Editorial Commentary

Examining combination of etodolac and dexamethasone improves preemptive analgesia in third molar surgery: a randomized study

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Combination of etodolac and dexamethasone improves preemptive analgesia in third molar surgery: a randomized study (1)

This study investigated the preemptive analgesic effectiveness of 8 mg dexamethasone (DEX) and 300 mg etodolac (ETO) in reducing post operative pain after third molar extractions. It was a triple blinded crossover study with 40 participants divided into 3 arms with 20 mandibular third molars extractions in each arm. The arms were DEX + ETO, ETO alone and DEX alone; the study drugs were administered 1 hour prior to the surgical extraction of mandibular third molars. The primary outcomes included pain measured on a Visual Analog Scale (VAS) at 6 h, 12 h, 24 h, 48 h, 72 h and 7 d post operative time points and the number of rescue analgesics (750 mg paracetamol q6h) used. Secondary end points measured included edema and trismus at 48 h and 7 d. The age range was 18–35 and the level of impaction of the third molars was controlled (Class I&II and position A/B per the Pell and Gregory systems). There was a single surgeon with a standardized local anesthesia, surgical protocol and suture closure for all 60 teeth extracted. The VAS scores and edema/trismus measurements were collected by the same individuals using precision equipment.

Exclusion criteria included ingestion of medications in the prior 21 days, post operative alveolitis or complications (1 tooth was eliminated), and allergies to the medications being studied. However, it was unclear if surgical difficulty, surgical time, preoperative pain levels from periodontal disease or other conditions of the mouth/dentition were considered.

The reported result from this study was DEX + ETO arm had the lowest VAS measurements and need for rescue analgesics. This was statistically significant ($P<0.001$ and $P<0.014$) from the other arms. Secondary end point measurements at 48 h (trismus and edema) were not significantly different among the arms, but at 7 d, the ETO arm had the highest trismus measurement in statistically significant fashion ($P<0.05$).

Preemptive analgesia and its evolution over a century

To better understand the goals of Ramires *et al.*, it would be helpful to review the concept of preemptive analgesia as it was first introduced and how it evolved over time. The concept of preventing postoperative pain by preoperative interventions was first introduced by Crile (2) in 1913 who demonstrated that post-surgical central nociceptive hyperexcitability could be blunted by utilizing inhaled nitrous oxide and local anesthesia in abdominal surgery. Hutchins and Reynolds (3) in 1947 showed how preoperative local anesthesia reduced hyperalgesia and referred pain at the maxillary sinus after dental surgery. Wall (4) and Woolf (5) characterized and demonstrated the concept of central sensitization and introduced the positive effect of analgesics (6). Kissin (7,8) defined how preemptive analgesia prevented central hyperexcitability and how analgesic effectiveness and efficacy could be measured with pre incisional and post incisional VAS scores.

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Gordon *et al.* (9) demonstrated that preoperative blocks with bupivacaine reduced or eliminated the afferent barrage from noxious stimuli during extraction of third molars under general anesthesia that contributed to postoperative analgesia. Dahl and Møiniche (10) made an important contribution which concluded that various drugs could be used for preemptive analgesia and highlighted its role in reducing chronic post operative pain. Katz *et al.* (11) broadened preemptive analgesia to "preventive analgesia" which was further expanded upon by Vadivelu *et al.* (12). This suggests interventions can be studied in pre, intra and post surgical timeframes.

A selected literature search of contemporary and related publications is shown in *Table 1*. In summary, preemptive analgesia in oral surgery has been studied using non-pharmacological, corticosteroids, non-steroidal anti-inflammatory, opioid and central active analgesic drugs. Specific to DEX and ETO used in this study, previous studies showed significant lower pain reported with DEX and ETO together as well as alone or in combination with other medications.

Cetira Filho *et al.* (20) conducted a systematic review of 31 articles published between 1978–2018 and a meta-analysis of 10 placebo controlled studies investigating preemptive non-steroidal anti-inflammatory drugs (NSAID) use with removal of third molars. The meta analysis was somewhat limited due to high heterogeneity in study methodologies with different NSAIDs studied and varying surgical protocols. However with an n=151 statistically significant pain reduction was observed at 1 h and 6 h (P<0.001). This did not apply to all NSAIDs—naproxen, diclofenac and ketoprofen likely due to their pharmacokinetics (half-life

Table 1 A brief review of the other contemporary literature on preemptive analgesia in oral surgery

Author and year	Type of study	Studied N and groups	Studied medications	Results
Lebrun *et al.* 2006 (13)	Prospective placebo controlled RCT—Level 2	84 patients (I) 30 patients placebo group (II) 31 patients IV ketamine pre operative (III) 23 patients IV ketamine post operative	Ketamine—IV 300 µg/kg	No statistically significant differences between the groups, pre, post and placebo groups in reducing rescue analgesics in PACU or POD 1/2
Gelesko *et al.* 2011 (14)	Multicenter retrospective comparative study—Level 3	206 patients (I) 51 patients Cryotherapy group ('05-'09) (II) 63 patients minocycline group ('03-'04) (III) 92 patients control group ('02-'06)	Cryotherapy (24 hour cold wrap) Minocycline (topical application)	Statistically significant decreases in highest post operative pain in both treatment groups
Baygin *et al.* 2011 (15)	Double-blind, prospective, placebo controlled RCT—Level 2	45 pediatric patients (I) 15 patients IBU PO (II) 15 patients paracetamol PO (III) 15 patients control group	IBU 100 mg/5 cc Paracetamol 250 mg/5 cc	Both study groups had statistically significant lower pain scores and IBU had even lower pain at 15 min (P<0.05) and 4 h (P<0.009) compared to Paracetamol
Bauer *et al.* 2013 (16)	Split mouth, Double-blind, prospective, placebo controlled RCT—Level 2	47 patients with 94 impacted third molars (I) IBU 600 mg *vs.* placebo (II) dexamethasone 8 mg + IBU 600 mg *vs.* placebo	IBU 600 mg DEX 8 mg	G1 (IBU *vs.* placebo) showed no statistically significant differences. G2 showed DEX + IBU had statistically significant decrease in pain and rescue analgesics

Table 1 *(continued)*

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Table 1 *(continued)*

Author and year	Type of study	Studied N and groups	Studied medications	Results
Silva de Oliviera *et al.* 2016 (17)	Split mouth, Double-blind, prospective, RCT—Level 2	20 patients with 40 impacted third molars	DEX 4 mg	Statistically significant reduction in edema and trismus in ETO group at day 2 and day 7. Statistically insignificant lower post operative pain scores in ETO group
		(I) dexamethasone pre operative, IBU post operative	IBU 600 mg	
		(II) dexamethasone pre operative, ETO post operative	ETO 300 mg	
Momesso *et al.* 2021 (18)	Triple-blind, prospective, RCT—Level 2	100 patients		DEX + ETO and DEX + KET as statistically significant in reducing immediate post op pain. DEX + ETO group also had lower need for rescue analgesics compared to all other groups
		(I) 20 patients DEX group	ETO 300 mg	
		(II) 20 patients DEX + ETO group	KET 10 mg	
		(III) 20 patients DEX + KET group	LOX 60 mg	
		(IV) 20 patients DEX + LOX group	IBU 600 mg	
		(V) 20 patients DEX + IBU group	DEX 8 mg	
Santos *et al.* 2021 (19)	Split mouth, Triple-blind, prospective, placebo controlled RCT—Level 2	100 patients with 200 impacted third molars		IBU and NIM most efficacious in reducing pain at the T6 h, T12 h and T24 h
		(I) 20 patients Acetaminophen *vs.* Placebo	Acetaminophen 1,000 mg	All medications other than Acetaminophen had statistically significant reduction in edema
		(II) 20 patients IBU *vs.* placebo	IBU 600 mg	
		(III) 20 patients Ketoprofen *vs.* placebo	Ketoprofen 100 mg	
		(IV) 20 patients NIM *vs.* placebo	NIM 100 mg	
		(V) 20 patients DEX *vs.* placebo	DEX 4 mg	

RCT, randomized controlled trial; PACU, post-anesthesia care unit; POD, post-operative day; PO, per oral; IBU, ibuprofen; DEX, dexamethasone; ETO, etodolac; KET, ketorolac; LOX, loxoprofen; NIM, nimesulide.

>6 h). This is one of very few Level 1 evidence describing the effectiveness of NSAIDs in preemptive analgesia.

Yamaguchi and Sano (21) conducted an expansive review of prospective randomized controlled trials (RCTs) investigating preemptive analgesia. Drawing a distinction between central and peripheral sensitization and arguing that the area of tissue damage is crucial in the efficacy of preemptive analgesics, they highlight how this concept might need to be altered for third molar extractions. Abdominal or thoracic surgery where extensive tissue damage is present, inhibiting central sensitization becomes crucial. Conversely, these authors argue that in third molar extraction, the smaller wound penetrating through bone likely produces post operative pain largely through peripheral sensitization. While preemptive NSAIDs do reduce post operative pain in third molar extraction through

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some inhibition of central sensitization, combining this with a post-surgical dose of analgesics before peripheral sensitization occurs may lead to better post operative pain reduction.

Commentary regarding the Ramires *et al.* (1) publication on DEX and ETO in preemptive analgesia

Strengths in study design

Ramires *et al.* (1) was an admirable venture in studying the efficacy of DEX and ETO in reducing post operative pain. The single operator model with uniform procedural protocols, clear exclusion criteria, careful case selection with standardized outcome measures and following COHORT all lend credence to the findings of the publication. The original authors are also very considerate of the body of work preceding their publication in selecting DEX and ETO specifically due to their higher efficacy when compared to other NSAIDs (17,18) or NSAIDs without steroids (16).

Weaknesses in study design

The demographics and n are rather skewed and small in this study. With 30/40 participants being females and an n of 60 teeth with no clear exclusion criteria based on surgical difficulty or necessary surgical time which could affect post operative pain. Despite having sufficient power (0.8), the data only shows a 25–50% relative difference per Moher *et al.* (22). Bell (23) discusses how DELTA researchers have comprehensive guidance to improve trial design in medical literature. Furthermore the 3 study groups of DEX + ETO, DEX and ETO missing a true placebo control group, making number needed to treat (NNT) impossible to calculate. Furthermore, the lack of a postsurgical group that received the same medications raises the question of whether preemptive analgesic effect was being studied or simply the efficacy of certain medications or combinations in reducing post operative pain. Given that timing of medications and the presurgical and postsurgical groups are crucial to defining preemptive analgesia, this omission reduces the validity of the conclusion that DEX + ETO is a good and efficacious preemptive analgesia regimen. Contemporary studies (18,19) with an n=100 individuals and 5 study groups shows that for such a common procedure getting a large study sample is possible. Another important consideration is that this wasn't a split mouth study despite a lot of similar contemporary literature incorporating this design to reduce confounding variables through matching (17,19).

Areas of further study

Though standardization of cases is important, the relatively uncomplicated teeth (limited to Class I/II and position A/B in the Pell and Gregory system) also raises the question of how efficacious such preemptive analgesia would be for Class III or Position C teeth which require more aggressive dissection and osteotomies. Another consideration is how efficacious preemptive analgesia can be if other extractions or implant placement are done simultaneously. Presumably those procedures are less commonly associated with severe post operative pain, however what the introduction of multiple surgical sites do to an otherwise successful preemptive analgesia regimen requires more study.

Utilizing the preventive analgesia model described by Katz *et al.* (11) and Vadivelu *et al.* (12), a further area of study would be to see if the DEX + ETO regimen, moderate IV sedation, and multimodal postoperative pain control could be synergistic in reducing central sensitization (5) and peripheral sensitization (4,21). This is especially interesting since IV ketamine, fentanyl and dexmedetomidine are commonly used in moderate sedations by practitioners and can provide varying levels of analgesia. Ketamine is of particular interest since NMDA receptor blockade leading to blunting of the afferent barrage (5,8,9,10,12) but also being shown to have no significant preemptive analgesia (13).

Conclusions

This is an exciting area of study with meaningful developments especially for the head and neck surgical region. The publication shows that achieving considerable reduction in post operative pain is possible with careful case selection and an easily adopted PO medication regimen. The skewed demographics, small n and lack of a control group weaken the conclusion of DEX + ETO being highly efficacious in reducing post operative pain and need for rescue analgesics but suggest such techniques could be widely adopted moving forward.

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References

1. Ramires GAD, de Souza Santos AM, Momesso GAC, et al. Combination of etodolac and dexamethasone improves preemptive analgesia in third molar surgery: a randomized study. Clin Oral Investig 2021;25:2297-305.
2. Crile GW. The kinetic theory of shock and its prevention through anoci-association. Lancet 1913;182:7-16.
3. Hutchins HC, Reynolds OE. Experimental investigation of the referred pain of aerodontalgia. J Dent Res 1947;26:3-8.
4. Wall PD. The prevention of postoperative pain. Pain 1988;33:289-90.
5. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686-8.
6. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci Lett 1986;64:221-5.
7. Kissin I. Preemptive analgesia. Anesthesiology 2000;93:1138-43.
8. Kissin I. Preemptive analgesia. Why its effect is not always obvious. Anesthesiology 1996;84:1015-9.
9. Gordon SM, Dionne RA, Brahim J, et al. Blockade of peripheral neuronal barrage reduces postoperative pain. Pain 1997;70:209-15.
10. Dahl JB, Møiniche S. Pre-emptive analgesia. Br Med Bull 2004;71:13-27.
11. Katz J, Clarke H, Seltzer Z. Review article: Preventive analgesia: quo vadimus? Anesth Analg 2011;113:1242-53.
12. Vadivelu N, Mitra S, Schermer E, et al. Preventive analgesia for postoperative pain control: a broader concept. Local Reg Anesth 2014;7:17-22.
13. Lebrun T, Van Elstraete AC, Sandefo I, et al. Lack of a pre-emptive effect of low-dose ketamine on postoperative pain following oral surgery. Can J Anaesth 2006;53:146-52.
14. Gelesko S, Long L, Faulk J, et al. Cryotherapy and topical minocycline as adjunctive measures to control pain after third molar surgery: an exploratory study. J Oral Maxillofac Surg 2011;69:e324-32.
15. Baygin O, Tuzuner T, Isik B, et al. Comparison of pre-emptive ibuprofen, paracetamol, and placebo administration in reducing post-operative pain in primary tooth extraction. Int J Paediatr Dent 2011;21:306-13.
16. Bauer HC, Duarte FL, Horliana AC, et al. Assessment of preemptive analgesia with ibuprofen coadministered or not with dexamethasone in third molar surgery: a randomized double-blind controlled clinical trial. Oral Maxillofac Surg 2013;17:165-71.
17. Silva de Oliveira JC, Grossi de Oliveira GA, Bassi AP. Comparative Assessment of the Effect of Ibuprofen and Etodolac on Edema, Trismus, and Pain in Lower Third Molar Surgery: A Randomized Clinical Trial. J Oral Maxillofac Surg 2016;74:1524-30.
18. Momesso GAC, Grossi-Oliveira GA, Silva WPP, et al. A triple-blind randomized clinical trial of different associations between dexamethasone and non-steroids anti-inflammatories for preemptive action in third molar extractions. Sci Rep 2021;11:24445.
19. Santos BFE, Costa FO, Pinto Júnior AAC, et al. Postoperative pain and edema control following different protocols of preemptive analgesia in the surgical removal of impacted third molars: A triple-blind parallel randomized placebo-controlled clinical trial. J Craniomaxillofac Surg 2021;49:694-704.
20. Cetira Filho EL, Carvalho FSR, de Barros Silva PG, et al. Preemptive use of oral nonsteroidal anti-inflammatory drugs for the relief of inflammatory events after surgical removal of lower third molars: A systematic review with meta-analysis of placebo-controlled randomized clinical trials. J Craniomaxillofac Surg 2020;48:293-307.
21. Yamaguchi A, Sano K. Effectiveness of preemptive

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analgesia on postoperative pain following third molar surgery: Review of literatures. Jpn Dent Sci Rev 2013;49:131-8.
22. Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. JAMA 1994;272:122-4.
23. Bell ML. New guidance to improve sample size calculations for trials: eliciting the target difference. Trials 2018;19:605.

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