

# Comparative effect of sodium dipyrone and sodium dipyrone associated to caffeine to control post-tooth extraction pain\*

*Efeito comparativo entre a dipirona sódica e a dipirona sódica associada à cafeína no controle da dor pós-exodontia*

Carllini Barroso Vicentini<sup>1</sup>, Juliana Cama Ramacciato<sup>2</sup>, Rubens Gonçalves Teixeira<sup>2</sup>, Francisco Carlos Groppo<sup>3</sup>, Rogério Heládio Lopes Motta<sup>2</sup>

\*Received from the School of Dentistry São Leopoldo Mandic. Campinas, SP.

## ABSTRACT

**BACKGROUND AND OBJECTIVES:** Adequate postoperative pain control is a challenge among surgical specialties, in spite of recent advances in analgesic techniques and analgesics. Caffeine has been used as therapeutic adjuvant to potentiate analgesic efficacy of some drugs, however there are still no scientific investigation reports on the association with sodium dipyrone in the postoperative period of dental procedures. So, this study aimed at observing and comparing the efficacy of sodium dipyrone alone or in association with caffeine to control postoperative pain of dental procedures, considering hemodynamic parameters of patients as indicators of anxiety and pain during surgery.

**METHODS:** This is a crossover and double-blind study involving 50 young and healthy patients (25 males and 25 females) referred for bilateral extraction of impacted mandibular third molars. Operated side, patient's gender and analgesic drug used were randomized. Visual analog scale scores were submitted to Friedman test ( $\alpha = 0.05$ ) to compare pain intensity at defined intervals (preoperative, immediate postoperative, 1, 2, 4 and 12 hours, 1, 2, 3 and 7 days after surgery). Blood pressure and heart rate were measured in the preoperative period, after anesthetic injection and in the postoperative period (Friedman test,  $\alpha = 0.05$ ).

**RESULTS:** Patients have referred mild pain in the first two postoperative days and there has been no statistically significant difference between the analgesic efficacy of sodium dipyrone alone or in association with caffeine in different evaluated intervals. Most cardiovascular changes were within normality, considering anxiety and stress induced by surgery.

**CONCLUSION:** The therapeutic protocol proposed in this

study has not shown statistically significant difference between sodium dipyrone associated or not to caffeine to control post-tooth extraction pain.

**Keywords:** Caffeine, Dipyrone, Pain, Third molar, Tooth extraction.

## RESUMO

**JUSTIFICATIVA E OBJETIVOS:** O adequado controle da dor pós-operatória constitui um desafio entre as especialidades cirúrgicas, a despeito dos recentes avanços das técnicas de analgesia e dos analgésicos. A cafeína tem sido utilizada como adjuvante terapêutico para potencializar a eficácia analgésica de alguns fármacos, porém ainda não existe relatos de investigação científica da associação com a dipirona sódica em dor pós-operatória em procedimentos odontológicos. Dessa forma, o objetivo deste estudo foi observar e comparar a eficácia da dipirona sódica isolada e da dipirona sódica associada à cafeína no controle da dor pós-operatória em cirurgia dental, considerando os parâmetros hemodinâmicos dos pacientes como indicador de ansiedade e de dor durante a cirurgia.

**MÉTODOS:** Estudo cruzado e duplo encoberto incluiu 50 pacientes jovens e saudáveis (25 homens e 25 mulheres) com indicação de exodontia bilateral de terceiros molares mandibulares impactados. O lado operado, o gênero do paciente e o fármaco analgésico usado foram randomizados. Os escores obtidos pela escala analógica visual, foram submetidos ao teste de Friedman ( $\alpha = 0,05$ ) para comparação das intensidades dolorosas em intervalos definidos (pré-operatório, pós-operatório imediato, 1, 2, 4 12 horas, 1, 2, 3 e 7 dias após as cirurgias) e as alterações nos parâmetros de pressão arterial e frequência cardíaca foram mensurados no pré-operatório, após a injeção anestésica e no pós-operatório (teste de Friedman,  $\alpha = 0,05$ ).

**RESULTADOS:** Os pacientes experimentaram dor leve nos dois primeiros dias de pós-operatório e não houve diferença estatisticamente significativa entre a eficácia analgésica da dipirona sódica isolada e da dipirona sódica associada à cafeína nos diferentes intervalos medidos. A maioria das alterações cardiovasculares observadas estava dentro da normalidade, considerando a ansiedade e estresse induzido pela cirurgia.

**CONCLUSÃO:** O protocolo terapêutico proposto neste estudo não demonstrou diferença estatística significativa na eficiência analgésica da dipirona sódica associada ou não a cafeína no controle da dor pós-exodontia.

**Descritores:** Cafeína, Dipirona, Dor, Exodontia, Terceiro molar.

1. Tocantinense Institute Presidente Antonio Carlos. Porto Nacional, TO, Brazil.  
2. School of Dentistry São Leopoldo Mandic. Campinas, SP, Brazil.  
3. State University of Campinas; School of Dentistry. Piracicaba, SP, Brazil.

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Correspondence to:  
Rogério Heládio Lopes Motta  
Rua José Rocha Junqueira, 13  
13414-903 Campinas, SP  
E-mail: rogeriomotta@yahoo.com

## INTRODUCTION

Pain is a major biological phenomenon for body's defense, however it is uncomfortable for patients. It is inherent to some dental procedures, especially surgical procedures such as third molar extraction, being its intensity related to surgery extension<sup>1,2</sup>.

Impacted third molar extraction surgery in general produces moderate to severe postoperative discomfort due to the release of chemical inflammatory mediators caused by the manipulation of soft, bone and dental tissues. Post-oral surgery pain has major impact on patients' quality of life and has potential effect on physiological parameters variation, thus needing effective control<sup>3-5</sup>.

Sodium dipyrone is usually indicated to control postoperative pain, with satisfactory results due to its peripheral action mechanism which is different from other analgesic drugs. Dipyrone seems to act by desensitizing peripheral nociceptors, with direct inflammatory hyperalgesia block. This desensitizing mechanism probably involves potassium channels block and nitric oxide-FMPC pathway activation in the nociceptor<sup>6-8</sup>. However, there are few studies evaluating its clinical efficacy for dental surgical procedures, be it alone or in association<sup>3</sup>.

Caffeine has been reported as adjuvant drug when combined to analgesics and anti-inflammatory drugs to control tension pain and migraine<sup>9-11</sup>. Caffeine antinociceptive effect occurs by the blockade of adenosine receptors, which are important for nociceptors sensitization in pain signal transmission. Caffeine also changes cyclooxygenase enzymes activity in certain sites, improving the analgesic action of several drugs indicated to control acute and chronic pain<sup>12-15</sup>.

Considering the need for adequate postoperative pain control after impacted third molar extraction, and the effectiveness of the synergistic association of caffeine to analgesic and anti-inflammatory drugs to treat acute and chronic pain in other body regions, we question caffeine's adjuvant effect with sodium dipyrone to control pain in a dental clinical model<sup>16-19</sup>. This study aimed at evaluating the clinical relevance of caffeine associated to sodium dipyrone to control postoperative pain of impacted third molar surgeries, considering patients' hemodynamic parameters control.

## METHODS

This is a crossover, randomized and double-blind study carried out between May and December 2011, with a sample of 50 patients of both genders (25 males and 25 females), aged between 18 and 25 years, without systemic changes that would contraindicate surgical procedures. All volunteers had indication for bilateral lower third molars extraction, with similar impaction patterns according to Pell & Gregory (Class I and II and position B) and Winter (Vertical and Mesio-angulated) classification<sup>20</sup>. A clinical card was developed for data collection were data on patient's identification, medical and dental history, results of preoperative exams (X-Rays, red

blood cells count, leukocytes count, coagulation time, renal and hepatic function), surgery date and time, operatory time, operated side during the session, number of needed anesthetic tubetes, group of analgesic drug used during the session and hemodynamic parameters were recorded.

For adequate patients' control and higher fidelity of results, a randomized clinical trial was proposed (generated at [www.randomization.com](http://www.randomization.com)) for the operated side, patient's gender and analgesic therapy used, based on items 8 to 10 of the 2001 Cochrane Collaboration, Manchester, UK checklist (CONSORT)<sup>21</sup>. Postoperative analgesic therapy protocol was divided in two study groups: Group 1 – tablet of 500 mg sodium dipyrone (Magnopyrol®, São Paulo, Brazil) and Group 2 – tablet of 500 mg sodium dipyrone associated to 65 mg caffeine (Cafilisador®, São Paulo, Brazil), double-blindly distributed, being the identification of groups disclosed to the surgeon and to patients only after collection of results.

All volunteers were submitted to two surgical procedures by the same surgeon with proven experience and with interval of 21 days between them<sup>22</sup>. This crossover (Split-mouth) study has determined that during each surgery the same patient would receive one proposed analgesic technique – sodium dipyrone alone for one surgery and sodium dipyrone associated to caffeine for the other.

For each surgical procedure, patients received 1 g amoxicillin (Amoxil®, Rio de Janeiro, Brazil) and 4 mg dexamethasone (Decadron®, Campinas, Brazil) one hour before surgery. Patients were asked to vigorously mouthwash with 0.12% chlorhexidine (Proderma®, Piracicaba, Brazil) for 1 minute, went through extraoral antiseptis with 2% chlorhexidine (Proderma®, Piracicaba, Brazil) and received postoperative recommendations about diet, rest and oral hygiene<sup>23</sup>.

For tooth extraction, routine materials and tools needed for this surgical practice were used, in addition to strict compliance with asepsis principles. Anesthetic block was induced in lower alveolar, lingual and buccal nerves with 2% lidocaine with 1:100.000 epinephrine (Alphacaine®, Rio de Janeiro, Brazil)<sup>24</sup>. Sulcular incision was made with knife blade 15 (MedGoldman®, São José, Brazil) and after detachment a mucoperiosteum flap was obtained. Osteotomy and dental section were performed with rotary tool and abundant sterile saline irrigation. Nylon thread 3.0 (Polysuture®, São Sebastião do Paraíso, Brazil) was used for suture.

After surgery, all patients have received a bottle with eight 500 mg sodium dipyrone tablets (Group 1) or 500 mg sodium dipyrone associated to 65 mg caffeine (Group 2) and an oral prescription every 6 hours for two days. Volunteers were evaluated in return consultation at 1, 2 and 7 postoperative days and were oriented not to use any other drug class.

Hemodynamic systolic and diastolic blood pressure and heart rate parameters were measured with gauged digital equipment (G-Tech®, Providencie, U.S.A), were recorded and compared in different periods (preoperative, post-anesthetic, surgery completion, second and seventh postoperative days)<sup>25</sup>.

Pain was evaluated with the visual analog scale (horizontal 100-mm line) printed on 10 pages of a booklet with filling

guidelines on the cover. Each page of this booklet represented one pain measurement moment (preoperative, immediate postoperative, 1, 2, 4 and 12 hours, 1, 2, 3 and 7 postoperative days). Patients were oriented to mark the horizontal line at the point related to their pain intensity, being zero no pain and 10 the worst possible pain<sup>2,5,26</sup>.

Volunteers were oriented to personally deliver the booklet with filled visual analog scales in the return consultation at 7 postoperative days. Their pain intensity marks were then measured with gauged digital caliper rule (Pantec®, São Bernardo do Campo, Brazil), considering the distance from the zero mark to the point recorded by patients in every measurement moment. All volunteers have filled the booklet according to investigator's orientation and at determined times, and have returned the postoperative evaluation when requested. In addition, volunteers were daily followed up by telephone.

All patients were informed about the objectives of the research and have signed the Free and Informed Consent Term (FICT).

### Statistical analysis

This study has used descriptive statistics techniques through absolute and percentage distributions and inferential statistical methods. Paired t test, Wilcoxon test and Friedman test were used with significance level of 5% and calculations were obtained with the software BioEstat 5.0 (Mamirauá Foundation, Belém, PA).

This study was approved by the Ethics Committee for Research with human beings, Dental Research Center and School of Dentistry São Leopoldo Mandic (Process 2010/0124), in compliance with the Declaration of Helsinki and Resolution 196/1996.

## RESULTS

No adverse effect was reported in the two studied periods. Among observed patients, none had to use analgesics for more than 48 hours or to use other support analgesics. All volunteers have returned for evaluation consultations and no complications were recorded.

Data analysis has shown that surgery duration was not influenced (paired t test) by the operated side ( $p = 0.0846$ ), by the order of surgeries ( $p = 0.4537$ ) or by gender ( $p = 0.0548$ ). Surgery duration has also not differed between treatments ( $p = 0.2449$ ), as shown in Figure 1. In addition, it was possible to observe that mean time needed for surgery was below 45 minutes, both when dipyrone was used alone ( $36.3 \pm 4.6$  min) and when associated to caffeine ( $37.4 \pm 5.8$  min) (Figure 1). Similarly, the number of anesthetic tubetes used was not influenced (Wilcoxon test) by the operated side ( $p = 1.0000$ ), order of surgeries ( $p = 0.2622$ ), gender ( $p = 0.332$ ) and treatments ( $p = 0.2622$ ), being that in 94% of surgeries under dipyrone and in 86% of those under dipyrone associated to caffeine three tubetes were used. Remaining surgeries used four tubetes.

There has been significant increase (Friedman test,  $p < 0.05$ )

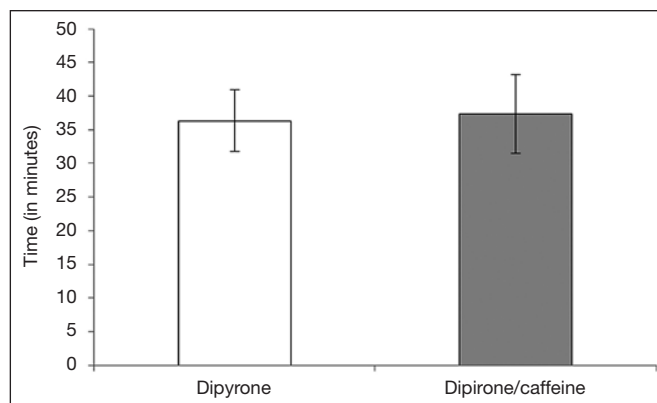


Figure 1 – Surgery duration (mean  $\pm$  standard deviation) as a function of treatments used.

in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the period “after anesthesia” as compared to remaining periods, for both treatments. However, the comparison (Wilcoxon test) between SBP and DBP obtained for both treatments has shown no statistically significant differences ( $p > 0.05$ ) in any evaluated period (Figure 2).

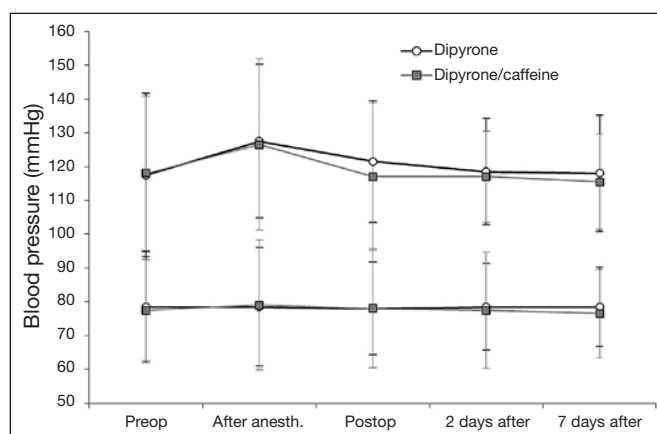


Figure 2 – Median  $\pm$  interquartile deviation of systolic blood pressure (upper lines) and diastolic blood pressure as a function of treatments.

Figure 3 shows heart rate (HR) behavior along studied periods. Data analysis (Friedman test) has shown significant HR increase ( $p < 0.05$ ) in the period “after anesthesia” for both treatments, being that such increase has remained in the immediate postoperative period, returning to baseline values in following periods. There have been no statistically significant differences (Wilcoxon test) between treatments considering each studied time period separately.

It has been observed that mean pain levels remained below 30 mm for both treatments in all periods, thus showing the efficacy of both treatments which had identical behavior with regard to reported pain during the period. There has been significant pain increase (Friedman,  $p < 0.05$ ) from the immediate postoperative period to one day, when values returned to baseline levels (Figure 4).

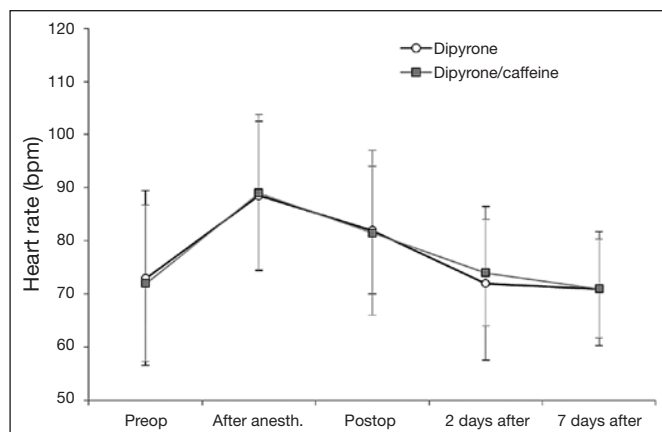


Figure 3 – Median  $\pm$  interquartile deviation of heart rate as a function of treatments.

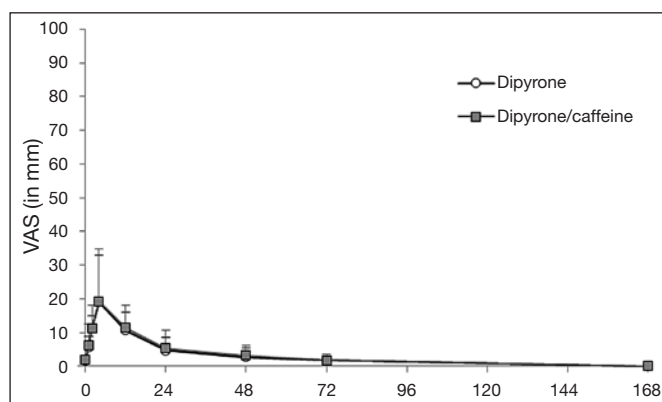


Figure 4 – Median  $\pm$  interquartile deviation of visual analog scale scores as a function of treatments and periods of time.

## DISCUSSION

Pain is an expected physiological phenomenon during dental surgeries and is related to nociceptors sensitization and inflammatory mediators release at tissue injury produced by surgical procedures. Similar studies to our research have observed that pain measurement by the visual analog scale in the postoperative period of impacted teeth surgery corresponds to the clinical model more commonly used and broadly accepted to evaluate the effect of analgesic drugs in Dentistry<sup>1-5,26</sup>.

Pain induced by impacted third molar extraction surgery may be influenced by several factors, such as the invasive character of such procedure, anxiety with regard to pain expectation, possible complications and major impact on quality of life in the immediate postoperative period<sup>2,28</sup>. Hemodynamic parameters in this study were the reference for indirect evaluation of patients' anxiety. No anxiolytic drug was indicated due to their major impact on postoperative pain perception<sup>25,27,28</sup>. Blood pressure and HR results had values close to physiological parameters, and minor changes observed might be associated to the surgical moment, not indicating severe anxiety able to interfere with pain perception with regard to tested treatments. Studies with similar clinical design confirm ob-

served inferences about the interaction of hemodynamic patterns with anxiety and pain perception<sup>25</sup>.

Control of surgical time and perioperative complications was reported as a major factor to evaluate pain induced by impacted third molar extraction when two therapeutic modalities are compared<sup>2,5,24,25</sup>. Our results showed no statistically significant differences in surgical time and amount of anesthetic tubetes used with regard to operated side, patient's gender and analgesic drug used. Steroid anti-inflammatory drugs are often preemptively used in impacted tooth extraction for the adequate control of edema, trismus and postoperative pain<sup>30,31</sup>. The interference of steroids on patients' pain perception is an unavoidable limitation of this study, considering that their prescription is classic and necessary for Dentistry invasive surgical procedures<sup>32</sup>.

Clinical studies with criteria similar to those adopted by this research have shown that analgesic and anti-inflammatory coverage are important in the first 48 postoperative hours and that the addition of adjuvants seems to improve the analgesic effect of classic drugs prescribed for dental surgeries<sup>2,5,13,28,30,31</sup>. Caffeine has been associated as analgesic adjuvant to treat chronic and tension pain. Comparative studies have shown that caffeine associated to drugs such as paracetamol, ibuprofen, acetylsalicylic acid and naproxene, improves absorption and plasma distribution of such drugs and contributes to the inhibition of hyperalgesia inflammatory mediators release<sup>11,16,17,33,34</sup>. With regard to caffeine adjuvant analgesic effect for sodium dipyron in different situations, results are not consistent because there are few controlled, prospective and randomized studies<sup>18,19</sup>.

Sodium dipyron is widely used to control inflammatory pain, especially in the postoperative period of general surgeries<sup>35</sup>. Its analgesic efficiency may be attributed to the peripheral action mechanism which is different from other commonly used drugs<sup>6-8</sup>. The addition of caffeine seems to modify the effect of sodium dipyron to control pain, however action mechanisms of such association are still not clear<sup>16-19</sup>. Analysis of results obtained in this study show that caffeine/dipyron association had no differentiated postoperative analgesic effect for impacted third molar extraction surgeries and due to the scarcity of publications about the subject new controlled clinical trials are suggested.

## CONCLUSION

The therapeutic protocol proposed by this study has not shown statistically significant difference in analgesic efficiency of sodium dipyron associated or not to caffeine to control post tooth extraction pain.

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