Hematological changes associated with the use of dipyrone versus paracetamol after dental extractions: a double-blind randomized clinical trial.

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Study Design:

This is a double-blind, randomized clinical trial with a split-mouth crossover design, in which each of the 50 participants will undergo two bilateral dental extractions at different time points, with a minimum interval of 21 days between them. Participants will receive dipyrone during one period and paracetamol during the other for postoperative pain control, thus serving as their own controls.

Abstract:

Introduction: Dipyrone is widely used in Dentistry to control postoperative pain, particularly after low- and moderate-complexity tooth extractions. Among its adverse effects, agranulocytosis stands out as an idiosyncratic reaction that is not necessarily dependent on dose or duration of exposure. It is characterized by severe neutropenia (<500 cells/mm³) and may predispose patients to severe or fatal infections. For this reason, the drug has not been approved for clinical use in the United States. Paracetamol is a notable analgesic alternative, widely accepted because of its more stable hematological profile, although it is associated with hepatotoxicity in cases of overdose. Objective: To compare hematological changes associated with the use of dipyrone and paracetamol in the postoperative period of patients undergoing dental extractions. Materials and methods: A double-blind, randomized clinical trial with a split-mouth crossover design involving 50 patients undergoing two dental extractions at different time points, with no specific tooth predetermined for extraction, so that each procedure serves as a control for the other. Surgeries will be performed at least 21 days apart. Each participant will receive paracetamol (750 mg) during one period and dipyrone (500 mg) during the other, serving as their own control. Blood samples will be collected preoperatively and on the eighth postoperative day after each intervention. A complete blood count and biochemical parameters will be assessed, including aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, creatinine, and urea. Participants will be monitored for pain progression, blood pressure changes, adverse reactions, and analgesic preference. Expected results: Possible hematological changes associated with the use of dipyrone and paracetamol for postoperative pain management after dental extractions are expected to be identified.

Keywords:

Dipyrone; Paracetamol; Hematological tests.

Introduction (Literature Review):

Dipyrone (metamizole) is a drug with recognized analgesic and antipyretic properties, widely used in several countries to control acute pain and fever. Despite its established clinical efficacy, its use remains controversial because of its association with agranulocytosis, a rare but potentially fatal adverse reaction described in classic epidemiological studies such as the International Agranulocytosis and Aplastic Anemia Study (1986) and later discussed by Hedenmalm and Spigset (2002). For this reason, it was withdrawn from the market in countries such as the United States in the 1970s, although it remains widely marketed in Latin America and Europe (Fidelis et al., 2025). In Brazil, it is available in several pharmaceutical forms—oral solution, syrup, injectable solution, tablets, and suppositories—and is classified as an over-the-counter

medication (Knappmann, Melo, 2010). Its widespread availability reinforces the need for monitoring its hematological safety.

As a therapeutic alternative, paracetamol (acetaminophen) is noteworthy as an analgesic and antipyretic with a profile considered more stable from a hematological standpoint. It is widely available on the market, inexpensive, and frequently dispensed without a prescription, making it a common choice in several clinical settings. Under normal conditions of use (up to 3–4 g/day in adults), it is well tolerated. The main safety concern regarding its use is dose-dependent hepatotoxicity, widely described in the literature, particularly in cases of overdose or cumulative use in patients with other risk factors (Tsang, Chan, Tse, 2024).

Recent clinical studies with laboratory monitoring have shown that the use of certain analgesics may be associated with hematological and biochemical changes detectable in serial tests, even in healthy individuals (Blaser et al., 2021; de Souza et al., 2018; Zinzi et al., 2025). These changes may involve variations in leukocyte, hemoglobin, hematocrit, and platelet levels, as well as changes in other complete blood count parameters, which, although generally mild and transient, may reflect individual biological responses to the drugs administered. In addition, changes in biochemical markers, such as liver enzymes and indicators of renal function, have been described both during therapeutic use and in situations involving greater exposure or individual susceptibility, reinforcing the relevance of laboratory monitoring, particularly in surgical settings.

To date, no clinical trials have been identified that use paracetamol as a comparator drug when analyzing possible hematological changes induced by dipyrone in individuals undergoing tooth extractions. Considering that dental extractions are among the most frequently performed procedures in Dentistry and that these drugs are widely prescribed for postoperative pain control, investigating their laboratory impact is relevant (Andrade, 2006). Therefore, this research is justified by the need to produce clinical evidence to support safer therapeutic decisions, contributing to the rational use of analgesics and the reduction of potential risks associated with postoperative pain management in Dentistry.

Hypothesis:

Dipyrone is associated with a greater number of hematological changes than paracetamol in the postoperative period following dental extractions.

Primary Objective

To identify hematological changes associated with the use of dipyrone and paracetamol in the postoperative period of patients undergoing dental extractions.

Secondary Objective

To compare hematological changes associated with the use of dipyrone and paracetamol in the postoperative period of patients undergoing dental extractions, as well as to assess biochemical parameters related to liver and kidney function, the occurrence of adverse reactions, and possible blood pressure changes during the postoperative period.

Proposed Methodology:

The study will involve 50 participants undergoing dental extractions. Recruitment will be continuous and based on the spontaneous demand of patients attending the Oral and Maxillofacial Surgery Clinic of the UFJF School of Dentistry who require bilateral extractions in similar anatomical positions (contralateral anterior or posterior teeth). Participants will be invited in person by the researchers, who will explain the study and provide the Informed Consent Form (ICF). Secondary data from medical/dental records, such as medical history and radiographs, will be used after the ICF has been signed.

After providing consent, participants will be allocated to the test group (dipyrone) or control group (paracetamol) using Random Allocation Software 2.0. The medications will be prepared by a compounding pharmacy registered with ANVISA and funded by the researchers. The capsules will have similar appearance, odor, and taste. They will be dispensed by the researchers in coded containers according to the randomization sequence, with no external identification of their contents, ensuring participant and researcher blinding and allocation concealment. At the end of the study, the integrity of blinding will be assessed.

Tooth extractions will be performed by undergraduate students under the planning and supervision of the faculty researcher, following a standardized clinical protocol. The supplies required for the surgeries will be provided by the UFJF clinic, as they are part of the institution's routine care. Two 3.6-mL cartridges of 2% lidocaine hydrochloride with 1:100,000 epinephrine will be used in a standardized manner for the pterygomandibular and buccal nerve blocks. The surgical record will include the type of dental impaction (Pell and Gregory, 1933) and the degree of surgical difficulty (Pozos et al., 2006).

On one side, patients will receive 750 mg of paracetamol immediately after surgery (control group). On the contralateral side, they will receive 500 mg of dipyrone (test group). They will be instructed to take these medications every 6 hours for 7 days. If the pain becomes unbearable, they should replace these medications with rescue medication (30 mg of codeine phosphate combined with 500 mg of paracetamol). These participants will not be excluded from the statistical analysis, in accordance with the intention-to-treat (ITT) principle. At home, patients will record: the time when soft-tissue anesthesia wears off; pain progression, using the Visual Analog Scale, assessed immediately and at 2, 24, 48, 72, 96, 120, 144, and 168 hours after the end of surgery; blood pressure changes; adverse reactions; and the side with better recovery.

Three blood samples will be collected: before the first tooth extraction; on the 8th postoperative day after the first surgery; and on the 8th postoperative day after the contralateral surgery. The blood collection on the 8th postoperative day is scheduled because the 7-day medication course will have ended, allowing hematological changes to be assessed at the end of exposure, as described by De Souza et al. (2018), and in parallel with the study designs of Watkins et al. (2006) and Blaser et al. (2021). Stamer et al. (2017) provides no evidence that later blood collections are superior for the purpose of this research. Blood collection and laboratory analyses will be performed by a qualified private company hired by the researchers, at no cost to participants. The complete blood count will be analyzed, including red blood cell parameters, white blood cell count, and platelet count, in addition to liver and kidney function tests through measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, creatinine, and

urea. Results will be compared within each patient and between the different groups. Blood samples will preferably be collected at participants' homes. If this is not possible, transportation to the laboratory and reimbursement of transportation expenses will be provided.

The clinical trial will be registered on ClinicalTrials.gov before recruitment.

Inclusion Criteria:

Healthy patients of both sexes, aged 18 to 60 years, with an indication for bilateral tooth extraction in similar positions.

Exclusion Criteria:

Patients with a history of allergy to dipyrone or paracetamol. Patients whose forms contain insufficient or improperly completed data. Patients who do not return for the second tooth extraction. Patients who report the use of warfarin, bupropion, efavirenz, methadone, cyclosporine, tacrolimus, sertraline, valproate, methotrexate, acetylsalicylic acid, as well as other nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and corticosteroids used continuously (for a period of 7 days or longer) before surgery. Patients with systemic conditions that may interfere with hematological outcomes, such as diagnosed hematological diseases, coagulopathies, severe liver or kidney diseases, and active autoimmune diseases at the time of care.

Risks:

The risks involved in this research are foreseeable and classified as minimal because they arise exclusively from the additional procedures performed for research purposes and do not include risks related to dental treatment, which would be indicated regardless of participation in the study.

Blood collection may cause discomfort, mild pain, bruising, bleeding, dizziness, or malaise. Occupational risks associated with handling sharp instruments must also be considered. Therefore, blood samples will be collected by a qualified professional familiar with biosafety standards and responsible for managing any complications. Possible hematological changes will be monitored through a complete blood count, with special attention to leukocyte, neutrophil, hemoglobin, and platelet counts, based on the reference values for the tests. The researchers responsible will communicate the test results to participants in person during the scheduled study follow-up visits or, when necessary, by telephone, as soon as the laboratory results are released. If relevant hematological changes are identified, the participant will be examined and referred for specialized medical care when necessary, in accordance with National Health Council Resolution No. 466/2012, item IV.3.

The risk of a breach of confidentiality will be minimized by coding participants' data. These data will be stored in password-protected digital files. Physical documents will be kept in a secure institutional environment, with access restricted to the researchers responsible, and used exclusively for scientific purposes related to the research, in accordance with Law No. 13,709/2018 (Brazilian General Data Protection Law – LGPD). When necessary for the conduct of the research, data may be shared exclusively among members of the

research team, while remaining coded and protected by access controls to ensure confidentiality, integrity, and security, in accordance with the guidelines of Official Circular Letter No. 02/2021/CONEP. All information will be stored for a minimum of 5 years after the end of the study. After this period, the data may be deleted, anonymized, or retained when necessary to comply with legal or regulatory obligations or to exercise rights, as provided for in Articles 15 and 16 of Law No. 13,709/2018 (LGPD). All participants will be informed in advance about the objectives, procedures, risks, and benefits of the research and will participate only after signing the ICF, also in accordance with National Health Council Resolution No. 466/12.

Benefits:

The research may provide potential direct benefits to participants through the clinical and laboratory monitoring performed during the study, including blood tests before and after the surgical procedures, contributing to the early identification of possible hematological, hepatic, or renal changes. Participants will be informed of their test results as soon as the analyses have been completed and, if clinically relevant changes are identified, they will receive guidance and be referred for specialized medical care when necessary. Furthermore, the study results may expand scientific knowledge about the hematological safety of dipyrone in the dental setting, particularly in comparison with paracetamol, providing relevant evidence to support evidence-based clinical decision-making. Thus, in the medium and long term, the findings may benefit healthcare professionals and patients undergoing dental surgery by contributing to the safer and more rational use of analgesics in the dental postoperative period.

Data Analysis Methodology:

The study design followed the model of a double-blind, randomized, two-period, two-sequence (AB/BA) crossover clinical trial.

The sample size was calculated using G*Power software, version 3.1.9.7, considering a crossover design with paired measurements, a medium effect size ($d = 0.5$), a 5% significance level ($\alpha = 0.05$), and 90% statistical power ($1-\beta = 0.90$), resulting in a minimum sample of 44 participants completing the protocol in full. However, 50 participants will be recruited (25 per sequence), allowing for an approximate 14% margin to compensate for possible follow-up and methodological losses resulting from withdrawals, non-adherence to the protocol, failure to comply with the washout period, or technical infeasibility of laboratory samples, thereby ensuring that the study's statistical power is maintained.

The data will be analyzed according to the intention-to-treat (ITT) principle. Randomization, generated by an independent researcher using a computerized random-number table, will be kept in a sealed envelope until the final data analysis.

Continuous variables will be summarized using the mean and standard deviation (for normally distributed data) or the median and interquartile range (for non-normally distributed data). Normality will be assessed using the Shapiro–Wilk test and visual inspection of Q–Q plots. Categorical variables will be described using absolute and relative frequencies.

A Linear Mixed-Effects Model will be used to compare the effects of the treatments (dipyrone vs. paracetamol) on hematological, hepatic, and renal parameters. This model will include the administered treatment, study period (1

or 2), and allocation sequence (AB or BA), as well as the treatment-by-period interaction, as fixed effects. The participant-specific random effect will be included to account for the correlation between repeated measurements from the same individual. This will be the main analysis to test the hypothesis of equivalence or difference between the drugs, controlling for potential period effects and indirectly assessing the presence of a carryover effect through the significance of the treatment-by-period interaction. If the model assumptions are not met, data transformation or an equivalent nonparametric analysis (Wilcoxon signed-rank test for paired samples) will be used.

Treatment safety will be assessed by comparing the incidence of adverse events between the dipyrone and paracetamol periods, using Fisher's exact test for independent data or McNemar's test for paired events, depending on the nature of the data. Blood pressure and surgical complications will be compared between periods using paired t-tests or equivalent nonparametric tests.

The effectiveness of the 21-day washout period will be assessed by comparing baseline (pre-surgery) values from the first and second periods using a paired t-test. Treatment adherence will be calculated as the percentage of capsules taken relative to the number prescribed and will be considered adequate if ≥85%.

All analyses will be conducted using the R statistical software, version 4.3.1 (R Foundation for Statistical Computing), with the lme4 package for mixed-effects models and ggplot2 for visualization. A p-value <0.05 will be considered statistically significant. For multiple laboratory outcomes, results will be interpreted with caution, and a Bonferroni correction will be applied to the predefined primary outcomes.

Primary Outcome:

Change in complete blood count parameters (total leukocyte count, neutrophils, hemoglobin, hematocrit, and platelets) between the preoperative period and the eighth postoperative day following the use of dipyrone or paracetamol.

Secondary Outcome:

Difference in the changes in complete blood count parameters (total leukocytes, absolute neutrophils, hemoglobin, hematocrit, and platelets) between the dipyrone and paracetamol treatment periods, considering the difference between preoperative values and those obtained on the eighth postoperative day, as well as biochemical parameters related to liver and kidney function (AST, ALT, GGT, alkaline phosphatase, creatinine, and urea), the occurrence of adverse reactions associated with the use of the medications, and possible blood pressure changes recorded during the postoperative period.

Sample Size in Brazil:

50.

Will secondary data sources (medical/dental records, radiographs, demographic data, etc.) be used?

(X) Yes ( ) No

Please provide the number of individuals who will be approached in person, recruited, or undergo any type of intervention:	Number: 50

Groups into which the study participants will be divided

Group	No. of participants	Interventions to be performed
Group A (Paracetamol – Dipyrone)	25	Participants will undergo tooth extraction and use paracetamol postoperatively, followed by a 21-day washout period and, subsequently, a new tooth extraction with dipyrone use. Blood samples will be collected and clinical assessments performed according to the study protocol.
Group B (Dipyrone – Paracetamol)	25	Participants will undergo tooth extraction and use dipyrone postoperatively, followed by a 21-day washout period and, subsequently, a new tooth extraction with paracetamol use. Blood samples will be collected and clinical assessments performed according to the study protocol.

Implementation Schedule:

Stage	Start (DD/MM/YYYY)	End (DD/MM/YYYY)
Submission and review of the project by the Research Ethics Committee (CEP)	20/08/2026	30/09/2026
Implementation of the methodology	01/10/2026	31/07/2027
Interpretation and analysis of results	15/09/2027	30/11/2027
Manuscript writing	01/12/2027	31/01/2028

Financial Budget:

Item	Quantity	Amount in Brazilian Reais (R$)
Compounded medications (dipyrone + paracetamol)	50 kits (1 per participant)	3.650,00

A4 paper and photocopies (printing of the ICF)	100 sheets and copies	200,00
Blood collection and laboratory tests (including collection logistics and transportation reimbursement when necessary)	150 collections (3 per participant)	10.500,00
Surgical masks	2 boxes	30,00*
Surgical gowns	100 units	300,00*
Silk suture thread	2 boxes	100,00*
Scalpel blades	1 box	50,00*
Disposable caps	100 units	15,00*
Anesthetic (lidocaine)	2 boxes	400,00*
Surgical gloves	2 boxes	100,00*
Surgical drapes	100 units	350,00*

*The dental supplies used in the surgical procedures are provided by the Oral and Maxillofacial Surgery Clinic of the UFJF School of Dentistry, as they are part of the institution's routine care and therefore do not represent additional financial costs to the researchers or participants.

Funding:

Funded by the researchers.

Is a waiver of the Informed Consent Form (ICF) requested?

( ) Yes (X) No

Will samples be retained for storage in a biobank?

( ) Yes (X) No