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Review Article

**EFFECTIVENESS OF ORAL ANALGESICS IN CONTROL OF
DENTAL PAIN: A SYSTEMATIC REVIEW*****Mohammed Faraj Alsalem¹, Ali Mohammed Almakrami², Jaber Mahdi Alyami³,
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National College, ⁵Qassim University. ⁶Alfarabi colleges**Abstract:****Introduction:**

Trauma to either soft and hard tissues are usually associated with surgical dental extraction and deep cavity preparations, often accompanied with pain and swelling. The aim of this review was to review clinical trials investigating the effectiveness of oral analgesics in control of dental pain.

Materials and methods: A web search was conducted in MEDLINE database and the resultant studies were screened for eligibility criteria including clinical trials conducted among human subjects in the last 5 year. The trials should aim to assess the effect of the analgesics in the control of postoperative dental pain. The full articles were retrieved for the eligible studies and the secondary screening was conducted to exclude the ineligible studies based on the full text reading.

Results: Our search identified eligible 49 articles underwent full-text review and 8 met our inclusion criteria enrolling 2406 patients. Codeine 60mg added to a paracetamol 1000 mg/ibuprofen 400 mg regimen does not improve analgesia following third molar surgery. Tramadol/Acetaminophen decreased pain over time from time point 6 hours. Pain intensity was significantly lower over 24 hours with ER naproxen sodium vs. placebo. Etoricoxib was more effective than Paracetamol/ Acetaminophen and the placebo.

Conclusion: Because of the absence of strong evidence, no clear evidence whether the foundational non-steroidal anti-inflammatory (NSAIDs) are more compelling than paracetamol at reducing pain related with dental treatment.

Keywords: Analgesics, Dental, Surgery, Operative, Efficacy.

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INTRODUCTION:

The postoperative dental pain was reported to range from moderate to severe pain in the first day [1]. The pain usually reaches the peak 6 to 8 hours after conventional local anesthetic administration [2]. Trauma to either soft and hard tissues are usually associated with surgical dental extraction and deep cavity preparations, often accompanied with pain and swelling [3].

One of the treatment options to be used as pain relievers for surgical teeth extraction and cavities preparations are nonsteroidal anti-inflammatory drugs (NSAIDs) [4]. The postoperative pain intensity can be reduced and delayed by the reduction in the pain triggers (prostaglandins) amount secreted into the injuries site [5]. The time leading to the amplification of the pain intensity increased by the accumulation of prostaglandins secreted from the injured tissues [6]. Other NSAIDs acts by different mechanisms, such as Diclofenac which acts by antagonizing the chemical substances called cyclooxygenase (COX) enzymes. Locations of damage or mischief are viewed as the ordinary place for generation of the prostaglandins, which cause pain and inflammation. By blocking the impact of COX chemicals, less amount of prostaglandins are formed and as an outcome less pain and inflammation are felt [7].

There are 2 formulas of Diclofenac in the market; Diclofenac sodium and Diclofenac potassium. The absorption of Diclofenac potassium to patient's blood stream is faster than Diclofenac sodium (citation). As a rule, the earlier the analgesic absorbed the quicker the onset of action will be. Thus, Diclofenac potassium is a fast acting analgesic and useful for the patients who are required immediate relief of pain [7].

A study by Ferraiolo and Veitz-Keenanb [8] compared various pain killers after the extraction of third molar. Information with respect to the degree of analgesia and the requirement for extra pain killers were gathered at 6 hours post surgically. The result of this investigations uncovered that ibuprofen has more efficacy than paracetamol at doses of 200 mg to 512 mg and 600 mg to 1000 mg, respectively. Krishnan *et al.* [9] done investigation with deeply carious teeth on 40 healthy patients aged from 18-50 years old, who have been referred for extraction under local anesthesia (LA) of lower molars. The study sample was divided into two groups, one group was assigned to receive transdermal diclofenac patches while the other group were assigned to receive oral diclofenac for management of postoperative pain. The pilot

study found that effectiveness of transdermal diclofenac was equal to oral diclofenac in control of postoperative pain. Bauer *et al.* [9] study showed that ibuprofen alone was inadequate to avert pain in surgery of third molar. However, the combining of ibuprofen and dexamethasone has more efficacy in the central nervous system.

The most frequently used drug combination for the management of moderate-to-severe acute pain is codeine/acetaminophen because of its effectiveness and low side effects profile [10]. However, the combination of tramadol/acetaminophen has also been suggested as other option to manage acute pain [11]. The utilization of tramadol has been demonstrated compelling in treating a few instances of intense and persistent pain. Nonetheless, the advantages of its utilization in the treatment of intense pain of dental origin are not well known (citation).

The aim of this review was to review clinical trials investigating the effectiveness of oral analgesics in control of dental pain.

METHODS:

A web search was conducted in MEDLINE database using this strategy (dental pain OR toothache OR dental decay OR periodontitis) AND (analgesics OR paracetamol OR opioids OR NSAIDs OR acetaminophen OR anticonvulsants) AND (Effectiveness OR efficacy). The resultant studies were screened for eligibility criteria including clinical trials conducted among human subjects in the last 5 year. The trials should aim to assess the effect of the analgesics in the control of postoperative dental pain. The full articles were retrieved for the eligible studies and the secondary screening was conducted to exclude the ineligible studies based on the full text reading. The data were extracted from included studies for characteristics such as sample size and type of dental disease such as dental caries, gingivitis, postoperative, dental abscess, facial pain. Type of analgesics including doses of analgesic and comparison drug (if present), in addition to the effectiveness of studied analgesics. The data were presented in the table and discussed in a narrative approach.

RESULTS:

Our search identified eligible 49 articles underwent full-text review and 8 met our inclusion criteria enrolling 2406 patients (Table 1). The largest sample size was 701 recruited in the study done by Yue *et al.* [12] and smallest sample size was 26 in the study conducted by Santini *et al.* [13]. All included studies

were double-blind randomized controlled trials (12-18). Regarding the cause of postoperative pain, surgical removal of at least one impacted mandibular third molar extraction of one or two impacted third molars (at least one partial mandibular bony impaction in Laurora et al., [14], third molar extraction in Clarence et al., [15], Yue et al., [12], Brown et al., [16] and finally fixed orthodontic appliance treatment in Gupta et al., [17].

Concerning the type and dose of analgesic investigated in the included studies, paracetamol 1000 mg, ibuprofen 400 mg, codeine 60mg investigated in a study of Best et al. [18], while codeine 30 mg plus acetaminophen 500 mg or tramadol hydrochloride 37.5 mg plus acetaminophen 500 mg in Santini et al. [13]. Oral ER Naproxen sodium 660 mg (single dose) or immediate-release (IR) Naproxen sodium 220 mg three times a day in Laurora et al. [14], Naproxen submicron particle capsules 200 or 400 mg, Naproxen tablets 250 or 500 mg in Clarence et al. [15]. A single dose of FD-APAP 1000 mg, FD-APAP 500 mg, or a single dose of FD-APAP 1000 mg, standard APAP 650 mg in Yue et al. [12].

Etoricoxib 120 mg once daily or Etoricoxib 90 mg once daily, Ibuprofen 600 mg every 6 hours and Acetaminophen 600 mg/Codeine 60 mg every 6 hours in Brown et al. [16] and Paracetamol/Acetaminophen 500mg thrice daily and Etoricoxib 60mg once daily in Gupta et al. [17].

The primary outcome was the pain scores in all included studies. It was assessed using visual analogue scale (VAS) in all included studies except in Laurora et al. [14] and Yue et al. [12] who used primary efficacy endpoint of 24 hours summed pain intensity difference (SPID). The secondary outcomes included total pain relief (TOTPAR) and use of rescue medication, as in study of Clarence *et al.* [15]. The primary efficacy parameter was patient-reported total pain relief over 0 to 12 hours following administration of study medication.

Regarding the effectiveness of studied analgesics, Codeine 60mg added to a paracetamol 1000 mg/ibuprofen 400 mg regimen does not improve analgesia following third molar surgery in Best *et al.* [18]. For the Codeine/Acetaminophen group, there was a significant reduction in the scores 12, 24, 48, and 72 hours after treatment ($P < 0.05$). In the Tramadol/Acetaminophen group, the scores significantly decreased over time from time point 6 hours in a study of Santini *et al.* [13]. Pain intensity was significantly lower over 24 hours with ER

naproxen sodium vs. placebo ($p < 0.001$), with significant relief from 15 min, ER naproxen sodium was non-inferior to IR naproxen sodium, reducing pain intensity to a comparable extent over 24 h in Laurora et al., [14]. Naproxen submicron particle capsules 200 mg (25.9 ± 2.0 ; 95% CI 21.9–29.8), (Naproxen tablets 250 mg (24.4 ± 2.0 ; 95% CI (28.3–20.4) Naproxen submicron particle capsules 400 mg (31.9 ± 2.0 ; 95% CI (35.8–28.1 and naproxen tablets 500 mg 95% ; 2.0 ± 28.5) CI 24.7–32.4) groups experienced greater pain relief over 12 h compared with placebo ($P < 0.001$) in Clarence et al., [15]. FD-APAP 1000 mg demonstrated significantly greater effect compared with FD-APAP 500 mg, APAP 650 mg, and placebo for all efficacy measurements, including sum of pain relief and pain intensity difference, total pain relief, sum of pain intensity difference, pain intensity difference, and pain relief score during 6 hours after the dose in Yue et al., [12].

Average pain recall scores were lower than placebo for all active treatments on Day 2 but only for Etoricoxib 120 and 90 mg on day 3 in Brown et al., [16] and finally The three groups' results were statistically significant ($p < 0.001$) and Etoricoxib proved to be more effective than Paracetamol/Acetaminophen and the placebo; the Paracetamol/Acetaminophen was more also effective than the placebo in Gupta et al., [17]. Concerning the side effects of the analgesics, control participants (18%) intervention participants (6%) in Best et al., [18], there was no difference between the groups regarding the frequency of adverse reactions in Santini et al. [13].

Once daily ER naproxen sodium was generally safe and well tolerated, with a similar safety profile to IR naproxen sodium tid in Laurora et al., [14], adverse events were generally similar across all treatment groups in Clarence et al., [15], nausea and vomiting were among the most common adverse events with higher frequency in the A/C group in Brown et al., [16] and finally the side effects not reported in Yue et al. [12] and Gupta et al. [17].

DISCUSSION:

Control of postoperative pain with Many analgesics is essential for successful dental treatment and the current presentation of new drugs gives considerably more alternatives from which to pick [19]. The purpose of this review is to review the evidence regarding the analgesics used to control dental pain. Many trials provided the evidence of APAP efficacy for control of moderate pain emerging from headache

[20], musculoskeletal conditions [21], dysmenorrhea [22], and dental pain [23-26]. Pain following third molar extraction is an exceptionally precise model that can build up important adequacy contrasts amongst medications and has been utilized already to describe the impacts of over-the counter analgesics, including APAP. Acetaminophen has not been in an NSAIDs classification and its analgesic mechanism of action has been unknown historically [27].

NSAIDs and Acetaminophen works partially by antagonizing prostaglandin formation through the blocking of cyclooxygenase 1 and cyclooxygenase 2, with extra action connected to the nervous system by means of endogenous neurotransmitter frameworks [28]. Less gastrointestinal and cardiovascular adverse events associated with acetaminophen than NSAIDs. Its needed to treat number is more than the rest of NSAIDs, for acetaminophen 500 mg having a number expected to treat of 3.5 on the Oxford League table. Late confirmation recommends that joining ibuprofen and acetaminophen has a more noteworthy pain relieving impact than either medicate alone [29].

Pain relieving drug regimens that are compelling in instances of severe pain may not be as useful in instances of chronic pain [30]. There are different results regarding efficacy [13], this variation will be due partly to small sizes [31]. in addition since we realize that techniques for gathering side effects information strongly affect the revealed frequency, and on the grounds that strategies utilized changed [32]. There is a robust evidence of good viability for the analgesics usually endorsed by dental specialists, except for Dihydrocodeine where there was little confirmation altogether, and no persuading proof regarding adequacy. With the data accessible, standard measurements of NSAIDs and COX-2 inhibitors gave the best pain relieve [33].

Ibuprofen versus Paracetamol in dental trials concluded that ibuprofen was superior [34]. All data were measured using a visual analogue scale (VAS), with most studies comparing the effectiveness of drug interventions at 2 hours, 6 hours and 24 hours following dental pain. Both Paracetamol and NSAIDs were effective at reducing pain intensity at 2 hours, 6 hours and 24 hours after treatment compared with a placebo (12-18). Non-steroidal anti-inflammatory drugs (NSAIDs) were significantly more effective at reducing pain intensity than a control intervention at all-time points (14-18). There is moderate-quality evidence that the use of analgesics reduces the pain associated with dental treatment.

In the included study of tramadol and codeine [13]

with a results that agreed with a meta-analysis that used third molar extraction as a pain model [35], the Tramadol/Acetaminophen combination (75 mg/650 mg) was superior to the sole use of tramadol or acetaminophen and to placebo with regards to the intensity and duration of analgesia. Using the same pain model, Macleod, et al. [36] found that pain intensity was significantly lower after 12 hours in patients who received codeine/ acetaminophen (30 mg/1.0 mg) than reported for patients receiving acetaminophen alone.

Limitations of this review included the significant heterogeneity in the included studies, since they differed in the timing of drug administrations, the dose, and the time after administration when the effect was measured.

COCLUSION:

Because of the absence of strong evidence, no clear evidence whether the foundational non-steroidal anti-inflammatory (NSAIDs) are more compelling than paracetamol at reducing pain related with dental treatment. The findings of this review showed that there is a need for more long term, well designed and reported randomized controlled clinical studies to assess the efficacy of drug interventions with relation to NSAIDs and paracetamol with a clear inclusion and exclusion criteria, sufficient sample size, appropriate data analysis and side effects reporting.

Conflict of interests:

Authors declared no conflict of interests.

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Table (1); Summary of the findings regarding analgesics of postoperative dental pain

| Study | Sample size | Type of dental disease | Intervention | Comparison analgesics | Method of assessment | The effectiveness of studied analgesics | Side effects |
|-------|-------------|---|--|---|----------------------|--|---|
| [18] | 131 | Surgical removal of at least one impacted mandibular third molar requiring bone removal | Codeine 60mg added to a paracetamol 1000mg/ibuprofen 400mg regimen | Paracetamol 1000mg/ibuprofen 400mg | VAS | Codeine addition does not improve analgesia following third molar surgery | Control group (18%) Intervention participants (6%) |
| [13] | 26 | Acute peri-radicular abscess | Codeine (30 mg) plus acetaminophen (500 mg), every 4 h, for 3 days | Tramadol hydrochloride (37.5 mg) plus acetaminophen (500 mg), every 4 h, for 3 days | VAS | Intervention group had a significant reduction in the pain 12, 24, 48, and 72 hours after treatment. In the Tr/Ac group, the scores significantly decreased over time from time point 6 h. | The combination of Tr/Ac caused more adverse reactions as two patients had to stop using the medication. |
| [14] | 612 | Moderate to severe pain after extraction of one or two impacted third molars (at least one partial mandibular bony impaction) | Oral ER naproxen sodium 660 mg (single dose), or immediate-release (IR) naproxen sodium 220 mg 3 times per day | Placebo | SPID, and TOTPAR | Pain intensity was significantly lower over 24 h with ER naproxen sodium vs. placebo. ER naproxen sodium was non-inferior to IR naproxen sodium, reducing pain intensity to a comparable extent over 24 h. | Once daily ER naproxen sodium was generally safe and well tolerated, with a similar safety profile to IR naproxen sodium. |
| [15] | 254 | After third molar extraction | Naproxen submicron particle capsules 200 or 400 mg, naproxen tablets 250 or 500 mg | Placebo | SPID, and TOTPAR | Naproxen groups experienced greater pain relief over 12 h Compared with placebo | Adverse events were generally similar across all treatment groups |

| | | | | | | | |
|------|--|---|--|---|--|--|---|
| [12] | 701 | The postsurgical dental pain following third molar extraction | Paracetamol (APAP), a single dose of 1000 mg or 500 mg was given | Placebo | VAS | 1000 mg demonstrated significantly greater effect compared 500 mg, or placebo for all efficacy measurement. | Not reported |
| [16] | 588 | Third-molar Extraction Dental Pain | Etoricoxib 120 mg once daily, Etoricoxib 90 mg once daily, ibuprofen 600 mg every 6 hours and acetaminophen 600 mg/codeine 60 mg (A/C) every 6 hours | Placebo | AWRPA and GAS M | Average Pain Recall scores were lower than placebo for all active treatments on Day 2 but only for Etoricoxib 120 and 90 mg on Day 3 | Nausea and vomiting were among the most common adverse events with higher Frequency in the A/C group. |
| [17] | 45 | Patients undergo fixed appliance orthodontic treatment | Paracetamol/acetaminophen 500mg thrice daily; placebo in the form of empty Capsules; and etoricoxib 60mg once daily. | Group took 500 mg paracetamol Group took 60 mg etoricoxib; | VAS at time intervals of 2h after insertion of the appliance | Etoricoxib was more effective than paracetamol/acetaminophen and the placebo and the paracetamol/acetaminophen was more also effective than the placebo. | Not reported |
| [37] | 94 bilateral symmetrical third molar surgeries | Third molar surgeries | Ibuprofen group and ibuprofen + dexamethasone group | Placebo | VAS | There was no significant difference between ibuprofen and placebo for postoperative pain | |

VAS= Visual Analogue Scale, SPID=Summed pain intensity difference, TOTPAR= Total Pain, AWRPA=Average and Worst Recall Pain Assessments, GAS M=Global Assessments of Study Medication.