ("non injectable") OR TITLE-ABS-KEY ("gel anaesthetic") OR TITLE-ABS-KEY ("intrapocket anesthe*") OR TITLE-ABS-KEY ("dental anesthesia") OR TITLE-ABS-KEY ("local anesthetics") OR TITLE-ABS-KEY ("topical anesthe*") OR TITLE-ABS-KEY ("topical administration") OR TITLE-ABS-KEY (articaine) OR TITLE-ABS-KEY ("emla cream") OR TITLE-ABS-KEY (oraqix) OR TITLE-ABS-KEY (hurricaine) OR TITLE-ABS-KEY (ropivacaine)OR TITLE-ABS-KEY ("electronic anesthesia") OR TITLE-ABS-KEY ("injectable anesthe*") OR TITLE-ABS-KEY ("infiltration anesthesia") OR TITLE-ABS-KEY ("computerized anesthesia") OR TITLE-ABS-KEY ("traditional anesthesia") OR TITLE-ABS-KEY ("conventional anesthesia"))AND (LIMIT-TO (SUBJAREA , "**DENT**"))	
#1 AND #2		

Web of Science- 79 (07/04/2016)	
#1 TOPIC: (“dental scaling”) *OR* **TOPIC:** (gingivitis) *OR* **TOPIC:** (periodontitis) *OR* **TOPIC:** (“periodontal diseases”) *OR* **TOPIC:** ("periodontal maintenance") *OR* **TOPIC:** ("gingival tissue") *OR* **TOPIC:** ("periodontal tissue") *OR* **TOPIC:** ("periodontal pocket") *OR* **TOPIC:** ("periodontal recall")*OR* **TOPIC:** ("periodontal therapy") *OR* **TOPIC:** ("root planing") *OR* **TOPIC:** (SRP) *OR* **TOPIC:** ("periodontal treatment") *OR* **TOPIC:** (“ultrasonic scaler$”) *OR* **TOPIC:** ("nonsurgical periodontal")	**#2 TOPIC:** (“dental anesthesia”) *OR* **TOPIC:** (carticaine) *OR***TOPIC:** (Emla)*OR* **TOPIC:** (lidocaine) OR **TOPIC:**(prilocaine) OR **TOPIC:**(benzocaine) OR **TOPIC:**(tetracaine)*OR* **TOPIC:** ("Non injectable") *OR* **TOPIC:** ("Gel an*sthetic") *OR* **TOPIC:**("Intrapocket an*sthe*") *OR***TOPIC:** ("Dental an*sthesia”) *OR* **TOPIC:** ("Local an*sthetics") *OR* **TOPIC:** ("Topical an*sthe*") *OR* **TOPIC:** ("Topical administration") *OR* **TOPIC:** (“Emla cream") *OR* **TOPIC:** (articane) OR **TOPIC:** (Oraqix) *OR* **TOPIC:**(hurricaine) OR **TOPIC:**(ropivacaine) OR **TOPIC:** ("electronic an*sthesia") *OR***TOPIC:** ("injectable an*sthesia") *OR* **TOPIC:** ("infiltration an*sthesia") *OR* **TOPIC:** ("computerized an*sthesia") *OR* **TOPIC:**("traditional an*sthesia") *OR* **TOPIC:** ("conventional an*sthesia")
#1 AND #2	
Lilacs and BBO= 41 (07/04/16)	
#1 (MH: "dental scaling" OR MH:gingivitis OR MH:periodontitis OR MH: "periodontal diseases" OR "periodontal maintenance" OR "manutenção periodontal" OR "mantenimiento periodontal" OR "gingival tissue" OR "tecido gengival" OR "tejido gingival" OR "periodontal tissue" OR "tecido periodontal" OR "tejido periodontal" OR "periodontal pocket" OR "bolsa periodontal" OR "saco periodontal" OR "periodontal recall" OR "recuperação periodontal" OR "recuperación periodontal" OR "periodontal therapy" OR "terapia periodontal" OR "scaling and root planing" OR "scaling root planing" OR "raspagem e alisamento radicular" OR "raspado y alisado radicular" OR SRP OR RAP OR RAR OR "periodontal treatment" OR "tratamento periodontal" OR "tratamiento periodontal" OR "Root planing" OR "alisamento radicular" OR "alisado radicular" OR "ultrasonic scaler" OR "ultra som"OR "escarificador ultrasónico" OR "ultrasonic scalers" OR "ultra sônicos" OR "escarificador ultrasónicos" OR "non surgical periodontal" OR "periodontal não cirúrgico" OR "periodontal no quirúrgico")	**#2** (MH: "anesthesia, dental" OR MH:Carticaine OR MH:emla OR MH:lidocaine OR MH:prilocaine OR MH:benzocaine OR MH:tetracaine OR "No injectable" OR "não injetável" OR "no inyectable" OR "Gel anaesthetic" OR "Gel anesthetic" OR "gel anestésico" OR "Intrapocket anesthesia" OR "Intrapocket anaesthesia" OR "anestesia intrasulcular" OR "Intrapocket anesthetic" OR "Intrapocket anaesthetic" OR "anestésico intrasulcular" OR "Dental anesthesia" OR "Dental anaesthesia" OR "anestesia dental" OR "Local anesthetics" OR "Local anaesthetics" OR "anestésicos locais" OR "anestésicos locales" OR "Topical anesthetic" OR "Topical anaesthetic" OR "anestésico tópico" OR "Topical administration" OR "administração tópica" OR " administración tópica" OR Articaine OR articaína OR "Emla cream" OR "Emla creme" OR "Emla crema" OR Emla OR Oraqix OR Hurricaine OR Hurricaína OR Ropivacaine OR ropivacaína OR "electronic anesthesia" OR "anestesia eletrônica" OR "anestesia electrónica" OR "injectable anesthesia" OR "injectable anaesthesia" OR "anestesia injetável" OR "anestesia inyectable" OR "injectable anaesthetic" OR "injectable anesthetic" OR "anestésico injetável" OR "anestésico inyectable" OR "infiltration anesthesia" OR "infiltration anaesthesia" OR "anestesia infiltrativa" OR "computerized anesthesia" OR "computerized anaesthesia" OR "anestesia computadorizada" OR "anestesia computarizada" OR "traditional anesthesia" OR "traditional anaesthesia" OR "tradicional anestesia" OR "anestesia tradicional" OR "conventional anesthesia" OR "conventional anaesthesia" OR "convencional anestesia" OR "anestesia convencional")
#1 AND #2	
Cochrane Library = 273 (07/04/2016)	
#1 MeSH descriptor: [Dental Scaling] explode all trees **#2** MeSH descriptor: [Gingivitis] explode all trees **#3** MeSH descriptor: [Periodontitis] explode all trees **#4** MeSH descriptor: [Periodontal Diseases] explode all trees **#5** #1 OR #2 OR #3 OR #4 **#6** periodontal next maintenance:ti,ab,kw or gingival next tissue:ti,ab,kw or periodontal next tissue:ti,ab,kw or periodontal next pocket:ti,ab,kw or periodontal next recall:ti,ab,kw (Word variations have been searched) **#7** periodontal next therapy:ti,ab,kw or root near planing:ti,ab,kw or SRP:ti,ab,kw or periodontal near treatment:ti,ab,kw or ultrasonic near scaler*:ti,ab,kw (Word variations have been searched) **#8** nonsurgical next periodontal:ti,ab,kw (Word variations have been searched) **#9** #5 OR #6 OR #7 OR #8	**#1** MeSH descriptor: [Anesthesia, dental] explode all trees **#2** MeSH descriptor: [Carticaine] explode all trees **#3** MeSH descriptor: [Lidocaine] explode all trees **#4** MeSH descriptor: [Prilocaine] explode all trees **#5** MeSH descriptor: [Benzocaine] explode all trees **#6** MeSH descriptor: [Tetracaine] explode all trees **#7** #1 OR #2 OR #3 OR #4 OR #5 OR #6 **#8** non near injectable:ti,ab,kw or gel near anaesthetic:ti,ab,kw or intrapocket near anesthe*:ti,ab,kw or dental near anesthesia:ti,ab,kw or local near anesthetics:ti,ab,kw(Word variations have been searched) **#9** topical near anesthe*:ti,ab,kw or topical near anesthesia:ti,ab,kw or topical next administration:ti,ab,kw or articaine:ti,ab,kw or emla:ti,ab,kw(Word variations have been searched) **#10** oraqix:ti,ab,kw or hurricaine:ti,ab,kw or ropivacaine:ti,ab,kw or electronic near anesthesia:ti,ab,kw or injectable near anesthesia:ti,ab,kw(Word variations have been searched) #11 injectabled near anesthetic:ti,ab,kw or infiltration near anesthesia:ti,ab,kw or computerized next anesthesia:ti,ab,kw or traditional next anesthesia:ti,ab,kw or conventional near anesthesia:ti,ab,kw(Word variations have been searched) **#12** #7 OR #8 OR #9 OR #10 OR #11
#9 AND #12	

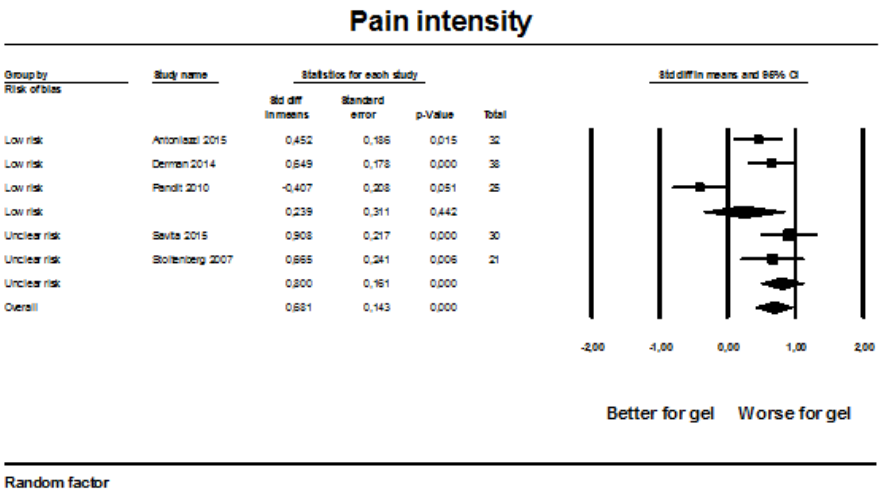
Table 2 - Summary of the studies included in this systematic review.

Study ID	Study design	Subjects' age mean±SD [range] (years)	No. of male subjects [%]	Total No. patients [drop-outs]	Presence of periodontal disease? [Severity]	Periodontal pocket depth (mm)	Topical anesthetic used	Injectable anesthetic used	Time anesthetic topic was left before treatment	Time used for SRP mean±SD (median)	Treatment phase (Type of SRP)	Outcomes evaluated		
												Was the patient's preference evaluated?	Was the need of rescue anesthesia evaluated? [type]	Pain
Antoniazzi et al 2015 (Antoniazzi et al.[29] 2015)	Split-mouth	49.4±9.4 [n.r.]	n.r. [n.r.]	41 [9]	Yes [gingivitis/ periodontitis]	≥5	Emla®: 5% [a] Benzotop®:2%[b]	2% lidocaine with epinephrine[h] 1:100,000	2 min	Emla®: 60.06 ±36.52 (n.r) Benzotop®: 61.25 ±36.32 (n.r) Injectable: 53.06 ±29.66 (n.r)	Non-surgical therapy (curettes)	No	Yes [the same anesthetic gel/ second application injectable anesthesia]	Absolute risk and pain intensity in VAS and VRS scales
Derman et al 2014 (Derman et al.[39] 2014)	Split-mouth	56±n.r. [27-73]	19 [50]	38 [5]	Yes [periodontitis]	≥4	Oraqix®:5% [c]	Articaine with epinephrine[i] 1:100,000	n.r.	n.r.	Non-surgical therapy (ultrasonic scaler /curettes)	Yes	Yes [were excluded]	Absolute risk and pain intensity in VAS and VRS scales
Pandit et al 2010 (Pandit et al.[40] 2010)	Split-mouth	n.r. [n.r.]	5 [20]	25 [0]*	Yes [chronic periodontitis]	≥5	Emla®: 5% [a] Patch® 20%, lidocaine[d]	Electronic Anesthesia	Emla: 5 min Patch: 5 a 13 min	n.r.	Non-surgical therapy (curettes)	Yes	Yes [the same anesthesia]	Absolute risk and pain intensity in VAS and VRS scales
Savita et al 2015 (Savita et al.[41] 2015)	Split-mouth	35.07 ± 6.44 [25-50]	21 [70]	30 [n.r.]	Yes [chronic periodontitis]	≥5	Precaine: 8% lidocaine + 0.8% dibucaine [e] Wocaine gel: 2% lidocaine[f]	2% Lidocaine[j]	n.r.	n.r.	Non-surgical therapy (n.r.)	No	n.r.	Absolute risk and pain intensity in VAS scales

Stoltenberg et al 2007 (Stoltenberg et al.[42] 2007)	Split-mouth	53±n.r. [32-78]	15 [71]	21 [6]	n.r.	≥5	Benzocaine gel: 20%[g]	2% lidocaine with epinephrine[h] 1:100,000	1- 2 min	Topic: n.r (55-130 min) Injectable: n.r (55-105 min)	Non-surgical therapy (ultrasonic scaler /curettes)	Yes	Yes [used infiltrative anesthesia]	Pain intensity in Heft Parker pain scales
Van Steenberghe et al 2004 (van Steenberghe et al.[8] 2004)	Cross-over	48 ±n.r. [25-72]	82 [48]	170 [13]	n.r.	3.6	Emla®: 5% [a]	2% lidocaine with adrenaline[k]	30 s	Topic: n.r (15-94 min) Injectable: n.r (10-85 min)	Non-surgical therapy (ultrasonic scaler /curettes)	Yes	Yes [the same anesthesia]	—

ID – identification; SD – standard deviation; n.r. – not reported; SRP- scaling and root planing; VAS (Visual Analog Scale):0 a 100-cm horizontal line with words "no pain" at one end and "worst pain" at the opposite end; VRS (Verbal Rating Scale): 0-4 - no pain, mild pain, moderate pain, severe pain, extremely severe pain; Heft-Parker scale:0- 170-cm horizontal line with words "no pain" at one end and "worst pain" at the opposite end;.*This information was obtained by e-mail contact with the author, -----: - not evaluated.

[a]Emla® 5%, AstraZeneca, RεD Södertälje, Sweden.
[b]Benzotop® 2%, DFL, Rio de Janeiro, RJ.
[c]Oraqix® 5%,Dentsply, York, PA, USA.
[d]Patch® 20% lidocaine: not report
[e]Precaine: 8% lidocaine + 0.8% dibucaine: not report
[f]Wocaine gel: 2% lidocaine: not report
[g]Benzocaine gel: 20%: not report
[h]2% lidocaine with epinephrine 1:100,000, Alphacaine; DFL, Rio de Janeiro, RJ, Brazil.
[l] Articaine with epinephrine 1:100,000: not report
[j]Lidocaine 2%: not report.
[k]Lidocaine 2% with adrenaline: not reported.



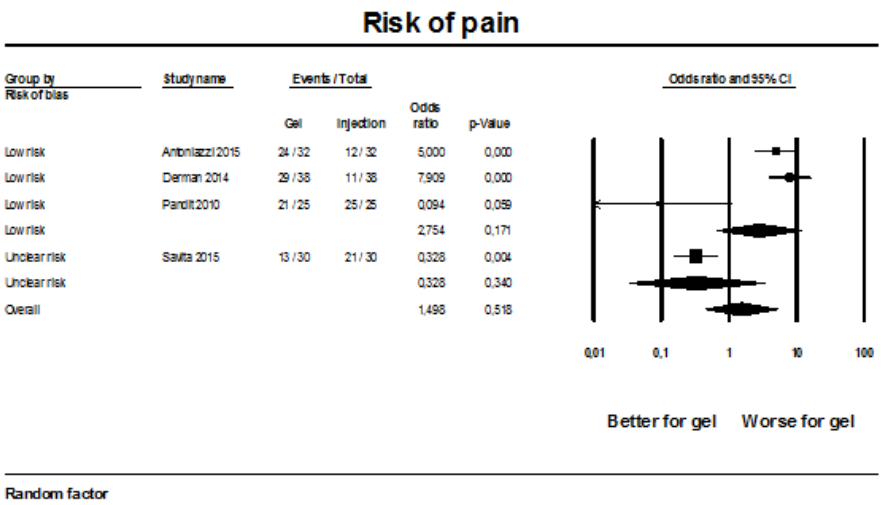
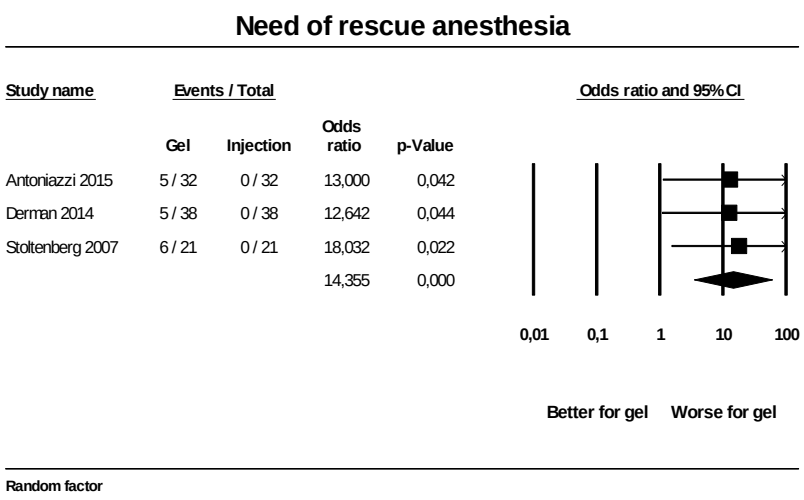


Fig. 3. Forest plots of the pain intensity measured with the VAS and Heft–Parker pain scales and the risk of pain.



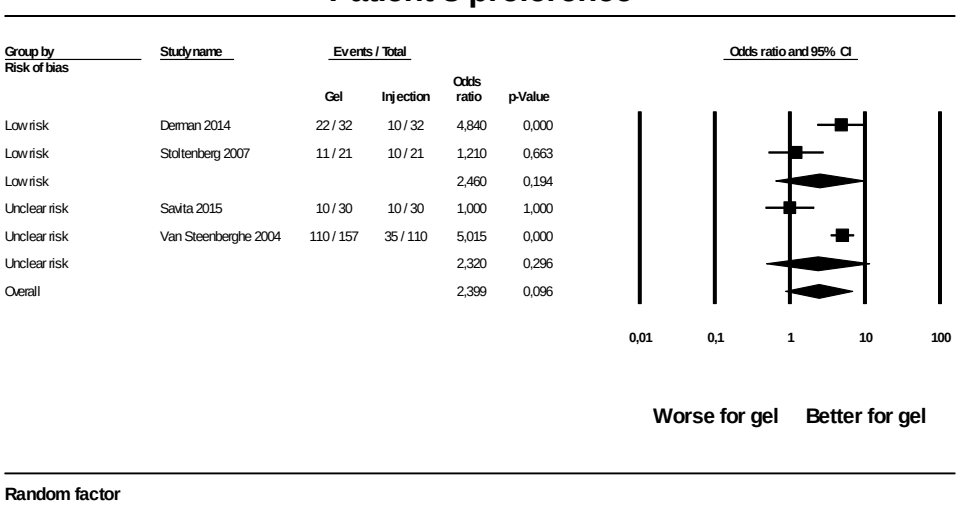


Fig. 4. Forest plots of the need for rescue anesthesia and the patient's preference.

REGISTRO DA PATENTE

TÍTULO: PROCESSO DE OBTENÇÃO DE BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA

STATUS: DEPOSITADA

NUMERO DO REGISTRO: BR 10 2016 007724 9

Avaliação Preliminar de Pedido de Patente

Nº .../20...
(preenchido pela Agência)

Fase I

1. Dados do Inventor

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2. Dados do Invento

Título Proposto (em português e inglês):

Desenvolvimento de um gel anestéstico fotoativado para uso odontológico.

Development of a light-cured anesthetic gel for use in dentistry.

Palavras-chave a serem utilizadas na Busca (em português e inglês):

Anestesia Dentária; Tetracaína; Medição da Dor; Benzocaína; Procaína; Propoxicaína; Lidocaína; Mepivacaína; Bupivacaína; Ropivacaína; Etidocaína; Prilocaína; Articaína.

Dental Anesthesia; Tetracaine; Pain Measurement; Benzocaine; Procaine; Propoxycaine; Lidocaine; Mepivacaine; Bupivacaine; Ropivacaine; Etidocaine; Prilocaine; Articaine.

Área de Pesquisa (em português e inglês):

Biomateriais e Odontologia

Biomaterials and Dentistry

Descrição sucinta do invento (em português e inglês):

O uso de anestesia terminal infiltrativa gera na maioria dos indivíduos algum medo e desconforto. Entretanto, o controle da dor e ansiedade é requisito importante para ganhar a confiança do paciente e garantir a aceitação do tratamento. O uso de anestésicos tópicos é uma alternativa para substituir o uso da agulha, reduzindo a ansiedade dos pacientes. Existe no mercado géis/cremes para uso tópico, porém, estes produtos comercialmente disponíveis apresentam efeito anestésico de curta duração, dificuldade de aplicação, sensibilidade gustativa desagradável e escoam com facilidade do local aplicado. Aliado ao fato de que, invariavelmente não são considerados substitutos da anestesia terminal infiltrativa. Em resumo, este

invento é uma alternativa viável e promissora para o controle da prevalência e da intensidade da dor de baixa intensidade nos tratamentos que requerem uso de anestesia terminal infiltrativa, sendo uma alternativa para substituição do uso da agulha. Além disso, apresenta maior duração anestésica, facilidade de aplicação e permanece apenas na região que se deseja trabalhar, não escoando para outras regiões.

The use of infiltrative anesthesia generates in most individuals, some fear and discomfort. However, the control of pain and anxiety is important requirement to get the patient's trust and acceptance to the treatment. The use of topical anesthetic is an alternative to replace the use of needle, reducing the anxiety of the patient. In the dental market, even though there are gels/creams for topical use, these commercially available products have anesthetic effect of short duration, difficulty of implementation, bitter taste sensitivity, and they flow easily from the application site. Furthermore they invariably are not considered substitutes of the terminal infiltrative anesthesia. In summary, this invention is a viable and promising alternative for controlling the prevalence of low- intensity pain in treatments requiring the use of infiltrative anesthesia as an alternative to replace the use of the needle. Moreover, it presents higher anesthetic duration, it is ease to apply and remains only in the area you want to work, instead of flowing to others regions.

Qual é o problema a ser resolvido pela referida proposta de invenção?

A anestesia não invasiva é um procedimento fundamental para o controle da dor e da ansiedade do paciente, possibilitando a aceitação dos procedimentos odontológicos. O uso de um anestésico tópico fotoativado permite a aplicação de um gel que após fotoativação não escoa para regiões indesejadas, portanto, anestesia apenas a região onde o produto é aplicado. Adere sobre a gengiva sem irritá-la, e permanece sobre o local, ocasionando um efeito anestésico lento, controlado e prolongado do anestésico enquanto ele está em contato com a mucosa.

Após remoção, o produto é facilmente eliminado não restando remanescentes, o que o torna seguro, por evitar ingestão. Por conter sais de longa duração em sua composição, permite uma ação anestésica

prolongada. Dessa forma, o uso de anestesia não invasiva fotoativada é um desafio tecnológico ainda não resolvido, com grande potencial comercial.

Dessa forma, o uso de anestesia tópica fotoativada contendo sais de longa duração em sua composição permite uma anestesia prolongada, dispensa o uso da agulha, além de anestesiar apenas a região onde o produto foi aplicado, já que a viscosidade do material impede com que ele escoe.

Como este problema é resolvido atualmente? Quais tecnologias são utilizadas para a resolução?

Não existe no mercado nenhum anestésico tópico que seja fotoativado, apresente longo tempo de duração e permaneça no local onde foi aplicado sem que haja o escoamento. Como alternativa atual, o cirurgião dentista utiliza anestesia terminal infiltrativa para procedimentos onde requer anestesia de longa duração. Porém, o uso de anestesia terminal infiltrativa pode gerar dor, desconforto e amortecimento de uma área muito maior que aquela na qual será realizada o procedimento. Existe no mercado anestésicos tópicos para a substituição do uso de agulha. Porém, nenhum desses anestésicos é fotoativado e não são capazes de permanecerem na região a ser aplicada sem que ocorra o escoamento. Os anestésicos tópicos comercializados apresentam dificuldade de administração, sabor desagradável, fácil escoamento e pouco tempo de ação. Todos esses inconvenientes da tecnologia atual foram considerados durante o desenvolvimento da nova tecnologia neste invento.

Qual a novidade ou o diferencial inovador proposto em relação ao existente no mercado? Existe algum interessado na nova tecnologia?

O diferencial do presente produto é a fotoativação do anestésico tópico, maior tempo de ação e a sua ação apenas na região onde o produto foi aplicado sem que ocorra o escoamento. Sobre o interesse por empresas, embora a nova tecnologia tenha mostrado resultados promissores, ainda não foi apresentada ao mercado.

Já houve alguma forma de divulgação do presente invento? Se sim, Qual? Quando? Onde?

Não.

_____

Declaro(amos) que todas as informações acima descritas são verdadeiras.

Nome [Inventor(es) e Parceiro]	**Assinatura**
Alessandra Reis	
Paulo Vitor Farago	
Alessandro Dourado Loguercio	
Letícia Maíra Wambier	

Nota: Após o preenchimento entregar na AGIPI, para fins de busca de anterioridade em bases de patentes.

Recebido na AGIPI em: .../ .../ ... .

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(assinatura/carimbo)

Fase II

3. Buscas de Anterioridade (a ser preenchido pela Agência)

Base de Busca	Nº da Patente	Título / Resumo

Nota: No caso de anterioridade positiva o presente invento não terá direito à proteção.

Buscas concluídas em: .../ .../ ... .

_____

4. Considerações sobre o Resultado das Buscas de Anterioridade
[a ser preenchido pelo(s) inventor(es)]

Nota: Se necessário, novas buscas poderão ser solicitadas. Para fins de avaliação mais detalhada sobre o estado da técnica, acessar a Base e analisar a íntegra do pedido de depósito.

_____

Declaro(amos) que todas as informações acima descritas são verdadeiras.

Em, ... / ... / ... .

Nome [Inventor(es) e Parceiro]	Assinatura

RESUMO

PROCESSO DE OBTENÇÃO DE BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA

A presente invenção refere-se ao processo de obtenção de barreira gengival fotoativada, para o uso em várias áreas da odontologia e medicina. Na odontologia está indicada na dentística, odontopediatria, endodontia, prótese e, periodontia. Já na medicina pode ser aplicada na dermatologia, otorrinolaringologia, urologia e ginecologia. De modo geral, pode ser aplicado antes de qualquer procedimento que requer a aplicação de anestesia local infiltrativa, proporcionando uma anestesia tópica com uma liberação controlada do fármaco, sendo uma estratégia para diminuir o estresse, ansiedade, dor e desconforto dos pacientes.

A formulação proposta é inovadora, já que é o primeiro anestésico tópico fotoativado, apresentando vantagens como: longo tempo de duração, fácil aplicação, dispensa o uso da agulha em procedimentos de baixa e moderada intensidade de dor, por ser fotoativado, não há escoamento do produto para áreas vizinhas, além disso, evita a deglutição do produto, diminuindo a ocorrência de efeitos colaterais, e, não apresenta gosto desagradável.

REIVINDICAÇÕES

PROCESSO DE OBTENÇÃO DE BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA

1. Processo de obtenção de barreira gengival anestésica fotoativada, caracterizado pela adição de um sal anestésico em uma barreira gengival no campo da odontologia e medicina;

2. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1, caracterizada pela utilização de sais anestésicos, tais como: tetracaína, benzocaína; procaína; propoxicaína; lidocaína; mepivacaína; bupivacaína; ropivacaína; etidocaína; prilocaína; articaína e associação entre sais anestésicos, em concentrações de 1 a 10%, para uso no campo da odontologia e medicina;

3. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1 e 2, caracterizada pela utilização de inibidores da fotoativação, tais como: BHT (hidroxitolueno butílico); hidroquinona; MHQ (metoxi-hidroquinona), em concentrações de 0,1 a 2%, para uso no campo da odontologia e medicina;

4. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1, 2 e 3, caracterizada pela utilização de monômeros, tais como:Bis-GMA (bisfenol glicidil metacrilato); UDMA (uretano dimetacrilato); TEGDMA (trietilenoglicol dimetacrilato); EGDMA (etilenoglicol dimetacrilato); HEMA (2-hidroxietil metacrilato); Bis-EMA (bisfenol-A etoxilado dimetacrilato), em concentrações de 10 a 80%, para uso no campo da odontologia e medicina;

5. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1 a 4, caracterizada pela utilização de fotoiniciador, tais como: canforoquinona; benzilo; BZ (benzil propanodiona); PPD (fenil propanodiona); 2-propanodiona, em concentrações de 0,1 a 2%, para uso no campo da odontologia e medicina;

6. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1 a 5, caracterizada pela utilização de co-iniciador, tais como: DABE (éster etílico do ácido *N,N*-dimetil-*para*-aminobenzoico); CEMA (N,N-metilanilina cianoetilo); DMAEMA (2-dimetilaminoetil metacrilato); DMPT (NN-dimetil-p-toluidina); DEPT (N, N-dietanol-p-toluidina), em concentrações de 0,1 a 2%, para uso no campo da odontologia e medicina;

7. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1 a 6, caracterizada pela utilização de carga inerte, tais como: partículas de sílica; partículas de quartzo; partículas de vidro, em concentrações de 5 a 30%, para uso no campo da odontologia e medicina.

PROCESSO DE OBTENÇÃO DE BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA

Campo da Invenção

A presente invenção refere-se à descrição do processo de obtenção de barreira gengival fotoativada contendo um sal anestésico, para o uso em várias áreas da odontologia e medicina. Na odontologia está indicada na dentística, odontopediatria, endodontia, prótese e, periodontia. Já na medicina pode ser aplicada na dermatologia, otorrinolaringologia, urologia e ginecologia. De modo geral, pode ser aplicado antes de qualquer procedimento que requer a aplicação de anestesia local infiltrativa, proporcionando uma anestesia tópica com uma liberação controlada do fármaco, sendo uma estratégia para diminuir o estresse, ansiedade, dor e desconforto dos pacientes.

A presente invenção está relacionada com vários procedimentos na área de atuação na odontologia como: colocação de grampos de isolamento absoluto, remoção de dentes decíduos em fase avançada de reabsorção radicular, na sondagem, raspagem e alisamento radicular. Em procedimentos protéticos e restauradores que exigem o afastamento gengival com fio retrator, diminui a presença e a intensidade de dor. Na medicina, pode ser utilizado para a aplicação de laser, remoção de nevus, passagem de sonda vesical, sonda nasogástrica, exames ginecológicos e cauterização de vasos nasais. Além disso, pode ser aplicado como anestésico tópico antes de qualquer procedimento prévio a punção da agulha, em todos os procedimentos invasivos que exigem o uso de anestesia terminal infiltrativa diminuindo o estresse, dor e proporcionando maior conforto ao paciente.

A formulação proposta é inovadora, já que é o primeiro anestésico tópico fotoativado, apresentando vantagens como: longo tempo de duração, fácil aplicação, por ser fotoativado, não há escoamento do produto para áreas vizinhas e nem a deglutição o que diminui a ocorrência de efeitos colaterais, além disso, como fica restrito a área onde é aplicado não apresenta gosto desagradável. Contudo a maior vantagem é o fato de dispensar o uso da anestesia infiltrativa em vários procedimentos da odontologia e medicina, isto

facilita a sua utilização em adultos, idosos, portadores de necessidades especiais e, especialmente crianças e adolescentes.

O anestésico tópico é uma estratégia viável e promissora para o controle da prevalência e da intensidade da dor, de baixa a moderada intensidade (até 5 em uma escala de 0 a 10 - *Visual Analogue Scale ou Escala Visual Análoga*), nos procedimentos odontológicos que requerem o uso da anestesia terminal infiltrativa, promovendo conforto ao paciente, aceitação a tratamentos futuros e ainda, com maior segurança ao clínico.

Fundamentos da Invenção e Estado da Arte

O controle da dor e ansiedade são requisitos importantes para ganhar a confiança do paciente e garantir a aceitação e continuidade do tratamento (Milgrom et al.1997; Karadottir et al. 2002; Monteiro et al. 2008). O uso de anestesia terminal infiltrativa é uma intervenção comum visando minimizar a dor e desconforto nos procedimentos odontológicos, no entanto, mais de 25% dos adultos têm medo de injeções, pois esse procedimento pode ser doloroso e gera em muitos indivíduos medo, ansiedade e amortecimentos em determinados locais, principalmente nos lábios, língua e nos tecidos circundantes, sendo até maior do que na área que será realizado o procedimento (Palotie et al. 2007; Al Habashneh et al. 2012). Este fato contribui para reduzir a tolerância e, faz com que alguns pacientes adiem o tratamento odontológico quando requer anestesia local infiltrativa convencional (Milgrom et al. 1997).

Estas observações apontam para a necessidade do desenvolvimento de técnicas anestésicas que substituam o uso da agulha, reduzindo a ansiedade dos pacientes (Donaldson et al.1995; Derman et al. 2013). A anestesia tópica é uma estratégia que minimiza a ansiedade, dor e desconforto dos indivíduos (Magnusson et al. 2003; Froes et al.2010; Derman et al. 2014). Diferentes géis e cremes para uso tópico têm sido comercializados (EMLA® creme [AstraZeneca, Cotia, SP, Brasil]; Oraqix® [Dentsply, York, PA, EUA]; Benzotop® [DFL, Rio de Janeiro, RJ, Brasil] e Hurricaine® [Beutlich LP, Waukegan, IL, EUA]) para tentar contornar esses problemas (Friedman et al. 2001; Al Habashneh et al. 2012; Derman et al. 2014). Porém, esses produtos não se mostraram eficientes na

redução da prevalência e intensidade da dor, e tem uma curta duração, permanecendo portanto como um desafio tecnológico a ser superado. Além disso, estas alternativas podem anestesiar diferentes áreas quando aplicados, possuem gosto desagradável e ainda, podem ser deglutidos, já que são soluções em gel, spray ou pomadas.

Na medicina é grande a necessidade de uso de anestésicos tópicos, principalmente na dermatologia para a realização de procedimentos entre eles: laser para depilação, retirada de tatuagens, rejuvenescimento. Acrescenta-se a aplicação de toxina botulínica, escleroterapia, entre outros. Essas intervenções podem causar dor e desconforto para o paciente (Friedman et al. 2001). Nessas situações o uso de anestésicos tópicos pode reduzir o desconforto, promovendo analgesia de rápida ação com efeitos colaterais mínimos (Friedman et al. 2001; Cantisani et al. 2014). A busca de um agente com essas características, ainda é um desafio, devido a dificuldade de difusão e distribuição adequada através da pele (Lener et al. 1997; Kleiber et al. 2002). O mesmo ocorre em pacientes submetidos à cirurgia ginecológica laparoscópica, que pode resultar em dor pós-operatória, sendo necessário o uso de anestésico tópico nas primeiras 48 horas (Saccardi et al. 2016).

Assim, até o presente momento, não existe no mercado nenhum anestésico tópico que reúna qualidades tais como: longo tempo de duração, não escoe permanecendo no local onde foi aplicado, caso seja fotoativado. Com isso, novos processos tecnológicos devem ser desenvolvidos, sendo a barreira gengival fotoativada uma estratégia viável e promissora para o controle da prevalência e da intensidade da dor de baixa e moderada intensidade nos procedimentos odontológicos e médicos que requerem o uso de uma agulha, tal como em anestesias terminais infiltrativas.

Descrição da Abordagem do Problema

A presente invenção refere-se a um processo de obtenção de um produto inédito que descreve a obtenção de uma formulação inovadora, contendo um sal anestésico associado a uma barreira gengival fotoativada, proporcionando uma anestesia tópica com uma liberação controlada do fármaco, sendo uma

alternativa para o controle da prevalência e da intensidade da dor de baixa e moderada intensidade, pois dispensa o uso da agulha para a anestesia terminal infiltrativa e, restringe a anestesia apenas as regiões onde o produto foi aplicado, já que o produto é fotoativado. Isto também impede que o anestésico escoe da região aplicada, gerando conforto ao paciente e segurança para o profissional, já que diminui potencialmente a deglutição e outros efeitos colaterais.

Considerando as desvantagens do uso de anestesia terminal infiltrativa, tais como: medo, ansiedade, dor, longo tempo de ação, amortecimento de regiões próximas da aplicação, gosto amargo e estimulação da salivação, a presente invenção relata o desenvolvimento de um anestésico que seja fotoativado, com propriedades adequadas para anestesias tópicas, gerando conforto ao paciente.

Atualmente no mercado, existem anestésicos tópicos que podem ser utilizados em pacientes que tem medo da agulha usada em anestesias terminais infiltrativas. Mas, os produtos comercializados apresentam algumas desvantagens como efeito anestésico de curta duração, dificuldade de aplicação, alto escoamento, são facilmente removidos com a saliva, gosto desagradável, e, não são substitutos de anestesia terminal infiltrativa (Friskopp et al. 2001; Donaldson et al. 2003).

Entre os diferenciais desta invenção, é que o anestésico tópico é fotoativado, ou seja, é um líquido-viscoso durante a aplicação, mas após a excitação dada por um aparelho de fotoativação em um comprimento de onda específico, ocorre à aproximação molecular da cadeia polimérica e a conversão dos monômeros em polímero, formando cadeias cruzadas, isso faz com que o anestésico fique rígido e permaneça grudado na região aplicada, até que seja mecanicamente removido de forma fácil e conveniente.

Portanto, a presente invenção permite superar os desafios tecnológicos existentes, corrigindo falhas dos anestésicos comercializados mantendo o produto no local com liberação lenta e contínua do sal anestésico. Isto pode aumentar a penetração nos tecidos orais e aumentar com isto a duração da ação anestésica, apesar de mantê-la localizada a uma pequena área. Aliado a isto, outras vantagens como facilidade de aplicação com nenhum escoamento para áreas vizinhas, redução da deglutição do produto que diminui a ocorrência de

efeitos colaterais, tornando-o mais seguro, e melhor conforto para o paciente já que não sentirá o gosto desagradável do produto.

Outra vantagem importante da invenção, é que pode ser utilizado em adultos, idosos, portadores de necessidades especiais, adolescentes e, especialmente crianças, em várias áreas da odontologia e medicina. Na odontologia, utiliza-se no isolamento absoluto para a colocação do grampo metálico, bem como no isolamento relativo quando associado ao uso do fio retrator. Além disso, pode ser utilizado na sondagem, raspagens e alisamento radiculares em pacientes que tenham doença periodontal com bolsas rasas e de média profundidade (≥ 5 mm). Pode também ser considerada uma alternativa para minimizar a dor na colocação de fios retratores, substituto da anestesia para extração de dentes decíduos com raízes esfoliadas.

Na medicina pode minimizar o desconforto em procedimentos estéticos, aplicação de laser, remoção de nevus e cauterização de vasos nasais, entre outros procedimentos.

Geralmente, pode ser aplicado antes de qualquer procedimento que requer a aplicação da anestesia terminal infiltrativa, proporcionando uma anestesia tópica antes da punção da agulha em procedimentos invasivos, tornando o invento um aliado ao cirurgião dentista e médico.

Citação das Figuras

A Figura 1, demonstra a média de dor em pacientes submetidos a diferentes tratamentos odontológicos, como raspagem e alisamento radicular (Raspagem), profundidade de sondagem periodontal (Sondagem), colocação de grampo para isolamento absoluto (Grampo adulto), e, crianças submetidas a colocação de grampo para isolamento absoluto (Grampo crianças), comparando o gel anestésico fotoativado com um gel placebo. Observe que em todos os casos mencionados ocorreu uma expressiva diminuição da dor quanto mensurada por uma escala VAS (*Visual Analogue Scale ou Escala Visual Análoga*) que avalia a dor de 0 a 10, onde 0 significa ausência de dor e 10 máxima dor mensurável.

Descrição Detalhada da Invenção

A partir do sal anestésico junto à uma barreira gengival, procurou-se formular um anestésico tópico potente, obtendo um produto com propriedades ideais para uso tópico em intervenções odontológicas e médicas, sendo um produto atrativo para os cirurgiões dentistas e médicos.

A obtenção da formulação foi feita a partir do uso de reagentes da matriz orgânica e inorgânica (Tabela 1), empregando os seguintes componentes: inibidor da fotoativação nas concentrações de 0,1 a 2%; monômero metacrílico de 10 a 60%; monômero metacrílico-uretânico entre 20 a 80%; sal anestésico entre 1 a 10%; fotoiniciador de 0,1 a 2%; co-iniciador de 0,1 a 2%; pigmento de 0,1 a 2%; e carga inerte entre 5 a 30%.

Em síntese, a formulação piloto, que exemplifica as composições abrangidas por este pedido de patente e, utilizada durante os ensaios clínicos, está apresentada na tabela 1.

TABELA 1 – FORMULAÇÕES DA BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA.

Reagentes da Barreira Gengival Anestésica Fotoativada (10 g)		
MATRIZ ORGÂNICA		
Composição	**Concentração (%)**	**Função**
BHT - (butil- hidroxitolueno)	0,1 – 0,2%	Inibidor
HEMA - (2-hidroxietil metacrilato)	25 – 35%	Monômero
UDMA - (uretano dimetacrilato)	45 – 55%	Monômero
CLORIDRATO DE TETRACAÍNA	4 – 6%	Sal anestésico
CANFOROQUINONA	0,1 – 0,5%	Fotoiniciador
DABE - (éster etílico do ácido *N,N*-dimetil-*para*-aminobenzoico)	0,1 – 0,5%	Co-iniciador
PIGMENTO	0,3 – 0,5%	Corante
MATRIZ INORGÂNICA		
Composição	**Concentração (%)**	**Função**
PARTÍCULAS DE SÍLICA	10– 15%	Carga inerte

Para fins de patente, considera-se como inibidores da fotoativação: BHT (hidroxitolueno butílico); hidroquinona; MHQ (metoxi-hidroquinona). Já os mônomeros, considera-se: Bis-GMA (bisfenol glicidil metacrilato); UDMA (uretano dimetacrilato); TEGDMA (trietilenoglicol dimetacrilato); EGDMA

(etilenoglicol dimetacrilato); HEMA (2-hidroxietil metacrilato); Bis-EMA (bisfenol-A etoxilado dimetacrilato).

Para fins de patente, considera-se como sais anestésicos: Tetracaína; Benzocaína; Procaína; Propoxicaína; Lidocaína; Mepivacaína; Bupivacaína; Ropivacaína; Etidocaína; Prilocaína; Articaína e associação entre os sais anestésicos.

Para fins de patente, considera-se como fotoiniciador: canforoquinona; benzilo; BZ (benzil propanodiona); PPD (fenil propanodiona); 2-propanodiona. E, o co-iniador, considera-se como: DABE (éster etílico do ácido *N,N*-dimetil-*para*-aminobenzoico); CEMA (N,N-metilanilina cianoetilo); DMAEMA (2-dimetilaminoetil metacrilato); DMPT (NN-dimetil-p-toluidina); DEPT (N, N-dietanol-p-toluidina). Já a carga inerte, considera-se: partículas de sílica; partículas de quartzo; partículas de vidro.

Tento em vista todas as dificuldades e limitações dos anestésicos existentes, essa formulação tende a suprir os comercializados atualmente, sendo de fácil uso, longa duração, fácil remoção que o torna seguro, evita a ingestão do produto devido sua viscosidade, permanece apenas nas regiões que serão realizados os procedimentos, dispensa uso da agulha, não apresenta sabor desagradável, tendo pelos resultados preliminares promissores, um grande potencial comercial.

Para conseguir uma formulação ideal, várias tentativas e testes foram realizados com os reagentes apresentados na Tabela 1, até se obter uma formulação ideal e que mantenha o máximo de suas propriedades anestésicas. Para avaliar a aceitação e eficácia anestésica, o anestésico tópico da barreira gengival fotoativada foi testada em 80 pacientes adultos e 60 crianças em diversas situações como raspagem e alisamento radicular, sondagem e colocação de grampos que auxiliam no isolamento absoluto em pacientes adultos, e, colocação de grampo para isolamento absoluto em crianças.

O primeiro teste foi realizado em adultos com bolsa periodontal de profundidade média (≥ 5 mm) e presença de doença periodontal, que necessitavam de tratamento de raspagem e alisamento radicular para remoção de cálculo. Aplicou-se o produto na região gengival e, após iniciado o procedimento, observou-se tolerância e baixo grau de estresse e ansiedade do

paciente. Além disso, o gel anestésico mostrou boa aceitação e bons resultados no controle da dor quando comparado a um gel placebo (Figura 1).

Para o segundo teste foram selecionados pacientes adultos que apresentavam doença periodontal com bolsas médias (≥ 5 mm), nesse caso apenas a sondagem periodontal foi realizada. Aplicou-se o anestésico fotoativado na margem gengival e a sondagem periodontal foi realizada em 6 pontos ao redor de todo o do dente (mésio-vestibular, vestibular, disto-vestibular, mésio-lingual, lingual e disto-lingual). Os resultados mostraram redução significante no nível da dor quando comparado a um gel placebo (Figura 1).

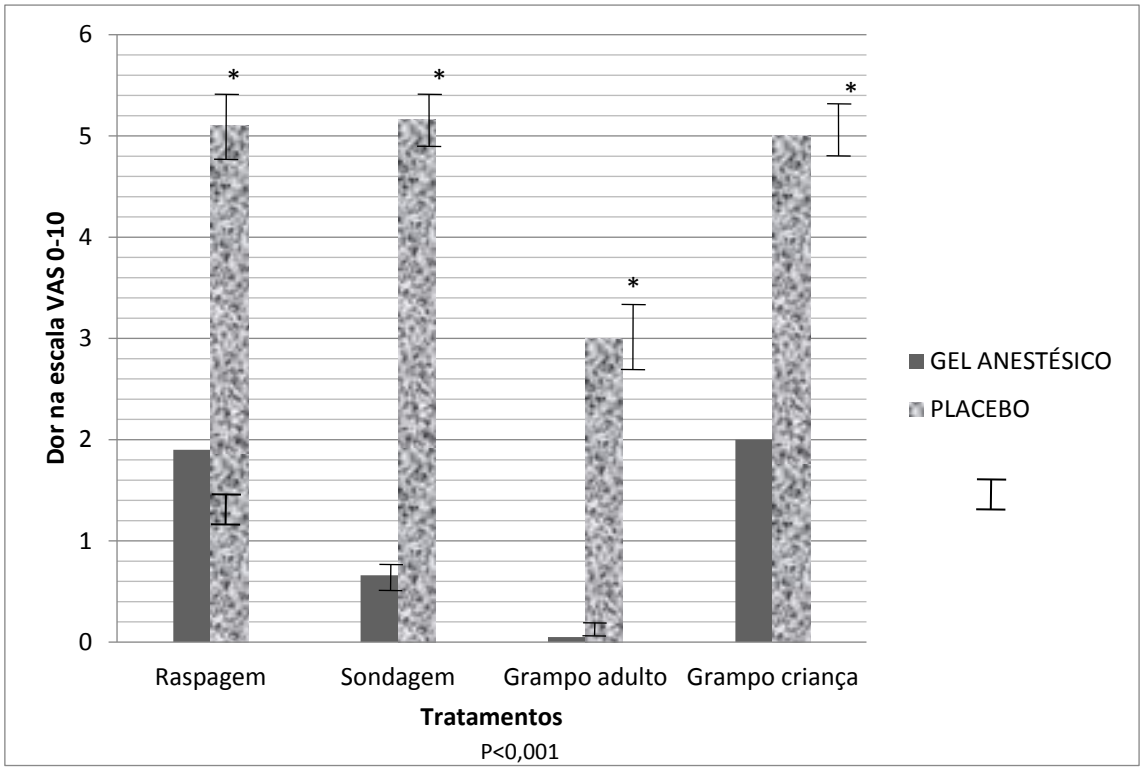
O terceiro teste foi realizado em adultos que necessitavam de procedimentos restauradores e que, em geral, exigem o uso de dique de borracha para evitar a contaminação da saliva. Para a adaptação do dique é necessário o uso de grampo metálico que exige, no mínimo, anestesia terminal infiltrativa na região. Neste caso, a mencionada anestesia foi substituída pela barreira gengival fotoativada e o grampo foi colocado em posição. No quarto teste, o mesmo procedimento descrito foi realizado em crianças. Tanto para crianças como para adultos que necessitam a colocação de grampo metálico para o isolamento absoluto, o gel anestésico mostrou boa aceitação e menor ansiedade, além de bons resultados no controle da dor quando comparado a um gel placebo (Figura 1).

Esses resultados confirmam que a estratégia diferencial adotada neste pedido de patente, a partir do uso de um anestésico tópico fotoativado, é extremamente interessante ao uso odontológico, podendo ser utilizado em várias áreas da odontologia, sendo uma estratégia viável ao uso clínico, com a vantagem de promover uma liberação controlada e prolongada do fármaco, efetividade no controle da dor e ansiedade, e ainda, prove segurança ao clínico e ao paciente.

Pode-se concluir que a barreira gengival anestésica fotoativada é efetiva no controle da dor, sua obtenção vai ser um avanço na odontologia e medicina, podendo ser empregado em várias áreas, bem como, promover conforto ao paciente e aceitação a tratamentos futuros que requer o uso de anestesia.

Figura 1. Média de dor (escala VAS de 0-10, onde 0 significa ausência de dor e 10 significa máxima dor mensurável) em pacientes submetidos a raspagem e

alisamento radicular (Raspagem), profundidade de sondagem periodontal (Sondagem), colocação de grampo para isolamento absoluto (Grampo adulto), e, crianças submetidas a colocação de grampo para isolamento (Grampo criança), utilizando o anestésico tópico fotoativado comparado a um gel placebo.



ARTIGO 3

TÍTULO: EFFICACY OF A THERMO-SENSITIVE LIPOSOMAL ANESTHETIC GEL FOR CLAMP PLACEMENT BEFORE RUBBER DAM ISOLATION FOR RESIN SEALANTS: A RANDOMIZED CLINICAL TRIAL

STATUS: SUBMETIDO

REVISTA: PEDIATRIC DENTISTRY

Efficacy of a thermo-sensitive liposomal anesthetic gel for rubber dam isolation: a clinical trial

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Abstract:

Objectives: This randomized clinical trial, split-mouth, triple-blind evaluated the efficacy of a newly developed anesthetic liposomal gel thermo-sensitive topical (experimental) to a placebo gel (control) for pain control in children, submitted to rubber dam isolation for the application of sealants. Methods: For this study, 81 children with 8 to 12 years was selected and received both treatments: anesthetic liposomal thermo-sensitive gel and the placebo gel. For the application of gels, the quarters were isolated with cotton rolls and administered agents non-invasively in the gum around the tooth with the aid of an applicator tip. After 2 minutes the clamp 26 was positioned on the first lower molars (FDI: 36 and 46), if there was pain report, it was removed and the procedure was performed using relative isolation. The absolute risk and intensity of pain was registered using scales of facial expression Wong-Baker and scale of 11 points (NRS). The data were evaluated with the McNemar test and Wilcoxon Signed Rank (alpha = 5%). Results: No statistically significant differences were observed for the risk of pain between groups (anesthetic gel: 22%, placebo 27%, p = 0.52). In relation to pain intensity, the groups differed according to the two pain scales used in this study (p = 0.013 for facial scale and p = 0.023 for the numerical scale) with positive results for the anesthetic gel. Conclusions: The liposomal thermo-sensitive anesthetic gel can reduce the pain intensity in children submitted to rubber dam isolation before resin sealant placement.

Keywords: Dental Anxiety. Anesthetics. Pit and Fissure Sealants.

Introduction

In Pediatric Dentistry, every effort must be made to avoid invasive procedures that can trigger fear and anxiety in children (Aapd, 2016). Local anesthesia is one of these procedures, although an essential measure in a large number of clinical situations for pain control (Kudo, 2005; Aapd, 2016). Topical anesthetics have been extensively studied as a replacement for local anesthesia in several procedures like scaling and root planning (Antoniazzi *et al.*, 2015), rubber dam clamp placement (Stecker *et al.*, 2002), periodontal probing (Winning *et al.*, 2012) among others.

Different anesthetic gels/creams for topical use that contains a mixture of anesthetic agents have been marketed (EMLA® cream – lidocaine 5% and prilocaine 5% [AstraZeneca, Cotia, SP, Brazil], Oraqix® - lidocaine 5% and prilocaine 5% [Dentsply, York, PA, USA], Benzotop® - benzocaine 20% [DFL, Rio de Janeiro, RJ], and Hurricaine® - benzocaine 20% [Beutlich LP, Waukegan, IL, USA]), (Donaldson *et al.*, 2003; Mayor-Subirana *et al.*, 2013; Wambier *et al.*, 2016). However, these commercially available products have short anesthetic effect duration and they are difficult to apply due to its low viscosity (Friskopp *et al.*, 2001; Van Steenberghe *et al.*, 2004; Franz-Montan *et al.*, 2007).

Aiming to circumvent these problems, we developed a new anesthetic gel, with thermo-sensitive properties and slow-delivery drug mechanism with liposomes. Thermo-sensitive substances are based on copolymers, known as poloxamers, these agents are fluids at room temperature, but their viscosity increase at body temperature (Allen e Cullis, 2013; Svirskis *et al.*, 2016). Liposomes are considered optimal drug carriers and allow controlled drug release (Batista *et al.*, 2007; Franz-Montan *et al.*, 2007; Allen e Cullis, 2013), which facilitates penetration of the product in the oral mucosa (Meechan, 2000). Local anesthetics encapsulated in liposomes have a higher effect duration with a decreased plasma levels and toxicity (Franz-Montan *et al.*, 2007; Allen e Cullis, 2013).

In order to test our new developed anesthetic gel, we designed the present clinical trial that studied the pain control after rubber dam clamp

placement in children. This procedure was selected because it is a common in daily practice and causes significant discomfort in patients (Lim e Julliard, 2004; Kudo, 2005; Yoon e Chussid, 2009). Approximately 64 to 80% of the children report pain during clamp placement (Lim e Julliard, 2004). This may generate anxiety and difficulties for behavior control and the acceptance of the treatment (Milsom *et al.*, 2003; Aapd, 2005; Kudo, 2005; Aminabadi *et al.*, 2012).

It does not feel right that the procedure to be used to control pain is the same procedure that can trigger anxiety. But this is the case when local anesthesia is used to control the pain in such a simple procedure like rubber dam placement for a pit and fissure treatment. Therefore, the development of anesthetic techniques that can replace the use of needle and the local anesthesia (Meechan, 2000; Herdevall *et al.*, 2003) might be a good alternative.

In face of that, the aim of this randomized clinical trial, split-mouth, triple-blind was to compare a new topical anesthesia with a liposomal thermo-sensitive gel that contains prilocaine and lidocaine at 5% (experimental) and a placebo (control) for rubber dam placement in children submitted to resin sealant treatment for pain control in children.

Material and Methods

Ethical approval

The clinical investigation was approved (protocol number 974.470) by the scientific review committee and by the committee for the protection of human participants of the local University.

Protocol registration

This article were prepared using the protocol established by the Consolidated Standards of Reporting Trials statement (Schulz *et al.*, 2011). This protocol was registered in the REBEC under the identification number RBR-3WWQC3.

Trial design, setting and locations of data collection

This was a randomized, split-mouth and placebo-controlled clinical trial with an equal allocation ratio. All procedures in the selected volunteers were

performed from March 24, 2015, to May 07, 2016, in the School of Dentistry at Local University and at school Center of Integral Care for Children and Adolescents (CAIC) associated to the Local University. The procedures were performed in a clinical environment.

Recruitment

Participants included in the clinical trial (convenience sampling), presented themselves for treatment at the School of Dentistry at the same University and at school Center of Integral Care for Children and Adolescents. No type of advertisement was done in any type of media.

Eligibility criteria

To be included in the trial, participants should be 8 to 12 years, should not have systemic diseases and should have two lower first permanent molars (FDI two-digit notation: teeth number 36 and 46) in need of sealant placement. Participants were excluded if their teeth were partially erupted or with active caries lesions in dentine that require restorative treatment. Children with a history of allergy, severe uncontrolled systemic disease (heart problems, neurological, kidney, liver or blood) or, any form of sensitivity or allergic reaction to amida-based anesthetics were not included. The tutors and the patients were informed with details about the research objectives and both signed an Informed Consent Form before any intervention.

Sample size calculation

The primary outcome of this study was the absolute risk of pain. The absolute risk of pain is the number of patients who reported pain at some period during the treatment. A total of 81 patients were required to have a 80% chance of detecting at the level of 5% significance, a reduction in the pain risk of 64% (Lim e Julliard, 2004) in the control group to 40% in the experimental group. All calculations for determining the sample size were carried out with a specific program, freely available online, for this purpose (www.sealedenvelope.com).

Random sequence generation and allocation concealment

The resin sealants were applied in the first lower molars (36 and 46 FDI two-digit notation) of each patient. The gel to be used in each tooth was

determined by simple randomization. The random sequence was generated by the same software used for sample size calculation, which is freely available online (www.sealed.envelope.com). An investigator who was not involved in the implementation of the study generated the random sequence.

Neither the operator nor the patients were aware of the gel that would be applied in their both teeth before the intervention. To conceal the allocation, the random sequence generated was individually placed in opaque, consecutively numbered and sealed envelopes, which were only opened by the operator immediately before the intervention. The group determined in the envelope was done in the right teeth while the other teeth received the complementary treatment.

Blinding

This was a triple-masked clinical trial, in which the patient, operator, and statistician were masked to the group assignment. A third researcher, not involved in the evaluation process, was responsible for the randomization process, delivery and guidance on the administration of the gels.

A single investigator handled the preparation of topical anesthetic gel. The thermo sensitive liposomal anesthetic gel was manipulated in two phases. First, the manipulation of the aqueous phase reagents was carried out. The following substances were mixed: poloxamer 407 (6.78 g), polaxamer 188 (2.40 g), sodium benzoate (0.1 g), purified water (30 mL). This mixture was kept in a refrigerator (4oC) for 12 hours. Then, the oil phase reagents were mixed. This phase is composed of: granulated lecithin (6.6 g), isopropyl palmitate (7.6 g), benzoic acid (0.12 g). The oil phase was stored for 12 h at room temperature.

After 12 h, the anesthetic agents were manipulated: lidocaine base (1.5 g), prilocaine base (1.5 g), ethanol (2.5 mL), hydrochloric acid (0.1 mL) and water (10 mL). The anesthetic agents were mixed with the reagents from the aqueous phase, homogenizing four times with a syringe. Thereafter, in another syringe, the products were transferred to the oil phase, extruding all of the reagents 10 times until the correct consistency of the gel was obtained (Table 1).

For the placebo gel, manipulation was carried out similarly, following all

the steps of topic anesthetic gel including the fact that the anesthetic agents (prilocaine and lidocaine 5 %) were not included. The gels was handled in the Pharmacy School of the Local University and they presented the same color and smell, whose details are informed in Table 1. The anesthetic gel and placebo were stored in the refrigerator (4°C) and used within 60 days after preparation.

After handling, both gels were transferred to insulin syringes to prevent foreknowledge of the group assignment during application. The syringes were marked only with numbered codes so that neither the operators nor the patients could identify them.

Study intervention

The first tooth to be treated was the tooth # 36 (FDI two-digit notation). The envelope containing group description to be performed in each patient's, was opened only at this moment.

The quadrants were isolated with cotton rolls and the anesthetic or placebo gels were placed with the aid of a syringe and applicator tip (size 0.80x30 mm; BD PrecisionGlide^{TM}, Curitiba, Brazil) in the gingival tissue around the tooth to be sealed. The gel extended approximately 2 mm beyond the gingival marginal. The gel was left in place for 2 min and the clamp # 26 (SS White, Rio de Janeiro, RJ, Brazil) was positioned with a door-clamp gripper for adaptation check. At this moment, if the patient reported pain or discomfort, the clamp was removed and the procedure was performed after isolating the operative field with cotton rolls and saliva ejectors. Rubber dam was only installed after clamp placement in those patients that did not complain pain or discomfort.

The enamel surface was etched with 37% phosphoric acid for 30 s (Condac 37- FGM, Joinville, Brazil), followed by washing with water for 30 s and drying the surface with an air stream for 30 s. The resin sealant Fluroshield (Dentsply, Petrópolis, RJ, Brazil) was applied and light cured for 40 s with LED device (Radii-cal, SDI, Bayswater, Victoria, Australia) at 1,200mW/cm^2. Subsequently, the same procedure was carried out in the tooth # 46.

Assessment of the outcome

The absolute risk of pain was evaluated just after placement of clamp # 26 for adaptation, at the time of stimulus. In case the patient reported some pain or discomfort during clamp placement, the patient was considered to be sensitive to clamp placement through a dichotomous scale (yes/no). The pain intensity was further evaluated using two different pain scales:

1. Facial expression Wong-Baker scale (Viana *et al.*, 2006; Aminabadi *et al.*, 2012; Khatri e Kalra, 2012) (Figure 1). The patients should assign scores from 0 to 5 (0 = no pain, 1 and 2 = mild pain, 3 = moderate pain, 4 = severe pain, 5 = unendurable pain) to express their pain intensity. One calibrated evaluated, blinding to the group assign, was responsible to evaluate this scale.
2. Numerical scale of 11 points (Numeric Rating Scale- NRS), (Scopel *et al.*, 2007). In this scale, participants should chose and point the number ranging from 0 (no pain) to 10 (unbearable pain).

Statistical analysis

We performed the analysis following the intention-to-treat protocol, and we involved all participants who were randomly assigned (Schulz et al. 2011). We compared the absolute risk of pain for both groups using the McNemar's test (α= 0.05). We calculated the relative risk with the confidence interval for the effect size.

We performed the comparison of pain intensity (numerical scale and Wong-Baker Faces scale) using the Wilcoxon Signed Rank test, as the data did not follow not normal distribution. In all statistical tests, the significance level was set at 0.05. We performed all analyses by using the software Sigma Plot version 11.0 (Systat Software Inc., San Jose, CA, USA).

Results

Characteristics of the included participants

A total of 345 participants were examined in a dental chair to check if they meet the inclusion and exclusion criteria but only 81 met the eligibility criteria. The mean age (years) of the participants of this study was 10.8 ± 0.5. The ages of the participants ranged from 8 to 12 years, and the percentage of girls was 52%.

Risk of pain

In terms of the absolute risk of pain, no significant difference was observed between groups as seen in Table 2 (p = 0.52). It can be observed that 18 patients presented pain using the anesthetic gel (22%) and 22 presented pain using the placebo gel (27%). Although no statistical differences were detected, a larger number of patients reported pain when the placebo gel was used.

In terms of pain intensity (Table 3), the groups differed statistically under the two pain scales used in this study (p = 0.023 for NRS scale and p = 0.013 for Wong Baker faces). These data show that the anesthetic gel presented positive results when compared to placebo where the children reported low intensity pain using the different scales.

Adverse effect

No adverse effects were observed or related by patients.

Discussion

The population of this study was composed of school children aged 8 to 12 since that the occlusal pit and fissure caries accounts for the majority of lesions in the age group of 8 to 15 year olds (Misra *et al.*, 2007; Kalnina e Care, 2016). Sealants can be applied with cotton rolls isolation and saliva ejector but rubber dam isolation has several advantages. Increased retention rates of fissure sealants due to the better isolation from saliva and contaminants, and protection from aspiration are some of them (Eidelman *et al.*, 1983; Lim e Julliard, 2004; Ammann *et al.*, 2013).

However, as mentioned in the introduction, placement of a rubber dam clamp may cause significant discomfort to pediatric patients. The use of a

potent topic anesthetic quickly absorbed into the dental papilla (keratinized tissue) is an alternative to replace the infiltrative anesthesia for most of the children that is afraid and anxious to injections (Stecker *et al.*, 2002; Lim e Julliard, 2004; Kudo, 2005).

In this study, we developed an anesthetic gel, which had in their composition poloxamers control the product flow ability during application and it increases viscosity at body temperature on the application site, reducing dilution and swallowing (Franz-Montan *et al.*, 2007). This experimental gel also contains liposomes that permits a controlled release of drugs and makes the product safer for use (Allen e Cullis, 2013).

Both gels (liposomal anesthetic and placebo gel) lead to similar risks of pain. In other words, the sensation of pain related to the clamp placement was not avoided by the anesthetic gel. However, the intensity of pain was diminished when the active gel was used. Similar results were found in the literature, whenanother anesthetic gel (Emla- AstraZeneca, RεD Södertälje, Sweden) was compared to a placebo (Lim e Julliard, 2004). Others studies that compared different topical anesthetic products one another, such as Oraqix (Dentsply, York, PA, USA.) vs. benzocaine (DFL, Rio de Janeiro, RJ.), (Yoon e Chussid, 2009) and DentiPatch vs. benzocaine(Stecker *et al.*, 2002) did not show significant differences in pain perception between products, although, showed better results for the gels. However, a recent published systematic review that compared anesthetic gels against placebo used for scaling and root planing yielded the conclusion of this study (Wambier *et al.*, 2016).

Ideally, the anesthetic gel should provide a control release of the anesthetic salt; it should allow increased absorption in the mucosa with longer effect duration. Additionally the product should have an easy application, viscosity control and be free of side effects. Some of the available products in the market does not possess all these characteristics, being the short effect action (Benzocaine) and difficulty application due to high flow ability (Emla, DentiPatch and Oraqix) their main disadvantages (Meechan, 2000; Lim e Julliard, 2004). These characteristics were not evaluated in present study, as we did not compare the experimental gel herein tested against other available

anesthetic gels presented in the market. Further studies should be conducted to investigate these features.

The use of scales to assess patients' pain is a useful tool as it is a patient-centered outcome. They facilitate communication between patient and health team (Viana *et al.*, 2006; Castarlenas *et al.*, 2016). This study used the scale of 11 points and the Wong-Baker faces to address the reproducibility of the pain assessment in two different pain scales. The Wong-Baker faces are especially useful for pediatric patients to assess the intensity of pain, as it is an easy scale to be understood for children (Viana *et al.*, 2006; Castarlenas *et al.*, 2016).

The isolation clamp stabilizes the rubber dam and the selection of the clamp varies according to the dental anatomy group (Stecker *et al.*, 2002; Cazacu, 2014). In this study, we used the clamp # 26, as only totally erupted teeth were included in the sample. Other studies also used clamp #14 (Lim e Julliard, 2004) or #14A as they are also indicated for partially erupted molars (Yoon e Chussid, 2009).

The liposomal anesthetic gel has a bitter taste and the possibility of cushioning feel during the treatment, and these characteristics are limitations of this gel. To minimize these problems the gel was applied with after isolation of the field with cotton rolls. In case of excess gel, the cotton rolls absorb it minimizing the contact of the product with neighboring soft tissues. Other limitation was that both treatments were performed in the same clinical session. When the patient was anxious and had pain during the treatment of the first tooth, they could have had an increased tendency to over express the painful sensation in the other teeth. However, the adequate randomization of the products minimizes and even eliminated the influence of this experimental design on the findings of the study. To eliminate this influence even further, infiltrative anesthesia were not applied when the patient felt pain during clamp placement and the sealant was placed after isolation of the operative field with cotton rolls and saliva ejector.

Further studies comparing anesthetic gels with different compositions and characteristics should be focus of other investigations. In this study we

observed that the use of a liposomal thermo-sensitive anesthetic gel could be an alternative to reduce the pain intensity in children submitted to rubber dam placement.

Conclusion

It is concluded that the liposomal thermo-sensitive anesthetic gel can reduce the perceived pain intensity related to clamp placement for rubber dam isolation before resin sealant placement in children.

Acknowledgments

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Table 1: Reagents used for the manufacture of anesthetic gel.

Phases/Anesthetics	Composition	Proportion	Handling
Oil	Lecithingranulate Isopropylpalmitate Benzoicacid	22%	The reactants were mixed in a beaker, sealed with aluminum paper and stored at room temperature for 12 hours.
Aqueous	Poloxamer 407 (Lutrol ® 127) Poloxamer 188 (Lutrol ® F68) Sodium benzoate GPS Purified Water	73%	The solutions were mixed in a beaker after 12 hours handling of oily and aqueous phases
Anesthetics	lidocaine base prilocaine base Ethanol Hydrochloric acid GPS Purified Water	5%	The solutions were mixed in a beaker after 12 hours handling of oily and aqueous phases
After the handling of anesthetic agents, all reagents were transferred to 60 mL syringes. The solutions were homogenised with the reagent of the aqueous phase, this mixture was homogenised with the oil phase reagents performing the extrusion 10 times until ready anesthetic gel.			

Table 2: Comparison of the number of patients who experienced pain rubber dam clamp placement in both groups along with the absolute and the risk ratio (*).

Treatment	Pain (number of patients)		Absolute risk (95% CI)	Risk ratio (95% CI)
	Yes	No		
Liposomal	18	63	22 (15 – 32)	0.8 (0.5 – 1.4)
Placebo	22	59	27 (19 – 38)	

McNemar's test (p = 0.52)

Table 3: Means ± standard deviations, medians and interquartile ranges of the pain intensity for both groups using the two pain scales.

Pain scale	Means ± standard deviation		Medians (interquartile range)		p-value*
	Liposomal	Placebo	Placebo	Liposomal	
Numerical scale	1.2 ± 1.5	1.8 ± 2.3	1 (0 – 2.2)	1 (0 – 2)	0.023
Wong-Baker faces	0.7 ± 0.9	1.0 ± 1.1	1 (0 – 2)	0 (0 – 1)	0.013

**Wilcoxon Signed Rank test.*

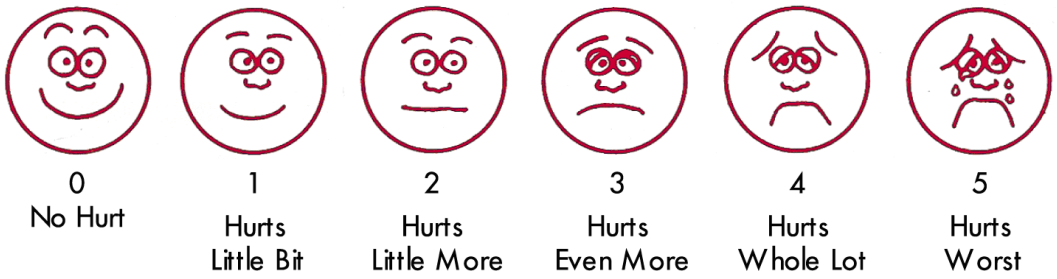

Figure 1: Wong-Baker Faces Scale

ARTIGO 4

TÍTULO: EFFICACY OF A NEW LIGHT-CURED ANESTHETIC GEL FOR CLAMP PLACEMENT BEFORE RUBBER DAM ISOLATION IN CHILDREN: A TRIPLE-BLINDED RANDOMIZED CONTROLLED CLINICAL TRIAL

STATUS: SUBMETIDO

REVISTA: AMERICAN JOURNAL OF DENTISTRY

Efficacy of a new light-cured anesthetic gel for clamp placement before rubber dam isolation in children: a triple-blinded randomized controlled clinical trial

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Abstract:

Objective: To evaluate the efficacy of a new light-cured anesthetic gel for pain control associated with the clamp placement for rubber dam isolation in children. **Methods:** Eighty-two children in need of sealant placement on the first permanent mandibular molars were selected to took part in this randomized, split-mouth, triple-blinded study. Before rubber dam placement, the light-cured anesthetic gel (test) or a placebo gel (control) was applied on the gingival margins of the molars. The hemi-arches were isolated with cotton rolls and the gels were applied; the anesthetic gel was light-cured. After 30 seconds, clamp #26 was positioned on tooth 36 or 46. If there was pain, the clamp was removed and rescue anesthesia was applied. The absolute risk and intensity of pain were registered using three scales: facial expression (Wong-Baker), observational (Flacc) and numerical (NRS). Data were analyzed by McNemar's test and Wilcoxon Signed Rank (alpha = 5%). **Results:** Differences were detected for the risk of pain between groups (P= 0.0002) and for the different intensity of pain scales used (P<0.001) with positive results for the anesthetic gel.

Clinical Significance: The new developed light-cured topical anesthetic is an alternative to infiltrative anesthesia for pain control during clamp adaptation for rubber dam isolation. Its use helps to overcome the fear of needles, which can trigger pain, anxiety and discomfort for the majority of the patients, hampering the behavior management in children.

Introduction

Topical anesthesia is a strategy that minimizes anxiety, pain and patient discomfort [1]. Different gels and creams for topical use have been marketed (EMLA® cream[a]; Oraqix®[b]; Benzotop®[c] and Hurricaine®[D]) to circumvent these problems [1]. These products have some disadvantages as short anesthetic effect, difficult application due to high flow ability and they can be easily washed out by saliva leaving an unpleasant taste[2-4].

In order to overcome the shortcomings of the available gels, our research team developed a topical light-cured anesthetic gel with a more powerful anesthetic salt. Additionally, the light-cured property makes application easier, without flowing to neighboring areas, avoiding the swallowing or unpleasant taste. All these features make this gel a suitable substitute for the available products.

Such a product was designed for use in several clinical situations like periodontal probing/scaling and root planning, placement of retraction cords, dental extraction of exfoliating primary teeth and clamp adaptation for rubber dam use, among others usages.

This is the first of a sequence of clinical trials designed to test this new product in children. It was planned to test the efficacy of the light-cured anesthetic gel in controlling or even avoiding the discomfort related to rubber dam clamp placement.

Nearly 60 to 90% of schoolchildren has experienced carious lesions in their permanent teeth[5, 6] and the progression of dental caries can be prevented through on invasive treatments, like resin based pit and fissures resin sealants[7].

This material can be applied under isolation with cotton rolls and saliva ejectors. But the use of rubber dam isolation is a more reliable way to prevent saliva contamination [2, 8].

Rubber dam isolation for sealant placement is especially important when treating children with active tongue movements and saliva excess to ensure the efficacy of this procedure [3, 9, 10]. On the other hand, the use of the metallic clamps to stabilize the rubber dam can produce discomfort. In the majority of cases (64 to 80% of children)[2], it is handled with local anesthesia.

Infiltrative anesthesia is the most common anesthesia for pain control in soft and hard tissues [11, 12]. However, many patients report anxiety, pain from injections and fear of needles. Approximately 18% of patients are “very much" afraid of needles [13]. Discomfort associated with the duration of the anesthesia is another drawback of such type of analgesia [13, 14]. All of these can be avoided with the use of a more powerful topical anesthetic.

To the extent of the authors’ knowledge, this is the first paper to introduce a light-cured topical anesthetic gel. Therefore, this study aims to compare this experimental gel to a placebo, analyzing the risk and intensity of pain, as well as the need of rescue anesthesia in children submitted to the placement of clamps for rubber dam isolation for sealant placement. The null hypothesis tested was that there was no difference when light-cured topical anesthetic gel or placebo gel were used.

Material and Methods

Ethical approval

This clinical investigation was approved (protocol number 974.502) by the scientific review committee and by the committee for the protection of human participants of the local university.

Protocol registration

We prepared this article using the protocol established by the Consolidated Standards of Reporting Trials statement - CONSORT (Schulz et al. 2011). This protocol was registered in the Brazilian clinical trials registry under the identification number RBR-6DYTYF.

Trial design, settings and locations of data collection

This was a triple-blind, randomized, split-mouth and placebo-controlled clinical trial with an equal allocation ratio. All procedures in the selected volunteers were performed from March 16, 2015, to April 15, 2016, in the School of Dentistry at Local University.

Recruitment

Participants included in the clinical trial presented themselves for treatment at the School of Dentistry at the local University (convenience sampling). No type of advertisement was done in any type of media.

Eligibility criteria

In order to be included in the trial, participants should be between 8 to 12 years old, without systemic diseases and present two lower first permanent molars (FDI two-digit notation: teeth number 36 and 46) with need of sealant placement to prevent carious lesions in deep fissures or to arrest the progression of non-cavitated carious lesions[15]. Participants were excluded if their teeth were partially erupted or exhibited active dentine carious lesions that require restorative treatment or if they had cognitive impairment that could prevent the correct assessment of pain. Children with a history of allergy, any form of sensitivity or allergic reaction to anesthetics based on esters were not included. The parents and the patients were informed with details about the research objectives and both signed an Informed Consent Form before any intervention.

Sample size calculation

The primary outcome of this study was the absolute risk of pain. The absolute risk of pain is the number of patients who reported pain at some period during the treatment. A total of 77 patients were required to have a 80% chance of detecting at the level of 5% significance, a reduction in the pain risk of 64% in the control group ^{2} to 42% in the experimental group. All calculations for determining the sample size were carried out with a specific program, freely available online, for this purpose (www.sealedenvelope.com).

Random sequence generation and allocation concealment

The resin sealants were applied in the teeth 36 and 46 of each patient. The gel to be used in each tooth were determined by simple randomization. The random sequence was generated by a software freely available online (www.sealedenvelope.com) by an investigator who was not involved in the

implementation of the study.

Neither the operator nor the patient had knowledge of the gel that would be applied to both teeth. For this purpose, the random sequence generated was individually placed in opaque, consecutively numbered and sealed envelopes, which were only opened by the operator one minute before the intervention. The group determined in the envelope was directed to the right tooth while the left molar received the other treatment.

Blinding

This was a triple-masked clinical trial, in which the patient, operator, and statistical were masked to the group assignment. A third researcher, not involved in the evaluation process, was responsible for the randomization process, delivery and guidance on the administration of the light cured gels.

The preparation of the topical light-cured anesthetic gel was handled by a single investigator (Patent –BR 10 2016 007724 9)[16]. The placebo gel manipulation was carried out similarly, following all the steps of the light-cured anesthetic gel without the addition of the anesthetic agents. The light-cured gels were handled in the Pharmacy School of the local University with the reagents: tetracaine hydrochloride (5%), inhibitor, monomers, photoinitiator, co-initiator, dye and inert load.

After manipulation, both gels were transferred to dark syringes to avoid contact with light and to prevent foreknowledge of the group assignment during application. The syringes were marked only with numbered codes so that neither the operators nor the patients could identify them.

Study intervention

The first tooth to be treated was the 36. The envelope-containing group, generated by random sequence, was opened immediately before the begging of the procedure.

The protocol consisted on the isolation of the quadrants with cotton rolls and the placement of the anesthetic or placebo gels, with the aid of a syringe, in the gingival tissue around the tooth to be sealed. The gel extended approximately

2 mm beyond the gingival margin (similar to the gingival protection barrier used in in-office bleaching procedures). The gel was left untouched for 15 seconds before being light-curing with a LED device (Radii-cal[e]) with a intensity of 1.200mW/cm^2,in both sides of the tooth (buccal and lingual). After 30 s, the clamp #26 (Duflex-SS White [f]) was positioned with a door-clamp gripper for adaptation check. At this moment, if the patient reported pain or discomfort, the clamp was removed and an infiltrative anesthesia (2% lidocaine with epinephrine 1:100,000 [g]) was applied as rescue anesthesia. Rubber dam was installed after clamp placement.

After isolation with rubber dam and tooth prophylaxis, the enamel surface of the molar was etched with 37% phosphoric acid for 30 s (Condac 37 [h]), followed by washing with water (30 s) and drying the surface with air jet (30 s). The resin sealant Fluroshield [i] was applied and light cured for 40 s with LED device at 1,200mW/cm^2. Subsequently, the same procedure was carried out in the tooth 46 in the same clinical appointment.

Assessment of the outcome

The absolute risk of pain was evaluated just after the #26 clamp adaptation and prior to rubber dam placement through a dichotomous scale(yes/no).If the patient reported some pain or discomfort during clamp placement, the pain intensity was evaluated using three different pain scales:

1. Facial expression Wong-Baker scale[13, 14, 17] (Figure 1). The patients should assign scores from0 to 5 (0 = no pain, 1 and 2 = mild pain, 3 = moderate pain, 4 = severe pain, 5 = unendurable pain) to express their pain intensity.

2. Numerical scale of 11 points (Numeric Rating Scale- NRS)[2]. In this scale, participants should chose a number ranging from 0 (no pain) to 10 (unbearable pain).

3. The observational Flacc scale. This scale enables an assessment of pain using body language, even without verbalization. The patient's movements were recorded with scores ranging from 0 to 10 [18, 19] by a calibrated and blinded operator.

Statistical analysis

We performed the analysis following the intention-to-treat protocol, and we involved all participants who were randomly assigned[20]. We compared the absolute risk of pain and need of rescue anesthesia for both groups using the McNemar's test (α= 0.05). We calculated the relative risk and the need of rescue anesthesia along with the confidence interval for the effect size.

We performed the comparison of the pain intensity (numerical scale, scale Wong-Baker Faces and the observational Flacc) using the Wilcoxon Signed Rank Tests, considering that normal distribution was not observed for these data. For all statistical tests, the significance level was 0.05. We performed all analyses using the software Sigma Plot version 11.0 [j] .

Results

Characteristics of included participants

A total of 392 participants were evaluated to check if they meet the inclusion and exclusion criteria; dental exams were done in a dental chair (Figure 2). The mean age (years) of the participants of this study was 10.4 ± 1.0 ranging from 8 to 12 years and the percentage of boys was 52%.

Adherence to the protocol and drop-outs

Treatment was performed in all participants that were randomized. No missing data was observed. Figure 2 depicts the participant flow diagram in the different phases of the study design.

Risk of pain

In regard to the absolute risk of pain, a significant difference was observed between groups (Table 1; p = 0.0002). The experimental gel showed a significant lower risk of pain during clamp placement and a reduced need of rescue anesthesia (Table 2; p = 0.01). In regard to the pain intensity (Table 3), the groups differed statistically under the three pain scales used in this study (p <0.001).Lower pain intensity was observed for the group receiving the experimental gel.

Rescue anesthesia

When considering the need of rescue anesthesia, a significant difference was observed between groups (Table 2; p = 0.01). The experimental gel showed a significant lower necessity of rescue anesthesia during clamp placement; only four children required rescue anesthesia after the use of anesthetic gel and 12 after the use of placebo.

Adverse effects

No adverse effects were observed or related by patients during this study.

Discussion

The null hypothesis was rejected. We showed that the experimental light-cured anesthetic gel reduced the risk and intensity of pain as well as the need of rescue anesthesia compared to a placebo gel during clamp placement in children undergoing sealant placement with rubber dam isolation.

Preliminary studies have already demonstrated that the use of an effective topical anesthesia instead of an infiltrative anesthesia can reduce the fear and anxiety of pediatric patients after clamp placement for rubber dam isolation [2, 9, 14, 21]. These findings are in line with the present clinical trial. But some important differences should be pointed out when comparing the present study with others [2, 3, 9].

The first feature that strengthen our results is that the present study presents a higher effect size for all outcomes, due to the number of participants included. Our study also showed the percentage of patients who reported pain related to the placement of the clamp, which is not reported by the others in the literature.

Another distinction is the anesthetic salt used in our experimental gel. Tetracaine is considered a very potent anesthetic agent and exhibits longer duration due to the prolonged connection with the sodium channel of the nerve fibres [22-24]. Other commercial anesthetic gels such as Oraqix and Emla contains lidocaine and prilocaine as theirs active ingredients[2, 9]. Benzocaine gel and Hurricaine contains benzocaine [3, 9]. DentiPatch is a transmucosal anaesthetic

patch that contains lidocaine [3]. These anesthetics are less potent than tetracaine for topical analgesia [4, 24].

We might expect additional benefits with the use of this light-cured gel. Although this was not the focus of the present investigation, by light-curing the gel into place, there is no swallowing of the product when compared to any commercial gel available in the market and the anesthetic effect is restricted to the regions where the product is applied, since the product do not flow from the applied site. Therefore, a slow, sustained and continuous release of the anesthetic salt may have occurred, which prolonged even further the anesthetic effect of the product. This, however, should be focus of future studies.

The scales to assess patients' pain can facilitate the communication between patients and dentists [18, 25, 26]. This study evaluated the intensity of pain using three scales: facial expression Wong-Baker, a numerical scale and the observational scale Flacc. The first two pain scales are normally recommended for pediatric patients, as they are easy to understand. Flacc scale provides a simple framework for quantifying pain behaviors in children just by watching their movements [14, 25]. All the three pain scales reached similar conclusions. Others studies also used different scales (VAS, NRS and face scales) to evaluate the pain caused by the rubber dam clamp[2, 3, 9]. Similar results to ours were observed in one study that used facial pain scale [2].

Finally, we should not deny the limitations of this study. Since both teeth of each patient were treated in the same day, one may think that a pain experience in the first treatment could affect the pain experience during clamp placement in the other side tooth. Notwithstanding, there is a very low likelihood that this design has affected the conclusions herein observed, as the study was well randomized.

Therefore, the light-cured anesthetic gel can be an alternative to infiltrative anesthesia. By doing so, we might observe a reduction of anxiety that needles usually causes[11, 14], being this product an ally in pediatric dentistry. However, further studies comparing the patient’s preference and anxiety produced by analgesia with topical gel and infiltrative anesthesia should be conducted.

We can conclude that the use of a light-cured anesthetic gel can significantly reduce the risk and intensity of pain as well as the need of rescue anesthesia during rubber dam clamp placement

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Legends

Figure 1 -Facial expression Wong-Baker scale

Figure 2 – Flow diagram of the split-mouth clinical trial, including detailed information regarding the excluded participants

Table 1: Comparison of the number of patients who experienced pain during rubber dam clamp placement in both groups along with the absolute and the risk ratio (*).

Table 2: Comparison of the number of patients who required rescue anesthesia in both groups along with the absolute and the risk ratio (*).

Table 3: Means ± standard deviations, medians and interquartile ranges of the pain intensity for both groups using the three pain scales.

Table 1: Comparison of the number of patients who experienced pain during rubber dam clamp placement in both groups along with the absolute and the risk ratio (*).

Treatment	Pain (number of patients)		Absolute risk (95% CI)	Risk ratio (95% CI)
	Yes	No		
Gel	28	54	34 (25 – 44)	0.6 (0.4 – 0.9)
Placebo	46	36	56 (45 – 66)	

McNemar's test (p = 0.0002).

Table 2: Comparison of the number of patients who required rescue anesthesia in both groups along with the absolute and the risk ratio (*).

Treatment	Pain (number of patients)		Absolute risk (95% CI)	Risk ratio (95% CI)
	Yes	No		
Gel	4	78	5 (2 – 11)	0.3 (0.1 – 0.9)
Placebo	12	70	14 (9 – 24)	

McNemar's test (p = 0.01)

Table 3: Means ± standard deviations, medians and interquartile ranges of the pain intensity for both groups using the three pain scales.

Pain scale	Means ± standard deviation		Medians (interquartile range)		p-value*
	Gel	Placebo	Placebo	Gel	
Facial expression Wong-Baker (0-5)	0.9 ± 1.0	1.7 ± 1.3	1 (1 – 2)	1 (0 – 1)	p<0.001
Numerical (0-11)	1.4 ± 1.6	2.7 ± 2.2	2(1 – 4)	1 (0 – 2)	
Observational Flacc (0-10)	0.4 ± 0.7	1.0 ± 1.1	1 (0 – 2)	0 (0 – 1)	

**Wilcoxon Signed Rank test.*

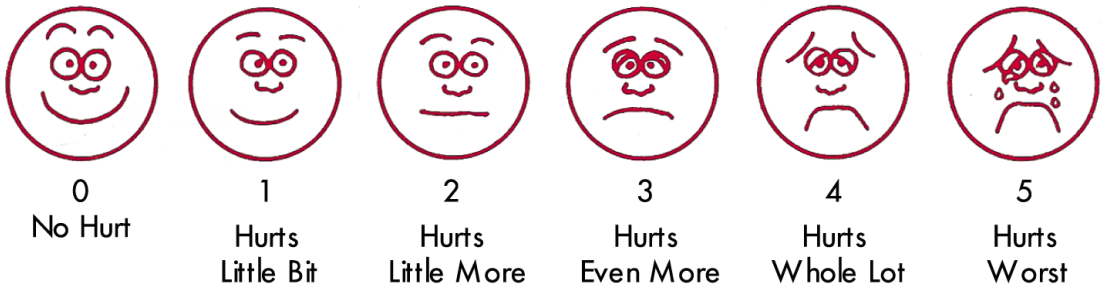

Figure 1: Facial expression Wong-Baker scale

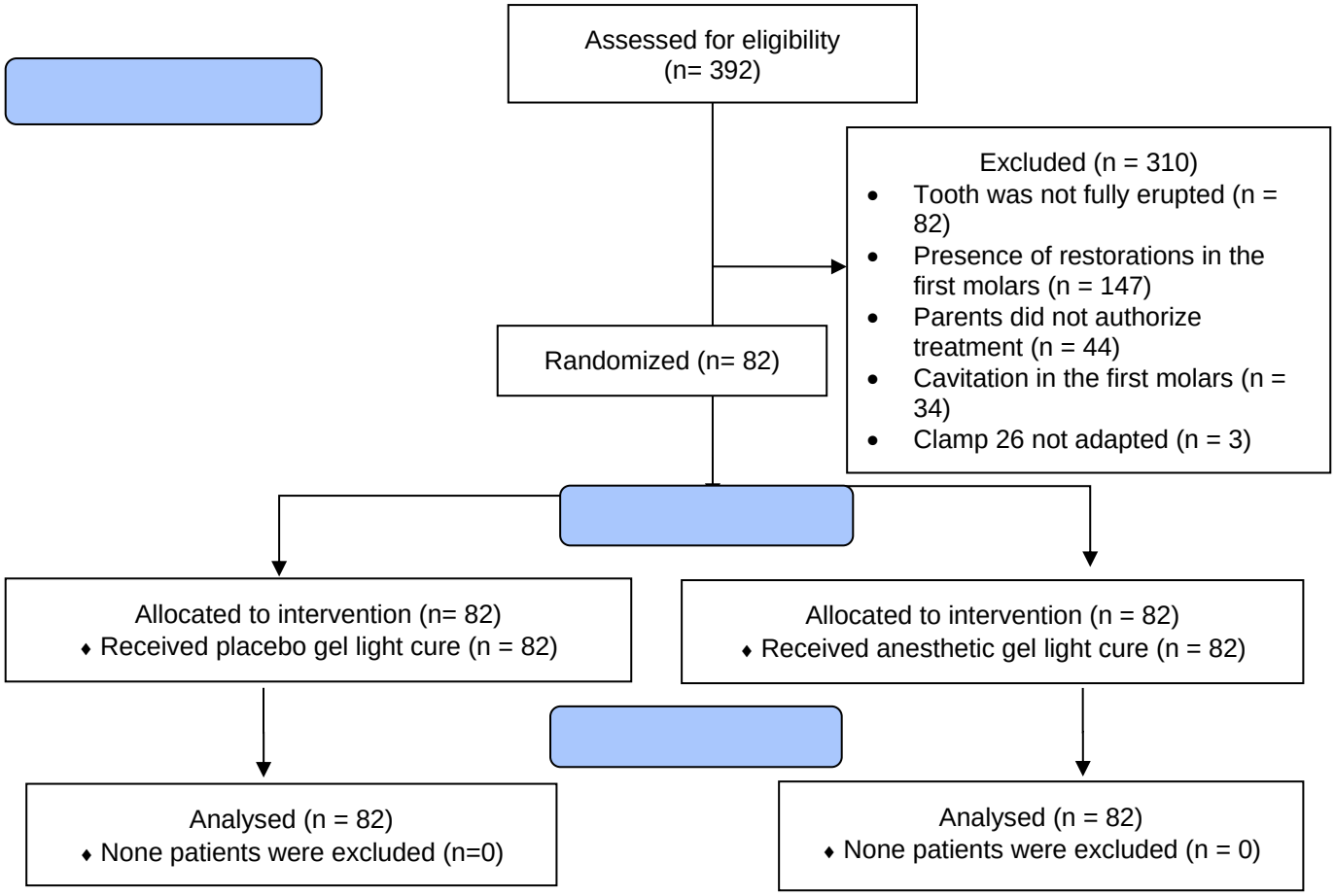

Figure 2: Flow diagram of the split-mouth clinical trial, including detailed information regarding the excluded participants.

ARTIGO 5

TÍTULO: Efficacy of a new anesthetic light-cured gel for clamp placement before rubber dam isolation for restorative treatment of non-carious lesions: a triple-blind randomized clinical trial

STATUS: SUBMETIDO

REVISTA: OPERATIVE DENTISTRY

Efficacy of a new anesthetic light-cured gel for clamp placement before rubber dam isolation in non-carious lesions: a triple-blind randomized clinical trial

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Abstract:

Objectives: To evaluate the efficacy of a new anesthetic light-cured gel for pain control in adults, submitted to the rubber dam isolation for the restorative treatment of non-carious cervical lesions (NCCL). **Methods:** This study was a randomized, split-mouth, triple-blind controlled trial. The sample was composed of 50 adults with at least one pair of non-carious cervical lesions, located in the same arch but on opposing sides. Each tooth received one anesthetic light-cured gel (experimental gel) or the placebo (control gel). The quarters were isolated with cotton rolls and the gels applied in the gum around the tooth with the aid of an applicator tip and the anesthetic gel was light-cured. After 30 seconds, the clamp #212 was positioned on the teeth, if there was pain report, it was removed and an injectable anesthesia was applied before rubber dam isolation as anesthesia rescue. The absolute risk and intensity of pain were registered using two methods: scale VAS and VRS. The data were analyzed by McNemar's test and Wilcoxon Signed Rank (alpha = 5%). **Results:** The odds ratio for pain (OR = 3.5; 95% CI 1.1 to 14.6) was statistically significant (p = 0.0339). However, there was a significant difference between light-cured anesthetic gel and placebo gel groups for both scales (p < 0.001). On average, pain intensity was 1 units (VAS) lower in the anesthetic group than in the placebo group (95% CI [-2.3 to -0.3]). For the VRS, the anesthetic gel was 0.4 units lower than placebo (95% CI [-0.9 to 0.07]).

Conclusions: The light-cured anesthetic gel, instead of a placebo, can significantly reduce the risk and intensity of pain during rubber dam clamp for restorative treatment of non-carious cervical lesions.

Keywords: Anesthetics; Dental Restoration, Permanent; Dental Materials; Dentin Sensitivity.

Introduction

The prevalence of non-carious cervical lesions (NCCLs) has increased especially in the elderly population [1, 2]. For instance, in the Chines population the prevalence of NCCLs was reported to be 63% [3]. This high proportion of patients with cervical lesions gave rise to the need of restorative treatment in these dental areas.

The restorative treatment can be performed with different restorative materials [4-6], but adhesive systems and composite resins are the most commonly used due to their better esthetic properties [7]. However, adhesive systems are sensitive to moisture and contaminants such as saliva [8], gingival fluid and blood [9, 8, 10]. Adequate moisture control can be solved by using rubber dam isolation, which avoids external contamination and may increase the longevity of restorations [11-13].

Unfortunately, rubber dam is kept in place by a metal clamp that also aim to retract the gingival tissue for explosion of the gingival margin of the NCCL. This procedure may be painful requiring the use of anesthesia for patient's comfort during the procedure [14]. A recent study demonstrated that approximately 70% of the patients under treatment of NCCLs required anesthesia for clamp placement [10].

The most common way to make this procedure less painfull is by using injectable anesthesia [15]. The problem that arises here is that approximately 18% of patients are "very much" afraid of needles [16], which places an obstacle for restorations of NCCLs under rubber dam isolation. Apart from that the greater area of numbing produced by the injectable anesthesia, the pain during puncture and its longer duration are also additional disadvantages that lead patients to reject injectable anesthesia [17, 18].

The restorative procedure in NCCLs is usually performed fastly and it is not painful as they usually do not require cavity preparation. Therefore, topical anesthesia could be an alternative to produce analgesia for clamp placement.

Topical anesthetics have played a great role in dentistry in alleviating the fear of patients, eliminating pain, and providing pain control [14].

In the dental market, there are some available topical anesthetics, used to replace injectable anesthesia, in some dental procedures such as probing [19], scaling and root planning [20, 21], clamp placement in children [22, 23] and placement of mini implants in orthodontics [24]. However, these available products have a very short time of action (10-15 min) [25-27], they flow to the neighboring areas causing its unpleasant anesthesia and it can be easily washed out by saliva [22, 28, 29]. In this way, it would be interesting to produce an anesthetic gel capable of overcoming such disadvantages and still capable to replace the injectable anesthesia in some dental procedures.

This paper presents an alternative for topical anesthesia based in a newly developed anesthetic gel. We developed a topical light-cured anesthetic gel using a more potent anesthetic salt than the ones used in the commercially available products. This triple-blind randomized clinical trial evaluated the efficacy of this new anesthetic gel compared to a placebo in the risk and intensity of pain of adults submitted to clamp placement for rubber dam isolation before treatment of NCCLs.

Material and Methods

Ethical approval

The Scientific review committee and the Committee for the protection of human participants of the present university approved this randomized clinical trial under protocol number 974.479.

All participants included were in need of sealant placement. Therefore, clamp testing would be required in all participants. All participants included were in need of sealant placement. Therefore, clamp testing would be required for all participants. All procedures were explained to the parents, especially the sensations that she/he would probably feel.

Protocol registration

We registered this research protocol in the Brazilian clinical trials registry (REBEC) under the identification number RBR-6HXHX7. The article was written based on the CONSORT (Consolidated Standards of Reporting Trials) statement [30]

Trial design, settings and locations of data collection

We conducted a triple-blind randomized, split-mouth and placebo-controlled clinical trial with an equal allocation ratio. The study was performed from September 18, 2015, to November 11, 2016, in the dental clinics of the School of Dentistry of the local university.

Recruitment

Participants included in the clinical trial (convenience sampling), presented themselves for treatment at the School of Dentistry at the local University. No type of advertisement was done in any type of media.

Eligibility criteria

For inclusion in the trial participants should beat least 18 years old, with good general health and oral health. The participants should have at least one pair of non-carious cervical lesions (NCCLs) without undercuts. These lesions should belocated in the same arch but on opposing sides and in need of restorative treatment (to avoid excessive dental wear and to eliminate hypersensitivity). The NCCLs should be similar size, depth and location of the gingival margin.

Participants were excluded if the teeth with NCCLs were endodontically treated. Participants with gingivitis, periodontitis and dental mobility, and bruxism habits were also excluded. Adults with a history of allergy; any form of sensitivity or allergic reaction to ester-based anesthetics were also excluded.

Sample size calculation

The primary outcome of this study was the absolute risk of pain caused by clamp placement. The risk of pain caused by clamp placement was reported to be 70% in an earlier study [10]. Therefore, at least 40 patients were required to detect a difference in the pain risk of 30% with a power of 80% and a significance

level of 5%. All calculations for determination of the sample size were carried out with freely available online program for this purpose (www.sealedenvelope.com).

The sample size calculation was performed without accounting for the potential correlation between the paired treatment outcomes. This approach resulted in a larger sample size than if the correlation coefficient between treatment outcomes is not zero. We performed this approach because published within-person trials do not report this correlation coefficient, and thus, we opted for being conservative.

Random sequence generation and allocation concealment

The gel to be used in each tooth was determined by simple randomization. The random sequence was generated in the same website used for sample size calculation (www.sealedenvelope.com) by an investigator who was not involved in the implementation of the study.

The random sequence generated was individually placed in opaque, consecutively numbered and sealed envelopes, which were only opened by the operator one minute before the intervention. The envelope contained the group to be used in teeth located in the quadrant with the lowest two-digit FDI numbering system (World Dental Federation), while the other teeth received the alternate treatment.

Blinding

This was a triple-masked clinical trial, in which the patient, operator, and statistician were masked to the group assignment. The delivery and guidance on the administration of the light-cured gelswas performed by a researcher not involved in the implementation.

A single investigation prepared the topical light-cured anesthetic gel following the description of the Patent –BR 10 2016 007724 9 [31]. The formulation of the placebo gel was carried out similarly following all the steps of the light-cured anesthetic gel except for the inclusion of the anesthetic salt. The light-cured gels were handled in the Pharmacy School of the local University with the following reagents: tetracaine hydrochloride (5%), inhibitor, monomers, photo-initiator, co-initiator, dye and inert load. The gels had a viscosity similar to that

used in light-cured gingival barriers.

After handling, both gels were transferred to dark syringes to avoid contact with light and to prevent foreknowledge of the group assignment during application. The syringes were marked only with numbered codes so that neither the operators nor the patients could identify them.

Study intervention

One researcher was responsible for application of the gels and placement and adaptation of rubber dam clamp. Another researcher was responsible for the restorative treatment.

First, patients were instructed on all steps of the treatment and the possible sensations he/she would probably feel during clamp adaptation. We made it clear that if there was any discomfort an injectable anesthesia would be applied.

The quadrants were isolated with cotton rolls and the anesthetic gel or placebo gel was placed, with the aid of a syringe,in the gingival tissue around the tooth to be restored. The gel extended approximately 2 mm beyond the gingival margin in both sides (facial and lingual). The gel was left in place for 15 s and then light-cured for 15 s with a LED light-curing unit (Radii-cal, SDI, Bayswater, Victoria, Australia) set at 1.200mW/cm^2. The clamp #212 (Duflex-SS White, Rio de Janeiro, RJ, Brazil) was positioned with a door-clamp gripper for adaptation check. At this moment, we asked the patient if he/she felt pain or discomfort. In case of positive answer, the clamp was removed and an injectable anesthesia (2% lidocaine with epinephrine 1:100,000 - Alphacaine; DFL, Rio de Janeiro, RJ, Brazil) was applied. Rubber dam was then installed after clamp placement.

Then, the enamel surface was etched with 37% phosphoric acid for 15 s (Condac 37- FGM, Joinville, SC, Brazil), followed by water washing (15 s) and drying with an air stream (10 s). Two coats of the two-step etch-and-rinse adhesive Ambar (FGM, Joinville, SC, Brazil) was applied and the solvent evaporated with an air stream for 5 s. The adhesive was light cured for 20 s with the same light curing device. The composite resin Opallis (FGM, Joinville, SC, Brazil) was incrementally placedand each increment light-cured for 20 s. The restorative steps were performed by a calibrated investigator.

Both gels were used in the same clinical appointment in the different sides of the same arch.

Assessment of the outcome

All outcomes were collected just after placement of the clamp #212 for adaptation, as it is the most critical phase in terms of painful sensation during the procedure. The odds of having pain was obtained for each group in a 2 X 2 table for paired data to allow calculation of the odds ratio. The pain intensity was further evaluated using two different pain scales:

1. Visual analogue scale (VAS) [32]. This scale is a 10-cm horizontal line with scores of 0 and 10 at their ends, where 0 = no pain and 10 = unbearable pain. The patient should mark with a vertical line across the horizontal line of the scale the intensity of the pain. Then, the distance in mm from the zero and was measured with the aid of a millimeter ruler.

2. Verbal Rating Scale (VRS) [33, 34, 20]. The patient was asked to indicate the numerical value of the degree of pain using a five-point Numeric Rating Scale (NRS) where 0 = none, 1 = mild, 2 = moderate, 3 = considerable and 4 = severe.

Statistical analysis

We performed the analysis following the intention-to-treat protocol, and we involved all participants who were randomly assigned [30]. We compared the odds of pain for both groups by using the McNemmar's test (α= 0.05). We calculated the odds ratio with the confidence interval for the effect size.

We performed the comparison of pain intensity (VAS and VRS) using the Wilcoxon Signed Rank test, as data did not follow not normal distribution. Correlation coefficients for the paired data for each outcome was calculated. In all statistical tests, the significance level was set at 0.05. We performed all analyses by using the software Sigma Plot version 11.0 (Systat Software Inc., San Jose, CA, USA).

Results

Characteristics of included participants

A total of 120 adults were examined in a dental chair to check if they meet the inclusion and exclusion eligibility criteria but only 50 met the eligibility criteria (Figure 1). The mean age (years) of the participants of this study was 40.4 ± 1.0 years old. The participant's age ranged from 25 to 66 years; the percentage of men was 40% and the most treated teeth were the two low first premolars (FDI two-digit notation: teeth number 34 and 44), which representing 36% of the sample.

Adherence to the protocol and drop-outs

Treatment was performed in all participants that were randomized. No missing data was observed. Figure 1 depicts the participant's flow diagram in the different phases of the study design.

Odds and intensity of pain

A total of 28 patients presented pain in the placebo group, and from these total, fourteen patients reported pain exclusively in the placebo group. Twenty-two patients reported pain in the light-cured group, and from these total of 22, four experienced pain only in the light-cured group. In comparative terms, the odds ratio for pain (Table 1; OR = 3.5 95% CI 1.1 to 14.6) was in average 2.5 times lower for the experimental gel, and a statistically significant difference between groups were detected (Table 2; $p = 0.034$). The phi correlation coefficient for pairs of binary data was low but significant ($r = 0.33$; $p = 0.019$).

Pain was positively correlated in both groups, being the correlation moderate for the VAS scale (Table 1, $r = 0.50$; $p < 0.0001$) and weak for the VRS scale (Table 1; $r = 0.43$; $p = 0.001$). There was a significant average difference between experimental and placebo groups for both pain the numerical scale (Table 2; $p = 0.005$) and VRS scales ($p = 0.015$). On average, pain intensity was 1 units (VAS) lower in the light-cured group than in the placebo group (95% CI -2.3 to -0.3; Table 2). For the VRS scale, the light-cured gel was 0.4 units lower than placebo (95% CI [-0.87 to-0.07], Table 2). The groups differed statistically under the two pain scales ($p=0.005$ VAS and $p= 0.015$ for VRS scale, Table 3).

Adverse effects

No adverse effects were observed or related by patients during this study.

Discussion

This study demonstrated that the newly developed light-cured anesthetic gel is effective in controlling the risk and intensity of pain related to clamp placement. This finding is a result of this well-designed trial that followed the principles of proper randomization, allocation and blinding of operator, patient and statistician, reducing selection and performance bias [35].

We have used tetracaine, instead of prilocaine and lidocaine commonly used formulation of other commercially available gels, as tetracaine is more potent [36, 28] than the aforementioned ones. This higher analgesia effectiveness of this salt is due to the fact that tetracaine is of the ester group [15] and its long duration is related to its hydrophobicity that promotes a prolonged interaction with the sodium channel binding site, determining a higher power than other anesthetics [37, 18].

For instance, Oraqix (Dentsply, York, PA, USA) which is a topical anesthetic gel that uses thermo setting agents [38, 39, 23] and Emla (AstraZeneca, RεD Sodertalje, Sweden) which is a eutectic mixture of local anesthetics [22, 40] contain lidocaine and prilocaine as active ingredients [41, 21]. DentPatch (Noven Pharmaceuticals, Inc., Miami, FL, USA) is a transmucosal anesthetic that contains just lidocaine [42, 29]. Benzotop (DFL, Rio de Janeiro, RJ, Brazil), Hurricaine (Clarben, Madrid, Spain) contain only benzocaine as the active ingredient [41, 20]. Benzocaine has inferior analgesia potential than lidocaine and prilocaine [41, 20] but they are very common and widely used in dentistry [14, 25].

These formulations are presented as spray, ointment, gel and adhesive [43, 44, 29]. The spray form is not easy to apply on restrict sites and is difficult to measure the dose to be dispensed [44, 45]. Although the gel and ointment can be dispensed in pre-calculated doses [41, 26], all these formulations are subjected to saliva dilution. The patch may not be effective due to its unfavorable bioadhesion, leading to move from the applied place [43, 29].

All these anesthetic salts produce analgesia by reversibly blocking nerve conduction at the site of application producing temporary loss of sensation in a limited area due to the prolonged connection with the sodium channel of the nerve fibres [18]. The anesthetic effect is dependent on the concentration of the anesthetic salt at the site of application [37].

Although we have not compared this experimental gel with others in the market, from a clinical standpoint, it is clear that the light-cured gel does not flow away from the applied site. This avoids dilution of the product by saliva and remains in the site to be anesthetized. This is an advantage of this experimental product compared to the commercially available ones.

Other study showed that 70% of patients reported pain when adapting #212 clamp or retraction cord to perform NCCL restorations, and it was necessary to apply injectable anesthesia most of the time [10]. Therefore, the performance of our newly developed topical anesthetic gel is an exciting finding. It showed to be effective in pain control, therefore is an alternative to replace injectable anesthesia in most of the cases, overcoming the patient's fear of needles and the numbness related to local anesthesia.

Some studies have tested the adaptation of clamp in children submitted to rubber dam isolation for the placement of sealants [22, 29, 23], with positive results for anesthetic gel, corroborating with the findings of our study. It is known that due to the anatomy of non-carious, which often present subgingival margins, there is need of gingival retraction which requires an effective gel containing a potent anesthetic salt.

Our study presents some limitations, because we have evaluated the intensity and risk of pain, which is subjective and dependent of individual interpretation [46, 47]. When the patient reported pain on the first side treated, there was a tendency to feel pain on the opposite side. As the gels were randomized, this bias was minimized. Further well-delineated clinical studies should be conducted to compare the use of different gels for clamp adaptation in non-carious lesions to minimize pain, provide comfort for the patient, and facilitate the clinical procedures.

Conclusion

The new light-cured anesthetic gel was effective to reduce the risk and intensity of pain during rubber dam clamp for restorative treatment of non-carious cervical lesions.

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Table 1: Matched tabulation of outcomes with the two treatments along with the odds ratio (*).

		Placebo			Odds ratio
		Positive	Negative	Total	(95% CI interval)
Light-cured anesthetic gel	Positive	14	14	28	3.5 (1.1 to 14.6)
	Negative	4	18	22	
	Total	18	32	50	

McNemar's test (p = 0.0339). Correlation coefficient between paired data = 0.33 (p = 0.019).

Table 2: Means ± standard deviations, medians and interquartile ranges of the pain intensity for both groups using the two pain scales and the correlation coefficient of the paired data.

Pain scale	Means ± standard deviation		Mean difference (95% confidence interval)	Correlation coefficient (p-value)
	Gel	Placebo		
VAS (0-10 cm)	2.4 ± 2.9	3.4 ± 2.8	-1 (-2.3 to -0.3)	0.50 (p <0.0001)
VRS (0-4)	0.8 ± 1.0	1.2± 1.1	-0.4 (-0.9 to -0.07)	0.43 (p = 0.001)

**Wilcoxon Signed Rank test.*

Table 3 – Medians and interquartile range of the pain intensity for both groups using the two pain scales

Pain scale	Medians (interquartile range)		p-value*
	Placebo	Gel	
VAS (0-10 cm)	3 (1.0 – 5.6)	1.2 (0 - 3.8)	0.005
VRS (0-4)	1 (0 – 2)	0 (0 – 1)	0.015

**Wilcoxon Signed Rank test.*

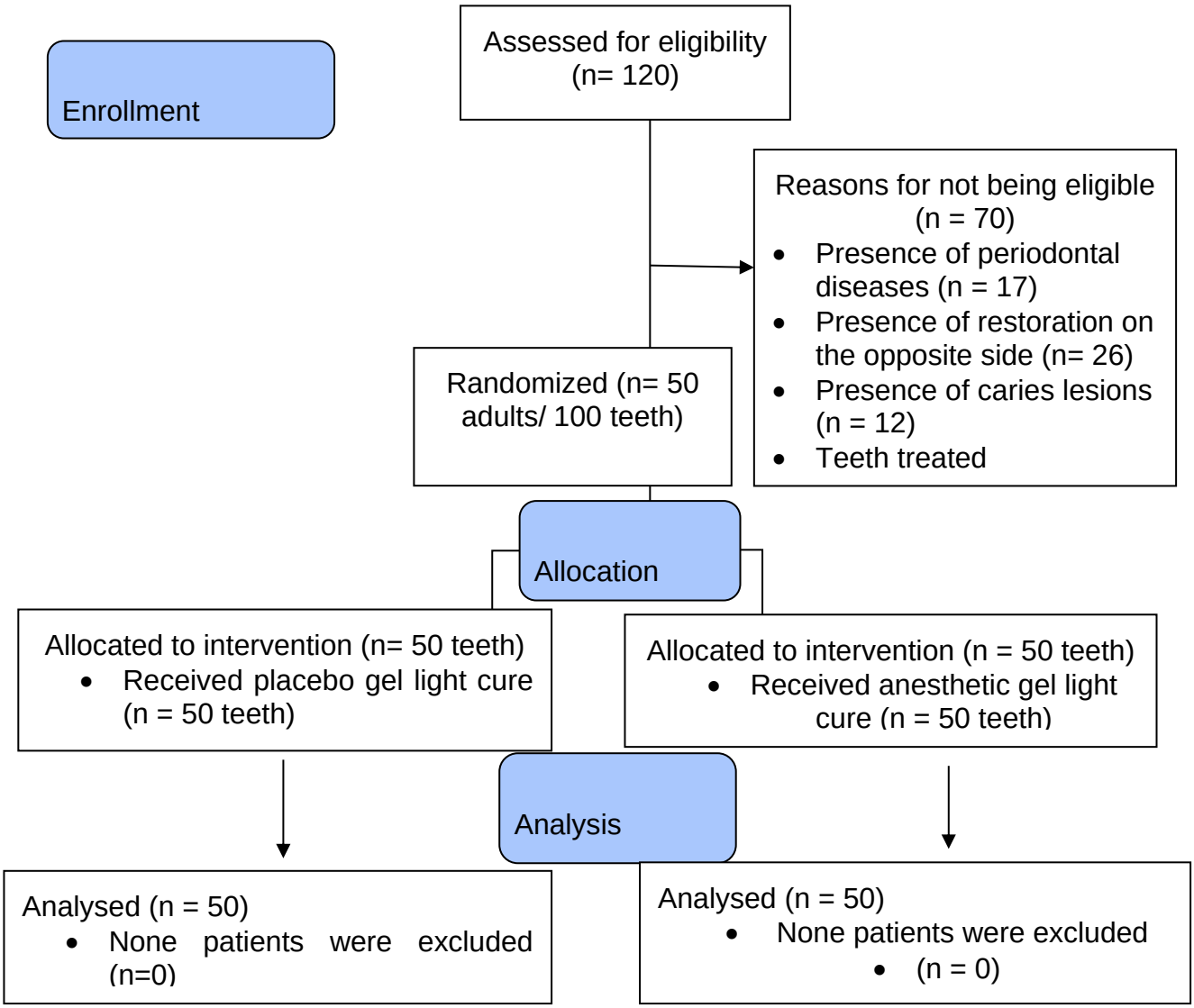

Figure 1: Flow diagram of the split-mouth clinical trial, including detailed information regarding the excluded participants.

5 DISCUSSÃO

Nessa tese, foram desenvolvidas duas revisões sistemáticas com meta-análises para comparar o efeito de “anestesia tópica versus placebo” e “anestesia infiltrativa versus anestesia tópica” durante RAP em pacientes adultos. Além dessas revisões sistemáticas, foram elaborados três estudos clínicos randomizados triplo cegos, incluindo crianças e adultos. Nesses pacientes foram testados dois tipos de géis anestésicos formulados especialmente para essas pesquisas, sendo um lipossomal termossensível e o outro fotoativado. Quanto ao produto fotoativado, foi registrada uma patente (Wambier et al.[27] 2016), tendo em vista seus diferentes componentes ativos e a consistência do gel anestésico formulado. Evitar e aliviar a dor são ações fundamentais para o bom desempenho profissional que permitem adquirir a confiança dos pacientes (Kudo[3] 2005, Milgrom et al.[4] 1997), fato que nos motivou no desenvolvimento dessas pesquisas.

A partir dos estudos realizados, constatamos que um anestésico tópico pode ser uma alternativa para substituir a anestesia infiltrativa em alguns procedimentos odontológicos como na sondagem, RAP e na adaptação de grampos para o uso de isolamento absoluto em adultos e crianças.

Os procedimentos de RAP, de modo geral, geram desconforto à maioria dos pacientes submetidos ao tratamento periodontal não cirúrgico (van Steenberghe et al.[8] 2004, Magnusson et al.[13] 2004, John et al.[43] 2017), fazendo com que a anestesia infiltrativa seja uma prática comum para a realização desses procedimentos, contudo tanto a RAP quanto a anestesia infiltrativa podem ocasionar ansiedade, medo e freqüência limitada às consultas odontológicas (Antoniazzi et al.[29] 2015).

Na revisão sistemática sobre anestésicos tópicos, primeira da literatura a comparar géis anestésicos tópicos com um placebo, o objetivo foi verificar a capacidade que esses produtos possuem de reduzir o risco e a intensidade da dor, bem como a necessidade de anestesia de resgate durante a sondagem ou RAP (Wambier et al.[9] 2016).

A dúvida com relação a efetividade dos anestésicos tópicos decorre dos diferentes resultados apresentados na literatura. Estudos demonstraram que o uso de anestesia tópica para a RAP foi superior ao placebo (Magnusson et al.[13] 2004, Mayor-Subirana et al.[35] 2013) e também há relatos de ocorrência de dor com a necessidade de anestesia terminal infiltrativa após a aplicação de anestesia tópica (Jeffcoat et al.[33] 2001, Magnusson et al.[34] 2003, Donaldson et al.[44] 2003).

Os resultados apontados em nossa revisão sistemática foram favoráveis aos anestésicos tópicos, mostrando que a anestesia tópica apresenta potencial de reduzir o risco e a intensidade da dor durante a RAP. Contudo, esses dados (risco e a intensidade da dor) foram heterogêneos na análise estatística e provavelmente isto se deve aos diferentes efeitos do tratamento, influenciado pela variabilidade nas intervenções e diversidade metodológica das pesquisas.

Diferentes anestésicos tópicos foram empregados nos estudos primários e, portanto de eficácia variável. Sob o ponto de vista da aceitação dos pacientes os resultados obtidos nesta revisão foram extremamente interessantes, permitindo concluir que os anestésicos tópicos pode ser uma alternativa durante a sondagem e RAP em pacientes adultos (Wambier et al.[9] 2016).

Por outro lado, poderia ser levantada a questão se a anestesia infiltrativa é mais eficaz do que a tópica no controle da dor em procedimentos periodontais (Antoniazzi et al.[29] 2015). Assim, a segunda revisão sistemática e meta-análise avaliou esse tema, levando em conta que a literatura é controversa nesta questão específica. Nessa revisão não consideramos o cegamento dos participantes como item principal dos domínios-chave, uma vez que a anestesia injetável poderia ser facilmente identificada pelos pacientes.

Existe estudo no qual a anestesia tópica mostrou efeito equivalente no controle da dor em comparação com a anestesia injetável, e foi melhor do que um placebo nos procedimentos de RAP (Antoniazzi et al.[29] 2015) enquanto em outras pesquisas foi demonstrado que a anestesia local infiltrativa controlava a dor de forma mais eficaz do que um gel tópico (van Steenberghe et al.[8] 2004, Stoltenberg et al.[42] 2007, Derman et al.[45] 2014). A anestesia infiltrativa bloqueia as fibras nervosas ao se ligar a receptores específicos nos canais de sódio, o

que resulta no bloqueio da dor na extremidade (Narahashi et al.[46] 1970, Strichartz [47] 1976).

Existem variáveis a serem consideradas que podem influenciar nos resultados dos diversos estudos em relação a dor do paciente. Por exemplo, a profundidade de bolsa (Winning et al.[38] 2012, John et al.[43] 2017, Svensson et al.[48] 1994), a destruição periodontal (Canakci et al.[49] 2002), força empregada pelo operador (Canakci e Canakci[50] 2007), o uso de instrumentos periodontais apropriados (Hakkinen et al.[51] 2000, Yang et al.[52] 2016) também exercem influência na intensidade de dor (Tunkel et al.[53] 2002). Além desses fatores, é importante lembrar que a dor é uma experiência individual, que pode ser influenciada por efeitos psicológicos e físicos (Hurter et al.[1] 2014, Renton[2] 2015). Esses são os diversos graus de dificuldade que os clínicos devem superar em sua prática diária, buscando avaliar a opção de trabalho mais confortável aos pacientes.

A anestesia injetável apresenta maior duração em comparação com a anestesia tópica (AAPD[17] 2016, Derman et al.[45] 2014, Sadove et al.[54] 1951), e também produz um efeito vasoconstritor que aumenta o tempo da ação anestésica (Becker e Reed[55] 2012, Haas[56] 2002), enquanto os anestésicos tópicos têm uma capacidade limitada de penetração, uma vez que precisam ultrapassar as células queratinizadas que protegem a camada externa da mucosa oral (Garg et al.[57] 2016). Ainda apresentam um curto tempo de ação (Milgrom et al.[4] 1997, AAPD[17] 2016), em torno de 15-20 min (Friskopp et al.[20] 2001), enquanto a anestesia infiltrativa permanence por mais de uma hora (Fakheran Esfahani et al.[58] 2015). Portanto, este breve período de analgesia pode limitar o uso de géis anestésicos tópicos (van Steenberghe et al.[8] 2004).

Nossos resultados da revisão sistemática mostraram que a anestesia infiltrativa foi superior à anestesia tópica durante a RAP, pois reduziu a intensidade da dor e a necessidade de anestesia de resgate. Quanto ao risco de dor, não foi detectada diferença significativa entre os métodos. Isto significa que, em algum momento do tratamento, os pacientes sentiram dor independentemente do método de analgesia empregado. Embora a anestesia

injetável tenha produzido menor intensidade de dor durante RAP comparada com a anestesia tópica, a punção da agulha pode ter sido desconfortável (List et al.[59] 2014, Milam e Giovannitti[60] 1984). Na prática clínica, os pacientes podem ser informados sobre as vantagens e desvantagens de cada método.

Os estudos clínicos (3, 4 e 5) foram delineados com todo cuidado para evitar riscos de viés. É importante ressaltar que alguns itens como randomização, ocultação da alocação e cegamento são essenciais para evitar viés e tornam os estudos de boa qualidade (Mogensen[61] 2012). A randomização, quando executada corretamente, garante as mesmas chances para todos os participantes de serem alocados no grupo teste ou no grupo controle, isto significa que fatores prognósticos conhecidos e desconhecidos estão equilibrados entre os grupos (Higgins et al.[26] 2011). Tão importante quanto a randomização, é a ocultação da alocação, passo necessário para proteger o processo de randomização, uma vez que o tratamento a ser alocado não é conhecido antes que o paciente seja incluído no estudo (Higgins et al.[26] 2011). Já o cegamento dos participantes ou avaliadores, evita o viés de desempenho (Higgins et al.[26] 2011).

O anestésico tópico ideal deve permitir uma maior absorção na mucosa, ser de fácil aplicação e com viscosidade adequada para ficar concentrado no local desejado, evitando que escorra para as áreas vizinhas e evidentemente deve ser livre de efeitos colaterais, oferecendo segurança para sua administração (Allen e Cullis, 2013).

Desta forma, com o objetivo de superar as falhas mencionadas, para esta pesquisa foram formulados os dois géis anestésicos: lipossomal termossensível e fotoativado. Esses géis anestésicos foram testados em crianças com a mesma metodologia (estudos 3 e 4). Foram aplicados ao redor da gengiva de primeiros molares permanentes inferiores para adaptação do grampo 26, colocação do dique de borracha e posterior selamento. Cada gel experimental foi comparado com um gel placebo.

O gel anestésico encapsulado em lipossomas tem em sua composição poloxameres com propriedade de aumentar sua viscosidade à temperatura

corporal (Franz-Montan et al.[21] 2007), enquanto a presença de lipossomas permite uma liberação controlada de fármacos tornando o produto mais seguro (Allen e Cullis[62] 2013). Essa liberação controlada de fármacos, poderia ainda aumentar a duração de sua ação anestésica, sendo uma vantagem em relação aos produtos comercializados.

Nos testes realizados esse gel experimental foi efetivo para reduzir a intensidade da dor. Por outro lado, o gel fotoativado foi duplamente efetivo, pois reduziu a intensidade da dor, bem como o risco de dor. Este gel foi patenteado (Wambier et al.[27] 2016), e é o primeiro gel anestésico que pode ser fotoativado, formando uma barreira ao redor da gengiva.

Esse novo anestésico tópico fotoativado foi elaborado (Wambier et al.[27] 2016) na expectativa de corrigir algumas falhas dos produtos já comercializados, ele possui na sua composição a tetracaína que é um sal potente (Meechan[23] 2000, Giordano et al.[63] 2015). A longa duração de ação está relacionada com sua hidrofobicidade (permite a permanência do fármaco no tecido que circunda um nervo por um longo período). A hidrofobicidade promove uma interação prolongada com o sítio de ligação no canal de sódio, determinando uma maior potência que outros sais anestésicos (Becker e Reed[55] 2012, Kumar et al.[64] 2015, Carvalho[65] 1994).

Pelo fato de ser fotoativado, o novo gel permanece no local aplicado, sem se deslocar para áreas vizinhas, evitando a diluição pela saliva, qualidade positiva em relação as outras formulações (Lim e Julliard[11] 2004, Mayor-Subirana et al.[35] 2013, Pandit et al.[40] 2010, Svensson et al.[48] 1994). Além disto, apresenta maior duração devido à conexão prolongada com o canal de sódio das fibras nervosas (Shavit et al.[66] 2016, Eidelman et al.[67] 2005, Romsing et al.[68] 1999).

Embora os componentes ativos sejam diferentes (o lipossomal termossensível contém lidocaína com prilocaína e o fotoativado tetracaína), os resultados foram favoráveis para os dois anestésicos tópicos, sendo que o fotoativado acrescentou o menor risco de dor, conforme comentado.

O gel fotoativado foi testado em crianças para adaptação do grampo 26 e em adultos para adaptação do grampo 212, mostrando resultados positivos (menor risco e intensidade de dor). Foi observada correlação entre as escalas e os pacientes apontaram para os menores números. Este fato é interessante clinicamente, pois permite realizar procedimentos não invasivos ou minimamente invasivos sem a necessidade de utilizar anestesia infiltrativa, tornando o tratamento mais confortável para o paciente e mais fácil para o dentista.

Um artigo publicado anteriormente (Loguercio et al.[69] 2003), informou que 70% dos pacientes relataram dor para a colocação do grampo 212, sendo necessário aplicar anestesia infiltrativa na maior parte dos casos. Estudos preliminares já demonstraram que o uso de uma anestesia tópica potente pode substituir uma anestesia infiltrativa para reduzir o medo e a ansiedade de pacientes pediátricos para colocação do grampo e dique de borracha (Lim e Julliard[11] 2004, Yoon e Chussid[70] 2009).

Existe uma variedade de anestésicos tópicos que podem ser utilizados, embora a pomada a base de benzocaina seja a mais empregada na Odontologia, este tipo de sal anestésico tem potencial de analgesia inferior em comparação com a lidocaína e a prilocaína (Antoniazzi et al.[29] 2015, Rosivack et al.[71] 1990, Al-Melh e Andersson[72] 2007), e esse sais são menos eficientes e menos potentes do que os produtos à base de tetracaína (Meechan[23] 2000, Romsing et al.[68] 1999), utilizada na formulação do gel fotoativado.

Os anestésicos comercializados são disponibilizados na forma de spray, pomada, gel e adesivo (Stecker et al.[22] 2002, Roh et al.[73] 2016), tais como: EMLA® pomada [AstraZeneca, Cotia, SP] que contém lidocaína/prilocaína a 5%, Oraqix® gel [Dentsply, York, PA, EUA] com lidocaína / prilocaína a 5% que utiliza um sistema termoestável reversível, Patch™ adesivo transmucoso (DentiPatchTM, Inc., Miami, FL, EUA) com 10% ou 20% de lidocaína, Benzotop® [DFL, Rio de Janeiro, RJ, Brasil] e Hurricaine® [Beutlich LP, Waukegan, IL, USA] que são pomadas compostas por benzocaína à 20%. No entanto, todos esses anestésicos são menos potentes do que a tetracaína para analgesia tópica (Wambier et al.[9] 2016, Meechan[23] 2000, Romsing et al.[68] 1999).

A forma de spray apresenta alguma dificuldade na aplicação e não permite controlar ou medir a dose a ser dispensada (Roh et al.[73] 2016, Sharma et al.[74] 2014). O gel e a pomada são mais recomendados porque podem ser dispensados por doses pré-calculadas (Stoltenberg et al.[42] 2007, Sadove et al.[54] 1951, Roh et al.[73] 2016). O adesivo pode não ser tão eficaz devido à sua bioadesão desfavorável, podendo se deslocar (Stecker et al.[22] 2002, Koppolu et al.[75] 2016).

Vale mencionar que os géis experimentais foram comparados com géis placebos preparados de forma semelhante sem o sal anestésico na composição. Assim, em futuras pesquisas, devem-se comparar os diversos anestésicos tópicos disponíveis no mercado com os formulados nessa tese, e, em diferentes situações clínicas, bem como, com outros números de grampos para isolamento absoluto.

A evolução dos anestésicos tópicos representou um grande avanço na odontologia, proporcionando conforto aos pacientes que apresentam medo da anestesia infiltrativa, portanto estudos sobre esse tema devem ter continuidade para que o profissional tenha opções de escolha conforme a real necessidade de seus pacientes.

6 CONCLUSÃO

Os anestésicos tópicos mostraram ser uma alternativa para substituir a anestesia infiltrativa durante o uso do grampo de isolamento absoluto, raspagem e alisamento radicular, conforme verificado nas revisões sistemáticas e nos estudos clínicos. Acrescenta-se ainda que o gel fotoativado patenteado apresenta um potencial diferenciado para o controle do risco e intensidade de dor em crianças e adultos, oferecendo uma nova opção de trabalho na clínica odontológica.

6.1 A anestesia tópica é superior ao placebo, reduzindo o risco, a intensidade da dor e a necessidade de anestesia resgate nos procedimentos de sondagem e RAP.

6.2 A anestesia infiltrativa é superior a anestesia tópica para os procedimentos de sondagem e RAP, pois reduziu a intensidade da dor e a necessidade de anestesia de resgate. Contudo, as anestesias tópicas e infiltrativa são semelhantes quanto ao risco de dor e preferência dos pacientes.

6.3 O gel anestésico liposomal termossensível é efetivo para reduzir a intensidade da dor em crianças submetidas ao isolamento absoluto para aplicação de selantes.

6.4 O gel anestésico fotoativado é efetivo para reduzir o risco, a intensidade da dor, bem como a necessidade de anestesia de resgaste em crianças submetidas ao isolamento absoluto para aplicação de selantes.

6.5 O gel anestésico fotoativado é efetivo para reduzir o risco, a intensidade da dor em adultos submetidos ao isolamento absoluto para restaurações de lesões cervicais não cariosas.

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ANEXO A

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Does the intra-pocket anesthesia influence the pain during probing/ scaling and root planning compared to placebo in adult patients? A systematic review.

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.
A anestesia não inavasiva influencia na dor durante a sondagem e raspagem/alisamento radicular comparado a um placebo em pacientes adultos? Uma revisão sistemática

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
03/01/2015

4 Anticipated completion date
Give the date by which the review is expected to be completed.
01/06/2015

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Leticia Wambier

7 Named contact email
Enter the electronic mail address of the named contact.
marcelo_gumy@hotmail.com

8 Named contact address
Enter the full postal address for the named contact.
Senador Pinheiro Machado, 267, Ponta Grossa, Paraná -Brazil. CEP:84010-310

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
554299124364

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
Universidade Estadual de Ponta Grossa

Website address:
www.uepg.br

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Miss	Leticia	Wambier	UEPG
Professor	Ana Claudia	Chibinski	UEPG
Miss	Juliana	Larocca de Geus	UEPG
Professor	Denise	Stadler Wambier	UEPG
Professor	Alessandro	Loguercio	UEPG
Professor	Alessandra	Reis	UEPG

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
none

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
Does the intra-pocket anesthesia compared to a placebo influence the pain during probing and/or scaling and root planning in adult patients with periodontal disease?

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
To identify trials to be included for this review, we will search on the electronic databases MEDLINE via PubMeb, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO) and Cochrane Library. We will hand-search the reference lists of all primary studies for additional relevant publications and the related articles link of each primary study in the PubMed database without restrictions to publication date or languages. No restrictions will be placed on the publication date or languages, and all relevant studies will be translated and reviewed. We will search the abstracts of the annual conference of the International Association for Dental Research (IADR) and their regional divisions (1990–2014) and will get in touch with authors of relevant abstracts for further information. We will explore the grey literature using the database System for Information on Grey literature in Europe (SIGLE), and dissertations and theses using the ProQuest Dissertations and Theses Fulltext database, as well as the Periódicos Capes Theses database. To locate unpublished and ongoing trials related to the review question, we will search the following clinical trials registry: Current Controlled Trials (www.controlled-trials.com), International Clinical trials registry plataform

(http://apps.who.int/trialsearch/), the ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). The search strategy will be appropriately modified for each database and performed by two reviewers to idebtify eligible studies. Full text versions of the papers that appeared to meet the inclusion criteria will be retrieved for further assessment and data extraction.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
No

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
periodontal disease; periodontal pocket

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Inclusion: Adult patients with periodontal diseases that can be treated with probing, scaling and root planning. Adult patients without periodontal disease submited to dental probing only. Exclusion: pacients who took analgesics or anti-inflammatory drugs before probing and/or scaling and root planning.

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Pacients that undergo probing, scaling and root planning after application of a topical anesthetic.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Pacients that undergo probing, scaling and root planning after application of a placebo.

22 Types of study to be included initially
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Inclusion: We will include randomized clinical trials (RCTs) that compare the pain during probing and/or scaling and root planning with intra-pocket anesthesia versus placebo in adult patients of any age group. The intensity of pain will be the primary outcome of the study. We will include only parallel or split-mouth clinical trials in humans. Exclusion: Non-controlled clinical trials, editorial letters, pilot studies, historical reviews, in vitro studies, cohort, observational and descriptive studies, such as case reports and case series will be excluded.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
1) Randomized clinical trials (full-text articles or abstracts published in dental meetings);

24 Primary outcome(s)
Give the most important outcomes.
Pain intensity and risk during probing and/or scaling and root planning, taken immediately after or during the procedure.

Give information on timing and effect measures, as appropriate.
Different types of pain scales will be accepted to assess the intensity of pain after periodontal treatment.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
None

Give information on timing and effect measures, as appropriate.

26 Data extraction, (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Articles will be selected by title and abstracts according to the previously described search strategy. Articles that appear in more than one database will be considered only once. Full-text articles will also be obtained when the title and abstract have insufficient information to make a clear decision. Subsequently, two reviewers will classify those which met the inclusion criteria. To handle with such a large number of studies, we will use a study ID for each eligible study, combining first author and year of publication. Any disagreement between the reviewers over the eligibility of particular studies will be resolved through discussion with a third reviewer.

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Quality assessments of the selected trials will be evaluated by two independent reviewers, using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins et al.20 2011). The assessment criteria contain six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. During data selection and quality assessment, any disagreements between the reviewers will be solved through discussion, and if needed, by consulting a third reviewer. The quality assessment will be pilot tested using a sample os study reports to ensure that the criteria will be consistent to the research quesion.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
The extracted data will be analyzed using Revman (Review Manager version 5.3 softwar, Cochrane Collaboration, Copenhagen, Denmark). Data from eligible studies will be either dichotomous or ordinal.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned.

Review general information

30 Type of review
Select the type of review from the drop down list.
Intervention

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Brazil

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.
Not applicable.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
No

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Not applicable.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
periodontal pocket

scaling and root planning

intrapocket anesthesia

topical anesthetic

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
Not applicable.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.
None.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

ANEXO B

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Does the intra-pocket anesthesia influence the pain during scaling and root planning compared to injectable anesthesia in adult patients? A systematic review.

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.
A anestesia não inavasiva influencia na dor durante a raspagem e alisamento radicular comparado a anestesia infiltrativa em pacientes adultos? Uma revisão sistemática

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
23/02/2016

4 Anticipated completion date
Give the date by which the review is expected to be completed.
06/12/2016

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started √

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Leticia Wambier

7 Named contact email
Enter the electronic mail address of the named contact.
marcelo_gumy@hotmail.com

8 Named contact address
Enter the full postal address for the named contact.
Senador Pinheiro Machado

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
554299124364

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
Universidade Estadual de Ponta Grossa

Website address:
www.uepg.br

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Miss	Leticia	Wambier	UEPG
Miss	Juliana	de Geus	UEPG
Miss	Thaynara	Boing	UEPG
Professor	Ana Claudia	Chibinski	UEPG
Professor	Denise	Wambier	UEPG
Professor	Alessandro	Loguercio	UEPG
Professor	Alessandra	Reis	UEPG

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
None

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
Does the intra-pocket anesthesia compared to a injectable anesthesia influence the pain during scaling and root planning in adult patients with periodontal disease?

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
To identify trials to be included for this review, we will search on the electronic databases MEDLINE via PubMeb,Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO) and Cochrane Library. We will hand-search the reference lists of all primary studies for additional relevant publications and the related articles link of each primary study in the PubMed database without restrictions to publication date or languages. No restrictions will be placed on the publication date or languages, and all relevant studies will be translated and reviewed. We will search the abstracts of the annual conference of the International Association for Dental Research (IADR) and their regional divisions (1990–2014) and will get in touch with authors of relevant abstracts for further information. We will explore the grey literature using the database System for Information on Grey literature in Europe (SIGLE), and dissertations and theses using the ProQuest Dissertations and Theses Fulltext database, as well as the Periódicos Capes Theses database. To locate unpublished and ongoing trials related to the review question, we will search the following clinical trials registry:

Current Controlled Trials (www.controlled-trials.com), International Clinical trials registry plataform (http://apps.who.int/trialsearch/), the ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). The search strategy will be appropriately modified for each database and performed by two reviewers to idebtify eligible studies. Full text versions of the papers that appeared to meet the inclusion criteria will be retrieved for further assessment and data extraction.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.
No

I give permission for this file to be made publicly available
Yes

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Periodontics; Periodontal diseases

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Inclusion: Adult patients with periodontal diseases that can be treated with scaling and root planning. Patients who took analgesics or antiinflammatory drugs regularly.

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Application of topical intrapocket anesthesia before scaling and root planning.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Application of a injectable anesthesia before scaling and root planning.

22 Types of study to be included initially
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Inclusion: We will include randomized clinical trials (RCTs) that compare the pain during scaling and root planning with intra-pocket anesthesia versus injectable anesthesia in adult patients of any age group. We will include only parallel or split-mouth clinical trials in humans. Non-controlled clinical trials, editorial letters, pilot studies, historical reviews, in vitro studies, cohort, observational and descriptive studies, such as case reports and case series will be excluded.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Randomized clinical trials (full-text articles or abstracts published in dental meetings);

24 Primary outcome(s)
Give the most important outcomes.
1) Pain intensity will be measured during and/or immediately scaling and root planning. 2) Risk of pain will be measured during and/or immediately scaling and root planning. Different types of pain scales will be accepted such as VAS, Heft Parker scale and VRS.

Give information on timing and effect measures, as appropriate.
Pain intensity will be measured during and/or immediately scaling and root planning. Different types of pain scales will be accepted such as VAS, Heft Parker scale and VRS.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
The need of rescue anesthesia during scaling and root planning will be a secondary dichothomores outcome.

Give information on timing and effect measures, as appropriate.
Only during scaling and root planning.

26 Data extraction, (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Articles will be selected by title and abstracts according to the previously described search strategy. Articles that appear in more than one database will be considered only once. Full-text articles will also be obtained when the title and abstract have insufficient information to make a clear decision. Subsequently, two reviewers will classify those which met the inclusion criteria. To handle with such a large number of studies, we will use a study ID for each eligible study, combining first author and year of publication. Any disagreement between the reviewers over the eligibility of particular studies will be resolved through discussion with a third reviewer.

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Quality assessments of the selected trials will be evaluated by three independent reviewers (L.M.W, J.L.G and T.F.B), using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins et al.20 2011). The assessment criteria contain six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias. During data selection and quality assessment, any disagreements between the reviewers will be solved through discussion, and if needed, by consulting a fourth reviewer (A.R). The quality assessment will be pilot tested using a sample os study reports to ensure that the criteria will be consistent to the research question. We will consider three out of the six domains in the Cochrane risk of bias tool as key domains for the assessment of the risk of bias. At the study level, studies will be judged to at "low" risk of bias if there are adequate sequence generation, allocation concealment and blinding (operators and participants). If one or the two criteria not is adequate, the study will be considered at 'high' risk of bias.When the study is judged as 'unclear' in their key domains, we will try to contact the authors to obtain more information to allow a definitive 'low' or 'high' risk.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
The extracted data will be analyzed using Revman (Review Manager version 5.3 softwar, Cochrane Collaboration, Copenhagen, Denmark). Data from eligible studies will be either dichotomous (absolute risk of pain and need of rescue anesthesia) or continuous (pain intensity).Only studies classified at "low" risk of bias in the key domains will enter into the meta-analysis. The outcomes will summarized by calculating the Hedge's g standardize mean difference for the continuous data and the odds ratio for dichotomous data. For both summary measures, the 95% confidence interval (CI) will be calculated.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned.

Review general information

30 Type of review
Select the type of review from the drop down list.
Intervention

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Brazil

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.
Not applicable.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Not applicable.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
scaling and root planning

intrapocket anesthesia

anesthesia local

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
Not applicable.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.
None

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

ANEXO C

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação clínica da sensibilidade transoperatória em crianças submetidas ao tratamento preventivo utilizando anestesia tópica com novo gel anestésico

Pesquisador: Alessandra Reis

Área Temática:

Versão: 1

CAAE: 42035314.1.0000.0105

Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 974.470

Data da Relatoria: 26/02/2015

Apresentação do Projeto:

Avaliação clínica da sensibilidade transoperatória em crianças submetidas ao tratamento preventivo utilizando anestesia
tópica com novo gel anestésico

Objetivo da Pesquisa:

Analisar o efeito da anestesia tópica não-invasiva com gel anestésico lipossomal termossensível no controle da dor em crianças de 7 a 12 anos
submetidas ao isolamento absoluto para a aplicação de selantes resinosos.

Avaliação dos Riscos e Benefícios:

Riscos:

Desconforto durante a prova do grampo 26, e caso isso ocorra, será aplicada anestesia infiltrativa.

Benefícios:

Substituição da anestesia infiltrativa por uma tópica e aplicação do selante resinoso em pacientes que possuem essa indicação.

Endereço: Av. Gen. Carlos Cavalcanti, nº 4748. UEPG, Campus Uvararanas, Bloco M, Sala 100.
Bairro: Uvaranas **CEP:** 84.030-900
UF: PR **Município:** PONTA GROSSA
Telefone: (42)3220-3108 **E-mail:** coep@uepg.br

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

Continuação do Parecer: 974.470

Comentários e Considerações sobre a Pesquisa:

Pesquisa bem delineada e exequível.

Considerações sobre os Termos de apresentação obrigatória:

Corretos.

Recomendações:

Aprovado.

Conclusões ou Pendências e Lista de Inadequações:

Aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

PONTA GROSSA, 05 de Março de 2015

Assinado por:
ULISSES COELHO
(Coordenador)

Endereço: Av. Gen. Carlos Cavalcanti, nº 4748. UEPG, Campus Uvararanas, Bloco M, Sala 100.
Bairro: Uvaranas **CEP:** 84.030-900
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ANEXO D

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação clínica da dor transoperatória em crianças submetidas ao tratamento preventivo utilizando um novo anestésico tópico fotoativado

Pesquisador: Alessandra Reis

Área Temática:

Versão: 1

CAAE: 42035115.0.0000.0105

Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 974.502

Data da Relatoria: 26/02/2015

Apresentação do Projeto:

Avaliação clínica da dor transoperatória em crianças submetidas ao tratamento preventivo utilizando um novo anestésico
tópico fotoativado

Objetivo da Pesquisa:

Analisar o efeito de uma novo anestésico tópico no controle da dor em crianças de 8 a 12 anos submetidas ao isolamento absoluto para a aplicação de selantes resinosos

Avaliação dos Riscos e Benefícios:

Riscos:

Desconforto durante a prova do grampo 26, e caso isso ocorra, será aplicada anestesia infiltrativa.

Benefícios:

-Substituição da anestesia infiltrativa por uma anestesia tópica; -Aplicação do selante resinoso em pacientes que possuem essa indicação

Comentários e Considerações sobre a Pesquisa:

Pesquisa condizente com o histórico da equipe.

Endereço: Av. Gen. Carlos Cavalcanti, nº 4748. UEPG, Campus Uvararanas, Bloco M, Sala 100.
Bairro: Uvaranas **CEP:** 84.030-900
UF: PR **Município:** PONTA GROSSA
Telefone: (42)3220-3108 **E-mail:** coep@uepg.br

UNIVERSIDADE ESTADUAL DE PONTA GROSSA - UEPG

Continuação do Parecer: 974.502

Considerações sobre os Termos de apresentação obrigatória:

Estão corretos.

Recomendações:

Aprovado.

Conclusões ou Pendências e Lista de Inadequações:

Aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

PONTA GROSSA, 05 de Março de 2015

Assinado por:
ULISSES COELHO
(Coordenador)

Endereço: Av. Gen. Carlos Cavalcanti, nº 4748. UEPG, Campus Uvararanas, Bloco M, Sala 100.
Bairro: Uvaranas **CEP:** 84.030-900
UF: PR **Município:** PONTA GROSSA
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ANEXO E

RBR-3wwqc3
Avaliação clínica da sensibilidade transoperatória em crianças submetidas ao tratamento preventivo utilizando anestesia tópica com novo gel anestésico.

Data de registro: 6 de Ago. de 2016 às 16:22
Last Update: 23 de Ago. de 2016 às 10:56

Tipo do estudo:

Intervenções

Título científico:

PT-BR
Avaliação clínica da sensibilidade transoperatória em crianças submetidas ao tratamento preventivo utilizando anestesia tópica com novo gel anestésico.

EN
Clinical evaluation of intraoperative sensitivity in children undergoing preventive treatment using topical anesthesia with new anesthetic gel.

Identificação do ensaio

Número do UTN: U1111-1186-2169

Título público:

PT-BR
Investigação clínica da dor durante o tratamento de selante utilizando uma anestesia tópica.

EN
Investigation of clinical pain during sealing treatment using topical anesthesia.

Acrônimo científico:

Acrônimo público:

Identificadores secundários:

974.470
Órgão emissor: Comitê de Ética em Pesquisa da Universidade Estadual de Ponta Grossa

42035314.1.0000.0105
Órgão emissor: Plataforma Brasil/Sistema Nacional de Ética em Pesquisa

Patrocinadores

Patrocinador primário: Universidade Estadual de Ponta Grossa

Patrocinadores secundários:

Instituição: Universidade Estadual de Ponta Grossa

Fontes de apoio financeiro ou material:

Instituição: Universidade Estadual de Ponta Grossa

Condições de saúde

Condições de saúde ou problemas:

PT-BR	EN
Cárie dentária; Restauração Dentária Permanente; Anestesia Dentária; Dor	Dental caries; Dental Restoration, Permanent; Anesthesia, Dental; Pain

Descritores gerais para as condições de saúde:

PT-BR	ES	EN
C07: Doenças estomatognáticas	**C07:** Enfermedades estomatognáticas	**C07:** Stomatognathic diseases

Descritores específicos para as condições de saúde:

PT-BR	ES	EN
C07.793.720.210: Cárie Dentária	**C07.793.720.210:** Caries Dental	**C07.793.720.210:** Dental Caries
E06.323.428: Restauração Dentária Permanente	**E06.323.428:** Restauración Dental Permanente	**E06.323.428:** Dental Restoration, Permanent
E03.155.141: Anestesia Dentária	**E03.155.141:** Anestesia Dental	**E03.155.141:** Anesthesia, Dental
C10.597.617: Dor	**C10.597.617:** Dolor	**C10.597.617:** Pain

Intervenções

Categorias das intervenções

Other

Intervenções:

PT-BR	EN
O selante resinoso será realizado nos dentes 36 e 46 de 80 pacientes. Um anestésico tópico lipossomal termossensível (grupo experimental) ou um placebo (grupo controle) a ser usado em cada um desses dentes será determinado por aleatorização por meio de blocos de tamanho de 2 e 4, em um envelope selado haverá a indicação do tratamento do dente 36, sendo o outro tratamento aplicado no dente 46. Serão realizados 80 selantes utilizando o grupo controle (gel placebo) e 80 selantes utilizando o grupo experimental (gel anestésico tópico lipossomal termossensível). Para a aplicação do anestésico tópico ou do placebo, os quadrantes serão isolados com rolos de	The resin sealant will be held on 36 and 46 teeth of 80 patients. A topical anesthetic liposomal thermosensitive (experimental group) or a placebo (control group) to be used in each of these teeth will be determined by randomization using blocks of size 2 and 4, in a sealed envelope will be the treatment indication tooth 36, the other treatment applied to the tooth 46. sealants 80 will be performed using the control group (placebo gel), and sealants 80 using the experimental group (topical anesthetic thermosensitive liposome gel). For the application of topical anesthetic or placebo quarters will be isolated with cotton rolls and agents applied around the tooth and gingiva (collar 1 to 2 mm) with the aid of an

algodão e os agentes aplicados ao redor do dente e gengiva (colarinho de 1 a 2 mm) com o auxílio de uma ponta aplicadora. Após três minutos, o grampo 26 será posicionado com uma pinça porta-grampo para verificação da adaptação do mesmo, neste momento o risco da dor será avaliado através de uma escala dicotômica de prevalência, e a intensidade será avaliada através de diferentes escalas (escala de expressão facial Wong-Baker, numérica de 11 pontos e observacional de Flacc). A aplicação do selante resinoso será realizada primeiramente no dente 36. Após isolamento com o dique de borracha, a superfície do esmalte será condicionada com ácido fosfórico 37% por 30 segundos, seguida de lavagem com água e secagem da superfície com jato de ar. O selante resinoso será aplicado e fotoativado por 40 segundos. O mesmo procedimento será realizado no dente 46.

applicator tip. After three minutes, the clip 26 is positioned with a door-clip forceps to check the adjustment of the same, this time the pain of the risk will be assessed through a dichotomous scale prevalence, and intensity will be assessed using different scales (scale facial expression Wong-Baker, numerical 11 points and observational FLACC). The application of resin sealant is first carried out on the tooth 36. After isolation with a rubber dam, the enamel surface is etched with 37% phosphoric acid for 30 seconds, followed by washing with water and drying the surface with compressed air. The resin sealant is applied and light cured for 40 seconds. The same procedure will be performed on tooth 46.

Descritores para as intervenções:

PT-BR
E03.155.086.231: Anestesia Local

ES
E03.155.086.231: Anestesia Local

PT-BR
E06.323.428: Restauração Dentária Permanente

ES
E06.323.428: Restauración Dental Permanente

PT-BR
C10.597.617: Dor

ES
C10.597.617: Dolor

PT-BR
F01.470.132.300: Ansiedade ao Tratamento Odontológico

ES
F01.470.132.300: Ansiedad al Tratamiento Odontológico

PT-BR
D25.339.773: Selantes de Fossas e Fissuras

ES
D25.339.773: Selladores de Fosas y Fisuras

Recrutamento

Situação de recrutamento: Recruitment completed

País de recrutamento
Brazil

Data prevista do primeiro recrutamento: 2015-04-13

Data prevista do último recrutamento: 2016-04-15

Tamanho da amostra alvo:	Gênero para inclusão:	Idade mínima para inclusão:	Idade máxima para inclusão:
80	-	8 Y	12 Y

Critérios de inclusão:

PT-BR
Crianças de 8 a 12 anos com boa saúde geral e bucal; os dentes 36 e 46 deverão estar totalmente erupcionados e ter indicação de selante.

EN
Children 8 to 12 years with good general and oral health; the teeth 36 and 46 should be fully erupted and have sealant indication.

Critérios de exclusão:

PT-BR
Dentes que não estão totalmente erupcionados ou com lesões de cárie que necessitam de restauração; também serão excluídos pacientes com história de alergia; sensibilidade ou qualquer forma de reação alérgica aos anestésicos a base de amida; portadores de doença sistêmica grave não controlada como problemas cardíacos; neurológicos; renais; hepáticos ou sanguíneos e ainda pacientes não colaboradores.

EN
Teeth are not fully erupted or carious lesions that require restoration; also a history of allergy patients are excluded; any form of sensitivity or allergic reaction to anesthetics amide base; severe systemic disease patients not controlled as heart problems; neurological; kidney; liver or blood and even patients not employees.

Tipo do estudo

Desenho do estudo:

PT-BR
Ensaio clínico de tratamento, randomizado controlado, paralelo, triplo-cego, dois braços.

EN
Clinical trial treatment, randomized controlled, parallel, triple-blind, two-arm.

Programa de acesso expandido	Enfoque do estudo	Desenho da intervenção	Número de braços	Tipo de mascaramento	Tipo de alocação	Fase do estudo
Nenhum	Treatment	Parallel	2	Triple-blind	Randomized-controlled	N/A

Desfechos

Desfechos primários:

PT-BR
Desfecho esperado: Número de pacientes que relatam dor durante a colocação de um grampo para isolamento absoluto após a aplicação de um anestésico tópico lipossomal termossensível, através de auto-relato. Este número será transformado em percentual de pacientes com dor e será denominado de risco absoluto de dor.

EN
Expected outcome: Number of patients reporting pain during the placement of a staple for absolute isolation after application of a topical anesthetic liposomal thermosensitive through self-report. This number will be transformed into percentage of patients with pain and is called absolute risk of pain.

Desfechos secundários:

PT-BR
Desfecho esperado: A intensidade da dor será avaliada através de escala de

EN
Expected outcome: The intensity of the pain will be assessed by scale of facial

expressão facial de Wong-Baker (0-5) e uma escala numérica de 11 pontos (0-10) e será apresentada como média e desvio padrão.

expression Wong-Baker (0-5) and a numeric scale of 11 points (0-10) and will be presented as mean and standard deviation.

PT-BR

Desfecho esperado: O risco da dor será avaliado através de escala dicotômica (sim ou não) e será apresentada como média e desvio padrão.

EN

Expected outcome: The pain of the risk will be assessed by dichotomous scale (yes or no) and will be presented as mean and standard deviation.

Contatos

Contatos para questões públicas

Nome completo: Alessandra Reis

Endereço: Av. General Carlos Cavalcanti, 4748.

Cidade: Ponta Grossa / Brazil

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E-mail: reis_ale@hotmail.com

Filiação: Universidade Estadual de Ponta Grossa

Contatos para questões científicas

Nome completo: Alessandra Reis

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Cidade: Ponta Grossa / Brazil

CEP: 84030-900

Fone: +55 (42) 3220 3741

E-mail: reis_ale@hotmail.com

Filiação: Universidade Estadual de Ponta Grossa

Contatos para informação sobre os centros de pesquisa

Nome completo: Alessandra Reis

Endereço: Av. General Carlos Cavalcanti, 4748.

Cidade: Ponta Grossa / Brazil

CEP: 84030-900

Fone: +55 (42) 3220 3741

E-mail: reis_ale@hotmail.com

Filiação: Universidade Estadual de Ponta Grossa

Links adicionais:

Download no formato ICTRP

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ANEXO F

RBR-6dytyf
Avaliação clínica da dor transoperatória em crianças submetidas ao tratamento preventivo utilizando um novo anestésico tópico fotoativado

Data de registro: 6 de Ago. de 2016 às 15:27
Last Update: 16 de Ago. de 2016 às 09:24

Tipo do estudo:

Intervenções

Título científico:

PT-BR
Avaliação clínica da dor transoperatória em crianças submetidas ao tratamento preventivo utilizando um novo anestésico tópico fotoativado

EN
Clinical evaluation of intraoperative pain in children undergoing preventive treatment using a new topical anesthetic photoactivated

Identificação do ensaio

Número do UTN: U1111-1186-2065

Título público:

PT-BR
Investigação clínica da dor durante o tratamento de selantes em crianças utilizando um novo anestésico tópico fotoativado

EN
Clinical research of pain during treatment sealants in children using a new topical anesthetic photoactivated

Acrônimo científico:

Acrônimo público:

Identificadores secundários:

974.502
Órgão emissor: Comitê de Ética em Pesquisa da Universidade Estadual de Ponta Grossa

42035115.0.0000.0105
Órgão emissor: Plataforma Brasil/Sistema Nacional de Ética em Pesquisa

Patrocinadores

Patrocinador primário: Universidade Estadual de Ponta Grossa

Patrocinadores secundários:

Instituição: Universidade Estadual de Ponta Grossa

Fontes de apoio financeiro ou material:

Instituição: Universidade Estadual de Ponta Grossa

Condições de saúde

Condições de saúde ou problemas:

PT-BR	EN
Cárie dentária; Restauração Dentária Permanente; Anestesia Dentária; Dor; Ansiedade ao Tratamento Odontológico; Selantes de Fossas e Fissuras	Dental caries; Dental Restoration, Permanent; Anesthesia, Dental; Pain; Dental Anxiety; Pit and Fissure Sealants

Descritores gerais para as condições de saúde:

PT-BR	ES	EN
C07: Doenças estomatognáticas	**C07:** Enfermedades estomatognáticas	**C07:** Stomatognathic diseases

Descritores específicos para as condições de saúde:

PT-BR	ES	EN
C07.793.720.210: Cárie Dentária	**C07.793.720.210:** Caries Dental	**C07.793.720.210:** Dental Caries
E06.323.428: Restauração Dentária Permanente	**E06.323.428:** Restauración Dental Permanente	**E06.323.428:** Dental Restoration, Permanent
E03.155.141: Anestesia Dentária	**E03.155.141:** Anestesia Dental	**E03.155.141:** Anesthesia, Dental
C10.597.617: Dor	**C10.597.617:** Dolor	**C10.597.617:** Pain
F01.470.132.300: Ansiedade ao Tratamento Odontológico	**F01.470.132.300:** Ansiedad al Tratamiento Odontológico	**F01.470.132.300:** Dental Anxiety
D25.339.773: Selantes de Fossas e Fissuras	**D25.339.773:** Selladores de Fosas y Fisuras	**D25.339.773:** Pit and Fissure Sealants

Intervenções

Categorias das intervenções

Other

Intervenções:

PT-BR	EN
Grupo experimental: O selante resinoso será realizado nos dentes 36 e 46 de 80 pacientes. Um anestésico tópico fotoativado a ser usado em cada um desses dentes	Experimental group: The resin sealant will be held on 36 and 46 teeth of 80 patients. A photoactivated topical anesthetic to be used in each of these teeth will be determined by

será determinado por aleatorização por meio de blocos de tamanho de 2 e 4, em um envelope selado haverá a indicação do tratamento do dente 36, sendo o outro tratamento aplicado no dente 46. Para a aplicação do anestésico tópico fotoativado, os quadrantes serão isolados com rolos de algodão e os agentes aplicados ao redor do dente e gengiva (colarinho de 1 a 2 mm) com o auxílio de uma ponta aplicadora. O produto será imediatamente fotoativado com auxílio de um aparelho fotopolimerizador por 30 segundos. Após a fotoativação do produto, o grampo 26 será posicionado com uma pinça porta-grampo para verificação da adaptação do mesmo, neste momento o risco da dor será avaliado através de uma escala dicotômica de prevalência, e a intensidade será avaliada através de diferentes escalas (escala de expressão facial Wong-Baker, numérica de 11 pontos e observacional de Flacc). A aplicação do selante resinoso será realizada primeiramente no dente 36. Após isolamento com o dique de borracha, a superfície do esmalte será condicionada com ácido fosfórico 37% por 30 segundos, seguida de lavagem com água e secagem da superfície com jato de ar. O selante resinoso será aplicado e fotoativado por 40 segundos. O mesmo procedimento será realizado no dente 46.
Grupo controle: Serão efetuados os mesmos passos já descritos acima mas utilizando um placebo. O selante resinoso será realizado nos dentes 36 e 46 de 80 pacientes. Um placebo fotoativado a ser usado em cada um desses dentes será determinado por aleatorização por meio de blocos de tamanho de 2 e 4, em um envelope selado haverá a indicação do tratamento do dente 36, sendo o outro tratamento aplicado no dente 46. Para a aplicação do placebo fotoativado, os quadrantes serão isolados com rolos de algodão e os agentes aplicados ao redor do dente e gengiva (colarinho de 1 a 2 mm) com o auxílio de uma ponta aplicadora. O produto será imediatamente fotoativado com auxílio de um aparelho fotopolimerizador por 30 segundos. Após a fotoativação do placebo, o grampo 26 será posicionado com uma pinça porta-grampo para verificação da adaptação do mesmo, neste momento o risco da dor será avaliado através de uma escala dicotômica de prevalência, e a intensidade será avaliada através de diferentes escalas (escala de expressão facial Wong-Baker, numérica de 11 pontos e observacional de Flacc). A aplicação do selante resinoso será realizada

randomization via second size blocks and 4, in a sealed envelope will be an indication of treatment of the tooth 36, the other treatment applied to the tooth 46. the application of topical anesthetic photoactivated, the quadrants are isolated with cotton rolls and agents applied around the tooth and gingiva (collar 1 to 2 mm) with the aid of an applicator tip. The product will immediately light cured with the aid of a curing light for 30 seconds. After curing the product, the clip 26 is positioned with a door-clip forceps to check the adjustment of the same, this time the pain of the risk will be assessed through a dichotomous scale prevalence, and intensity will be assessed using different scales (range of facial expression Wong-Baker, numerical 11 points and observational FLACC). The application of resin sealant is first carried out on the tooth 36. After isolation with a rubber dam, the enamel surface is etched with 37% phosphoric acid for 30 seconds, followed by washing with water and drying the surface with compressed air. The resin sealant is applied and light cured for 40 seconds. The same procedure will be performed on tooth 46.
Control group: the same steps will be made already described above but using a placebo. The resin sealant will be held on 36 and 46 teeth of 80 patients. A placebo photoactivated to be used in each of these teeth will be determined by randomization via second size blocks and 4, in a sealed envelope will be an indication of treatment of the tooth 36, the other treatment applied to the tooth 46. application of photoactivated placebo quarters will be isolated with cotton rolls and agents applied around the tooth and gingiva (collar 1 to 2 mm) with the aid of an applicator tip. The product will immediately light cured with the aid of a curing light for 30 seconds. After curing the placebo, the clamp 26 is positioned with a door-clip forceps to check the adjustment of the same, this time the pain of the risk will be assessed through a dichotomous scale prevalence, and intensity will be assessed using different scales (range of facial expression Wong-Baker, numerical 11 points and observational FLACC). The application of resin sealant is first carried out on the tooth 36. After isolation with a rubber dam, the enamel surface is etched with 37% phosphoric acid for 30 seconds, followed by washing with water and drying the surface with compressed air. The resin sealant is applied and light cured for 40 seconds. The same procedure will be performed on tooth 46.

primeiramente no dente 36. Após isolamento com o dique de borracha, a superfície do esmalte será condicionada com ácido fosfórico 37% por 30 segundos, seguida de lavagem com água e secagem da superfície com jato de ar. O selante resinoso será aplicado e fotoativado por 40 segundos. O mesmo procedimento será realizado no dente 46.

Descritores para as intervenções:

PT-BR	ES
E03.155.141: Anestesia Dentária	**E03.155.141:** Anestesia Dental
C07.793.720.210.220: Fissuras Dentárias	**C07.793.720.210.220:** Fisuras Dentales
E06.323.428: Restauração Dentária Permanente	**E06.323.428:** Restauración Dental Permanente
C10.597.617: Dor	**C10.597.617:** Dolor
D25.339.773: Selantes de Fossas e Fissuras	**D25.339.773:** Selladores de Fosas y Fisuras

Recrutamento

Situação de recrutamento: Recruitment completed

País de recrutamento
Brazil

Data prevista do primeiro recrutamento: 2015-03-10

Data prevista do último recrutamento: 2016-03-07

Tamanho da amostra alvo:	Gênero para inclusão:	Idade mínima para inclusão:	Idade máxima para inclusão:
80	-	8 Y	12 Y

Critérios de inclusão:

PT-BR	EN
Crianças de 8 a 12 anos com boa saúde geral e bucal; os dentes 36 e 46 deverão estar totalmente erupcionados e ter indicação de selante.	Children 8 to 12 years with good general and oral health; the teeth 36 and 46 should be fully erupted and have sealant indication.

Critérios de exclusão:

PT-BR
Dentes que não estejam erupcionados ou com lesões de cárie que necessitam de restauração; também serão excluídos pacientes com história de alergia; sensibilidade ou qualquer forma de reação alérgica aos anestésicos a base de éster e aos componentes da fórmula; portadores de doença sistêmica grave não controlada como problemas cardíacos; neurológicos; renais; hepáticos ou sanguíneos e ainda pacientes não colaboradores.

EN
Teeth that are unerupted or carious lesions that require restoration; also a history of allergy patients are excluded; any form of sensitivity or allergic reaction to anesthetics and ester-based components of the formula; severe systemic disease patients not controlled as heart problems; neurological; kidney; liver or blood and even patients not employees.

Tipo do estudo

Desenho do estudo:

PT-BR
Ensaio clínico de tratamento, randomizado controlado, paralelo, triplo-cego, dois braços.

EN
Clinical trial treatment, randomized controlled, parallel, triple-blind, two-arm.

Programa de acesso expandido	Enfoque do estudo	Desenho da intervenção	Número de braços	Tipo de mascaramento	Tipo de alocação	Fase do estudo
Nenhum	Treatment	Parallel	2	Triple-blind	Randomized-controlled	N/A

Desfechos

Desfechos primários:

PT-BR
Desfecho esperado: Número de pacientes que relatam dor durante a colocação de um grampo para isolamento absoluto após a aplicação de um anestésico tópico fotoativado, através de auto-relato. Este número será transformado em percentual de pacientes com dor e será denominado de risco absoluto de dor.

EN
Expected outcome: Number of patients reporting pain during the placement of a staple for absolute isolation after application of a topical anesthetic photoactivated through self-report. This number will be transformed into percentage of patients with pain and is called absolute risk of pain.

Desfechos secundários:

PT-BR
Desfecho esperado: A intensidade da dor será avaliada através de escala de expressão facial de Wong-Baker (0-5) e uma escala numérica de 11 pontos (0-10) e será apresentada como média e desvio padrão.

EN
Expected outcome: The intensity of the pain will be assessed by scale of facial expression Wong-Baker (0-5) and a numeric scale of 11 points (0-10) and will be presented as mean and standard deviation.

PT-BR
Desfecho esperado: O risco da dor será avaliado através de escala dicotômica (sim ou não) e será apresentada como média e desvio padrão.

EN
Expected outcome: The pain of the risk will be assessed by dichotomous scale (yes or no) and will be presented as mean and standard deviation.

Contatos

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Links adicionais:

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ANEXO G

INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL

07/04/2016 870160012830 14:44

00.000.2.2.16.0230044.0

Pedido nacional de Invenção, Modelo de Utilidade, Certificado de Adição de Invenção e entrada na fase nacional do PCT

Número do Processo: BR 10 2016 007724 9

Dados do Depositante (71)

Depositante 1 de 1

Nome ou Razão Social: UNIVERSIDADE ESTADUAL DE PONTA GROSSA
Tipo de Pessoa: Pessoa Jurídica
CPF/CNPJ: 80257355000108
Nacionalidade: Brasileira
Qualificação Jurídica: Instituição de Ensino e Pesquisa
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Dados do Pedido

Natureza Patente: 10 - Patente de Invenção (PI)

Título da Invenção ou Modelo de Utilidade (54): PROCESSO DE OBTENÇÃO DE BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA

Resumo: A presente invenção refere-se ao processo de obtenção de barreira gengival fotoativada, para o uso em várias áreas da odontologia e medicina. Na odontologia está indicada na dentística, odontopediatria, endodontia, prótese e, periodontia. Já na medicina pode ser aplicada na dermatologia, otorrinolaringologia, urologia e ginecologia. De modo geral, pode ser aplicado antes de qualquer procedimento que requer a aplicação de anestesia local infiltrativa, proporcionando uma anestesia tópica com uma liberação controlada do fármaco, sendo uma estratégia para diminuir o estresse, ansiedade, dor e desconforto dos pacientes. A formulação proposta é inovadora, já que é o primeiro anestésico tópico fotoativado, apresentando vantagens como: longo tempo de duração, fácil aplicação, dispensa o uso da agulha em procedimentos de baixa e moderada intensidade de dor, por ser fotoativado, não há escoamento do produto para áreas vizinhas, além disso, evita a deglutição do produto, diminuindo a ocorrência de efeitos colaterais e não apresenta gosto desagradável.

Figura a publicar: Fig.1

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Documentos anexados

Tipo Anexo	Nome
Portaria	Port159.pdf
resolução Cons de Adm	resca430 GEL ANESTESICO.pdf
Resumo	3 -final Le Resumo.pdf
Relatório Descritivo	2 - final Le Redação de Patente.pdf
Reivindicação	4 -final Le Reivindicações.pdf
Desenho	1- final Le Figuras patente.pdf
Comprovante de pagamento de GRU 200	Ordem de pagamento GEL ANESTESICO.pdf
gru	boleto GEL ANESTESICO.pdf

Acesso ao Patrimônio Genético

☑ Declaração Negativa de Acesso - Declaro que o objeto do presente pedido de patente de invenção não foi obtido em decorrência de acesso à amostra de componente do Patrimônio Genético Brasileiro, o acesso foi realizado antes de 30 de junho de 2000, ou não se aplica.

Declaração de veracidade

☑ Declaro, sob as penas da lei, que todas as informações acima prestadas são completas e verdadeiras.

Obrigado por acessar o Peticionamento Eletrônico

PETICIONAMENTO ELETRÔNICO

Este pedido foi enviado pelo sistema Peticionamento Eletrônico em 07/04/2016 às 14:44

Universidade Estadual de Ponta Grossa

PORTARIA R. Nº 159 DE 9 DE ABRIL DE 2015.

O REITOR DA UNIVERSIDADE ESTADUAL DE PONTA GROSSA, no uso de suas atribuições legais e estatutárias, *considerando* os termos do expediente autuado no Protocolo Geral da Universidade Estadual de Ponta Grossa onde se consubstanciou no *Processo nº 3921/2015,*

R E S O L V E:

Art. 1º Dispensar o servidor *Angelo Luiz Maurios Legat* do exercício da função gratificada FG - 02 – Chefe da Divisão de Treinamento e Desenvolvimento/PRORH, da Universidade Estadual de Ponta Grossa.

Art. 2º Designar o servidor *Angelo Luiz Maurios Legat* para o exercício da função gratificada FG - 02 – Chefe do Escritório de Propriedade Intelectual e Transferência de Tecnologia/AGIPI, da Universidade Estadual de Ponta Grossa.

Art. 3º Esta Portaria entrará em vigor na data de sua publicação, com efeitos retroagindo ao dia 1º de abril de 2015. Reitoria da Universidade Estadual de Ponta Grossa.

Carlos Luciano Sant'Ana Vargas
Reitor.

UEPG REITORIA | Av. Gal. Carlos Cavalcanti, nº 4748, Campus em Uvaranas - PABX (42) 3220-3000 / 3220-3200
Fax: (42) 3220-3233 - CEP 84030-900 - Ponta Grossa - Paraná

RESOLUÇÃO CA Nº 430, DE 6 DE OUTUBRO DE 2014.

a) Manifesta o interesse institucional no registro de patente nº 12/2014, do invento “Desenvolvimento de um gel anestésico fotoativado para uso odontológico”.

b) Aprova a liberação dos recursos financeiros para que a Agência de Inovação e Propriedade Intelectual gestione junto ao Instituto Nacional de Propriedade Intelectual – INPI o pedido de proteção dos direitos de invenção do referido produto.

O CONSELHO DE ADMINISTRAÇÃO, no uso de suas atribuições legais e estatutárias, na reunião do dia 6 de outubro de 2014, *considerando*

a Resolução UNIV nº 71, de 1º de dezembro de 2006;

o Regulamento da Agência de Inovação e Propriedade Intelectual da Universidade Estadual de Ponta Grossa, aprovado pela Resolução UNIV nº 31, de 27 de julho de 2011; e,

considerando mais, os termos do expediente protocolado no Protocolo Geral da Universidade Estadual de Ponta Grossa, onde se consubstanciou no *Processo nº* 16.166/2014*, aprovou* e eu, Vice-Reitora no exercício da Reitoria, sanciono a seguinte Resolução:

Art. 1º Fica manifestado o interesse institucional no registro da Patente nº 12/2014, do invento “Desenvolvimento de um gel anestésico fotoativado para uso odontológico”.

Parágrafo único: A autoria do referido invento é composta por:

		(contribuição) %
I -	*Alessandra Reis Silva Loguércio/Departamento de Odontologia*	*25%*
II -	*Paulo Vitor Farago/Departamento de Ciências Farmacêuticas*	*25%*
III -	*Alessandro Dourado Loguércio/Departamento de Odontologia*	*25%*
IV-	*Letícia Maíra Wambier/Departamento de Odontologia*	*25%*

Art. 2º Fica aprovada a liberação dos recursos financeiros, para que a Agência de Inovação e Propriedade Intelectual gestione junto ao Instituto Nacional de Propriedade Intelectual – INPI o pedido de proteção dos direitos de invenção do produto referido no *caput* do Art. 1º, deste ato legal.

Art. 3º Esta Resolução entrará em vigor na data de sua publicação. Reitoria da Universidade Estadual de Ponta Grossa.

Gisele Alves de Sá Quimelli,
Vice-Reitora no Exercício da Reitoria.

RESUMO

PROCESSO DE OBTENÇÃO DE BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA

A presente invenção refere-se ao processo de obtenção de barreira gengival fotoativada, para o uso em várias áreas da odontologia e medicina. Na odontologia está indicada na dentística, odontopediatria, endodontia, prótese e, periodontia. Já na medicina pode ser aplicada na dermatologia, otorrinolaringologia, urologia e ginecologia. De modo geral, pode ser aplicado antes de qualquer procedimento que requer a aplicação de anestesia local infiltrativa, proporcionando uma anestesia tópica com uma liberação controlada do fármaco, sendo uma estratégia para diminuir o estresse, ansiedade, dor e desconforto dos pacientes. A formulação proposta é inovadora, já que é o primeiro anestésico tópico fotoativado, apresentando vantagens como: longo tempo de duração, fácil aplicação, dispensa o uso da agulha em procedimentos de baixa e moderada intensidade de dor, por ser fotoativado, não há escoamento do produto para áreas vizinhas, além disso, evita a deglutição do produto, diminuindo a ocorrência de efeitos colaterais e não apresenta gosto desagradável.

PROCESSO DE OBTENÇÃO DE BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA

Campo da Invenção

001 A presente invenção refere-se à descrição do processo de obtenção de barreira gengival fotoativada contendo um sal anestésico, para o uso em várias áreas da odontologia e medicina. Na odontologia está indicada na dentística, odontopediatria, endodontia, prótese e periodontia. Já na medicina pode ser aplicada na dermatologia, otorrinolaringologia, urologia e ginecologia. De modo geral, pode ser aplicado antes de qualquer procedimento que requer a aplicação de anestesia local infiltrativa, proporcionando uma anestesia tópica com uma liberação controlada do fármaco, sendo uma estratégia para diminuir o estresse, ansiedade, dor e desconforto dos pacientes.

002 A presente invenção está relacionada com vários procedimentos na área de atuação na odontologia como: colocação de grampos de isolamento absoluto, remoção de dentes decíduos em fase avançada de reabsorção radicular, na sondagem, raspagem e alisamento radicular. Em procedimentos protéticos e restauradores que exigem o afastamento gengival com fio retrator, diminui a presença e a intensidade de dor. Na medicina, pode ser utilizado para a aplicação de laser, remoção de nevus, passagem de sonda vesical, sonda nasogástrica, exames ginecológicos e cauterização de vasos nasais. Além disso, pode ser aplicado como anestésico tópico antes de qualquer procedimento prévio a punção da agulha, em todos os procedimentos invasivos que exigem o uso de anestesia terminal infiltrativa, diminuindo o estresse, dor e proporcionando maior conforto ao paciente.

003 A formulação proposta é inovadora, já que é o primeiro anestésico tópico fotoativado, apresentando vantagens como: longo tempo de duração, fácil aplicação, por ser fotoativado, não há escoamento do produto para áreas vizinhas e nem a deglutição o que diminui a ocorrência de efeitos colaterais, além disso, como fica restrito a área onde é aplicado não apresenta gosto desagradável. Contudo a maior vantagem é o fato de dispensar o uso da anestesia infiltrativa em vários procedimentos da odontologia e medicina, isto facilita a sua utilização em adultos, idosos, portadores de necessidades especiais e, especialmente, em crianças e

adolescentes.

004 O anestésico tópico é uma estratégia viável e promissora para o controle da prevalência e da intensidade da dor, de baixa a moderada intensidade (até 5 em uma escala de 0 a 10 - *Visual Analogue Scale ou Escala Visual Análoga*), nos procedimentos odontológicos que requerem o uso da anestesia terminal infiltrativa, promovendo conforto ao paciente, aceitação a tratamentos futuros e ainda, com maior segurança ao clínico.

Fundamentos da Invenção e Estado da Arte

005 O controle da dor e ansiedade são requisitos importantes para ganhar a confiança do paciente e garantir a aceitação e continuidade do tratamento (Milgrom et al.1997; Karadottir et al. 2002; Monteiro et al. 2008). O uso de anestesia terminal infiltrativa é uma intervenção comum visando minimizar a dor e desconforto nos procedimentos odontológicos, no entanto, mais de 25% dos adultos têm medo de injeções, pois esse procedimento pode ser doloroso e gera em muitos indivíduos medo, ansiedade e amortecimentos em determinados locais, principalmente nos lábios, língua e nos tecidos circundantes, sendo até maior do que na área que será realizado o procedimento (Palotie et al. 2007; Al Habashneh et al. 2012). Este fato contribui para reduzir a tolerância e, faz com que alguns pacientes adiem o tratamento odontológico quando requer anestesia local infiltrativa convencional (Milgrom et al. 1997).

006 Estas observações apontam para a necessidade do desenvolvimento de técnicas anestésicas que substituam o uso da agulha, reduzindo a ansiedade dos pacientes (Donaldson et al.1995; Derman et al. 2013). A anestesia tópica é uma estratégia que minimiza a ansiedade, dor e desconforto dos indivíduos (Magnusson et al. 2003; Froes et al.2010; Derman et al. 2014). Diferentes géis e cremes para uso tópico têm sido comercializados (EMLA® creme [AstraZeneca, Cotia, SP, Brasil]; Oraqix® [Dentsply, York, PA, EUA]; Benzotop® [DFL, Rio de Janeiro, RJ, Brasil] e Hurricaine® [Beutlich LP, Waukegan, IL, EUA]) para tentar contornar esses problemas (Friedman et al. 2001; Al Habashneh et al. 2012; Derman et al. 2014). Porém, esses produtos não se mostraram eficientes na redução da prevalência e intensidade da dor, e tem uma curta duração, permanecendo portanto como um

desafio tecnológico a ser superado. Além disso, estas alternativas podem anestesiar diferentes áreas quando aplicados, possuem gosto desagradável e ainda, podem ser deglutidos, já que são soluções em gel, spray ou pomadas.

007 Na medicina, é grande a necessidade do uso de anestésicos tópicos, principalmente na dermatologia para a realização de procedimentos entre eles: laser para depilação, retirada de tatuagens, rejuvenescimento. Acrescenta-se a aplicação de toxina botulínica, escleroterapia, entre outros. Essas intervenções podem causar dor e desconforto para o paciente (Friedman et al. 2001). Nessas situações o uso de anestésicos tópicos pode reduzir o desconforto, promovendo analgesia de rápida ação com efeitos colaterais mínimos (Friedman et al. 2001; Cantisani et al. 2014). A busca de um agente com essas características, ainda é um desafio, devido a dificuldade de difusão e distribuição adequada através da pele (Lener et al. 1997; Kleiber et al. 2002). O mesmo ocorre em pacientes submetidos à cirurgia ginecológica laparoscópica, que pode resultar em dor pós-operatória, sendo necessário o uso de anestésico tópico nas primeiras 48 horas (Saccardi et al. 2016).

008 Assim, até o presente momento, não existe no mercado nenhum anestésico tópico que reúna qualidades tais como: longo tempo de duração, não escoe permanecendo no local onde foi aplicado, caso seja fotoativado. Com isso, novos processos tecnológicos devem ser desenvolvidos, sendo a barreira gengival fotoativada uma estratégia viável e promissora para o controle da prevalência e da intensidade da dor de baixa e moderada intensidade nos procedimentos odontológicos e médicos que requerem o uso de uma agulha, tal como em anestesias terminais infiltrativas.

Descrição da Abordagem do Problema

009 A presente invenção refere-se a um processo de obtenção de um produto inédito que descreve a obtenção de uma formulação inovadora, contendo um sal anestésico associado a uma barreira gengival fotoativada, proporcionando uma anestesia tópica com uma liberação controlada do fármaco, sendo uma alternativa para o controle da prevalência e da intensidade da dor de baixa e moderada intensidade, pois dispensa o uso da agulha para a anestesia terminal infiltrativa e, restringe a anestesia apenas as regiões onde o produto foi aplicado, já que o

produto é fotoativado. Isto também impede que o anestésico escoe da região aplicada, gerando conforto ao paciente e segurança para o profissional, já que diminui potencialmente a deglutição e outros efeitos colaterais.

010 Considerando as desvantagens do uso de anestesia terminal infiltrativa, tais como: medo, ansiedade, dor, longo tempo de ação, amortecimento de regiões próximas da aplicação, gosto amargo e estimulação da salivação, a presente invenção relata o desenvolvimento de um anestésico que seja fotoativado, com propriedades adequadas para anestesias tópicas, gerando conforto ao paciente.

011 Atualmente existem no mercado, anestésicos tópicos que podem ser utilizados em pacientes que tem medo da agulha usada em anestesias terminais infiltrativas. Mas, os produtos comercializados apresentam algumas desvantagens como efeito anestésico de curta duração, dificuldade de aplicação, alto escoamento, são facilmente removidos com a saliva, gosto desagradável e, não são substitutos de anestesia terminal infiltrativa (Friskopp et al. 2001; Donaldson et al. 2003).

012 Entre os diferenciais desta invenção, é que o anestésico tópico é fotoativado, ou seja, é um líquido-viscoso durante a aplicação, mas após a excitação dada por um aparelho de fotoativação em um comprimento de onda específico, ocorre à aproximação molecular da cadeia polimérica e a conversão dos monômeros em polímero, formando cadeias cruzadas, isso faz com que o anestésico fique rígido e permaneça grudado na região aplicada, até que seja mecanicamente removido de forma fácil e conveniente.

013 Portanto, a presente invenção permite superar os desafios tecnológicos existentes, corrigindo falhas dos anestésicos comercializados mantendo o produto no local com liberação lenta e contínua do sal anestésico. Isto pode aumentar a penetração nos tecidos orais e aumentar com isto a duração da ação anestésica, apesar de mantê-la localizada a uma pequena área. Aliado a isto, outras vantagens como facilidade de aplicação com nenhum escoamento para áreas vizinhas, redução da deglutição do produto que diminui a ocorrência de efeitos colaterais, tornando-o mais seguro, e melhor conforto para o paciente já que não sentirá o gosto desagradável do produto.

014 Outra vantagem importante da invenção, é que pode ser utilizado em adultos, idosos, portadores de necessidades especiais, adolescentes e,

especialmente crianças, em várias áreas da odontologia e medicina. Na odontologia, utiliza-se no isolamento absoluto para a colocação do grampo metálico, bem como no isolamento relativo quando associado ao uso do fio retrator. Além disso, pode ser utilizado na sondagem, raspagens e alisamento radiculares em pacientes que tenham doença periodontal com bolsas rasas e de média profundidade (≥ 5 mm). Pode também ser considerada uma alternativa para minimizar a dor na colocação de fios retratores, substituto da anestesia para extração de dentes decíduos com raízes esfoliadas.

015 Na medicina pode minimizar o desconforto em procedimentos estéticos, aplicação de laser, remoção de nevus e cauterização de vasos nasais, entre outros procedimentos.

016 Geralmente, pode ser aplicado antes de qualquer procedimento que requer a aplicação da anestesia terminal infiltrativa, proporcionando uma anestesia tópica antes da punção da agulha em procedimentos invasivos, tornando o invento um aliado ao cirurgião dentista e médico.

Citação das Figuras

017 A Figura 1, demonstra a média de dor em pacientes submetidos a diferentes tratamentos odontológicos, como raspagem e alisamento radicular (Raspagem), profundidade de sondagem periodontal (Sondagem), colocação de grampo para isolamento absoluto (Grampo adulto), e, crianças submetidas a colocação de grampo para isolamento absoluto (Grampo crianças), comparando o gel anestésico fotoativado com um gel placebo. Observe que em todos os casos mencionados ocorreu uma expressiva diminuição da dor quanto mensurada por uma escala VAS (*Visual Analogue Scale ou Escala Visual Análoga*) que avalia a dor de 0 a 10, onde 0 significa ausência de dor e 10 máxima dor mensurável.

Descrição Detalhada da Invenção

018 A partir do sal anestésico junto à uma barreira gengival, procurou-se formular um anestésico tópico potente, obtendo um produto com propriedades ideais

para uso tópico em intervenções odontológicas e médicas, sendo um produto atrativo para os cirurgiões dentistas e médicos.

019 A obtenção da formulação foi feita a partir do uso de reagentes da matriz orgânica e inorgânica (Tabela 1), empregando os seguintes componentes: inibidor da fotoativação nas concentrações de 0,1 a 2%; monômero metacrílico de 10 a 60%; monômero metacrílico-uretânico entre 20 a 80%; sal anestésico entre 1 a 10%; fotoiniciador de 0,1 a 2%; co-iniciador de 0,1 a 2%; pigmento de 0,1 a 2%; e carga inerte entre 5 a 30%.

020 Em síntese, a formulação piloto, que exemplifica as composições abrangidas por este pedido de patente e, utilizada durante os ensaios clínicos, está apresentada na tabela 1.

TABELA 1 – FORMULAÇÕES DA BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA.

Reagentes da Barreira Gengival Anestésica Fotoativada (10 g)		
MATRIZ ORGÂNICA		
Composição	**Concentração (%)**	**Função**
BHT - (butil- hidroxitolueno)	0,1 – 0,2%	Inibidor
HEMA - (2-hidroxietil metacrilato)	25 – 35%	Monômero
UDMA - (uretano dimetacrilato)	45 – 55%	Monômero
CLORIDRATO DE TETRACAÍNA	4 – 6%	Sal anestésico
CANFOROQUINONA	0,1 – 0,5%	Fotoiniciador
DABE - (éster etílico do ácido *N,N*-dimetil-*para*-aminobenzoico)	0,1 – 0,5%	Co-iniciador
PIGMENTO	0,3 – 0,5%	Corante
MATRIZ INORGÂNICA		
Composição	**Concentração (%)**	**Função**
PARTÍCULAS DE SÍLICA	10– 15%	Carga inerte

021 Para fins de patente, considera-se como inibidores da fotoativação: BHT (hidroxitolueno butílico); hidroquinona; MHQ (metoxi-hidroquinona). Já os mônomeros, considera-se: Bis-GMA (bisfenol glicidil metacrilato); UDMA (uretano dimetacrilato); TEGDMA (trietilenoglicol dimetacrilato); EGDMA (etilenoglicol dimetacrilato); HEMA (2-hidroxietil metacrilato); Bis-EMA (bisfenol-A etoxilado dimetacrilato).

022 Para fins de patente, considera-se como sais anestésicos: Tetracaína; Benzocaína; Procaína; Propoxicaína; Lidocaína; Mepivacaína; Bupivacaína; Ropivacaína; Etidocaína; Prilocaína; Articaína e associação entre os sais anestésicos.

023 Para fins de patente, considera-se como fotoiniciador: canforoquinona; benzilo; BZ (benzil propanodiona); PPD (fenil propanodiona); 2-propanodiona. E, o

co-iniador, considera-se como: DABE (éster etílico do ácido *N,N*-dimetil-*para*-aminobenzoico); CEMA (N,N-metilanilina cianoetilo); DMAEMA (2-dimetilaminoetil metacrilato); DMPT (NN-dimetil-p-toluidina); DEPT (N, N-dietanol-p-toluidina). Já a carga inerte, considera-se: partículas de sílica; partículas de quartzo; partículas de vidro.

024 Tento em vista todas as dificuldades e limitações dos anestésicos existentes, essa formulação tende a suprir os comercializados atualmente, sendo de fácil uso, longa duração, fácil remoção que o torna seguro, evita a ingestão do produto devido sua viscosidade, permanece apenas nas regiões que serão realizados os procedimentos, dispensa uso da agulha, não apresenta sabor desagradável, tendo pelos resultados preliminares promissores, um grande potencial comercial.

025 Para conseguir uma formulação ideal, várias tentativas e testes foram realizados com os reagentes apresentados na Tabela 1, até se obter uma formulação ideal e que mantenha o máximo de suas propriedades anestésicas. Para avaliar a aceitação e eficácia anestésica, o anestésico tópico da barreira gengival fotoativado foi testado em 80 pacientes adultos e 60 crianças em diversas situações como raspagem e alisamento radicular, sondagem e colocação de grampos que auxiliam no isolamento absoluto em pacientes adultos, e, colocação de grampo para isolamento absoluto em crianças.

026 O primeiro teste foi realizado em adultos com bolsa periodontal de profundidade média (≥ 5 mm) e presença de doença periodontal, que necessitavam de tratamento de raspagem e alisamento radicular para remoção de cálculo. Aplicou-se o produto na região gengival e, após iniciado o procedimento, observou-se tolerância e baixo grau de estresse e ansiedade do paciente. Além disso, o gel anestésico mostrou boa aceitação e bons resultados no controle da dor quando comparado a um gel placebo (Figura 1).

027 Para o segundo teste foram selecionados pacientes adultos que apresentavam doença periodontal com bolsas médias (≥ 5 mm), nesse caso apenas a sondagem periodontal foi realizada. Aplicou-se o anestésico fotoativado na margem gengival e a sondagem periodontal foi realizada em 6 pontos ao redor de todo o do dente (mésio-vestibular, vestibular, disto-vestibular, mésio-lingual, lingual e disto-lingual). Os resultados mostraram redução significante no nível da dor quando comparado a um gel placebo (Figura 1).

028 O terceiro teste foi realizado em adultos que necessitavam de procedimentos restauradores e que, em geral, exigem o uso de dique de borracha para evitar a contaminação da saliva. Para a adaptação do dique é necessário o uso de grampo metálico que exige, no mínimo, anestesia terminal infiltrativa na região. Neste caso, a mencionada anestesia foi substituída pela barreira gengival fotoativada e o grampo foi colocado em posição. No quarto teste, o mesmo procedimento descrito foi realizado em crianças. Tanto para crianças como para adultos que necessitam a colocação de grampo metálico para o isolamento absoluto, o gel anestésico mostrou boa aceitação e menor ansiedade, além de bons resultados no controle da dor quando comparado a um gel placebo (Figura 1).

029 Esses resultados confirmam que a estratégia diferencial adotada neste pedido de patente, a partir do uso de um anestésico tópico fotoativado, é extremamente interessante ao uso odontológico, podendo ser utilizado em várias áreas da odontologia, sendo uma estratégia viável ao uso clínico, com a vantagem de promover uma liberação controlada e prolongada do fármaco, efetividade no controle da dor e ansiedade, e ainda, prove segurança ao clínico e ao paciente.

030 Pode-se concluir que a barreira gengival anestésica fotoativada é efetiva no controle da dor, sua obtenção vai ser um avanço na odontologia e medicina, podendo ser empregado em várias áreas, bem como, promover conforto ao paciente e aceitação a tratamentos futuros que requer o uso de anestesia.

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REIVINDICAÇÕES

PROCESSO DE OBTENÇÃO DE BARREIRA GENGIVAL ANESTÉSICA FOTOATIVADA

1. Processo de obtenção de barreira gengival anestésica fotoativada, caracterizado pela adição de um sal anestésico em uma barreira gengival no campo da odontologia e medicina;

2. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a reivindicação 1, caracterizada pela utilização de sais anestésicos, tais como: tetracaína, benzocaína; procaína; propoxicaína; lidocaína; mepivacaína; bupivacaína; ropivacaína; etidocaína; prilocaína; articaína e associação entre sais anestésicos, em concentrações de 1 a 10%, para uso no campo da odontologia e medicina;

3. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a reivindicação 1 e 2, caracterizada pela utilização de inibidores da fotoativação, tais como: BHT (hidroxitolueno butílico); hidroquinona; MHQ (metoxi-hidroquinona), em concentrações de 0,1 a 2%, para uso no campo da odontologia e medicina;

4. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a reivindicação 1 a 3, caracterizada pela utilização de monômeros, tais como:Bis-GMA (bisfenol glicidil metacrilato); UDMA (uretano dimetacrilato); TEGDMA (trietilenoglicol dimetacrilato); EGDMA (etilenoglicol dimetacrilato); HEMA (2-hidroxietil metacrilato); Bis-EMA (bisfenol-A etoxilado dimetacrilato), em concentrações de 10 a 80%, para uso no campo da odontologia e medicina;

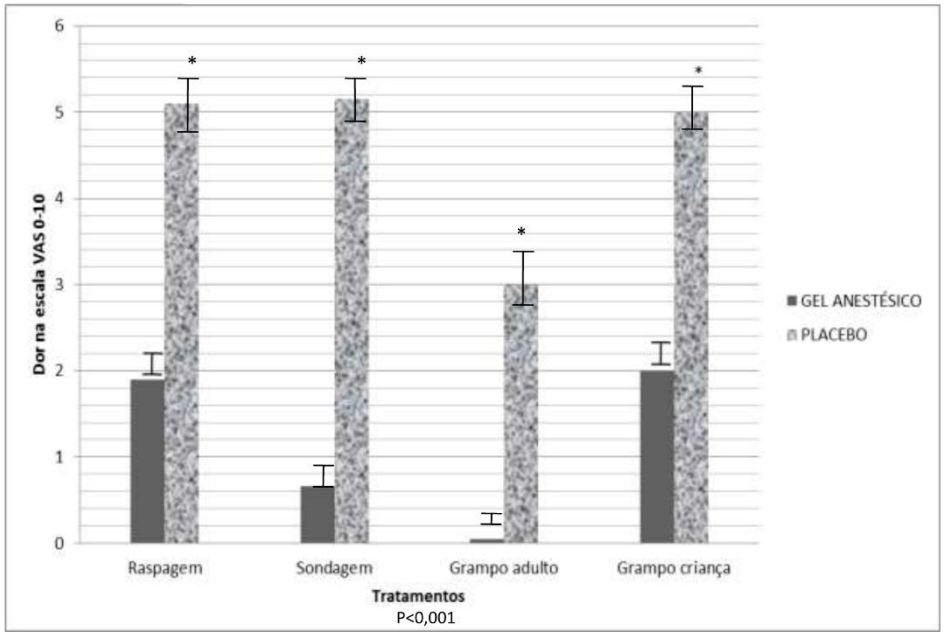
5. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1 a 4, caracterizada pela utilização de fotoiniciador, tais como: canforoquinona; benzilo; BZ (benzil propanodiona); PPD (fenil

propanodiona); 2-propanodiona, em concentrações de 0,1 a 2%, para uso no campo da odontologia e medicina;

6. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1 a 5, caracterizada pela utilização de co-iniciador, tais como: DABE (éster etílico do ácido *N,N*-dimetil-*para*-aminobenzoico); CEMA (N,N-metilanilina cianoetilo); DMAEMA (2-dimetilaminoetil metacrilato); DMPT (NN-dimetil-p-toluidina); DEPT (N, N-dietanol-p-toluidina), em concentrações de 0,1 a 2%, para uso no campo da odontologia e medicina;

7. Processo de obtenção de barreira gengival anestésica fotoativada, de acordo com a revendicação 1 a 6, caracterizada pela utilização de carga inerte, tais como: partículas de sílica; partículas de quartzo; partículas de vidro, em concentrações de 5 a 30%, para uso no campo da odontologia e medicina.

Figura 1


6
5
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Dor na escala VAS 0-10
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Raspagem
Sondagem
Grampo adulto
Grampo criança
Tratamentos
P<0,001
GEL ANESTÉSICO
PLACEBO

ESTADO DO PARANA
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Sacador/Avalista

Corte na linha pontilhada

Autenticação mecânica - Controle Cedente

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ANEXO H

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PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação clínica da dor transoperatória em adultos submetidos ao tratamento restaurador de lesões não cariosas utilizando um novo anestésico tópico

Pesquisador: Alessandra Reis

Área Temática:

Versão: 1

CAAE: 42035215.7.0000.0105

Instituição Proponente: Universidade Estadual de Ponta Grossa

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 974.479

Data da Relatoria: 26/02/2015

Apresentação do Projeto:

Avaliação clínica da dor transoperatória em adultos submetidos ao tratamento restaurador de lesões não cariosas utilizando um novo anestésico tópico

Objetivo da Pesquisa:

Analisar o efeito de um novo anestésico tópico fotoativado no controle da dor em adultos submetidos ao isolamento absoluto para a realização de lesões cervicais não cariosas de classe V.

Avaliação dos Riscos e Benefícios:

Riscos:

A etiologia das lesões cervicais não cariosas é bastante variável, com o aumento da população idosa, a prevalência dessas lesões aumentou

(Bartlett e Shah1 2006, Wood et al.2 2008). Essas lesões podem ser restabecidas com o uso de materiais restauradores (Zander-Grande et al.3

2014, Loguercio et al.4 2003). Porem, os materiais restauradores como os sistemas adesivos e as resinas compostas, são sensível a umidade

(Cobanoglu et al.5 2013, Aboushelib6 2011). O controle adequado da umidade pode ser resolvido

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Telefone: (42)3220-3108 **E-mail:** coep@uepg.br

com a utilização de isolamento absoluto, evitando
contaminações externas e garantindo a longevidade das restaurações (Owens7 2006, Ammann et al.8 2013, Daudt et al.9 2013). No entanto, a
utilização de grampo e dique de borracha causa desconforto e sensibilidade nos pacientes (Donaldson e Meechan10 1995, Lim e Julliard11 2004,
Yoon e Chussid12 2009). O uso de anestesia terminal infiltrativa reduz o desconforto gerado pela colocação do grampo, porém este procedimento
por si só gera na maioria dos indivíduos algum medo e desconforto (Karadottir et al.13 2002, van Steenberghe et al.14 2004, Milgrom et al.15 1997).
Tais observações apontam para a necessidade do desenvolvimento de técnicas anestésicas que substituam o uso da agulha, reduzindo assim a
ansiedade dos pacientes (Derman et al.16 2013, Friskopp et al.17 2001, Mayor-Subirana et al.18 2013). Diferentes géis e cremes para uso tópico
têm sido comercializados (EMLA® creme [AstraZeneca, Cotia, SP, Brasil]; Oraqix® [Dentsply, York, PA, EUA]; Benzotop® [DFL, Rio de Janeiro, RJ,
Brasil] e Hurricaine® [Beutlich LP, Waukegan, IL, EUA]), e podem ser uma estratégia à substituição da agulha (Donaldson e Meechan10 1995,
Derman et al.19 2014, Magnusson et al.20 2003). Estes produtos apresentam algumas desvantagens como efeito anestésico de curta duração,
dificuldade de aplicação, alto escoamento e facilmente removidos com a saliva e gosto desagradável (Lim e Julliard11 2004, Friskopp et al.17 2001,
Mayor-Subirana et al.18 2013, Donaldson et al.21 2003, Winning et al.22 2012). A elaboração de um anestésico fotoativado poderia corrigir falhas
dos anestésicos comercializados mantendo o produto no local com liberação lenta e contínua do sal anestésico. Isto poderia aumentar a penetração
nos tecidos orais, aumentar a duração da ação. Aliado a isto, outras vantagens como facilidade de aplicação com nenhum escoamento para áreas
vizinhas, redução da deglutição do produto tornando-o mais seguro e melhor conforto para o paciente já que não sentiria o gosto desagradável do
produto.
Introdução:Tamanho da Amostra no Brasil: 50
Desconforto durante a prova do grampo 212, e caso isso ocorra, será aplicada anestesia infiltrativa.

Benefícios:

O uso de anestesia tópica fotoativada pode ser uma alternativa à substituição da anestesia infiltrativa, podendo este ser uma boa opção nos
tratamentos odontológicos, evitando trauma, ansiedade e anestesia de outras regiões. Além disso, todos os pacientes envolvidos no estudo receberão tratamento restaurador de classe V não carioso. Todos os procedimentos serão realizados por profissional qualificado, sem qualquer custo, melhorando as condições bucais dos pacientes.

Comentários e Considerações sobre a Pesquisa:

Pesquisa relacionada a trabalhos da equipe.

Considerações sobre os Termos de apresentação obrigatória:

Corretos.

Recomendações:

Aprovado.

Conclusões ou Pendências e Lista de Inadequações:

Aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

PONTA GROSSA, 05 de Março de 2015

Assinado por:
ULISSES COELHO
(Coordenador)

ANEXO I

RBR-6hxhx7
Avaliação clínica da dor transoperatória em adultos submetidos ao tratamento restaurador de lesões não cariosas utilizando um anestésico tópico fotoativado

Data de registro: 6 de Ago. de 2016 às 16:54
Last Update: 15 de Ago. de 2016 às 14:45

Tipo do estudo:

Intervenções

Título científico:

PT-BR
Avaliação clínica da dor transoperatória em adultos submetidos ao tratamento restaurador de lesões não cariosas utilizando um anestésico tópico fotoativado

EN
Clinical investigation of intraoperative pain in adults undergoing restorative treatment of non-carious lesions using a topical anesthetic photoactivated

Identificação do ensaio

Número do UTN: U1111-1186-2282

Título público:

PT-BR
Investigação clínica da dor durante o tratamento restaurador em adultos utilizando um anestésico tópico fotoativado

EN
Clinical research of pain during restorative treatment in adults using a topical anesthetic photoactivated

Acrônimo científico:

Acrônimo público:

Identificadores secundários:

974.479
Órgão emissor: Comitê de Ética em Pesquisa da Universidade Estadual de Ponta Grossa

42035215.7.0000.0105
Órgão emissor: Plataforma Brasil/Sistema Nacional de Ética em Pesquisa

Patrocinadores

Patrocinador primário: Universidade Estadual de Ponta Grossa

Patrocinadores secundários:

Instituição: Universidade Estadual de Ponta Grossa

Fontes de apoio financeiro ou material:

Instituição: Universidade Estadual de Ponta Grossa

Condições de saúde

Condições de saúde ou problemas:

PT-BR	EN
Cárie dentária; Falha de Restauração Dentária; Anestesia Dentária; Sensibilidade da Dentina	Dental caries; Dental Restoration Failure; Anesthesia, Dental; Dentin Sensitivity

Descritores gerais para as condições de saúde:

PT-BR	ES	EN
C07: Doenças estomatognáticas	**C07:** Enfermedades estomatognáticas	**C07:** Stomatognathic diseases

Descritores específicos para as condições de saúde:

PT-BR	ES	EN
C07.793.720.210: Cárie Dentária	**C07.793.720.210:** Caries Dental	**C07.793.720.210:** Dental Caries
E06.323.400: Falha de Restauração Dentária	**E06.323.400:** Fracaso de la Restauración Dental	**E06.323.400:** Dental Restoration Failure
E03.155.141: Anestesia Dentária	**E03.155.141:** Anestesia Dental	**E03.155.141:** Anesthesia, Dental
C07.793.266: Sensibilidade da Dentina	**C07.793.266:** Sensibilidad de la Dentina	**C07.793.266:** Dentin Sensitivity

Intervenções

Categorias das intervenções

Other

Intervenções:

PT-BR	EN
Os tratamentos restauradores não cariosos de classe V, serão realizados nas cervicais de premolares de 50 pacientes. O anestésico tópico fotoativado (grupo experimental) ou placebo fotoativado (grupo controle) a ser usado, será determinado por aleatorização por meio de blocos de 2 e 4, o tratamento a ser realizado estará lacrado em um envelope escuro, aberto apenas 1 min antes da intervenção. Antes da realização da intervenção será aplicado o anestésico experimental ou o placebo na região gengival dos dentes a serem tratados, os quadrantes serão isolados com rolos de algodão e os agentes administrados de maneira não invasiva ao	Treatments not carious V class will be held in cervical premolars of 50 patients. The topical anesthetic photoactivated (experimental group) or photoactivated placebo (control group) to be used will be determined by randomization via 2 and 4 blocks, the treatment being conducted is sealed in a dark envelope open only 1 min before intervention. Prior to the intervention will be applied the experimental anesthetic or placebo in the gingival area of ??the tooth to be treated, the quarters will be isolated with cotton rolls and agents administered noninvasively around the tooth and gum (collar 1mm) with the aid of an applicator tip. The product will immediately light cured with

redor do dente e gengiva (colarinho de 1mm) com o auxílio de uma ponta aplicadora. O produto será imediatamente fotoativado com auxílio de um aparelho fotopolimerizador por 30 segundos. Após 2 min o grampo 212 será posicionado com uma pinça porta-grampo, para verificação da adaptação do mesmo. A percepção da dor será avaliada logo após a prova do grampo 212, antes da colocação do dique de borracha, através de uma escala dicotômica de prevalência (sim/não), registrando os dados na ficha clínica. Já a intensidade da dor, só será avaliada caso o paciente relate dor ou desconforto. Nesse momento o grampo será removido e será utilizada a escala visual analógica (VAS), sendo atribuídos os escores 0 (nenhuma dor) a 10 (dor insuportável) e uma escala verbal de dor (VRS), com escores de 5 pontos, sendo (0= sem dor; 1= dor leve; 2= dor moderada; 3= dor intensa; 4= dor insuportável)na qual o paciente relatará sua dor. A intervenção será realizada primeiramente no quadrante 1 quando for arco superior, ou, quadrante 3 se for arco inferior. Após isolamento com o dique de borracha, a superfície do esmalte será condicionada com ácido fosfórico 37% por 15 s, seguida de lavagem com água e secagem da superfície com jato de ar. Dupla aplicação do adesivo, eliminação do solvente com jato de ar, fotoativação por 20 s, aplicação da resina composta seguida de fotoativação por 40 s. O mesmo procedimento será realizado no quadrante do lado oposto.

the aid of a curing light for 30 seconds. After 2 min clip 212 will be positioned with a door-clamp gripper to verify the adaptation of the same. The perception of pain will soon be evaluated after the test clip 212 before placing the rubber dam through a dichotomous scale prevalence (yes / no), recording the data in the medical record. The intensity of the pain will only be evaluated if the patient reports pain or discomfort. At that moment the clip will be removed and will be used the visual analog scale (VAS), and assigned scores 0 (no pain) to 10 (unbearable pain) and a verbal pain scale (VRS), 5-point scores, and (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain, 4 = unbearable pain) in which the patient will report their pain. The intervention will be performed first in quadrant 1 when superior arch or quadrant 3 if lower arch. After isolation with a rubber dam, the enamel surface is etched with 37% phosphoric acid for 15 sec, followed by washing with water and drying the surface with compressed air. Double application of the adhesive, the solvent removal with air jet, light curing for 20 s, application of composite resin followed by curing for 40 s. The same procedure will be performed in the quadrant opposite.

Descritores para as intervenções:

PT-BR	ES
E06.323.428: Restauração Dentária Permanente	**E06.323.428:** Restauración Dental Permanente
E06.780.346.737.125: Desgaste de Restauração Dentária	**E06.780.346.737.125:** Alisadura de la Restauración Dental
E03.155.141: Anestesia Dentária	**E03.155.141:** Anestesia Dental

Recrutamento

Situação de recrutamento: Recruitment completed

País de recrutamento

Brazil

Data prevista do primeiro recrutamento: 2015-03-15

Data prevista do último recrutamento: 2016-03-17

Tamanho da amostra alvo:	Gênero para inclusão:	Idade mínima para inclusão:	Idade máxima para inclusão:
50	-	18 Y	80 Y

Critérios de inclusão:

PT-BR
Pacientes com mais de 18 anos; com boa saúde geral e bucal; os dentes premolares deverão ter indicação de tratamento restaurador não cariosa na cervical; essas lesões não cariosas devem envolver dois dentes em quadrantes diferentes.

EN
Patients over 18 years; with good general and oral health; the premolar teeth should have restorative treatment indication not carious cervical; these non-carious lesions should involve two teeth in different quadrants.

Critérios de exclusão:

PT-BR
Dentes tratados endodonticamente; destruídos e com lesões de cárie; também serão excluídos pacientes com gengivites, periodontites e mobilidade dental; além disso, pacientes com história de alergia; sensibilidade ou qualquer forma de reação alérgica aos anestésicos a base de éster e aos componentes da fórmula; portadores de doença sistêmica grave não controlada (problemas cardíacos; neurológicos; renais; hepáticos ou sanguíneos); pacientes grávidas ou lactantes.

EN
Endodontically treated teeth; destroyed and caries; also excluded are patients with gingivitis; periodontitis and dental mobility; in addition, patients with a history of allergy; any form of sensitivity or allergic reaction to anesthetics and ester-based components of the formula; patients with severe uncontrolled systemic disease (heart problems; neurological; kidney; liver or blood); pregnant or lactating patients.

Tipo do estudo

Desenho do estudo:

PT-BR
Ensaio clínico de tratamento, randomizado controlado, paralelo, triplo-cego, dois braços.

EN
Clinical trial, randomized controlled, parallel, triple-blind, two-arm.

Programa de acesso expandido	Enfoque do estudo	Desenho da intervenção	Número de braços	Tipo de mascaramento	Tipo de alocação	Fase do estudo
Nenhum	Treatment	Parallel	2	Triple-blind	Randomized-controlled	N/A

Desfechos

Desfechos primários:

PT-BR
Desfecho esperado: Número de pacientes que relatam dor durante a colocação de um grampo para isolamento absoluto após a aplicação de um anestésico tópico fotoativado, através de auto-relato. Este número será transformado em percentual de

EN
Expected outcome: Number of patients reporting pain during the placement of a staple for absolute isolation after application of a topical anesthetic photoactivated through self-report. This number will be

pacientes com dor e será denominado de risco absoluto de dor.

transformed into percentage of patients with pain and is called absolute risk of pain.

Desfechos secundários:

PT-BR
Desfecho esperado: A intensidade da dor será avaliada através de escala numérica de 5 pontos (NRS 0-4) e da escala visual analógica VAS (0-100) e será apresentada como média e desvio padrão.

EN
Expected outcome: The intensity of the pain will be assessed using a scale of 5 points (NRS 0-4) and visual analogue scale VAS (0-100) and will be presented as mean and standard deviation.

PT-BR
Desfecho esperado: O risco da dor será avaliado através de escala dicotômica (sim ou não) e será apresentada como média e desvio padrão.

EN
Expected outcome: The pain of the risk will be assessed by dichotomous scale (yes or no) and will be presented as mean and standard deviation.

Contatos

Contatos para questões públicas

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