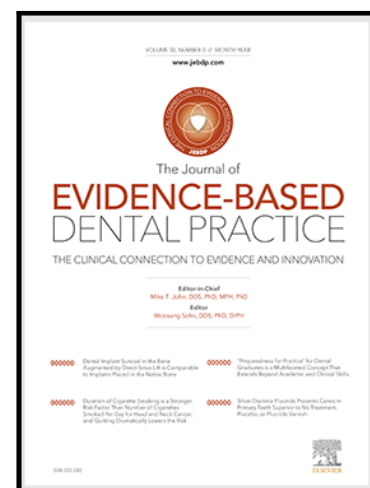


Journal Pre-proof

Comparative analgesic effects of single-dose preoperative administration of paracetamol (acetaminophen) 500 mg plus codeine 30 mg and ibuprofen 400 mg on pain after third molar surgery.

Gerardo La Monaca DDSPhD , Nicola Pranno DDSPhD ,
Susanna Annibali MDDDS , Antonella Polimeni MDDDS ,
Giorgio Pompa MDDDS , Iole Vozza DDSPhD ,
Maria Paola Cristalli DDSPhD



PII: S1532-3382(21)00086-5
DOI: <https://doi.org/10.1016/j.jebdp.2021.101611>
Reference: YMED 101611

To appear in: *The Journal of Evidence-Based Dental Practice*

Received date: 7 February 2021
Revised date: 8 June 2021
Accepted date: 14 June 2021

Please cite this article as: Gerardo La Monaca DDSPhD , Nicola Pranno DDSPhD ,
Susanna Annibali MDDDS , Antonella Polimeni MDDDS , Giorgio Pompa MDDDS ,
Iole Vozza DDSPhD , Maria Paola Cristalli DDSPhD , Comparative analgesic effects of single-
dose preoperative administration of paracetamol (acetaminophen) 500 mg plus codeine 30 mg and
ibuprofen 400 mg on pain after third molar surgery., *The Journal of Evidence-Based Dental Practice*
(2021), doi: <https://doi.org/10.1016/j.jebdp.2021.101611>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Elsevier Inc. All rights reserved.

Comparative analgesic effects of single-dose preoperative administration of paracetamol (acetaminophen) 500 mg plus codeine 30 mg and ibuprofen 400 mg on pain after third molar surgery.

Gerardo La Monaca^a, DDS, PhD, Nicola Pranno^{a,*}, DDS, PhD, Susanna Annibaldi^a, MD, DDS, Antonella Polimeni^a, MD, DDS, Giorgio Pompa^a, MD, DDS, Iole Voza^a, DDS, PhD, Maria Paola Cristalli^b, DDS, PhD,

^aDepartment of Oral and Maxillofacial Sciences, Sapienza, University of Rome, Rome, Italy

^bDepartment of Biotechnologies and Medical Surgical Sciences, Sapienza, University of Rome, Rome, Italy

*Corresponding author: Nicola Pranno, "Sapienza" University of Rome, 6, Caserta St., 00161, Rome Italy, Phone +39 06 49976651 Fax +39 06 44230811, E-mail nicola.pranno@uniroma1.it

ABSTRACT

Background: Efficacy and rapid onset of postsurgical oral pain relief are critical to improve clinical outcomes and reduce the risk of excessive dosing with analgesic drugs.

Purpose: To compare analgesic effects of preoperative administration of paracetamol 500 mg plus codeine 30 mg in single-tablet and effervescent formulation to ibuprofen 400 mg, and placebo in the management of moderate to severe postoperative pain after mandibular third molar surgery.

Materials and methods: One hundred twenty healthy outpatients aged 15 to 29 years undergoing surgical removal of one bony impacted mandibular third molar were enrolled in this, single-center, prospective, randomized, triple-blind parallel-group, placebo-controlled, clinical trial. Study participants were randomly assigned to three treatment arms. According to the concealed allocation, each patient 30 minutes before surgery received paracetamol 500 mg plus codeine 30 mg (group APAP/COD), ibuprofen 400 mg (group IBU) or placebo (group PLA). Rescue therapy allowed in the postoperative period was paracetamol 500 mg plus codeine 30 mg in groups APAP/COD and PLA and ibuprofen 400 mg in group IBU. Patients recorded on Numerical Rating Scale-11 (NRS-11) the pain intensity, total number of postoperative-supplement medications and time of the first intake, until 12-hours after surgery and over extra two days,

Results: Over postoperative three days, patients in the APAP/COD group (2.33 ± 1.99) displayed significantly ($p < 0.001$) less pain intensity than IBU (3.43 ± 2.47) and placebo (3.57 ± 2.62) groups. The first-day postoperative pain was significantly ($p < 0.001$) higher in group PLA than in groups APAP/COD and IBU, but not between the latter two groups. However, at 2 hours post-dose, the

IBU group displayed average pain intensity lower than APAP/COD group ($p>0.05$). On the next two days, pain intensity was significantly ($p<0.001$) lower in group APAP/COD than in groups IBU and PLA but failed to reach statistical significance between groups IBU and PLA.

Although the time to the first using rescue therapy was longer (445.88 ± 159.96 minute) in group IBU, compared to groups APAP/COD (392.67 ± 138.90 minutes) and PLA (323.00 ± 143.95 minutes), the number of supplemented tablets was significantly higher in group IBU (2.89 ± 2.13) than in groups APAP/COD (1.24 ± 1.79) ($p=0.001$) and PLA (1.53 ± 1.67) ($p=0.008$). No adverse events were registered for all groups.

Conclusions: Within the limits of the present study, over postoperative three days, a statistically significant intensity pain reduction and decreased rescue therapy consumption were recorded in the paracetamol-codeine group than to ibuprofen group. Nevertheless, lower pain intensity at 2 hours post-dose and longer time using rescue therapy was found in the ibuprofen group without statistical significance. No adverse events occurred over the studied period.

Keywords

acetaminophen, paracetamol-codeine combination, postsurgical dental pain, ibuprofen, placebo, third molar surgery.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

INTRODUCTION

In oral surgery, the onset of postoperative pain is induced by algogenic substances (neurokinins, prostaglandins, serotonin, histamine) generated or released from peripheral nerve endings and extraneural sources of soft and hard tissues injured.¹⁻³ These inflammatory response mediators, activating and sensitizing high-threshold nociceptors, cause peripheral sensitization, which through fibres A δ and C leads to central sensitization, in the dorsal horn of the medulla. Via the spinothalamic tract, the nociceptive stimulus reaches the thalamus, cerebral cortex, and other regions of Central Nervous System (hippocampus), where it is converted in a complex sensory, subjective and emotional sensation experienced by the patient as acute pain.⁴

To manage acute postoperative pain following third molar surgery, different drugs have been proposed. In an overview of Cochrane reviews on the efficacy of single-dose oral analgesics for acute postoperative pain in adults (often following the removal of wisdom teeth), 41 different medicines at various doses are examined.⁵ The oral analgesics can be categorized "mild", such as paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and celecoxib, or "moderate", which are weaker opioids such as codeine, and 'strong', which are strong opioids such as morphine, fentanyl or oxycodone.⁵ Paracetamol and NSAIDs are routinely worldwide used for the management of postoperative pain in oral surgery.^{6,7} Paracetamol has a weak anti-inflammatory activity, and its analgesic mechanism is complex and still not entirely clarified. In recent findings, paracetamol has been seen to have central actions on cerebral cyclooxygenase, descending opioidergic inhibitory and serotonin pathways, inhibition of peroxidase

but not cyclooxygenases. Furthermore, its analgesic activity may also involve an interaction with the endocannabinoid system.⁸ Effectiveness of paracetamol on pain is improved by the addition of codeine, which acts not only through the metabolism into morphine but also by itself and through its metabolites, such as norcodeine (NORC) and codeine-6- glucuronide (C-6-G).^{8,9} Ibuprofen exerts their anti-inflammatory and analgesic effects via inhibition of both families of cyclooxygenases (COX-1 and COX-2). These enzymes convert arachidonic acid generated from the surgical site's injured tissues to prostanoids (prostaglandins prostacyclin and thromboxanes), which play a crucial role in developing pain and inflammation.^{7,10} Oral strong opioids, instead, are less used as they produce a higher incidence of side effects in dental outpatients, including dizziness, drowsiness, psychomotor impairment, nausea/vomiting, constipation, and may cause addiction.⁴ Furthermore, preoperative administration of analgesics, resulting in immediate control of postoperative pain, could reduce the intensity and delay the onset. Waiting for the local anaesthesia to wear off and patients to experience severe pain before prescribing therapy provokes unnecessary discomfort and can affect the efficacy of the following treatment. Nevertheless, a single preemptive dose of analgesic is not enough for pain control in the postoperative period, thus analgesia should be extended for a few days after surgery.⁴

The present study was designed as a single-center, 2-stage, prospective, randomized, triple-blind parallel-group, placebo-controlled clinical trial. The aim was to compare the analgesic efficacy on pain after third molar surgery of preoperative administration of paracetamol 500 mg plus codeine 30 mg in single-tablet and effervescent formulation to ibuprofen 400 mg. The placebo used in the parallel control group was planned to measure the assay sensitivity and to compare side effects. The null hypothesis was that there would be no difference between the two analgesic drugs tested.

MATERIALS AND METHODS

Study Design

The study was designed as a single-center, 2-stage, prospective, randomized, triple-blind parallel-group, placebo-controlled, clinical trial and received prior Ethics-Committee approval by Policlinico Umberto I, "Sapienza" University of Rome, Italy (Reference 2704/21.02.2013) and was registered in ClinicalTrials.gov (NCT04730297).

In stage 1, the objective was to compare the efficacy on pain and tolerability of a single dose of paracetamol plus codeine, ibuprofen, or placebo in the operative day. During this period, it is easier to detect differences in the effectiveness of analgesic treatments due to more severe pain experienced by patients. The objective of stage 2 was to compare the efficacy and tolerability of the same drugs administered as rescue therapy up to 48 hours after stage 1.

The investigation was performed in accordance with standards of Good Clinical Practices for analgesic drugs and the principles of the 1964 WMA-Declaration of Helsinki on ethical principles for medical research involving human subjects and its later amendments. Trial preparation, execution and report followed the CONSORT Statement for improving the quality of reporting of randomized controlled trials.

Study population

Study participants were selected from outpatients referred for the prophylactic removal of bony impacted mandibular third molars to the Oral Surgery Unit, Policlinico Umberto I, "Sapienza" University of Rome, Italy, between January 2018 and September 2020. Subjects were eligible for

the study if they met the following criteria: 1) healthy status (ASA class I); 2) nonsmoker; 3) not pregnant or breastfeeding; 4) no medication consumption in the past 21 days; 5) good oral hygiene; 6) bony impaction of one mandibular third molars; 7) the presence of the first and second molars; 8) absence of pericoronitis or inflammation signs; 9) compliance to cooperate with the research protocol. Exclusion criteria were: 1) systemic diseases; 2) pregnancy or lactation; 3) smokers, 4) consumption of medications in the past 21 days; 3) history of intolerance or hypersensitivity to the study drugs; 4) allergy to local anesthetics; 5) any pre-existing pain and acute inflammatory or infectious conditions; 6) inability to understand or perform the study procedure.

Before achieving written informed consents, patients or parent or legal representative of children aged <18 years received detailed explanations on the mandibular third molar surgical removal and associated risks, possible adverse events of analgesic drugs, and experimental protocol. The subjects meeting the eligibility criteria were randomly allocated to Group: A paracetamol 500 mg plus codeine 30 mg; B ibuprofen 400 mg; C placebo (starch).

Randomization

Before the start of the study, analgesic treatment (paracetamol 500 mg plus codeine 30 mg, ibuprofen 400 mg) or placebo were assigned using a list of random numbers generated using CLINSTAT software (Martin Bland, York, UK). The concealed allocation was performed with consecutively numbered sealed opaque envelopes.

Blinding

Patients, surgeon, data collector and biometrician were unaware of the analgesic treatment (triple-blind design). Before starting surgery, patients were unaware of the analgesic treatment assigned, as an unblinded external study collaborator administered pre-emptive medications. Information in the decoding envelope on analgesic treatments was available at the end of the clinical and statistical analysis.

Surgical procedure

All surgeries were undertaken in outpatient setting and under local anaesthesia, with mepivacaine 3% without epinephrine for inferior alveolar and buccal nerve block, and mepivacaine, 2% with 1:100.000 epinephrine (Carbocaine, AstraZeneca, Italy) for soft tissues infiltration. All sessions were scheduled at 11.00 am to avoid any influence of circadian rhythms in pain diurnal variation. Interventions were carried out by the same expert oral surgeon (G.L.M) with a standardized technique, detailed in previous studies.¹¹⁻¹³ In brief, surgical procedures consisted in raising of the envelope mucoperiosteal flap; osteotomy and tooth sectioning; extraction of tooth sections; socket debridement; flap repositioning; suture (4/0 Ethilon, Ethicon S. p. A. Johnson & Johnson, Pratica di Mare, Rome, Italy), to be removed after one week. Chlorhexidine digluconate 0.2% (Corsodyl, GlaxoSmithKline Consumer Healthcare S.p.A. Baranzate, Milan, Italy) was used preoperatively as a mouth rinse for 2 minutes, and postoperatively as a spray to surgical site hygiene. Antibiotic therapy with amoxicillin 875 mg plus clavulanic acid 125 mg (Augmentin, GlaxoSmithKline S.p.A., Verona, Italy) was prescribed twice daily for seven days to prevent postoperative infections, which could affect pain intensity.¹⁴

Operative timing was measured from the incision to the suture conclusion. At the end of the surgery, patients were discharged, with postoperative instructions for brushing, soft food

consuming, and suppression of smoking in cases of smokers. Furthermore, they were asked to report any occurring adverse events (nausea, vomiting, headache, or dizziness).

Study Medication

According to the concealed allocation, study medications were administered 30 minutes before surgery. Group APAP/COD received effervescent single-tablet of paracetamol 500 mg plus codeine 30 mg (Co-Efferalgan - Bristol-Myers Squibb S.r.l., Rome, Italy) in 50 ml of water, group IBU ibuprofen 400 mg (Brufen 400 mg- Mylan S.p.A. Milano, Italy), and group PLA placebo (starch tablet). The inclusion of a placebo group in postoperative dental pain studies has been considered acceptable, due to the self-limiting nature of pain and the providing of effective therapy for subjects requiring additional pain relief.¹⁵

Rescue therapy, to assume at 6-hour intervals up to a maximum of four doses in 24 hours, was prescribed to patients in the postoperative period. Supplement medications were paracetamol 500 mg plus codeine 30 mg in Groups APAP/COD and PLA and ibuprofen 400 mg in Group IBU. No other analgesic drugs nor non-pharmacologic pain-relieving modalities were prescribed.

Outcome measures

Postoperative pain intensity was the primary outcome and was recorded on the Numerical Rating Scale-11 (NRS-11). This method, ranging from 0 (no pain or discomfort), 1–4 (mild pain), 5–6 (moderate pain) to 7–10 (severe pain), is considered valid and reliable for unidimensional self-assessment of postoperative pain intensity.¹⁶⁻¹⁸ Compared to other rating scales (Verbal Rating Scale and Visual Analogue Scale), the 11-response options of NRS, facilitating participants' ability to discriminate, increases their understanding, responsiveness, and compliance.¹⁵

Patients performed registrations at 1.00 pm (about 2 hours after surgery), 6.00 pm and 11:00 pm during the operation day, and at 8:00 am, 1:00 pm, 6:00 pm, and 11:00 pm over the next two days.^{16,18} After bony impacted third molars surgery under local anaesthesia, postoperative pain has a peak intensity after 6–8 hours and often lasts over several days.^{16,19} Furthermore, multiple observations are required to obtain accurate data on the onset and peak effect of test drugs.¹⁶ Secondary outcomes involved the number of patients requiring rescue therapy, timing to first postoperative use of analgesics, and the total amount of additional medications. Postoperative pain intensity, at pre-established timing, and any rescue analgesic intake were recorded by patients on pain diaries (one for each of three post-surgery days), which were to be returned at the suture removal.

Tolerability of the study drugs was assessed at both 1 and 2 stages with the frequency, nature and severity of the occurred adverse events.

Statistical analysis

A power analysis using the Wilcoxon matched-pairs signed-rank test with an α level of 0.05 and a medium effect size ($f=0.80$) showed that 80 subjects would be adequate to obtain 95% power in detecting a statistical difference between 2 groups in scores on the NRS-11 for postoperative pain, assuming a loss to follow-up of 20%. The power calculation was based on pain scores in a previous pilot study involving five patients for each group (3.25 ± 1.54 for ibuprofen and 2.09 ± 1.35 for paracetamol plus codeine).

The database was created using Excel (Microsoft, Redmond, WA, USA). Descriptive statistics, including mean \pm SD values, were calculated for each variable, and box plots were used to evaluate data outliers.

The Kruskal-Wallis H test was utilized to assess differences in pain intensity between the three treatment arms. The one-way ANOVA was applied to compare the timing of surgery, time to the first use of rescue medication and number of rescue analgesic medications between the three groups of patients. Pairwise comparisons were performed with Bonferroni correction for multiple comparisons. Data were evaluated with standard statistical analysis software (version 20.0, Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA). The cut-off for statistical significance of each test was $p \leq 0.05$.

RESULTS

Out of 120 subjects enrolled and equally randomized to the three treatment groups, 14 (10 males and 4 females) were excluded from the trial (6 in group APAP/COD, 2 in group IBU and 6 in group PLA) due to the incomplete compilation of pain diaries. All remaining 106 patients (66 females and 40 male) with ages ranged to 15 to 29 years (20.53 ± 3.57) were included in data analysis. There were no statistically significant differences in age ($p=0.876$) and gender ($p=0.729$).

Surgical time did not significantly differ between patients treated with paracetamol 500 mg plus codeine 30 mg ($25:11 \pm 7.52$ minutes), ibuprofen 400 mg ($21:37 \pm 8.58$ minutes), or placebo ($24:58 \pm 6.26$ minutes) ($p=0.422$).

Pain intensity score

Over three postoperative days, average pain intensity was significantly lower ($p < 0.001$) in the APAP/COD group (2.33 ± 1.99) than in IBU (3.43 ± 2.47) and PLA (3.57 ± 2.62) groups. On day one, postoperative pain was significantly higher ($p < 0.001$) in group PLA compared to groups APAP/COD and IBU ($p < 0.001$), but not between the latter two groups. On the next two days, pain intensity was significantly lower ($p < 0.001$) in group APAP/COD compared to groups IBU and PLA but failed to reach statistical significance between groups IBU and PLA. Data are illustrated in Fig. 1 and summarized in Table 1.

On the first postoperative day, the distribution of average pain intensity at 2 hours from drug administration was significantly higher in the PLA group than in APAP/COD ($p < 0.001$) and IBU ($p < 0.001$) groups and lower, but without statistical significance, in the IBU versus APAP/COD group ($p=0.827$) (Table 2). Pain intensity at 7 and 12 hours after drug intake was lower in patients of the APAP/COD group compared to those in IBU and PLA group (Table 2).

Maximum pain intensity recorded was mild in 20 (58.8%), moderate in 8 (23.5%) and severe in 6 (17.6%) patients receiving paracetamol plus codeine (group APAP/COD), mild in 12 (31.6%), moderate in 12 (31.6%) and severe in 14 (36.8%) patients receiving ibuprofen (group IBU), and mild in 6 (17.6%), moderate in 4 (11.8%) and severe in 24 (70.6%) patients receiving placebo (group PLA), with a statistically significant difference between groups APAP/COD and PLA ($p < 0.001$). No statistically significant difference was found between groups APAP/COD and IBU ($p=0.059$) and between groups IBU and PLA ($p=0.081$) (Table 3).

Rescue therapy

Ten out of 106 patients did not request rescue therapy, 5 in group APAP/COD, 3 in group IBU, and 2 in group PLA. The mean timing to first using rescue therapy was longer (445.88 ± 159.96 minute) in group IBU, compared to groups APAP/COD (392.67 ± 138.90 minutes), or PLA (323.00 ± 143.95 minutes). The difference was statistically significant ($p=0.012$) between groups IBU and PLA, but not between groups APAP/COD and IBU ($p=0.687$). The mean number of supplemented tablets was significantly higher in group IBU (2.89 ± 2.13) compared to groups APAP/COD (1.24 ± 1.79) ($p=0.001$) and PLA (1.53 ± 1.67) ($p=0.008$).

Tolerability

No adverse events were recorded 12 hours after surgery (stage 1) nor during the second and third postoperative day (stage 2), regardless of medications or placebo administered.

DISCUSSION

The present clinical trial aimed to compare the analgesic efficacy of paracetamol 500 mg plus codeine 30 mg in effervescent single-tablet and ibuprofen 400 mg when drugs were administered 30 minutes before mandibular third molar surgery. Paracetamol plus codeine achieved statistically significant overall pain intensity relief and decreased rescue therapy consumption over postoperative three days than ibuprofen. Nevertheless, lower pain intensity at 2 hours post-dose and longer timing to first using rescue therapy were found for ibuprofen. No adverse events occurred over the studied period.

The effectiveness of the paracetamol-codeine combination in different dosages and formulations has been documented.⁹ The synergy of the two drugs combined in a single-tablet is guaranteed by their pharmacodynamic parameters, which allow an action synchronous and of the same duration. The optimum adult dose of the two molecules in combination was estimated in 500 mg of paracetamol, corresponding to about 7 mg/kg, and 30 mg of codeine. This dosage, thanks to the synergistic action, improves analgesic efficacy and decreases adverse events when compared to the single components.⁸ Furthermore, fast-dissolving formulations allow faster absorption than standard tablets, and then they are more suitable to control acute pain, due to the quicker onset of action.²⁰ Lastly, preoperative administration of the analgesic drugs aims to delay the onset of pain and decrease the perceived postoperative pain, consumption of rescue medications and recovery time.²¹ Ibuprofen 400 mg in oral administration is commonly chosen in many clinical trials to compare other analgesics' efficacy in pain relief following third molars surgery.^{5,6} It has been shown to effectively manage postoperative pain in adults due to rapid absorbability, peak plasma concentration in 1-2 hours, and long-lasting effects up to 6 hours. Nevertheless, to suppress local tissue inflammatory response and prolonging analgesia, daily consumption of at least 1600 mg is needed.^{10,22}

Outcomes of the present investigation disagreed with those reported in the literature, which highlighted the superiority of ibuprofen to paracetamol, either alone or combined with codeine regardless of dosages.⁴⁻⁶

The average pain intensity over three postoperative days, significantly lower for paracetamol plus codeine than ibuprofen, may be explained both by the fixed-dose combination of two drugs in a single-tablet and the more rapid absorption. The efficacy of fixed-dose combinations and fast-acting formulations in achieving "good, and often long-lasting analgesia at relatively low doses" was previously reported in an overview of single-dose oral analgesics for acute postoperative pain in

adults.⁵ In this overview, the authors summarized the results of 39 Cochrane reviews investigating 41 individual drug interventions, with approximately 58,000 participants in 467 studies.⁵ The enhanced analgesic efficacy of effervescent formulation of paracetamol 500 mg-codeine 30 mg compound compared to equivalent doses of conventional tablets, was probably due to the speed of absorption, which led to more rapid time to peak blood levels and higher blood levels. The rate of absorption of paracetamol after oral administration depends on gastric emptying rate because the drug is primarily absorbed in the upper small intestine rather than in the stomach.²³ In many studies, the addition of putative prokinetic agents to paracetamol, such as sodium bicarbonate, has shown to fast the absorption when compared to conventional tablets. Results of pharmacokinetic analysis found an area under the blood concentration time-curve (AUC_0) and plasma concentration (C_{plasma}) higher and the time to reach C_{max} (T_{max}) shorter. Furthermore, the extent of absorption was equivalent for both formulations, with no statistically significant difference in maximum plasma concentration (C_{max}).²³⁻²⁵ It would be worthwhile in future research to compare effervescent APAP 500 mg/COD 30 mg to a solubilized formulation of ibuprofen 400 mg.

The lack of statistical differences between groups APAP/COD and IBU on the first-day pain might be affected by preemptive analgesic effects of the local anaesthesia. The regional nerve block, extending for 1-2 hours in the postoperative period, would not have the same influence on tested drugs according to their different pharmacokinetic parameters.^{26,27} After a single oral dose of ibuprofen 400 mg, the median time of maximum concentration (T_{max}) were 90 minutes, and the maximum observed plasma concentration (C_{max}) was 31.88 $\mu\text{g/mL}$. and lasts from 2 up to 6 hours.²⁸ After an effervescent single-tablet of paracetamol 500 mg plus codeine 30 mg, plasma concentration reaches the peak in 30 minutes and progressively decreases in 4-5 hours.^{7,22,23}

Pharmacokinetics could also explain lower pain intensity at 2 hours post-dose and longer time to the first use of rescue therapy in group IBU than in group APAP/COD. The latter outcome was in line with the median or mean time to use rescue medication reported in the overview of Moore et al.⁵ Furthermore, the delay in taking rescue therapy in the ibuprofen group versus the acetaminophen plus codeine group might be justified by the pain intensity at 2 hours post-dose lower for ibuprofen. Nevertheless, it cannot rule out that patients in the ibuprofen group, for whatever reason and regardless of pain intensity, may have waited longer to take additional rescue drug than the effervescent APAP/COD group. The benefits of analgesic treatment with paracetamol 500 mg plus codeine 30 mg were confirmed by the number of supplemented tablets on average higher in group IBU patients, taking ibuprofen 400 mg, than in groups APAP/COD and PLA.

Both drugs were well tolerated, and no side effects were recorded in all three groups. This data disagreed with information regarding adverse events (including nausea, vomiting, headache, and dizziness) reported in most studies.²⁸ Lacking side effects recorded in the present trial might be affected by the examined sample, consisting of healthy subjects relatively young and occasional consumer of analgesic drugs and the relatively small number of doses assumed. Furthermore, all surgeries were performed in outpatients under local anaesthesia, without intravenous or by inhalation sedation. Adverse events are more expected in older people undergoing more traumatic interventions and taking analgesics over several days.²⁹ However, side effects of paracetamol and codeine are uncommon, mild, transient, and associated with higher doses and long-term use.⁹ The risk of misuse, abuse, and addiction linked to opioid contain is more likely to happen with a long course and a higher dosage of codeine or other opioids (oxycodone, hydrocodone, tramadol). Similarly, ibuprofen, used in the short term and with low daily dosage, seems to be associated with a low risk of intolerance, allergy, and gastrointestinal, renal and hematologic complications.^{6,7}

Anyway, the effervescent combination of paracetamol plus codeine could perform a valid alternative for patients who must avoid ibuprofen because sensitive to asthma or specific allergies, at cardiovascular risk, in anticoagulant or lithium therapies or with a history of gastrointestinal ulcers or for subjects unable to swallow standard tablets.⁴

Nevertheless, outcomes in the present study should be interpreted with cautions as they could have been influenced by the sample size and method to evaluate pain intensity. The relatively small sample size may have decreased the statistical power, although, in the power analysis, it was adequate in detecting statistically significant differences in postoperative pain scores between tested groups. The method to evaluate pain intensity using NSR and self-report forms, compiled at home without stopwatches and reminders to complete assessment scales at the specific time points, might have been biased by patients' collaboration.

CONCLUSIONS

Both ibuprofen 400 mg and paracetamol 500 mg plus codeine 30 mg in single-tablet and effervescent formulation proved to have analgesic effects on postoperative pain after a third molar surgery. Within the limits of the present study, administration of paracetamol plus codeine compared to ibuprofen achieved statistically significant overall pain intensity relief and decreased rescue therapy consumption over postoperative three days. Nevertheless, lower pain intensity at 2 hours post-dose and longer timing to first using rescue therapy without statistical significance were found in the ibuprofen group. No adverse events occurred over the studied period.

In short, detailed pharmacotherapeutic information on the dose-response of this paracetamol-codeine fixed combination should be useful to drive clinicians in postoperative pain management to facilitate patient compliance, simplify prescribing and improve efficacy without increasing adverse effects.

Credit Author Statement

Polimeni A and Pompa G contributed to the conception and design of the study and critically revised the manuscript; Annibali S wrote the original and reviewed work. La Monaca G and MP Cristalli contributed to data acquisition, analysis, and interpretation, and drafted the manuscript; Pranno N and Voza I contributed to formal analysis, and interpretation, and drafted the manuscript;

All authors gave final approval and agree to be accountable for all aspects of the work.

Declaration of Competing Interests

The authors have stated that there are no conflicts of interest

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Ong CK, Seymour RA. Pathogenesis of postoperative oral surgical pain. *Anesth Prog.* 2003 Winter;50(1):5-17. PMID: 12722900; PMCID: PMC2007420.
2. Schaible HG, Richter F. Pathophysiology of pain. *Langenbecks Arch Surg.* 2004 Aug;389(4):237-43. doi: 10.1007/s00423-004-0468-9. Epub 2004 Mar 18. PMID: 15034717.
3. Dahl JB, Møiniche S. Pre-emptive analgesia. *Br Med Bull.* 2004 Dec 13;71:13-27. doi: 10.1093/bmb/ldh030. PMID: 15596866.
4. Hersh EV, Moore PA, Grosser T, Polomano RC, Farrar JT, Saraghi M, Juska SA, Mitchell CH, Theken KN. Nonsteroidal Anti-Inflammatory Drugs and Opioids in Postsurgical Dental Pain. *J Dent Res.* 2020 Jul;99(7):777-786. doi: 10.1177/0022034520914254. Epub 2020 Apr 14. PMID: 32286125; PMCID: PMC7313348.
5. Moore RA, Derry S, Aldington D, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2015 Sep 28;2015(9):CD008659. doi: 10.1002/14651858.CD008659.pub3. PMID: 26414123; PMCID: PMC6485441.
6. Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database Syst Rev.* 2013 Dec 12;(12):CD004624. doi: 10.1002/14651858.CD004624.pub2. PMID: 24338830.
7. Moore N D. In search of an ideal analgesic for common acute pain. *Acute Pain* 2009; 11(3-4): 129–37. doi: 10.1016/j.acpain.2009.09.003.
8. Mattia C, Coluzzi F. A look inside the association codeine-paracetamol: clinical pharmacology supports analgesic efficacy. *Eur Rev Med Pharmacol Sci.* 2015;19(3):507-16. PMID: 25720726.
9. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev.* 2009 Jan 21;2009(1):CD001547. doi: 10.1002/14651858.CD001547.pub2. PMID: 19160199; PMCID: PMC4171965.
10. Becker DE. Pain management: Part 1: Managing acute and postoperative dental pain. *Anesth Prog.* 2010 Summer;57(2):67-78; quiz 79-80. doi: 10.2344/0003-3006-57.2.67. PMID: 20553137; PMCID: PMC2886920.
11. La Monaca G, Voza I, Giardino R, Annibali S, Pranno N, Cristalli MP. Prevention of neurological injuries during mandibular third molar surgery: technical notes. *Ann Stomatol (Roma).* 2017 Nov 8;8(2):45-52. doi: 10.11138/ads/2017.8.2.053. PMID: 29299188; PMCID: PMC5749373.

12. Cristalli MP, La Monaca G, De Angelis C, Pranno N, Annibali S. Efficacy of Preoperative Administration of Paracetamol-Codeine on Pain following Impacted Mandibular Third Molar Surgery: A Randomized, Split-Mouth, Placebo-Controlled, Double-Blind Clinical Trial. *Pain Res Manag.* 2017;2017:9246352. doi: 10.1155/2017/9246352. Epub 2017 Feb 23. PMID: 28325960; PMCID: PMC5343255.
13. La Monaca G, Pranno N, Annibali S, Polimeni A, Pompa G, Cristalli MP. Effects of ibuprofen administration timing on oral surgery pain: A randomized clinical trial. *Oral Dis.* 2021 Jan 24. doi: 10.1111/odi.13781. Epub ahead of print. PMID: 33486855.
14. Annibali S, De Biase A, Pippi R, Sfasciotti GL; Italian Society of Odontostomatological Surgery. A consensus conference on management of the lower third molar. Italian Society of Odontostomatological Surgery. *Minerva Stomatol.* 2011 Oct;60(10):509-27. English, Italian. PMID: 22082856.
15. Cooper SA, Desjardins PJ, Turk DC, Dworkin RH, Katz NP, Kehlet H, Ballantyne JC, Burke LB, Carragee E, Cowan P, Croll S, Dionne RA, Farrar JT, Gilron I, Gordon DB, Iyengar S, Jay GW, Kalso EA, Kerns RD, McDermott MP, Raja SN, Rappaport BA, Rauschkolb C, Royal MA, Segerdahl M, Stauffer JW, Todd KH, Vanhove GF, Wallace MS, West C, White RE, Wu C. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. *Pain.* 2016 Feb;157(2):288-301. doi: 10.1097/j.pain.0000000000000375.
16. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, Fainsinger R, Aass N, Kaasa S; European Palliative Care Research Collaborative (EPCRC). Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage.* 2011 Jun;41(6):1073-93. doi: 10.1016/j.jpainsymman.2010.08.016. PMID: 21621130.
17. Gerbershagen HJ, Rothaug J, Kalkman CJ, Meissner W. Determination of moderate-to-severe postoperative pain on the numeric rating scale: a cut-off point analysis applying four different methods. *Br J Anaesth.* 2011 Oct;107(4):619-26. doi: 10.1093/bja/aer195. Epub 2011 Jun 30. PMID: 21724620.
18. Coulthard P, Patel N, Bailey E, Coulthard MB. Measuring pain after oral surgery. *Oral Surgery* 2014; 7(4): 203–8. doi:10.1111/ors.12075
19. Cooper SA, Desjardins PJ. The value of the dental impaction pain model in drug development. *Methods Mol Biol.* 2010;617:175-90. doi: 10.1007/978-1-60327-323-7_15. PMID: 20336423.
20. Yue Y, Collaku A, Brown J, Buchanan WL, Reed K, Cooper SA, Otto J. Efficacy and speed of onset of pain relief of fast-dissolving paracetamol on postsurgical dental pain: two randomized, single-dose, double-blind, placebo-controlled clinical studies. *Clin Ther.* 2013 Sep;35(9):1306-20. doi: 10.1016/j.clinthera.2013.07.422. Epub 2013 Aug 22. PMID: 23972577.
21. Katz J, Clarke H, Seltzer Z. Review article: Preventive analgesia: quo vadimus? *Anesth Analg.* 2011 Nov;113(5):1242-53. doi: 10.1213/ANE.0b013e31822c9a59. Epub 2011 Sep 30. Erratum in: *Anesth Analg.* 2011 Dec;113(6):1475. PMID: 21965352.
22. Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2009 Jul 8;2009(3):CD001548. doi: 10.1002/14651858.CD001548.pub2. PMID: 19588326; PMCID: PMC4171980.

23. Grattan T, Hickman R, Darby-Dowman A, Hayward M, Boyce M, Warrington S. A five way crossover human volunteer study to compare the pharmacokinetics of paracetamol following oral administration of two commercially available paracetamol tablets and three development tablets containing paracetamol in combination with sodium bicarbonate or calcium carbonate. *Eur J Pharm Biopharm.* 2000 May;49(3):225-9. doi: 10.1016/s0939-6411(00)00081-3.
24. Rygnestad T, Zahlsen K, Samdal FA. Absorption of effervescent paracetamol tablets relative to ordinary paracetamol tablets in healthy volunteers. *Eur J Clin Pharmacol.* 2000 May;56(2):141-3. doi: 10.1007/s002280050732. PMID: 10877008.
25. Ibáñez Y, Rodríguez JM., Luján M, Grattan TJ, Martin AJ, Burnett I. A pharmacokinetic study investigating the rate of absorption of a 500 mg dose of a rapidly absorbed paracetamol tablet and a standard paracetamol tablet. *Curr Med Res Opin.* 2006 Oct;22(10):1893-7. doi: 10.1185/030079906X132596. PMID: 17022846.
26. Gordon SM, Dionne RA, Brahim J, Jabir F, Dubner R. Blockade of peripheral neuronal barrage reduces postoperative pain. *Pain.* 1997 Apr;70(2-3):209-15. doi: 10.1016/s0304-3959(96)03315-5. PMID: 9150295.
27. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia II: recent advances and current trends. *Can J Anaesth.* 2001 Dec;48(11):1091-101. doi: 10.1007/BF03020375. PMID: 11744585.
28. Dewland PM, Reader S, Berry P. Bioavailability of ibuprofen following oral administration of standard ibuprofen, sodium ibuprofen or ibuprofen acid incorporating poloxamer in healthy volunteers. *BMC Clin Pharmacol.* 2009 Dec 4;9:19. doi: 10.1186/1472-6904-9-19. PMID: 19961574; PMCID: PMC2796637.
29. Moore RA, Derry S, Aldington D, Wiffen PJ. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2015, Issue 10. Art. No.: CD011407. DOI: 10.1002/14651858.CD011407.pub2.

Table 1. Comparison of average pain intensity (NRS-11) between patients receiving paracetamol 500 mg plus codeine 30 mg, ibuprofen 400 mg, or placebo before surgery.

	Paracetamol 500 mg - codeine 30 mg Group APAP/COD	Ibuprofen 400 mg Group IBU	Placebo Group PLA	<i>p</i>
Overall pain intensity	2.33 ± 1.99 ^a	3.43 ± 2.47 ^b	3.57 ± 2.62 ^b	<0.001*
Pain intensity on the first day	3.18 ± 1.17 ^a	3.61 ± 2.51 ^a	5.76 ± 2.53 ^b	<0.001*
Pain intensity on the second day	2.22 ± 1.88 ^a	3.57 ± 2.49 ^b	3.41 ± 1.75 ^b	<0.001*

Pain intensity on the third day	1.81 ± 1.77 ^a	3.16 ± 2.41 ^b	2.07 ± 2.31 ^b	<0.001*
---------------------------------	--------------------------	--------------------------	--------------------------	---------

Data expressed as the mean ± standard deviation.

Asterisks indicate significant differences, and each subscript letter denotes a subset of intervention categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 2. Comparison of average pain intensity (NRS-11) between patients receiving paracetamol 500 mg plus codeine 30 mg, ibuprofen 400 mg, or placebo before surgery.

	Paracetamol 500 mg - codeine 30 mg Group APAP/COD	Ibuprofen 400 mg Group IBU	Placebo Group PLA	<i>p</i>
Pain intensity after 2- hours drug intake	3.06 ± 2.64 ^a	2.74 ± 1.91 ^a	7.47 ± 2.39 ^b	<0.001*
Pain intensity after 7- hours drug intake	3.59 ± 1.81 ^a	4.47 ± 2.89 ^{ab}	5.24 ± 1.92 ^b	0.015*
Pain intensity after 12- hours drug intake	2.88 ± 1.97 ^a	3.63 ± 2.38 ^{ab}	4.59 ± 2.34 ^b	0.009*

Data expressed as the mean ± standard deviation.

Asterisks indicate significant differences, and each subscript letter denotes a subset of intervention categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 3. Comparison of pain intensity at 2-7-12 hours from drug administration between patients receiving paracetamol-codeine (group APA/COD), ibuprofen (group IBU), and placebo (group PLA)

Time after drug intake	Pain intensity	Patients (%) Group APAP/COD	Patients (%) Group IBU	Patients (%) Group PLA	P-value
2-hours	No Pain	8 (23.53) ^a	2(5.26) ^a	0 ^b	<0.001
	Mild	16 (47.06)	28 (73.69)	8(23.53)	
	Moderate	8 (23.53)	8 (21.05)	4(11.76)	
	Severe	2 (5.88)	0	22(64.71)	
7-hours	No Pain	0 ^a	0 ^{ab}	0 ^b	
	Mild	24 (70.59)	20 (52.63)	14(41.18)	

	Moderate	6 (17.65)	8 (21.05)	8(23.53)	0.033
	Severe	4 (11.76)	10 (26.32)	12(35.29)	
12-hours	No Pain	4 (11.77) ^a	2(5.26) ^{ab}	0 ^b	0.024
	Mild	22 (64.71)	22 (57.90)	18(52.94)	
	Moderate	6 (17.64)	8 (21.05)	6(17.65)	
	Severe	2 (5.88)	6 (15.79)	10(29.41)	

Data expressed as the mean \pm standard deviation.

Asterisks indicate significant differences, and each subscript letter denotes a subset of intervention categories whose column proportions do not differ significantly from each other at the 0.05 level.

Figure 1. Pain intensity score (NRS-11) in patients receiving ibuprofen 400 mg, paracetamol 500 mg/ codeine 30 mg or placebo recorded at specific time intervals over three days after surgery.

