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RENAN BORDINI CARDOSO

O EFEITO DO PARACETAMOL COM CODEÍNA EM COMPARAÇÃO AO PLACEBO NO DESCONFORTO CIRÚRGICO E NOS SINTOMAS DO TRANSTORNO DE ESTRESSE PÓS-TRAUMÁTICO APÓS A REMOÇÃO DO TERCEIRO MOLAR MANDIBULAR: UM ENSAIO CLÍNICO PROSPECTIVO RANDOMIZADO

PONTA GROSSA
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Orientador: Prof. Dr. Marcelo Carlos Bortoluzzi

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“Seja você quem for, seja qual for a posição social que você tenha na vida, a mais alta ou a mais baixa, tenha sempre como meta muita força, muita determinação e sempre faça tudo com muito amor e com muita fé em Deus, que um dia você chega lá. De alguma maneira você chega lá.” Ayrton Senna

RESUMO

CARDOSO, R.B. **O efeito do paracetamol com codeína em comparação ao placebo no desconforto cirúrgico e nos sintomas de transtorno de estresse pós-traumático após a remoção do terceiro molar mandibular: um estudo clínico prospectivo randomizado.** Orientador: Prof. Dr. Marcelo Carlos Bortoluzzi. Ponta Grossa, 2025. Tese (Doutorado em Odontologia), Universidade Estadual de Ponta Grossa, Ponta Grossa, 2025.

Este estudo investigou o efeito de uma única dose preventiva de 500 mg de paracetamol mais 7,5 mg de fosfato de codeína no desconforto cirúrgico, ansiedade, sintomas de transtorno de estresse pós-traumático e dor em cirurgias do terceiro molar mandibular. Os pacientes foram aleatoriamente designados e avaliados no pré-operatório usando o Inventário de Ansiedade Traço-Estado, Dental Anxiety Scale (DAS) e a escala visual analógica de ansiedade (Anxiety-VAS). Imediatamente após a cirurgia, os pacientes foram avaliados usando o questionário de autopercepção da cirurgia oral dentoalveolar, a escala visual analógica de dor (EVA-dor) e a Anxiety-VAS. Os pacientes também mantiveram um diário de dor pós-operatória em 3h, 6h, 9h, 12h e no início e no final do dia 1. Na revisão pós-operatória no sétimo dia, os pacientes completaram a Escala de Impacto do Evento – Revisada (IES-R) em relação à cirurgia. O estudo incluiu inicialmente 67 pacientes, com sete excluídos durante o processo de avaliação. Um total de 60 cirurgias envolvendo um único terceiro molar mandibular foram realizadas, distribuídas uniformemente entre o grupo paracetamol-codeína (n = 30) e o grupo placebo (n = 30). Os grupos foram semelhantes em idade, sexo, tempo cirúrgico e dificuldade da cirurgia de acordo com a Escala de Pederson. A ansiedade medida pelo STAI, DAS e Ansiedade-VAS não diferiu entre os grupos. A medicação preventiva testada mostrou eficácia semelhante ao placebo no controle da ansiedade e da dor, bem como no manejo do desconforto intraoperatório ou da dor pós-operatória. Um evento cirúrgico estressante específico foi observado em 8 pacientes (13%) com preocupação clínica e 8 pacientes (13%) com provável transtorno de estresse pós-traumático relacionado à cirurgia oral. O grupo de combinação paracetamol-codeína não apresentou melhora nas pontuações gerais do IES-R. Níveis mais altos de ansiedade pré-cirúrgica foram associados a pontuações mais altas do IES-R e maior desconforto e dor cirúrgicos.
Uma única dose preventiva de 500 mg de paracetamol mais 7,5 mg de fosfato de codeína não fornece benefícios na cirurgia do terceiro molar mandibular. Este estudo demonstrou uma ligação entre a ansiedade pré-operatória e o desconforto cirúrgico e o desenvolvimento de sintomas de transtorno de estresse pós-traumático.

Palavras-chave: Terceiro molar; Cirurgia oral; Dor; Transtorno de estresse pós-traumático

ABSTRACT

CARDOSO, R. B. **The Effect of Paracetamol/Codeine Compared to Placebo on Surgical Discomfort and Post-Traumatic Stress Disorder Symptoms Following Mandibular Third Molar Removal: A Prospective Randomized Clinical Trial** Advisor: Marcelo Carlos Bortoluzzi. Ponta Grossa, 2025. Thesis (Doctorate in Dentistry), State University of Ponta Grossa, Ponta Grossa, 2025.

This study investigated the effect of a single preemptive dose of 500 mg paracetamol plus 7.5 mg codeine phosphate on surgical discomfort, anxiety, post-traumatic stress disorder symptoms, and pain in mandibular third molar surgeries. Patients were randomly assigned and evaluated preoperatively using the State-Trait Anxiety Inventory, Dental Anxiety Scale (DAS), and anxiety visual analog scale (Anxiety-VAS). Immediately after surgery, patients were assessed using the self-perception questionnaire of dentoalveolar oral surgery, pain visual analog scale (Pain-VAS), and Anxiety-VAS. Patients also maintained a diary of postoperative pain at 3h, 6h, 9h, 12h, and at the beginning and end of day 1. At the postoperative review on the seventh day, patients completed the Impact of Event Scale – Revised (IES-R) regarding surgery. The study initially included 67 patients, with seven excluded during the evaluation process. A total of 60 surgeries involving a single mandibular third molar were performed, evenly distributed between the paracetamol-codeine group (n = 30) and the placebo group (n = 30).. The groups were similar in age, gender, surgical time, and difficulty of surgery according to the Pederson Scale. Anxiety measured by the STAI, DAS, and Anxiety-VAS did not differ among the groups. The preemptive medication tested showed similar effectiveness to placebo in controlling anxiety and pain, as well as in managing intraoperative discomfort or postoperative pain. A specific stressful surgical event was observed in 8 patients (13%) with clinical concern and 8 patients (13%) with probable post-traumatic stress disorder related to oral surgery. The paracetamol-codeine combination group did not show improved general IES-R scores. Higher levels of presurgical anxiety were associated with higher IES-R scores and greater surgical discomfort and pain. A single preemptive dose of 500 mg paracetamol plus 7.5 mg codeine phosphate does not provide benefits in mandibular third molar surgery. This study demonstrated a link between preoperative anxiety and both surgical discomfort and the development of post-traumatic stress disorder symptoms.

Keywords: Third Molar; Oral Surgery; Pain; Post-traumatic Stress Disorder

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

DS	Dry Socket
REBEC	Brazilian Clinical Trials Registry
TEPT	Transtorno De Estresse Pós-Traumático
CNPq	Conselho Nacional De Desenvolvimento Científico e Tecnológico
CAPES	Coordenação De Aperfeiçoamento De Pessoal De Nível Superior
ASA I	Normal Healthy Patient
NNT	Number Needed To Treat
ASA II	Patients With Mild Systemic Disease Without Substantial Functional Limitations
RCTs	Randomized Controlled Trials
SRs	Systematic Reviews
VCS	Verbal Category Scale
GLMM	Generalized Linear Mediation Model
OR	Odds Ratios
DAS	Dental Anxiety Scale
Anxiety-VAS	Anxiety Visual Analog Scale
Pain-VAS	Pain Visual Analog Scale
IES-R	Impact Of Event Scale – Revised
STAI	State-Trait Anxiety Inventory
STAI-S	State Anxiety
STAI-T	Trait Anxiety
VAS	Visual Analog Scales
CT	Computer Tomography
QCirDental	Questionnaire Of Dentoalveolar Oral Surgery
SD	Standard Deviations

LISTA DE SÍMBOLOS

=	Igual
±	Mais ou menos
<	Menor
>	Maior
%	Porcentagem
p	Valor da significância estatística

SUMÁRIO

1 INTRODUÇÃO

A remoção do terceiro molar, um dos procedimentos cirúrgicos orais e maxilofaciais mais comuns, é frequentemente acompanhada por significativo estresse psicológico, medo, ansiedade, desconforto e dor. O medo da dor, tanto durante quanto após a cirurgia sob anestesia local, é uma preocupação primordial para muitos pacientes. A ansiedade odontológica, um problema generalizado que afeta cerca de 25% dos adultos no Reino Unido e 20% nos EUA, tem sido consistentemente associada à intensidade e duração da dor em cirurgias orais. Indivíduos com ansiedade odontológica frequentemente exibem pensamentos, sentimentos e medos negativos, além de distúrbios do sono e alterações comportamentais, impactando negativamente sua qualidade de vida.

Experiências odontológicas negativas prévias são um dos principais fatores que contribuem para a ansiedade odontológica, aumentando a percepção da dor e cognições negativas em relação ao tratamento. Diversos fatores, incluindo características individuais (idade, sexo, experiências anteriores) e condições socioeconômicas, podem influenciar a presença do medo odontológico, com prevalência variando de 4,2% a mais de 50% em diferentes estudos. Essas variações podem refletir diferenças culturais, sociais e econômicas, bem como as metodologias de pesquisa empregadas.

A ansiedade pré-operatória é particularmente elevada em pacientes submetidos à remoção do terceiro molar, o procedimento mais comum em cirurgia oral. Essa ansiedade, embora tenda a diminuir após a cirurgia, pode complicar o procedimento, tornando-o mais desafiador para o cirurgião e resultando em sintomas pós-operatórios mais intensos. Além disso, a dor pós-operatória e suas complicações são reconhecidas como fatores de risco para o transtorno de estresse pós-traumático (TEPT), uma condição mental grave que pode ser desencadeada por eventos traumáticos, incluindo procedimentos cirúrgicos.

O TEPT é caracterizado por sintomas de intrusão, evitação e hipervigilância, e pode se desenvolver após experiências médicas e cirúrgicas que provocam medo intenso, impotência ou horror. Indivíduos com alta ansiedade e histórico de eventos médicos traumáticos são particularmente vulneráveis ao desenvolvimento de TEPT após cirurgias orais.

Apesar da alta prevalência de ansiedade e medo em cirurgias de terceiros molares, o impacto psicológico desses procedimentos, especialmente o potencial para TEPT, permanece pouco explorado. A maioria dos estudos se concentra em sintomas pós-operatórios, negligenciando a experiência intraoperatória, onde os principais fatores de estresse estão concentrados. A compreensão abrangente da experiência do paciente durante a cirurgia é crucial, pois essa fase expõe os pacientes a vulnerabilidades físicas e emocionais significativas, potencialmente contribuindo para o desenvolvimento de TEPT.

Diversas abordagens, incluindo protocolos farmacológicos e técnicas psicológicas, têm sido exploradas para melhorar o conforto do paciente e mitigar os efeitos negativos da cirurgia. A analgesia preemptiva, por exemplo, surge como uma estratégia promissora para o controle da dor e ansiedade antes do trauma cirúrgico.

2 PROPOSIÇÃO

2.1 PROPOSIÇÃO GERAL

Avaliar o uso de medicação analgésica preemptiva na redução dos níveis de ansiedade em pacientes submetidos a cirurgias de extrações dos terceiros molares.

2.2 PROPOSIÇÕES ESPECÍFICAS

Avaliar se os efeitos da medicação analgésica preemptiva podem reduzir o medo e ansiedade em pacientes submetidos a extrações dos terceiros molares e identificar possíveis pacientes com transtornos de estresse pós traumático bem como a possibilidade de desenvolvimento do mesmo.

Avaliar por meio de questionários a ansiedade, dor, percepção do paciente sobre o procedimento cirúrgico.

3 MATERIAIS E MÉTODO

A descrição abrangente dos materiais e método utilizados no artigo pode ser encontrada na próxima seção oferecendo aos leitores uma compreensão detalhada da metodologia empregada no estudo.

4 ARTIGO 1 - THE EFFECT OF PARACETAMOL/CODEINE COMPARED TO PLACEBO ON SURGICAL DISCOMFORT AND POST-TRAUMATIC STRESS DISORDER SYMPTOMS FOLLOWING MANDIBULAR THIRD MOLAR REMOVAL: A PROSPECTIVE RANDOMIZED CLINICAL TRIAL

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Introduction

Third molar removal is one of the most frequently performed procedures in oral and maxillofacial surgery, commonly associated with significant psychological stress, fear, anxiety, surgical discomfort, and pain and the fear of pain during and after oral surgery under local anesthesia is a primary concern for many patients[1-5]. Furthermore, numerous studies have consistently demonstrated that dental anxiety is closely linked to both the intensity and duration of pain experienced during and after oral surgeries[1,2,6-9]. These emotions may complicate the surgical procedure, making it more challenging for the surgeon to perform the procedure effectively and a more difficult and longer surgery is often associated with higher postoperative symptoms[1,4,10,11].

The combined emotional and physical challenges associated with dental surgery contribute to a substantial psychological burden on patients. Despite the prevalence of these issues, the psychological impact of dental procedures, particularly the potential for post-traumatic stress disorder, remains largely underexplored in the context of third molar extractions[12,13]. This research gap is noteworthy, especially considering that postoperative pain and its complications have been recognized as risk factors for post-traumatic stress disorder in oral and maxillofacial surgery and trauma[14,15]. Most studies on third molar surgeries have focused primarily on dental anxiety and postoperative symptoms such as pain and inflammation, with little attention given to intraoperative experiences, where the primary stress factors are concentrated. Surprisingly, no study has specifically explored the possibility that dental anxiety may contribute to triggering post-traumatic stress disorder symptoms in oral surgeries. A comprehensive understanding of the patient's experience during the surgery is necessary[16-18], as this phase exposes patients to considerable physical and emotional vulnerabilities, potentially contributing to the development of post-traumatic stress disorder symptoms.

Various approaches, including pharmacological protocols and psychological techniques, have been explored to improve patient comfort and counteract the negative effects of surgery, though most studies focus on managing postoperative symptoms[2,5,18]. Among these strategies, preemptive analgesia, such as a combination of paracetamol and codeine, offers a potential method for managing pain and anxiety before surgical trauma occurs[5,19].

The primary aim of this study was to evaluate whether a single preemptive dose of 500 mg paracetamol combined with 7.5 mg codeine phosphate effectively reduces surgical discomfort, anxiety, and the risk of post-traumatic stress disorder in patients undergoing mandibular third molar surgeries compared to placebo. It was hypothesized that the combination of 500 mg paracetamol and 7.5 mg codeine phosphate would significantly reduce pain, anxiety, and surgical discomfort, both during and immediately after the procedure.

Materials and Methods

This study was a randomized, placebo-controlled clinical trial designed to investigate the impact of a single preemptive dose of 500 mg paracetamol plus 7.5 mg codeine phosphate on surgical discomfort, anxiety, symptoms of post-traumatic stress disorder, and pain in mandibular third molar surgeries, when compared to placebo.

Clinical Criteria

The participants included in this study were referred by a dental school clinic for wisdom tooth removal between March 2023 and March 2024. Patients included in the study required surgical removal of a single mandibular third molar, which involved at least a surgical flap and osteotomy. Eligible participants were between 20 and 40 years old, female and male, and classified as American Society of Anesthesiologists (ASA) I or II. Additional inclusion criteria included the absence of signs and symptoms of infection at the surgical site and willingness to participate, as evidenced by the signing of the Informed Consent Form. Patients were excluded if they experienced a loss of follow-up, were non-cooperative, failed to complete postoperative diaries, or had intraoperative and postsurgical complications such as leaving dental roots in place, alveolar hemorrhage, alveolar osteitis, infection, or any other notable postoperative complications.

Medication Preparation

The preparation of the placebo and paracetamol-codeine combination was handled by a professional third party under strictly controlled conditions to ensure the integrity of the study. Both treatments were encased in capsules of identical color and weight to maintain blinding. These capsules were then sealed and labeled as

"Medication A" and "Medication B," with the coding recorded and securely maintained by the study administrator. This process ensured that neither the participants nor the researchers were aware of the treatment assignments, thus preserving the double-blind nature of the trial.

Randomization and Blinding

Participants were randomly allocated to either the placebo or paracetamol-codeine group through a random selection process. This was performed by having each participant draw a slip from an opaque bag containing the assignments for each group. This method ensured that neither the participants nor the researchers could predict or influence group allocation while maintaining the integrity of the randomization process. The trial participants, surgeons, and data collectors were blinded to the study group assignments.

Study Steps

During the initial evaluation, patients were selected for surgery based on a comprehensive assessment, including collection of demographic data and detailed medical history. A panoramic radiograph was obtained to assess the surgical site, and in cases where the mandibular third molar was in close proximity to the inferior alveolar nerve, a CT scan was requested for further evaluation.

Preoperative assessments consisted of the State-Trait Anxiety Inventory, Dental Anxiety Scale, and anxiety visual analog scale. After receiving the study medication, the patients completed these preoperative assessments (Time 1) before proceeding with the surgical procedure. The preemptive medication was administered approximately 30 ± 10 minutes prior to surgery.

Immediately after surgery, patients were evaluated using the self-perception questionnaire for dentoalveolar oral surgery, the pain visual analog scale, and the anxiety visual analog scale during the intraoperative period (Time 2). They were then discharged with postoperative instructions, including a diary to record pain levels at 3, 6, 9, and 12 hours (day 1), as well as at the beginning (pain day 2 morning) and end (pain day 2 evening) of the second day. Postoperative standard medication regimens included amoxicillin 500 mg every 8 hours for 7 days, paracetamol 500 mg every 8 hours for 3 days, and Potassium Diclofenac 50 mg every 8 hours for 3 days. For

patients with allergies, clindamycin 300 mg every 8 hours for 7 days and ibuprofen 600 mg every 8 hours for 3 days were prescribed.

On the seventh day, the patients returned for a follow-up visit, where their completed pain diaries were collected, and the healing process was reevaluated. During this visit, they also completed the Time 3 study protocol, which included the Impact of Event Scale – Revised to assess their psychological response to surgery.

Operators

All surgical procedures were performed by trained residents of the Oral and Maxillofacial Surgery Residency Program at the University Hospital. The residents were instructed about the research protocol, provided detailed information to the patients, assisted them in completing the questionnaires, and were supervised by two external evaluators throughout the entire process, from the surgery to the follow-up visit. Figure 1 outlines the key steps of the study and illustrates the flow of participants throughout the process, from initial enrollment and randomization to surgery, follow-up assessments, and final analysis.

Questionnaires

The Brazilian Portuguese version of Corah's Dental Anxiety Scale was used to assess dental anxiety. The questionnaire consisted of four questions, with responses rated on a scale from 1 (not anxious) to 5 (extremely anxious). Higher scores indicate higher levels of anxiety. Dental Anxiety Scale assesses the level of anxiety experienced by the respondents during dental treatment. Based on the Dental Anxiety Scale scores, patients were classified into one of the following categories: (a) low anxiety (4 points), (b) mild anxiety (5–10 points), (c) moderate anxiety (11–15 points), and (d) high anxiety (16–20 points)[9].

The State-Trait Anxiety Inventory (STAI) is a questionnaire designed to evaluate an individual's anxiety level. The inventory consists of 40 questions divided into two subscales: state anxiety (STAI-S) and trait anxiety (STAI-T). The STAI-S reflects a temporary emotional state characterized by feelings of worry, whereas the STAI-T indicates a persistent tendency to perceive situations as threatening. Each category comprises 20 items, with scores ranging from 20 to 80, with higher scores indicating elevated levels of anxiety. In general, scores between 20 and 40 indicate low anxiety,

scores between 41 and 60 indicate moderate anxiety, and scores between 61 and 80 indicate high anxiety[9].

Visual Analog Scales (VAS) are simple tools used to measure subjective experiences, such as pain or anxiety, on a continuum. They typically consist of a horizontal line ranging from "no sensation" at one end to "worst imaginable sensation" at the other end. Patients marked a point along the line that best reflected their current state. VAS is widely used in clinical settings due to its ease of use and ability to capture subtle changes in a patient's perceived intensity of symptoms[7]. Patients were evaluated preoperatively for anxiety about the procedure and immediately after the surgery for both pain and anxiety[12].

The Self-Perception Questionnaire of Dentoalveolar Oral Surgery (QCirDental) was developed to quantify the negative effects and discomfort experienced by patients during the immediate perioperative period of dentoalveolar surgeries. Its purpose is to assess the surgical procedure's associated discomfort and provide a measure of its impact on patients. The questionnaire is composed of 20 questions answered on a 0-10 scale of discomfort, with greater values indicating increased discomfort impact[16-18].

The Impact of Event Scale-Revised (IES-R) is a screening instrument for post-traumatic stress disorder symptomatology that demonstrates the best discriminant validity and diagnostic utility and can be used at any phase of symptom development (acute, chronic, and delayed). It consists of 22 questions with five response options (never, a little, moderately, often, and extremely) evaluating three symptom groups: Intrusion, Reliving traumatic events, Avoidance: Efforts to avoid trauma memories, Hyperarousal: Increased arousal, including irritability, difficulty sleeping, and hypervigilance. Higher scores indicate greater distress, and scores above certain thresholds suggest clinical concerns related to post-traumatic stress disorder. Scores of 24 or more: post-traumatic stress disorder is a clinical concern; scores of 33 and above suggest a probable post-traumatic stress disorder diagnosis; and scores of 37 or more may indicate a level of distress that could potentially suppress immune system functioning[15]. In this study, the follow-up period for assessing post-traumatic stress disorder symptoms was intentionally limited to one week, with the aim of capturing the immediate psychological impact of the surgical procedure.

Sample size

The sample size was calculated using G*Power (version 3.1.9.7). F tests were conducted using ANOVA with repeated measures, focusing on the interaction between within-subject and between-subject factors. Analysis was conducted *a priori* to determine the required sample size. The input parameters included an effect size (f) of 0.25, alpha error probability (α) of 0.05, and power (1-β) of 0.95. The number of groups was set to two, with two measurements taken (anxiety visual analog scale). The correlation among the repeated measures was 0.5, and the nonsphericity correction (ε) was 1. The output indicated a noncentrality parameter (λ) of 13.5, with a critical F value of 4.0. The degrees of freedom of the numerator and denominator were 1.0 and 52.0, respectively. The minimum total sample size required was 54 patients (27 per group), yielding an actual power of 0.95. To account for potential losses, an additional 25% of participants were included due of the risk of complications and dropouts associated with third molar surgeries.

Data analysis and Statistical Procedures

JAMOVI software (JAMOVI project, 2024, Version 2.5.3.0) was used for data analysis, employing descriptive and inferential methods. A two-tailed significance level of $p \leq 0.05$ was considered statistically significant. Variables were categorized as continuous, ordinal, or nominal, and appropriate statistical tests were selected based on their characteristics. Descriptive statistics summarized demographic and clinical characteristics, including age, gender, surgical time, and surgical difficulty (assessed by the Pederson Scale). Continuous variables were reported as means ± standard deviations (SD). Independent t-tests were used to compare continuous variables (anxiety scores and pain scores) between the paracetamol-codeine group and the placebo group. Assumptions of normality and homogeneity of variances were checked and validated prior to analysis. Chi-square tests (or Fisher's exact tests) were used to compare categorical variables between the paracetamol-codeine and placebo groups. The test evaluated differences in proportions of PTSD symptom classifications (no impact, clinical concern, probable PTSD). Repeated measures ANOVA was used to evaluate changes in anxiety and pain scores over multiple time points. This analysis assessed the effects of time (e.g., preoperative vs. postoperative anxiety) and the interaction between time and group (paracetamol-codeine vs. placebo). For pain

analysis, repeated measures ANOVA was applied to pain trajectories measured at six postoperative time points (3h, 6h, 9h, 12h, day 2 morning, and day 2 evening) to determine whether pain reduction patterns differed between the two groups. Assumptions of sphericity (Mauchly's test) and normality were checked and validated prior to analysis.

Results

The initial sample consisted of 67 patients, of which seven were excluded for various reasons: three due to loss of follow-up (1 for paracetamol-codeine group; 2 for placebo-controlled group), two for leaving dental roots in place (paracetamol-codeine group), and two due to postoperative complications (placebo-controlled group) (Fig. 1). The management of clinical data ensured a balanced distribution of patients between the groups. The final sample comprised 60 patients evenly divided into two groups: the paracetamol-codeine combination group and the placebo-controlled group. No differences were found between the two groups in terms of demographic characteristics (age and gender), surgical duration, or surgical difficulty assessed using the Pederson Scale (Table 1). Similarly, baseline dental anxiety levels measured using the State-Trait Anxiety Inventory, Dental Anxiety Scale, and Anxiety Visual Analog Scale (Anxiety-VAS) showed no differences between the groups prior to the administration of preemptive medication (Table 1).

The anxiety levels measured by the Anxiety-VAS before and immediately after surgery were compared between the two groups at both time points. The paracetamol-codeine group (pre-surgery Anxiety-VAS: 39.1, post-surgery Anxiety-VAS: 30.6; mean standard error: 4.7) did not show a significantly greater reduction in anxiety compared to the placebo group (pre-surgery Anxiety-VAS: 33.7, post-surgery Anxiety-VAS: 27.6; mean standard error: 4.2) ($p = 0.44$, repeated measures ANOVA).

The pain experienced during and shortly after the surgery (Pain-VAS) was similar between the paracetamol-codeine combination group (28 ± 27.5) and the placebo-controlled group (21 ± 20.7) ($p= 0.20$, t-test).

The ability of the paracetamol-codeine combination group to reduce intraoperative discomfort, as measured by the Self-Perception Questionnaire of Dentoalveolar Oral Surgery (Table 2), was similar to that of the placebo group ($p= 0.20$, t-test). The trajectory of pain reduction across six time points, from three hours post-

surgery to the end of the second day (Table 3), was similar between the preemptive medication (paracetamol-codeine combination) and placebo groups (p = 0.50, repeated measures ANOVA).

Post-traumatic stress disorder symptoms, as measured by the Impact of Event Scale – Revised in response to the specific surgical event, revealed that 8 patients (13%) fell within the range of clinical concern, and another 8 patients (13%) were identified with probable post-traumatic stress disorder related to oral surgery (Table 4). However, the preemptive medication (paracetamol-codeine combination group) resulted in a similar level of post-traumatic stress disorder development compared to the placebo group.

Discussion

Contrary to this hypothesis, the preemptive administration of paracetamol and codeine at the proposed dosage showed similar effectiveness to placebo in controlling anxiety or pain during and after third molar surgeries. Although some anxiety reduction was observed in both groups, the paracetamol-codeine combination group did not show statistically significant improvements compared to the placebo group in managing anxiety or discomfort, as evidenced by similar scores in Anxiety-VAS, Pain-VAS, and Self-Perception Questionnaire of Dentoalveolar Oral Surgery. Factors such as individual pain thresholds, real or *in vivo* surgical difficulty, and anxiety levels may have confounded the effects of medication, as suggested by the finding that higher presurgical anxiety was associated with higher surgical discomfort and immediate postoperative pain scores (Pain-VAS). Preoperative administration of paracetamol-codeine significantly reduced postoperative pain intensity and delayed the first request for rescue therapy compared to placebo, although they used a much higher dose of codeine (500 mg paracetamol plus 30 mg codeine)[19]. Notably, in the cited study, the rescue drug for the placebo group was also a placebo, meaning that these patients effectively received no analgesic coverage during the postoperative period. This raises ethical concerns regarding inadequate pain management, which may also explain the differences observed between the two studies. Pain relief differences were only apparent on the first postoperative day, suggesting a possible placebo effect[19].

Outcomes may vary based on factors such as the patient population, surgical context, and pharmacological protocols used. Moreover, the potential influence of the placebo

effect and the pain-relieving effects of the medication cannot be ruled out as factors contributing to the lack of an observed association between anxiety and postoperative pain (diary) in this study. This hypothesis is supported by an additional analysis (not included in the main results), which indicated that anxiety significantly affected immediate postoperative pain (Pain-VAS); however, this effect disappeared when mediated by the medications, whether in the placebo group or the paracetamol-codeine combination group, suggesting that both pharmacological and placebo responses may have played a role in alleviating postoperative anxiety-pain-related symptoms, and may indicate that the preemptive administration did not outperform the placebo effect.

Higher presurgical anxiety and increased surgical discomfort may also make surgery more traumatic for susceptible individuals. Previous studies have noted that anxiety levels during treatment are significantly associated with greater distress, characterized by higher scores for pain, anxiety, and emotional disturbance during the procedure[12]. This heightened anxiety and surgical discomfort may contribute to a higher risk of developing PTSD, emphasizing the importance of integrating psychological and pharmacological interventions to better address the emotional and physical aspects of 3Ms surgical experiences[1,8,9].

Disorders such as generalized anxiety, depression, acute stress reaction, and post-traumatic stress disorder (PTSD) are complex and largely understudied in the oral and maxillofacial field[14,15]. Moreover, few studies have specifically investigated the relationship between third molar surgery and the development of PTSD[12,13]. with even fewer studies have investigated the connection between third molar surgery and the development of post-traumatic stress disorder [12,13]. In this study, patients were evaluated for symptoms such as intrusive distressing memories, avoidance of thoughts or reminders of the surgery, nightmares, or flashbacks using the Impact of Event Scale – Revised questionnaire. The one-week follow-up aimed to identify early signs of trauma-related distress that could hinder the patient's emotional and psychological recovery from surgery, while considering the potential impact of preemptive medication. Approximately 27% of patients exhibited scores on the Impact of Event Scale – Revised, indicating either clinical concern or probable post-traumatic stress disorder-related symptoms, highlighting the psychological vulnerability of patients undergoing these procedures. A previous study[13] observed that the emotional impact

of third molar surgeries may be modest, with only 4% of the sample reporting a significant increase in dental anxiety or post-traumatic stress disorder one month post-surgery. However, from a clinical practice perspective, this seemingly small percentage is significant, suggesting that common and routine procedures can have a lasting psychological impact on a subset of patients. The findings of the present study underscore the complexity of managing anxiety and pain in dental surgeries, highlighting the intricate relationship between the various factors involved in these procedures.

Despite the growing concern about public health abuse due to the use of opioids, the rational prescription and use of these medications are still important for pain control in many situations. The single-dose paracetamol-codeine combination regimen, consisting of 500 mg of paracetamol combined with 7.5 mg of codeine phosphate, did not produce any noticeable adverse effects in the participants. Throughout the study, there were no reports of significant side effects, such as nausea, dizziness, drowsiness, constipation, headache, or excessive sedation, which are commonly linked to opioid use[5].

This study had some limitations that should be considered when interpreting the results. First, while the sample size was well-calculated and sufficient for the primary analyses, it may have limited the ability to perform certain secondary or exploratory analyses. For instance, the study might not have had enough statistical power to detect very small effect sizes or to conduct more detailed subgroup analyses (e.g., examining effects at specific surgical difficulty levels) that were not part of the primary objectives. Small effect sizes represent a missed opportunity to gain additional information for both clinical practice and future research. Second, the follow-up period for assessing post-traumatic stress disorder (PTSD) symptoms was limited to one week, which may not capture the full trajectory of PTSD development. An additional limitation related to PTSD is that participants were not screened for prior traumatic events that could have contributed to pre-existing PTSD, potentially influencing their response to the surgery. However, it was clearly communicated to participants that the questions on the Impact of Event Scale should be answered specifically regarding their surgical experience. Finally, the use of self-reported measures for pain and anxiety, while validated, may be subject to individual variability and reporting bias.

Conclusions

A single preemptive dose of 500 mg paracetamol plus 7.5 mg codeine phosphate showed similar effects in reducing anxiety, pain, or surgical discomfort during mandibular third molar surgeries compared to placebo. Notably, approximately 26% of the patients exhibited symptoms of clinical concern or probable post-traumatic stress disorder within seven days post-surgery, highlighting the psychological impact of these procedures.

Funding
None

Competing interests
None

Ethical approval

This study was approved by the Institutional Human Research Ethics Committee (#6.007.038) and registered at the Brazilian Clinical Trials Registry (ReBEC #RBR-3vskx79). Informed consent was obtained from each participant prior to their inclusion in the study.

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Appendix file

Figure 1: Study Flow Diagram

The diagram shows the progression of participants throughout the study. After the initial evaluation and baseline assessments, the participants were randomized into two groups: paracetamol-codeine (GCod) and placebo (GPla). Surgical intervention and follow-up assessments were also performed. The final analysis included 60 participants (group GCod, n=30; group GPla, n=30).

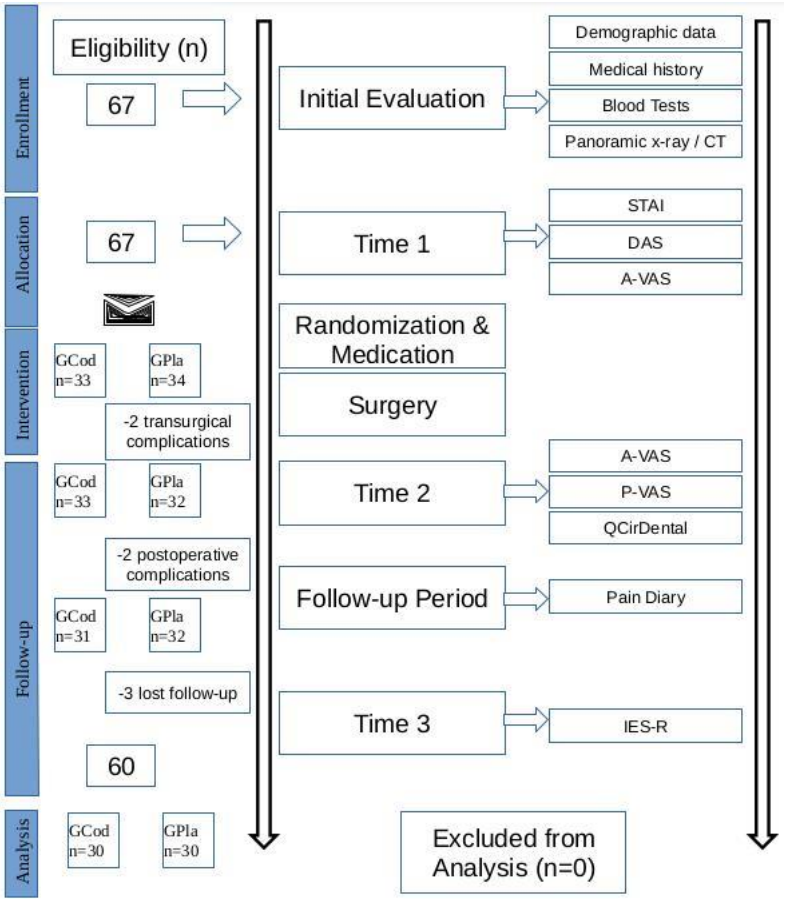

Table 1. Distribution of the patients by age, gender, surgical time, surgical difficulty according to the Pederson Scale, and preoperative anxiety levels in third molar surgery patients stratified by paracetamol-codeine combination and placebo-controlled groups.

Variables		Paracetamol-Codeine Combination Group	Placebo-Controlled Group
Age (Mean ± SD)		23.7 ±3.7	24.6 ±4.9
Gender			
	Female	20	24
	Male	10	6
Surgical Time			
	Up to 30 minutes	7	8
	Between 30-40 minutes	5	12
	Between 40-50 minutes	6	5
	Between 50-60 minutes	5	3
	More than 60 minutes	7	2
Difficulty Pederson Scale			
	Slightly Difficult	12	11
	Moderate Difficult	17	16
	Very Difficult	1	3
STAI-State (Mean ± SD)		41.3 ±6.9	39.9 ±7.9
STAI-Trait(Mean ± SD)		47.0 ±8.7	44.0 ±10.0
DAS (Mean ± SD)		10.0 ±3.1	9.2 ±3.7
Anxiety-VAS presurgical (Mean ± SD)		39.1 ±25.9	33.6 ±22.9

STAI-State: State-Trait Anxiety Inventory, State Domain.
STAI-Trait: State-Trait Anxiety Inventory, Trait Domain.
DAS: Dental Anxiety Scale.
Anxiety-VAS presurgical: Anxiety Visual Analog Scale.

Table 2: Self-perception questionnaire of dentoalveolar oral surgery scores and percentage of positive answers on discomfort after third molar surgeries stratified by paracetamol-codeine combination and placebo-controlled groups.

Self-perception questionnaire of dentoalveolar oral surgery scores	Paracetamol-codeine combination group		Placebo-controlled group	
	Mean score	Positive answers (%)*	Mean score	Positive answers (%)*
1. I felt nervous during the surgery	4.6	41.7	4.6	45.0
2. The comments the dentists made during my surgery	0.8	16.7	0.4	11.7
3. The fluids and blood in my mouth	1.7	28.3	1.8	26.7
4. The impression I had of the wounds in my mouth (bruises and cuts)	1.4	23.4	2.1	28.3
5. I was afraid of anesthesia	2.8	33.3	2	25.0
6. The pain I felt during the anesthesia	2.9	38.3	2.4	35.0
7. The pain I felt during the surgery	3.0	38.3	2.4	26.7
8. The sounds and noises of surgical instruments	2.8	30.0	2.4	25.0
9. The surgery time (The length of time the surgery took)	2.4	28.3	1.3	23.3
10. The lack of explanation of what was happening during the surgery	0.3	5.0	0.07	3.3
11. The dentist's lack of delicacy or care towards me during the surgery	0.5	10.0	0.2	3.3
12. I felt outraged during the surgery (for any related reason)	0.06	3.3	0.2	0.1
13. The surgeon's difficulty in finishing the surgery	0.9	15.0	0.1	3.3
14. During my surgery, I felt my privacy invaded (intimity)	0.03	1.7	0.0	0.0
15. The place, the surgical environment or atmosphere of the clinic	0.4	8.3	0.2	1.7
16. The different smells (for any related reason)	1.3	15.0	0.8	13.3
17. The materials or instruments they put in my mouth	1.5	23.3	1.4	26.7
18. I felt distressed during the surgery	3.1	35.0	2.7	28.3
19. The lack of explanations after finishing the surgery	0.03	1.7	0.0	0.0
20. The feeling of having lost my tooth or my tooth/teeth	1.1	15.0	0.2	5.0
Questionnaire Total Sum	32	- - -	25	- - -

*** Percentage of Positive Answers:** This represents the proportion of subjects whose responses were greater than zero on the QCirDental 0-to-10 question scale, indicating the percentage of patients who experienced any level of impact or discomfort based on the question.

Table 3: Pain levels over the period of 2 days starting at 3 hours after the surgery up to the end of the second day after the procedure, stratified by paracetamol-codeine combination group (GCod) and placebo-controlled group (GPla).

Pain measurements on time points	Paracetamol-Codeine Combination Group (Mean ± SD)	Placebo-Controlled Group (Mean ± SD)	p-value
Pain 3h - after the surgery (day 1)	4.03 ±2.9	4.23 ±3.1	0.79
Pain 6h - after the surgery (day 1)	4.03 ±2.7	3.53 ±2.7	0.48
Pain 9h - after the surgery (day 1)	3.20 ±2.8	2.87 ±2.5	0.63
Pain 12h - after the surgery (day 1)	2.70 ±2.9	2.33 ±2.1	0.59
Pain day 2 morning†	2.57 ±2.5	1.87±1.9	0.23
Pain day 2 evening††	2.57 ±2.5	2.23 ±2.1	0.58
ANOVA repeated measurements (between subjects - Group)			0.55

†Pain day 2 morning: beginning of the second postoperative day (morning).
††Pain day 2 evening: end of the second postoperative day (evening).

Table 4: Post-traumatic stress disorder (PTSD) measured using the Impact of Event Scale – Revised (IES-R), stratified by paracetamol-codeine combination group and placebo-controlled group.

Impact of Event Scale – Revised (IES-R)	Paracetamol-codeine combination group		Placebo-controlled group		p-value
	Number of Patients	Mean ± SD scores	Number of Patients	Mean ± SD scores	
Classification - No Impact	24	9.7 ±7.8	20	9.7 ±7.8	0.3†
Classification - Clinical Concern	2	25 ±1.4	6	27 ±2.6	
Classification - PTSD probable to suffering	4	52.5 ±11.9	4	50.5 ±13.7	
IES-R Scores (mean scores ±SD)		16.5 ±16.9		18.5 - 15.5	0.64††

†Chi-Square Test, based in the IES-R patient classification proportions.
††Student's T-Test, based on the IES-R total mean scores.

5 ARTIGO 2 - Prevalence and factors associated with dry socket following routine dental extractions

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Abstract

Background: Dry socket (DS) or fibrinolytic osteitis is a relatively common complication that can occur following tooth extraction. This study aimed to determine the prevalence of DS and identify its associated predictive and mediating variables.

Material and Methods: This study is classified as prospective observational, cross-sectional, and multicenter. Patients were consecutively selected in accordance with established criteria for tooth extraction. Data on patient demographics, surgical procedures and postoperative outcomes were collected. Nominal variables were analyzed using the Chi-Square Test, while associations involving ordinal values or considering counts or layers were examined using the Kendall's Tau-B Test or Mantel-Haenszel Test for trend. The GLM Mediation Model was employed to investigate potential mediation or indirect effects or potential underlying mechanisms of predictive variables on the development of DS. Two-tailed significance level of $p \leq 0.05$ was considered statistically significant.

Results: A total of 1,357 patients undergoing routine dental extractions were included. DS was observed in 13 patients (prevalence of 1%). DS was associated with younger patients (under 50 years old), longer procedures, and the presence of surgical accidents, but only when mediated by surgical complexity. Smoking, particularly in com bination with complex surgeries and surgical accidents, was associated with DS.

Postoperative pain for more than two days and reported at moderate to high levels, emerged as a potential warning sign for DS. The use of antibiotics was found to significantly reduce the risk of DS (RR reduction of 36% and absolute risk reduction of 0.63%).

Conclusions: Routine dental extractions revealed a 1% prevalence of dry socket. The obtained results suggests that DS is a multifactorial condition influenced by various factors, including gender, age, smoking, antibiotic prescription and surgical factors such as length, technique and accidents, nevertheless, those associations were observed mainly considering the influence of one variable on another.

Key words: Dry socket, oral surgery, pain, dental extractions, antibiotics, tooth extraction, alveolar osteitis.

Introduction

Dry socket (DS), also known as alveolar or fibrinolytic osteitis, is a relatively common complication that can occur following tooth extraction (1-9). It is characterized by the acute inflammation of the alveolar bone surrounding the extracted tooth, resulting in severe pain in the absence of infection or inflammation, typically appearing 2 to 4 days post-extraction. Clinical manifestations of DS encompass an empty socket with exposed bone, frequently containing food debris, mild swelling and redness of the gingiva, halitosis, and significant tenderness upon examination (3-6,8,10). The incidence of DS ranges from 1% to 5% for routine tooth extractions, but significantly higher rates have been reported for mandibular third molar extractions (1,4,5,7,9). As the occurrence of DS is more noTable in mandibular third molars, the majority of studies have focused on these procedures rather than regular or routine extractions, which are typically performed by general dentists.

The etiology of dry socket (DS) is not yet fully understood; however, the disintegration of the blood clot through fibrinolysis is widely accepted as the primary mechanism (2-5,11-14). Various factors have been associated with an increased risk of DS, although some of them remain controversial and may include difficult or traumatic extraction (6,15), poor oral hygiene (6,15), smoking (6-8,13,16), female gender (4,9), young patients (4), extraction site (15), previous DS (15) among other less frequently reported variables (12,13). Furthermore, a study using metagenomics to investigate the microbiome in DS sockets suggests that patients who develop DS

may harbor a distinct and specific microbiota, indicating that bacteria may have a significant role in the etiology of DS as well (2).

The present study was designed as an observational, cross-sectional, and multicentric investigation with the primary objective of assessing the prevalence of DS following routine tooth extractions. In addition to estimating the prevalence, the study aimed to identify and examine the predictive and mediating variables that may be associated with the development of DS. By exploring a diverse population, the study sought to provide a comprehensive understanding of the occurrence of DS and its potential influencing factors. Thus, the study's primary hypothesis is to test whether any of the examined variables demonstrate a statistically significant impact on the occurrence of DS.

Material and Methods

- Study design

The study was a prospective observational, cross-sectional, and multicenter investigation that aimed to determine the prevalence of dry socket (DS) and identify predictive and mediating variables or risk factors associated with its development. Ethical approval for the study was obtained from the University's Human Research Ethics Committees with the following registration numbers: UEPG-35061214.5.0000.0105 and UNOESC/HUST 250/2005. Informed consent was obtained from each participant prior to their inclusion in the study.

- Patient selection

Patients were consecutively selected in accordance with established criteria for tooth extraction. The inclusion criteria for the study were based on indications for tooth removal, such as irrecoverable teeth due to dental caries, periodontal disease, endodontics, prosthetic or orthodontic needs. Exclusion criteria included patients who had undergone surgery for impacted third molars, for extraction of deciduous teeth and lack of contact with the patient postoperatively or the inability to clinically check the occurrence of DS.

- Dental Extractions

Undergraduate dental students at the university's dental surgery clinics conducted all the exodontias. Stringent measures were taken to ensure strict control of microbiological contaminants throughout the procedures.

- Data Collection

A preoperative interview and anamnesis were firstly conducted. The postoperative outcomes of pain and inflammatory complications were assessed on the seventh postoperative day or whenever necessary, before or after this period. When faced with the presence of DS or any other surgical complication, the patients were followed up until the complete resolution of the problem. Telephone contact was used as a tool to collect symptoms from patients who were unable to return on the seventh day; however, no diagnosis was made under these circumstances.

- Criteria for Dry Socket (DS)

The criteria for DS was based on clinical condition (4,16). The clinical criteria for DS are as follows: (a) there is severe and persistent pain around the extraction site; (b) there is a partially or totally disintegrated blood clot with exposed alveolar bone; (c) halitosis is usually present. All diagnoses were always confirmed in a clinical setting by one oral and maxillofacial surgeon enrolled in the research. Doubts were resolved by consensus among the research team.

- Pain Evaluation

Pain levels were assessed on the seventh day after the surgery using a verbal category scale (VCS) with response options ranging from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe). This method facilitated a qualitative classification of pain and allowed patients to evaluate the cognitive and emotional dimensions associated with their pain throughout the entire postoperative period. By capturing patients' memories, perceptions, and the impact of pain and injury, this comprehensive approach provided a deeper understanding beyond pain intensity alone and enables a more comprehensive understanding of the patient's pain experience, taking into account their subjective perception and overall evaluation of the pain's significance (17).

- Data analysis and Statistical Procedures

The JASP software (JASP Team, 2023, Version 0.18.1; University of Amsterdam, Netherlands) and/or the JAMOVI software (JAMOVI project, 2023, Version 2.4.9) were utilized for data analysis, employing descriptive and inferential methods. Two-tailed significance level of $p \leq 0.05$ was considered statistically significant. The variables were categorized as continuous, ordinal, or nominal, and appropriate statistical tests were selected based on their characteristics, considering the distribution of the variables and checking the assumptions. Cases with missing sensitive data or lacking postoperative follow-up were excluded from the analysis. Surgical complexity was assessed by determining the necessity of flap elevation, osteotomy, and odontosection, resulting in an ordinal variable ranging from 0 to 3. Nominal variables were analyzed using the Chi-Square Test, while associations

involving ordinal values or considering counts or layers were examined using the Kendall's Tau-B Test or Mantel-Haenszel Test for trend. The GLM Mediation Model (JAMOVI- Advanced Mediation Models) was employed to investigate potential mediation or indirect effects or potential underlying mechanisms of predictive variables on the development of DS.

Results

The sample consisted of 1,357 routine dental extraction procedures. The majority of procedures were performed on male patients (714 or 52.6%), and the age ranged from 9 to 85 years (with a mean of 41 years, SD±15 years). One to three teeth were extracted per procedure (1 tooth: 1,023 surgeries; 2 teeth: 247 surgeries; 3 teeth: 87 surgeries). 20.4% of the patients reported having a systemic disease, while 22% were smokers.

Dry socket (DS) was observed in 13 patients (1%), with higher incidence among young female patients (average age of 35 years), although without statistically significant differences (proportion male-female 1:2.25; odds ratio for female =2.5). 5 DS cases were located in the anterior region of the maxilla, while 7 were found in the posterior region of the mandible, except for a single case that occurred in the canine area. 12 out of 13 cases of DS occurred in patients under 50 years old and the mean age of DS development was 34.7 (±11.1) years while for not having DS was 41.2

(±15.6). Epidemiological data of the study including the proportions and distributions of dental extractions and the development of dry socket can be seen on Table 1.

Regarding the surgical procedure, the average duration of the procedures was approximately 42 minutes (SD ± 27). As for the techniques employed, flap elevation was performed in 30% of cases [411], osteotomy in 12.7% [172], and odontosection in 13.5% [183]. The complexity of the procedure was determined by summing the requirements of the aforementioned techniques (as an ordinal measure ranging from 0 to 3). A higher value indicated a greater need for the utilization of all three techniques. The use of surgical flap, osteotomy and odontosection together was observed in 4.6% of the cases [62].

When the predictive variables were analyzed in isolation as a factor for DS development, it did not show statistically association with, sex, the presence of systemic disease, daily medication use (including contraceptives), contraceptives use (alone), or menstrual cycle influence. Habits such as tobacco, alcohol, and frequent consumption of mate tea (Ilex paraguariensis; a traditional South American beverage) also didn't show association with the development of DS when analyzed in a bivariated mode.

Among surgical factors, this complication occurred in single-tooth extraction procedures in all cases, and significantly occurred when odontosection was necessary (Pearson's Chi-square test, p =.001) or when the surgical technique involved a combination of flap elevation, osteotomy, and odontosection, indicating a more complex procedure (ordinal-by-ordinal Kendall Tau-B Test, p =.002). DS significantly occurred more often when the surgeon also reported a difficult or more complex dental extraction, independently of the technique complexity (Pearson's Chi-square test, p <.001) yet, the view of complexity by the surgeon and the technique complexity were associated (ordinal-by-ordinal Kendall Tau-B Test, p <.001). In 7.5% [102] of cases, intraoperative accidents or complications occurred, with root fractures being the most frequently reported. Among those cases, two individuals developed DS.

The duration of the surgery did not significantly influence DS development (NS); however, DS occurred more often in a slightly longer procedures (~42 minutes for cases without DS and ~47 minutes for cases with DS). In terms of the number of anesthetic cartridges used, 61.3% of procedures utilized up to 2 cartridges [832]. When more than 3 cartridges of local anesthetics (>5.4 ml) were used, there was a

statistically significant increase in the occurrence of DS (x2, p =.005). However, it is important to note that the amount of anesthetics used was also correlated with surgical time and surgical complexity (Spearman's rho Test, rs .26, p <.001; rs .18, p <.001), which could potentially confound the association between anesthetic dosage and DS incidence.

In this sample, antibiotics were prescribed to 11.5% of cases [156]. Regarding this perioperative prescriptions, it was observed that out of the 13 DS patients, 12 did not receive antibiotics during this phase as part of their regular prescription (unrelated to DS treatment). The use of antibiotics in this sample produced a relative risk reduction for DS of 36% and absolute risk reduction of 0.63%. However, a higher number needed to treat (NNT) indicates that approximately 278 patients would need to be treated with antibiotics to prevent one case of DS. It is important to note that this analysis does not take into consideration the nature of the study, the sample characteristics or the specific criteria for prescribing antibiotics. Antibiotics were significantly more prescribed for older (> 50 years old) patients (x2, p <.001), in procedures of greater complexity (Mantel-Haenszel Test for Trend, p =.001) and when surgical accidents occurred (x2, p =.008).

A Generalized Linear Mediation Model (GLMM) indicated that DS development, only when mediated by surgical complexity, may be influenced by age (GLMM, p =.019; younger patients), length of the procedure (GLMM, p =.014; longer surgeries) and, surgical accidents (GLMM, p =.016; occurrence of it). None of these variables, including surgical complexity and odontosection is related with DS when modulated by the presence of antibiotics. Statistical associations and odds ratios (OR) for DS using bivariable analysis, controlled analysis, or mediated by additional variables are presented in Table 2.

In bivariable analysis, tobacco use as a single variable (Yes/No) did not show an association with DS. However, when analyzing tobacco use as the amount of smoking (more than a pack of 20 cigarettes a day) and considering a more complex surgery, tobacco use was found to be associated with DS development (Mantel-Haenszel Test for Trend, p <.015). Additionally, a significant association was observed when surgical accidents occurred and the amount of smoking exceeded a pack (20 cigarettes) per day (Mantel-Haenszel Test for Trend, p =.004). These findings suggest

that the impact of tobacco use on DS development may be influenced by the quantity of smoking and the complexity of the surgical procedure.

A predictive or warning sign for DS development was the presence of reports of higher pain levels (ordinal-by-ordinal Kendall Tau-B test, p =.001), particularly if it persisted for more than two days (Pearson's Chi-square test, p <.001). All pain indicators for DS were reported as moderate (6 cases) or high (7 cases), despite the patients' utilization of analgesics.

Discussion

In the present study, we aimed to investigate the prevalence and associated factors of dry socket (DS) following tooth extractions. DS is a well-recognized and distressing complication that can occur after tooth extraction, causing considerable pain and discomfort for patients. Despite its clinical importance, the pathogenesis of dry socket (DS) remains elusive and probably multifactorial (6), which has hindered

the development of effective preventive measures and optimal management strategies.

Although previous studies, such as Oyri et al. (4), have reported a higher frequency of DS in female patients compared to males (6:1), the findings from this present study suggest that gender may not be an isolated significant factor in DS development, although it was observed with higher prevalence and odds ratio for women. Furthermore, the present study explored the potential influence of daily contraceptive use on DS development in women and yet it didn’t reach the significant level. Furthermore, the literature does not provide a clear indication or hypothesis regarding the reasons why women are more affected by this condition, while some other authors observes a ratio of 1:1 among man and woman (9). The association between gender and DS remains an intriguing aspect that requires further investigation.

Interestingly, our study findings revealed a significant association between the use of odontosection technique and the development of DS. Specifically, when this surgical procedure was employed, it led to a significantly higher incidence of DS in women, while no such association was observed in men. It is worth noting that DS is intricately linked to the process of fibrinolysis, which involves the degradation of blood clots. In the context of DS, bone exhibits fibrinolytic activity due to the release of

plasminogen activators (Pas) triggered by traumatic bone exposure. This complex cascade of inflammatory biochemical events ultimately leads to a decrease in bone formation, increased degradation of blood clots, and delays in wound healing (6). The association between odontosection and the development of dry socket (DS) may be attributed to additional trauma to the surrounding alveolar bone and soft tissues. The increased tissue trauma and manipulation associated with odontosection can lead to a more extensive inflammatory response, delayed healing, and compromised blood clot formation, all of which are known contributing factors to the development of DS.

The association between ostectomy and the development of dry socket (DS) showing a higher incidence in men but not in women, as observed in our study, is an interesting finding that suggests the influence of gender-technique-related factors. Hormonal differences, immune response variations, genetic predisposition, and other variables such as smoking and surgical complexity may contribute to the likelihood of DS development. Further research is needed to elucidate the precise mechanisms underlying these associations.

One important factor that has been extensively discussed in the literature is the impact of smoking on the increased risk of DS (6,8,12,16). Our findings suggest that smoking alone may not be a significant factor in the development of DS. However, our results indicate that smoking, particularly in individuals who consume more than 20 cigarettes a day, becomes a complicating factor when combined with complex surgeries, surgical accidents, and higher amounts of anesthetics used during the procedures. This suggests that the detrimental effects of smoking on DS development may be more pronounced in specific contexts and conditions.

The use of antibiotics to reduce postoperative complications is a subject of frequent discussion in dental literature, particularly in relation to third molar surgeries (7,18). Antibiotics have been proposed as a potential means to decrease the incidence of dry socket (DS), suggesting that specific microbiota may be linked to the pathophysiology of DS, or that antibiotics may act through alternative mechanisms to indirectly prevent blood clot dissolution (1,19). This could potentially involve inhibiting the fibrinolytic properties of certain microorganisms, preventing the dissolution of blood clots and impeding microbial invasion into the wound (6). The hypothesis suggests that bacteria or debris may stimulate the release of cytokines by monocytes/macrophages, which can up-regulate urokinase-type plasminogen activator (uPA) and plasminogen

activator inhibitor 1 (PAI-1), ultimately leading to clot lysis (2,3). However, it is important to note that Chow et al. (3) argue that current evidence does not support the routine administration of prophylactic antibiotics to prevent DS. Our understandings align with this perspective, as the number needed to treat (NNT) with antibiotics to prevent a single case of DS was exceptionally high. This highlights the need for judicious use of antibiotics and suggests that they should be reserved for specific situations, such as complex surgeries or patients with compromised health conditions. It is essential to consider the potential consequences of antibiotic overuse and misuse, as they contribute to the growing issue of antimicrobial resistance (20). The role of antibiotics in preventing DS and the underlying mechanisms involved require further research and clarification to establish more definitive recommendations in dental practice (5).

As anticipated, the presence of pain emerged as a significant marker for DS development in our study. The severity of pain experienced by patients may be attributed to the upregulation of TNF-α, a pro-inflammatory cytokine known to play a role in the delayed healing process. Studies have shown that elevated levels of TNF-α are associated with reduced bone formation and heightened pain perception, therefore, the intense pain reported by individuals with DS could be attributed, at least in part, to the increased expression of TNF-α and its impact on bone healing processes (6).

The presence of various risk factors associated with DS, such as gender, habits (e.g., smoking), surgical complexity, and the potential role of the microbiota, highlights the multifactorial nature of this inflammatory complication. While the exact etiology or the pathophysiology of DS remains unclear, the findings from this study support the notion that DS is a complex condition influenced by multiple factors.

- Study Limitations

The study may have limitations that should be considered. Firstly, the occurrence of dry socket (DS) was relatively low, which may limit the statistical power and precision of the findings. Additionally, the prescription of antibiotics for some patients could have influenced DS development to some extent. As an observational study, the findings are based on associations rather than causation. Unmeasured confounding factors, such as the use of antiseptics, could potentially have influenced the occurrence of dry socket.

Conclusions

In conclusion, our study involving 1,357 patients undergoing routine dental extractions revealed a 1% prevalence of dry socket. The obtained results suggests that DS is a multifactorial condition influenced by various factors, including gender, age, smoking, antibiotic prescription and surgical factors such as length, technique and accidents, nevertheless, those associations were observed mainly considering the influence of one variable on another.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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Appendix file

Table 4. Epidemiological data of the study including the proportions and distributions of dental extractions and the development of dry socket (DS) (n. 1,357).

Variable		**Extractions (%)**	**DS**
Sex	Male	714 (52.6%)	4
	Female	643 (47.4%)	9
Age	DS mean age	34.7 (mean age/extraction)	-
	Non-DS mean age	41.2 (mean age/extraction)	-
Ethnicity	Ethnically diverse white	1,046 (77%)	10
	African-Brazilian and non-white mixed	232 (17%)	2
	Native-Brazilian (Indian)	13 (1%)	0
	Other	66 (4.8%)	1
Reporting systemic disease	Yes	277 (20.4)	1
	No	1,080 (79.5)	12
Smoking	Yes	299 (22%)	2
	No	1,058 (78%)	11
Alcohol	Weekly	211 (15.5%)	1
	Not-Frequent	1,146 (84.5%)	12
Mate Tea (*Ilex paraguariensis*)	Weekly	667 (49.1%)	4
	Not-Frequent	690 (50.9%)	9
Contraceptive (only women)	Using	179 (13.2% of total)	4
	Not using	464 (34.2% of total)	5
Menstrual cycle (bleeding) (only women)	Yes	36 (2.6% of total)	0
	No	607 (44.7% of total)	9
Amount of teeth removed	1	1,023 (75.4%)	13
	2	247 (18.2%)	0
	3	87 (6.4%)	0
Surgical time (in minutes)	DS mean surgical time	46.3 (minutes/extraction)	-
	Non-DS mean surgical time	41.9 (minutes/extraction)	-
Surgical flap	Yes	411 (30.3%)	6
	No	946 (69.7%)	7
Odontosection	Yes	183 (13.5%)	6
	No	1,174 (86.5%)	7
Ostectomy	Yes	172 (12.7%)	4
	No	1,185 (87.3%)	9
Surgical Complexity	0	859 (63.3%)	3
	1	292 (21.5%)	5
	2	144 (10.6%)	4
	3	62 (4.6%)	1
Surgical accidents	Yes	102 (7.5%)	2
	No	1,255 (94.5%)	11
Amount of local anesthetics with vasoconstrictors	Up to 5.4 mL (3 cartridges)	1,235 (91%)	9
	More than 5.4 mL	122 (9%)	4
Antibiotics	Yes	156 (11.5%)	1
	No	1,201 (88.5%)	12
Pain	No Pain	865 (63.7%)	0
	Mild Pain	317 (23.4%)	0
	Moderate Pain	155 (11.4%)	6
	Severe Pain	20 (1.5%)	7
Pain endurance	Pain which persisted for more than 2 days	143 (10.5%)	13
	Pain which last up to 2 days	1,214 (89.5%)	0

Table 5. Statistical Associations and Odds Ratios for Dry Socket (DS) using Bivariable Analysis, Controlled (Chi Square Test with Layers, x2), or Mediated (General Linear Mediation Model, GLMM) by Additional Variables (n=1,357).

Variable		**DS Assoc.**	**Odds Ratio for DS**	**Variable for DS, controlled by**	**DS Assoc.**	**Odds Ratio for DS**
Sex	Male/Female	*p* =.11	Female= 2.5	Sex ***Layered by*** Odontosection	***p* =.050**	Female= 6.6
Female (only)	Contraceptive	*p* =.45	Yes= 2.1	NP	NP	NP
Age		*p* =.13	NP	Age ***Mediated by*** Sex	*p* =.18	NP
Systemic Disease -SD	Yes/No	*p* =.25	No = 3.1	SD ***Layered by*** Smoking	*p* =.23	Smoking= 0.95
Contraceptive	Yes/No	*p* =.06	Yes= 2.9	Contraceptive ***Layered by*** Odontosection	***p* =.004**	Odontosection yes= 8.3
Menstrual cycle (bleeding)	Yes/No	*p* =.55	No= 1.3	Menstrual cycle ***Layered by*** Smoking	*p* =.80	Smoking = 6.0
Smoking	Yes/No	*p* =.74	No= 1.5	Smoking ***Layered by*** Complex Surgery (3 points in the scale)	***p* =0.01**	NP
Surgical Time (ST)	Scalar	*p* =.58	NP	ST ***Mediated by*** Complex Surgery	***p* =.006**	NP
Odontosection	Yes/No	***p* <.001**	Yes= 5.6	Odontosection ***Layered by*** use of contraceptive	***p* <.001**	Contraceptive use= 24.6
Ostectomy	Yes/No	***p* =.048**	Yes= 3.1	Ostectomy ***Layered by*** sex	***p* <.001**	Male= 19.1
Surgical Complexity (SC)	Ordinal	***p* =.002**	NP	SC ***Layered by*** Age 50 years up or down	***p* =.016**	NP
Amount of local Anesthetics with vasoconstrictors (tubes of 1.8 ml)	Up to 3 tubes/ More than 3 tubes	***p* =.005**	More than 3= 4.6	Amount of anesthetic ***Layered by*** Tobacco amount (More than 20 cigarettes day)	***p* =.03**	NP
Surgical Accidents (SA)	Yes/No	*p* =.28	Yes= 2.2	SA ***Layered by*** Tobacco amount	***p* =.004**	More than 20 cigarettes day= 27.6
Antibiotics prescription (AP)	Yes/No	*p* =.66	Yes= .63	AP ***Layered by*** Complex Surgery (3 points in the scale)	*p* =.53	More complex surgery= .84

NP= Test not performed or does not apply. DS= Dry Socket. Mediated by = GLMM. Layered by = x^2.