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Evaluation of the efficacy of celecoxib and ibuprofen on postoperative pain, swelling, and mouth opening after surgical removal of impacted third molars: a randomized, controlled clinical trial

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Abstract. The objective of this study was to compare the efficacy of celecoxib and ibuprofen in reducing postoperative sequelae following the surgical removal of impacted mandibular third molars. Ninety-eight subjects who needed surgical extraction of an impacted mandibular third molar were selected for the study. All subjects were randomly allocated to receive one of the following treatments twice a day for 5 days after surgery: placebo ($n = 32$), ibuprofen ($n = 33$), or celecoxib ($n = 33$). The primary outcome chosen was postoperative pain, which was evaluated using the visual analogue scale (VAS) score recorded by each patient. The secondary outcomes chosen were changes in postoperative swelling and maximum mouth opening values compared to preoperative ones. Compared to placebo, treatment with celecoxib and ibuprofen resulted in improvements in the primary outcome. Furthermore, when compared to the other groups, patients in the celecoxib group showed a significant reduction in postoperative pain scores at 6 h ($P < 0.001$), 12 h ($P = 0.011$), and 24 h ($P = 0.041$) after surgery. Regarding swelling and maximum mouth opening values, there were no significant differences between the groups at each follow-up session. This study demonstrated that treatment with celecoxib decreased the incidence and severity of postoperative pain following third molar surgery compared to ibuprofen and placebo.

Key words: third molar surgery; ibuprofen; celecoxib; pain; swelling; trismus; randomized clinical trial.

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Third molar surgery is one of the most commonly performed oral and maxillofacial surgery procedures and is associated with a range of symptoms such as swelling, pain, and important oral inflammatory sequelae[1]. In response to the surgical extraction of the third molar, various inflammatory mediators are produced, including leukotrienes, prostaglandins, and platelet activating factors[2]. The release of these inflammatory mediators results in an increase in vasodilatation and vascular permeability of the surgical site, leading to peripheral oedema and local tissue alterations[3].

The management of these symptomatic sequelae, inflammatory mediators, and pain forms the basis of successful postoperative management[4]. Many strategies have been developed to reduce clinical signs and symptoms following third molar surgery, including the use of pharmacological therapy to inhibit the release of the inflammatory mediators responsible for this acute response[5].

Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are the most commonly used drugs in post-surgical oral and periodontal therapy due to their anti-inflammatory and analgesic properties[6]. Among the NSAIDs, those that inhibit the production of prostaglandin E2 (PGE2) and decrease the release of serotonin by the nervous system, producing a relatively strong reduction in inflammation at the systemic and topic level, are the most important[7].

It has been shown that NSAIDs mainly exert their anti-inflammatory action by inhibiting cyclooxygenases COX-1 and COX-2. However, as the inhibition of COX-1 is associated with a lack of gastric protection[8], a new class of NSAIDs, with selective anti-inflammatory activity through the inhibition of COX-2, has been developed in recent decades. In fact, selectively inhibiting the COX-2 enzyme provides excellent anti-inflammatory efficacy with almost no influence on the gastrointestinal tract[8]. However, although the efficacy of COX-2 inhibitors has been demonstrated extensively in patients with arthritis and rheumatoid arthritis[9], there is currently no robust evidence indicating the same efficacy of COX-2 inhibitors for the treatment of the acute phase postoperative discomfort after surgical extraction of impacted third molars[10,11].

A recent randomized controlled trial studied the effects of a COX-2 inhibitor, celecoxib (ranging from 25 mg to 400 mg), for the management of postoperative pain in patients undergoing third molar surgery[12]. The results of that pilot study showed efficacy in the management of the acute postoperative pain phase for celecoxib doses of 200 mg and 400 mg compared to the placebo[12]. Moreover, a similar clinical study which analysed the effectiveness of celecoxib compared with loxoprofen showed that celecoxib was equally effective to loxoprofen for postoperative pain discomfort after the surgical extraction of impacted mandibular third molars[13]. These preliminary results were validated by a Cochrane review that assessed the pain-relieving activity of another COX-2 inhibitor, etoricoxib[14]. When used as a single dose, etoricoxib showed good results in providing effective long-lasting analgesia at relatively low doses in the management of acute postoperative pain.

Considering these encouraging results, the aim of this study was to evaluate the effectiveness of celecoxib versus a commonly used anti-inflammatory drug and a placebo in the management of the perioperative discomfort after the surgical removal of mandibular third molars. The null hypothesis was that there would be no difference between the three protocols analysed.

Materials and methods

Study design

The study was designed as single-centre, randomized, triple-blind controlled clinical trial. The study was performed in accordance with the Declaration of Helsinki regarding medical research, as revised in 2016. Ethical approval was obtained at the beginning of the study from the Institutional Review Board of the University of Messina, and the study was registered at clinicaltrials.gov (ID: NCT03335684). Written informed consent was obtained from each patient, all of whom were informed about the study protocol (the randomized, blinded and controlled clinical trial study design, the nature of the surgical procedures, and the characteristics of the drugs used) and possible risks of the study (short- and long-term injuries linked to the surgical procedure and the possible allergic sequelae or complications linked to the drugs used) before any procedures were performed.

All subjects were consecutively and randomly recruited from normal healthy subjects (ASA I, according to the American Society of Anaesthesiology classification), aged ≥18 years, who required the surgical removal of an impacted third molar in the mandible. The enrolment of patients was performed between May 2017 and May 2018 in the Unit of Oral Surgery of the Department of Odontostomatology, University of Messina, Messina, Italy.

The inclusion criteria were: (1) age between 18 and 32 years; (2) good general health; (3) the presence of one impacted third molar in the mandible with a class II position, type B impaction[15]; (4) absence of pericoronitis or signs of inflammation during the last 30 days. Panoramic radiographs were used to determine tooth position. The exclusion criteria were: (1) the presence of any systemic disease; (2) consumption of oral contraceptives or other medications; (3) consumption of any immunosuppressive or anti-inflammatory drugs during the 3 months prior to the study; (4) status of pregnancy or lactation; (5) previous history of excessive drinking; (6) allergy to local anaesthetic; (7) smoking habit.

The study was performed according to the CONSORT guidelines (Consolidated Standards Of Reporting Trials) (Fig. 1; **Supplementary Material**, Appendix 1)[16]. Patients were excluded if they did not complete the study (both surgeries) or if they did not specifically follow the study protocol. Moreover, patients were excluded if any surgical time went over 40 minutes.

Sample size analysis and procedures

The sample size calculation was performed taking into account the identification of the three groups, with an effect size of 0.40, $\alpha = 0.050$, and with a power level of 0.80 for pain, which represented the primary variable selected for the analysis. The primary variable 'pain' presented a difference between groups of 0.60 (mean) and a standard deviation (SD) of 0.75. After an evaluation of these values, it was calculated that a minimum number of 31 patients in each group was necessary.

An inter-examiner reliability test was performed for the study, which showed an agreement of 85.3% ($\kappa = 0.62$) for the primary outcome (pain). Moreover, the intra-examiner agreement was evaluated by measurement of Cohen's kappa coefficient; this was $\kappa = 0.816$, indicating a high degree of reliability. The kappa coefficient was also calculated for the measurements taken at each follow-up session and an acceptable degree of reliability was established for every examination (intra-class correlation coefficient = 0.770).

In the first stage of the study, 119 patients (58 male, 61 female) from all patients who were referred to the Department of Odontostomatology of

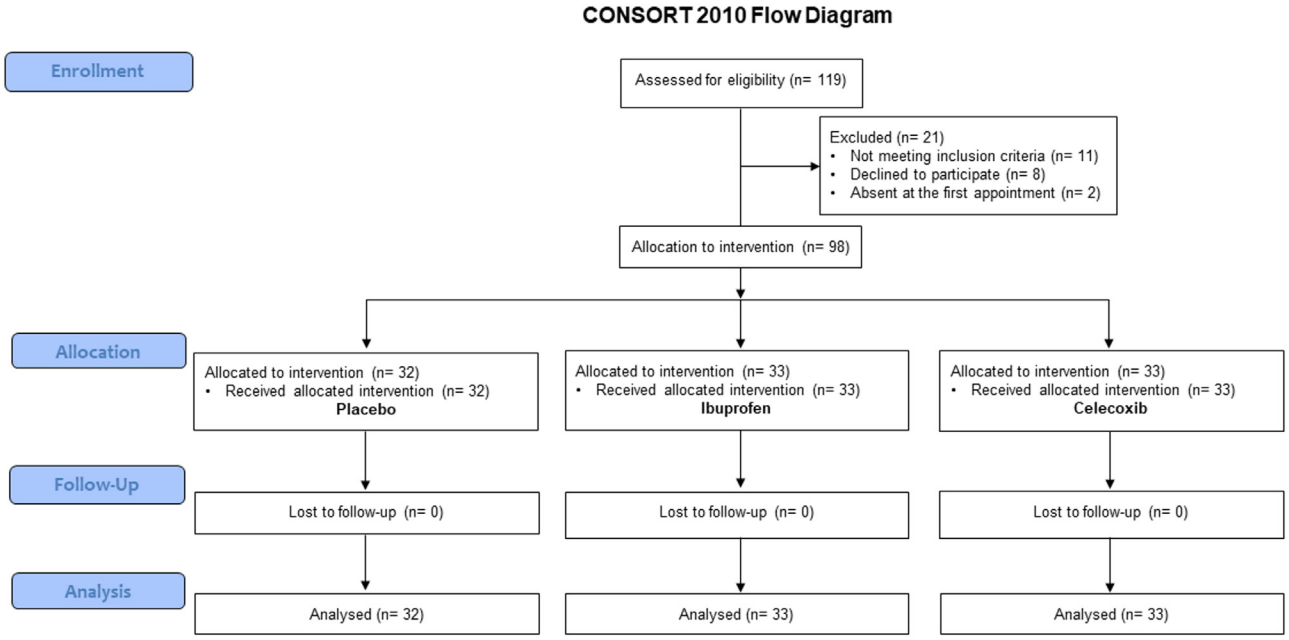

Fig. 1. Flowchart of patient recruitment into the study groups.

the University of Messina were recruited. After evaluation against the study criteria, 21 subjects (12 male, nine female) were excluded. These subjects did not meet the eligibility criteria ($n = 11$), refused to participate in the study ($n = 8$), or were absent at the baseline session ($n = 2$). Therefore, a final number of 98 patients were included in the analysis (Fig. 1).

All patients attended an initial preoperative screening consultation, which was performed by the same experienced clinician, who was blinded to the test medication administered. Patient data including age, sex, systemic diseases, coagulation and glycaemic parameters, and periodontal status were recorded preoperatively. The panoramic radiographs obtained prior to enrolment were examined to re-evaluate the tooth position, the degree of tooth impaction, and the degree of tooth/root formation of each third molar.

Each enrolled subject was assigned to one of three groups in accordance with the postoperative medication received: the placebo group patients ($n = 32$) were given a placebo capsule (sugar pill, Sucratol – placebo capsules) twice a day for 5 days; the ibuprofen group patients ($n = 33$) were given 400 mg ibuprofen twice a day for 5 days; the celecoxib group patients ($n = 33$) were given 200 mg celecoxib twice a day for 5 days. Before the procedure, each patient received 1 g amoxicillin with clavulanic acid as preoperative prophylactic therapy, 1 hour before surgery (Augmentin; GlaxoSmithKline, Milan, Italy).

All patients were allowed to extend the therapy up to 10 days if they presented a postoperative visual analogue scale (VAS) score for pain of ≥ 4 at 5 days after surgery[17]. No postoperative antibiotics were prescribed, but 0.12% chlorhexidine mouthwash three times a day for 7 days was prescribed for all enrolled subjects.

Randomization

The assignment of each patient to a study group was determined by means of a randomization technique using sealed and numbered envelopes; details of the sequence were concealed from all clinicians who participated in the study. An operator not involved in the subsequent experimentation generated a random allocation sequence, in a 1:1:1 ratio, for distribution of the patients to one of the three study groups. This was done with a permuted block design using a computer generator.

Before the start of each treatment, an operator who was not involved in the subsequent phases of the study or the data processing conducted the assignment of each sealed envelope (which contained the type of treatment and the patient's name and date of birth) to the therapist who subsequently prescribed postoperative therapy. The same operator who performed the statistical assignment phase was blinded to all patient clinical data and to the following analysis and evaluation of the data. For the codification of the single groups, it was decided, before the study, to assign the letter 'A' to the placebo treatment, the letter 'B' to the ibuprofen treatment, and the letter 'C' to the celecoxib treatment. Each envelope was used for each treatment assignment. In this phase, the type of treatment for each patient, useful for the subsequent statistical analysis, was registered. The patient, clinician, surgeon, and statistician who participated in the subsequent follow-up session were all blinded to the treatment data.

Treatment

All surgeries were performed by the same clinician in order to avoid any possible bias with regard to surgeon variability. Each enrolled subject underwent the same surgical extraction procedure, performed under similar clinical conditions. A local anaesthetic technique was employed that included inferior alveolar nerve blocks using mepivacaine 2% with epinephrine 1:100,000 (Molteni Farmaceutici S.p.A., Scandicci, Italy). The total amount of local anaesthetic used for the operation was recorded for each patient, by summing the number of dental cartridges used.

The same mucoperiosteal flap with subsequent osteotomy (useful for accessing the tooth) was performed in all patients. The bone was removed with a round bur in a straight hand-piece under continuous saline solution irrigation. In all subjects,

tooth sectioning and removal of the third molar was performed, following which granulation tissue was removed from the alveolar cavity. The surgical wound was closed using a 4–0 resorbable suture (Coated Vicryl (polyglactin 910); Ethicon, USA).

Immediately after surgery, postoperative therapy was carefully explained to each patient. They were instructed to follow a liquid and cold diet for the first 24 hours. Patients were also encouraged to maintain good oral hygiene and were informed of the possible symptomatology resulting from the surgical intervention. Possible surgical complications such as pain, swelling, and fever and the risks arising from the therapy including nausea, vomiting, or drug intolerance, were explained to all patients.

For the duration of the study, all patients were assisted by the surgical team in the event of any kind of postoperative problem, such as infection, uncontrolled pain, fever, or other complications due to the procedures, if necessary.

Outcomes

Immediately after surgery, details of each operation were documented, together with the total duration of surgery. The amount of postoperative pain was the primary outcome variable measured. This allowed the patient to describe their discomfort more objectively. The intensity of the primary pain variable was recorded using a 10-cm VAS, ranging from 0 (no pain) to 10 (maximum pain). Each subject was invited to register their perceived pain at 30 min, 2, 6, 12, 24, 48 hours, 7 and 10 days following surgery. At this stage, any additional analgesics or other drugs taken by each study participant were recorded.

The second outcome analysed was the appearance of postoperative swelling. For the analysis of this outcome, pre- and postoperative values (obtained at each follow-up session, i.e. at 24, 72 hours, 5, 7 and 10 days) of the different facial measurements were compared, as described previously[11] (Fig. 2): mandibular angle to tragus (distance MA–Tr), mandibular angle to external corner of the eye (distance MA–ECE), mandibular angle to nasal border (distance MA–NB), mandibular angle to labial commissure (distance MA–LC), and mandibular angle to soft pogonion (distance MA–SP).

For the clinical analysis of possible trismus, the maximum degree of mouth opening was measured. This was done at baseline, 24, 72 hours, 5, 7 and 10 days after surgery using a calibrated sliding caliper (TheraBite range of motion scales). The differences in the measurements compared to baseline were evaluated for each follow-up session.

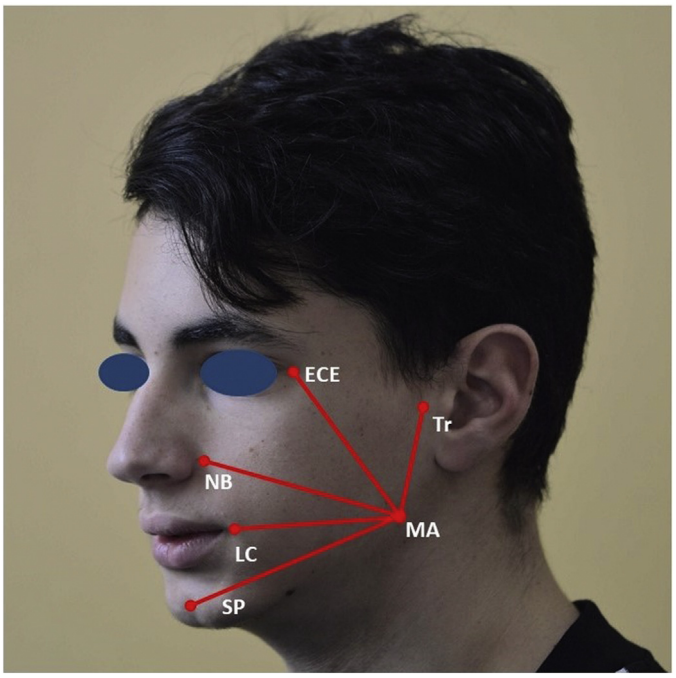

Fig. 2. Facial measurements taken in the study groups for the assessment of swelling. Red lines: mandibular angle to tragus (distance MA–Tr), mandibular angle to external corner of the eye (distance MA–ECE), mandibular angle to nasal border (distance MA–NB), mandibular angle to labial commissure (distance MA–LC), and mandibular angle to soft pogonion (distance MA–SP).

Statistical analysis

The Kolmogorov–Smirnov test revealed that the data examined were not normally distributed. Therefore, a non-parametric approach was taken for the analysis of the data. The Kruskal–Wallis test was applied to compare pain scores, facial distances, and maximum mouth opening among the three groups at each observation time point. The Mann–Whitney test was applied for two-by-two comparisons. The Friedman test was applied for the comparison of the measurements (pain scores, facial distances, and maximum mouth opening values) at the different observation time points within each group. The Wilcoxon test was used to perform two-by-two comparisons between time observations, for each follow-up session. Significance of the *P*-value was set at 0.05. The statistical analyses were performed using SPSS 17.0 for Windows statistical software (SPSS Inc., Chicago, IL, USA).

Results

All enrolled patients completed the study without any postoperative complications. The mean age of the 98 patients (48 male, 50 female) found to be eligible for the study was 28.9 ± 3.9 years. Thirty-two patients (17 male, 15 female) were randomly allocated to the placebo group, 33 patients (16 male, 17 female) to the ibuprofen group, and 33 patients (15 male, 18 female) to the celecoxib group. Postoperative healing was good in all patients, and no adverse events such as infections or abscesses were present during follow-up.

There were no significant differences between the groups regarding the quantity of dental anaesthetic used: placebo group, 2.9 ± 0.5; ibuprofen group, 2.4 ± 0.2; celecoxib group, 2.6 ± 1.1 ($P = 0.266$). The mean duration of surgery was similar in the three groups: 22.31 ± 6.64 min for the placebo group, 22.43 ± 5.31 min for the ibuprofen group, and 25.48 ± 5.35 min for the celecoxib group ($P = 0.169$). The osteotomy and tooth sectioning was performed without intraoperative accidents or complications in all enrolled patients.

The peak postoperative pain score was seen at 6 h in the placebo group, 12 h in the ibuprofen group, and 6 h in the celecoxib group (Fig. 3). Further comparison

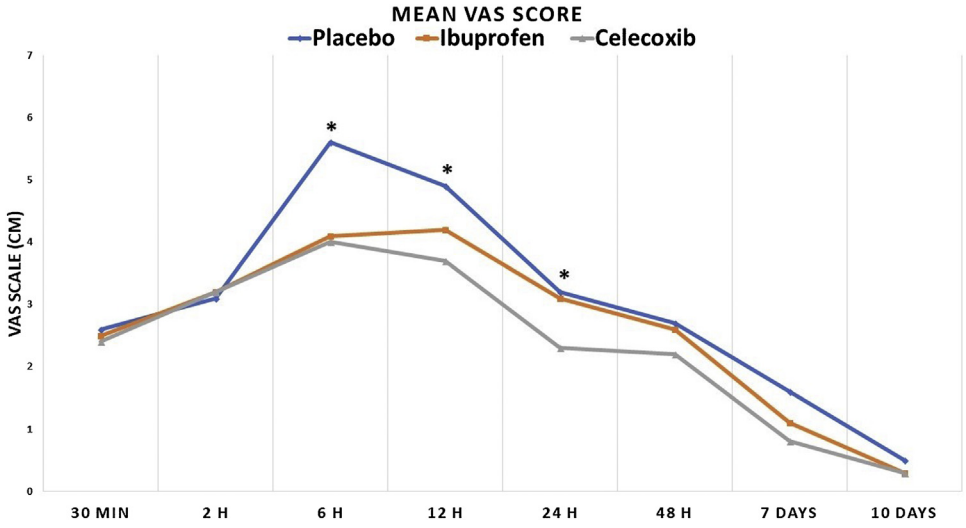

Fig. 3. Mean VAS pain intensity score in the study groups. Significance of comparisons between study groups: $*P < 0.05$.

between the groups showed that the mean VAS score was significantly lower in the celecoxib group at 6 h ($P < 0.001$), 12 h ($P = 0.011$), and 24 h ($P = 0.041$) following surgery compared to the other two groups, while it did not differ significantly at the other time points (Fig. 3).

Measurements of the facial distances, recorded pre- and postoperatively to determine the degree of swelling in the study groups, did not differ between the three groups at any of the observation time points ($P > 0.05$) (**Supplementary Material**, Appendix 2—Table S1). Moreover, the maximum mouth opening values did not differ significantly between the treatment groups at any of the observation time points ($P > 0.05$) (**Supplementary Material**, Appendix 2—Table S2). However, the comparison of maximum mouth opening between time points in each of the study groups highlighted statistically significant differences when the baseline values were compared to postoperative values: placebo group at 24 h ($P < 0.001$) and 5 days ($P = 0.004$); ibuprofen group at 24 h ($P < 0.001$) and 7 days ($P = 0.007$); celecoxib group at 24 h ($P < 0.001$), 72 h ($P = 0.008$), and 7 days ($P = 0.006$) (**Supplementary Material**, Appendix 2—Table S2). Moreover, in the celecoxib group, a significant difference in mean maximum mouth opening was demonstrated postoperatively when the value at 7 days was compared to the value at 24 h postoperative ($P = 0.006$).

Discussion

The aim of this study was to evaluate the effectiveness of ibuprofen and celecoxib in the prevention of perioperative discomfort after third molar surgery procedures. More specifically, it was sought to assess the efficacy of ibuprofen and celecoxib in the management of postoperative pain, facial swelling, and mouth opening compared to placebo. Treatment with celecoxib resulted in a significant decrease in the appearance and persistence of postoperative pain compared to ibuprofen and placebo.

During recent years, NSAIDs have been demonstrated to be effective among the anti-inflammatory drugs for the postoperative management of pain following the extraction of impacted third molars[18]. However, several studies have demonstrated adverse drug effects in patients on NSAIDs following their administration[18–20]. Olmedo et al.[21] reported that 37.3% of the patients who required adjunctive therapy with ketorolac or ketoprofen following third molar surgery presented adverse events such as drowsiness (10.7%), pyrosis (10.3%), and gastric lesions (8%).

Among the NSAIDs, potent, selective COX-2 inhibitors have been demonstrated to be efficacious for dental pain management[22,23]. Costa et al.[11] reported favourable effects using 120 mg etoricoxib as a preventive anti-inflammatory therapy in third molar surgery. Based on these pilot results, the present study was performed to analyse the effects of celecoxib compared to ibuprofen and placebo, as postsurgical therapy after the removal of impacted third molars. The results of this study showed that the postoperative administration of celecoxib significantly reduced postoperative pain compared to ibuprofen and placebo.

Morse et al.[24] evaluated the preventive analgesic effectiveness of ibuprofen compared to rofecoxib and a placebo. In that study, the authors observed that ibuprofen and rofecoxib provided similar results at 1, 3, and 4 hours after third molar surgery. Moreover, Yamashita et al.[13] found that when celecoxib was used to manage postoperative discomfort following third molar surgery, its efficacy with regard to the management of early stage acute pain was comparable to that of loxoprofen.

In the present study, celecoxib exhibited a substantial analgesic effect during the first postoperative week compared with ibuprofen and placebo. The group of patients who received celecoxib therapy showed a slight peak in postoperative pain at 6 h following the intervention; pain values then decreased continuously over the subsequent follow-up sessions. In contrast, the peak pain score occurred at 6 h in the placebo group and 12 h in the ibuprofen group and scores remained higher up to 48 hours following surgery. Moreover, the celecoxib group presented significantly lower mean pain scores at 6 hours ($P < 0.001$), 12 hours ($P = 0.011$), and 24 hours ($P = 0.041$) after surgery compared to the other groups, suggesting a better analgesic efficacy of celecoxib in the first phase of healing compared to the other treatments (Fig. 3). In this study, a 200 mg dose of celecoxib was found to be superior to a 400 mg dose of ibuprofen for the management of acute pain following the surgical removal of impacted third molars.

The results of this study are in agreement with those of other authors who have shown that celecoxib at a dose ranging

between 120 mg and 200 mg is effective in the short-term reduction (already at 2 hours) of the appearance of postoperative pain in patients undergoing dental procedures or third molar surgery[12,25].

With regard to swelling values, all groups presented comparable results. The swelling can be explained by the inflammatory and oedema responses that occur as a result of surgical trauma. This mechanism occurs mainly through the production of prostaglandins and cyclooxygenases, which are synthesized following arachidonic acid release from the cell membrane of cells at the surgical site[26]. In contrast to the results of the present study, some studies have previously shown that celecoxib, a COX-2 inhibitor, represents one of the best mediators, similar to other NSAIDs, for the reduction of the release of arachidonic acid, resulting in a clinical reduction in swelling[26,27].

The assessment of trismus, measured by comparing the maximum mouth opening values obtained at baseline to those obtained at each follow-up session, showed a significant decrease in the celecoxib group at 24, 72 hours and 7 days after surgery. These results are in accordance with the results of De Menezes and Cury[28], who performed a study in which patients took nimesulide, and Bjornsson et al.[29], who performed a study in which patients took ketoprofen, which both demonstrated that the use of NSAIDS resulted in a significant improvement in swelling and a reduction in trismus following third molar surgery. Positive effects of celecoxib include its association with fewer episodes of pyrosis and upper and lower gastrointestinal lesions compared to other NSAIDs such as diclofenac[30].

During the last few decades, different drugs have been proposed with the aim of reducing postoperative discomfort by helping to reduce pain and swelling following surgery without causing adverse effects. Identifying even more effective drugs or combinations of drugs for pain management following third molar surgery, with the purpose of discovering treatment strategies other than NSAIDs or corticosteroids, should be encouraged.

This study suggests that celecoxib used as postoperative therapy after third molar surgery shows favourable effects in the management of perioperative pain compared to ibuprofen and placebo. Celecoxib was found to be safe and simple to use in the postsurgical management of discomfort following third molar surgery. The results of this preliminary study are encouraging; however further research is required to provide a better understanding of the potential benefits of celecoxib in postoperative therapy following impacted third molar surgery.

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Competing interests

The authors declare that they have no conflict of interest or other benefits in relation to this article.

Ethical approval

This study followed the Declaration of Helsinki on medical protocol. The Institutional Review Board of the University of Messina approved the study protocol (#35-17).

Patient consent

Written informed consent was obtained from the patient for publication.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2019.02.006.

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