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Comparative analgesic effects of Ibuprofen, Celecoxib and Tramadol after third molar surgery: A prospective comparative study

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Abstract

This prospective comparative study included 200 healthy subjects who required surgical extraction of impacted mandibular third molars. The subjects were randomized into three equal groups and given appropriate doses of each drug immediately after extraction. They continued the drugs up to 48 hours after the extraction. Postoperative pain intensity was self-recorded by subjects at 4, 8, 16, 24 and 48 hours after the extraction, using a visual analogue scale (VAS). The mean VAS at each point of postoperative pain assessment was compared using one-way analysis of variance (ANOVA) among the three groups. The mean VAS score of the Celecoxib group (37.77) at 4 hours was the lowest. This was followed by the ibuprofen group with a mean VAS score of 44.20 Whereas, the subjects in the Tramadol group experienced the highest VAS score (58.26) at 4 hours. There was a statistically significant difference in the mean VAS scores at 4 hours after extraction when the three groups were compared ($p = 0.0039$). Celecoxib group also had the lowest mean VAS score. Celecoxib was the most effective analgesic of the three studied drugs in controlling postoperative pain after mandibular third molar extraction in our subjects. It was closely followed by ibuprofen while Tramadol was found to be the least effective. The outcomes of this study suggest that celecoxib can be prescribed for effective control of postoperative pain after third molar surgery. It also shows that ibuprofen can be an analgesic of choice for patients who are not at risk of gastrointestinal complications of non-steroidal anti-inflammatory drugs (NSAIDs).

Keywords: Celecoxib, Ibuprofen, Postoperative pain, Third molar surgery, Tramadol.

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1. Introduction

Pain is the most important symptom that brings the patient to the dentist. Analgesics are the drugs which relieve pain as a symptom, without affecting its cause. Analgesics most commonly prescribed in dentistry for pain relief include the non-steroidal anti-inflammatory drugs (NSAIDs) and various opioid-containing analgesic combinations [1]. Dental pain specifically third molar extraction is said to be one of the most acute postsurgical painful conditions [2].

The pain resulting from the removal of impacted third molar surgery is considered moderate to severe in intensity and is used as a parameter for evaluating the effectiveness of different drug therapies [3]. The surgical removal of impacted mandibular third molars is one of the most commonly performed dentoalveolar procedures in oral and maxillofacial surgery. In oral and maxillofacial surgery, acute postoperative pain is expected by both patients and medical person and can be usually explained by tissue damage, which promotes activation and sensitization of terminal nerve fibers [4].

Pain, trismus, and swelling are the most common postoperative complaints, and these influence a patient's quality of life in the days after surgery [5]

In addition to opioids, effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs), e.g. ketorolac, diclofenac, Tramadol, ibuprofen, indomethacin, tenoxicam in managing of postoperative pain has been confirmed NSAIDs, despite their inherent side effects, are widely used drugs—both prescribed and as self medication—because of their significant clinical spectrum and the relatively few complications with occasional use[6]. The advantages of the earliest possible administration of NSAIDs have been claimed by Seymour and Walton [7].

Most of the analgesic effects of NSAIDs have been attributed to their COX-2 inhibition, while their undesirable side effects have been attributed to their inhibition of COX-1 enzymes [8]. Ibuprofen and celecoxib are NSAIDs that exert their actions basically through inhibition of pro-inflammatory enzymes cyclooxygenase (COX).

Ibuprofen is a non-selective traditional NSAID (tNSAID) that nonspecifically inhibits both COX-1 and COX-2, while celecoxib, a newer drug, is a selective COX-2 inhibitor. COX-1, a constitutive enzyme is distributed throughout the body and is involved in the synthesis of protective prostaglandins in the gastric mucosa, kidneys and on platelets. COX-2, on the other hand, is expressed in a few specialized tissues and is only induced during inflammation. Therefore, when COX-2 is inhibited, prostaglandin formation is blocked. This leads to the prevention of inflammation and sensitization of peripheral nociceptors which are responsible for pain after third molar surgery.COX2-selective NSAIDs have commonly been used for their antiinflammatory and analgesic effects [9]. Bleeding and perforated gastroduodenal ulcers are among the most serious complications of NSAID therapy and may lead to significant morbidity, mortality, and financial costs [10].

Tramadol is a weak μ receptor agonist, imbuing the drug with opioid-like activity. In addition, tramadol inhibits the reuptake of norepinephrine and 5-hydroxytryptamine, an antidepressant-like action and thus activates monoaminergic spinal inhibition of pain [11].

This study aims to assess the effect of multiple doses of ibuprofen, a nonselective COX inhibitor, celecoxib, a COX-2 selective inhibitor and tramadol, a synthetic opioid in the control of pain among patients undergoing mandibular third molar surgery.

2. Material and method

2.1. Study Area:

The study is conducted at the Oral Surgery Department of the Educare Institute of Dental Sciences Chattipparamba.

2.2. Study design:

This prospective comparative study was done on 200 healthy subjects aged 20 to 45 years in the oral surgery department of the Educare Institute of Dental Sciences Chattipparamba between June 2018 and November 2018.

2.3. Study period: June to November 2018.

2.4. Study population:

Subjects underwent 3rd molar surgery, age 20 to 45 years, 200 patients enrolled in the study sample size.

2.5. Inclusion criteria:

Include subjects with at least one impacted mandibular third molar that was indicated for surgical extraction and confirmed by periapical radiographs (classified as mesioangular, distoangular, horizontal or vertical impaction), absence of uncontrolled medical or systemic conditions. Patient aged 20 to 45 years, with multiple transfusions, Those who agree to participate in the study.

2.6. Exclusion criteria:

Acute infection involving the mandibular third molar in question, unerupted mandibular third molar that is deeply buried in bone, uncontrolled medical or systemic disease, history of allergy or hypersensitivity to ibuprofen, celecoxib, tramadol, amoxicillin, and metronidazole, peptic ulcer

2.7. Ethical considerations:

Ethical clearance for the study was obtained from the Ethical Committee of Educare Institute of Dental Sciences, Chattipparamba. Written informed consent was freely obtained from each study participant following a clear explanation of the surgical procedure and study objectives.

2.8. Study procedure:

2.8.1 Sample Selection

A total of 200 healthy subjects aged 20 to 45 years were selected to participate in the study which was carried out in the oral surgery department of the Educare Institute of Dental Sciences Chattipparamba between June 2018 and November 2018.

The appropriate doses of each of the three medications: ibuprofen tablets; Celecoxib capsules and tramadol tablets were dispensed and kept in non-transparent sealed envelopes as follow: Tablets Ibuprofen 400 mg 8 hourly, caps celecoxib 400 mg start, then 200 mg 12 hourly and tablets tramadol 100 mg 8 hourly. There were 45 of such envelopes for each of the 3 study groups. There was no inscription of name or symbol on the tablets and capsules that could reveal the identity of any of the drugs. This assisted in ensuring the blinding of the patients to the medications.

Each envelope was labeled with a medication code number according to the randomization sequence that has been generated before the commencement of the study. The investigator was blinded to the medication patients were taking throughout the study as medication was handled by the independent observer.

2.8.2 Drug Administration

Patients were made to wait for postoperative monitoring in the recovery room where they were asked to pick one of the sealed non-transparent envelopes at random and the first dose of the enclosed oral medication was administered by the independent observer immediately after extraction. They were educated on how to take the remaining drugs at home and were given a telephone number of the independent observer which they called in case of any complaints related to the medications. Patients were instructed not to take any medications other than the ones already prescribed. The assigned analgesic was provided for every patient free of charge for a 48 hour period.

2.8.3 Postoperative Pain Assessment

Before the extraction, patients were given a visual analogue scale which comprised a horizontal line, 100mm in length with word descriptors at each end-point 0 at the left end representing "no pain" and points 100 at the right end representing "worst pain imaginable". They were then properly educated on how to record their pain intensity on the visual analogue scale by placing a vertical mark with a pen across the horizontal line of the VAS at the point they felt represented the pain they felt at intervals. Patients were then asked to record the pain intensity felt before the extraction, immediately after extraction thereafter, serially at 4, 8, 16, 24 and 48 hours after the extraction using the visual analogue scale. Patients were also asked to record any side effect or complication of the medication they felt and report to the independent observer administering the drug. Each patient was reviewed with their pain records 24 hours after the surgery, and subsequently at suture removal on the 7th postoperative day when they were also expected to submit their VAS recordings.

2.9. Statistical analysis:

The mean VAS at each point of follow-up was compared using one way ANOVA among the three groups with SNK or Turkey post hoc test when the F-test was significant. Regression methods for repeated data were used to determine the effect of other covariates in the determination of postoperative pain. Statistical significance was inferred at $p < 0.05$.

3. Results

The study recruited a total of 200 subjects 77 males (38.5 %) and 123 females (61.5%) whose ages ranged from 20 to 45 years with a mean 30.84 years. Demographic characteristics of the subjects between the three groups were similar for age and sex (Table 1). Pain intensities vary among the subjects after the third molar surgery between the three groups (Table 2).

Table 1: Distribution of patients by descriptive characteristics

Variable	Tramadol	Ibuprofen	Celecoxib
Mean age (years)	30.75	32.22	29.56
Sex(frequency)			
Male	24	27	26
Female	42	40	41

Figure 1: Age and gender distribution of the three groups

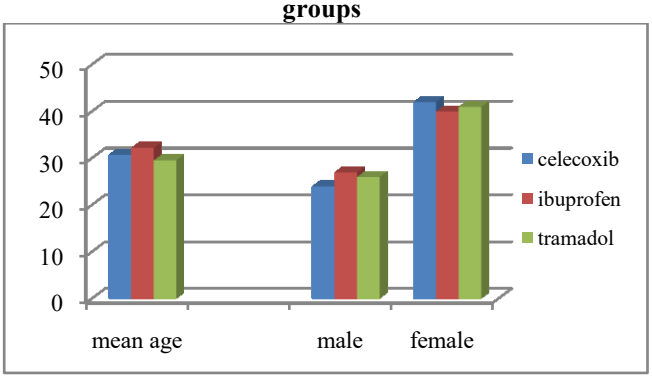
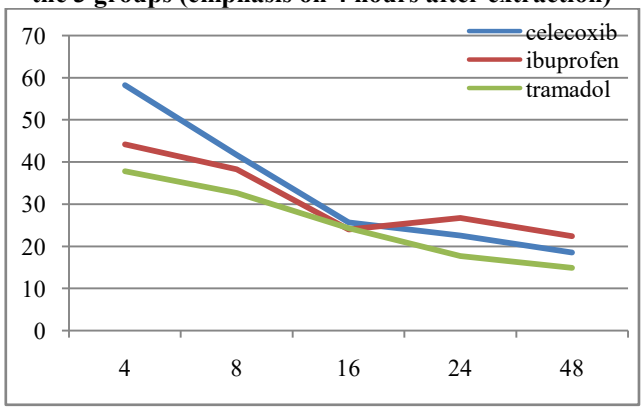


Table 2: Assessment of postoperative pain relief by mean VAS score

Time (Hr)	Tramadol	Ibuprofen	Celecoxib
4	58.26	44.20	37.77
8	41.71	38.37	32.62
16	25.61	24.02	24.24
24	22.50	26.72	17.67
48	18.54	22.42	14.84

Figure 2: Comparing pain intensities (VAS scores) in the 3 groups (emphasis on 4 hours after extraction)



The mean VAS score of the celecoxib group (37.77) at 4 hours was the lowest among the three groups. The Ibuprofen group was next with a mean VAS score of 44.20 whereas, the patients in the tramadol group

experienced the highest VAS score (58.26). There was a statistically significant difference in the mean VAS scores at 4 hours after the extraction when the three groups were compared ($p = 0.0039$).

The mean VAS score of the tramadol group at 8 hours was 41.71, while that of ibuprofen and celecoxib groups were 38.37 and 32.62 respectively.

The mean VAS score of the celecoxib (24.02) at 16 hours remained the lowest of the three, followed by ibuprofen (24.24) and tramadol (25.61).

At 24 hours, the celecoxib group still had the lowest mean VAS score (17.67), followed by tramadol (22.50) and ibuprofen (26.72). When celecoxib and ibuprofen groups were compared, the mean VAS scores of the ibuprofen group were higher than that of celecoxib except at 16 hours after the extraction.

There was no statistically significant difference in the two groups at all the time points after extraction.

4. Discussion

Our study compared the analgesic effects of multiple doses of celecoxib, tramadol, and ibuprofen on postoperative pain after third molar surgery over a period of 48 hours. The maximum pain intensity felt in all the groups was recorded at 4 hours and 8 hours after the extraction. This agreed with the findings of other studies that the postoperative pain after extraction is usually highest within the first 12 hours after the procedure [12,13]. The level of difficulty involved in the surgical removal of a mandibular impacted third molar depends on the type of impaction [14]. In our subjects, celecoxib was the most effective in controlling postoperative pain after mandibular third molar extraction throughout the 48 hour period. It was followed closely by ibuprofen, while tramadol produced the least analgesic effect.

Submucosal tramadol represents an effective, safe and reliable method of reducing postoperative acute facial pain after impacted third molar surgery as per the studies [15]. However, in this study, Tramadol produced the least pain relief with a considerable margin in our subjects compared with celecoxib and ibuprofen throughout the period of assessment. Robert *et al* [16] compared onset time for pain relief for tramadol and ibuprofen. They found out that patient receiving tramadol requires more time for the onset of pain relief compared to ibuprofen. These findings agree with our observation Where Tramadol produced the least pain relief with a considerable margin in our subjects compared with celecoxib and ibuprofen throughout the period of assessment. The lack of anti-inflammatory and antipyretic effects of tramadol, as well as its inability to prevent prostaglandin synthesis, limits its analgesic activity.

The result of this study demonstrated a far higher analgesic efficacy of celecoxib above tramadol. Ibuprofen also appeared to be more efficacious than tramadol. Studies have described satisfactory analgesic efficacy of tramadol following many dental procedures and it appears its adverse effect profile is more acceptable to ambulatory surgical patients when compared with the traditional opioids.

5. Conclusion

The result of this study showed that celecoxib and ibuprofen are more efficacious than tramadol in the control of postoperative pain following mandibular third molar extraction. Celecoxib, however, produced a better analgesic effect than ibuprofen when the two were compared. Tramadol, even though demonstrated remarkable pain relieving ability after mandibular third molar extraction was the least efficacious of the three. Celecoxib and ibuprofen appeared to be generally safe for treatment of acute postsurgical pain as no adverse effect was associated with their administration for the 48 hours postoperative period. The administration of tramadol in this study was significantly associated with adverse effects.

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