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Pain management in Oral and maxillofacial surgery – A review

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Abstract

Pain is a vital function of the nervous system in providing the body with a warning of potential or actual injury. It is both a sensory and emotional experience, affected by psychological beliefs about pain, fear or anxiety. Post-operative maxillofacial pain is the most commonly encountered in clinical practice and poses a great challenge to the practitioners. The methods of management are extensive and involve application of physical, chemical, and psychologic modalities aimed at preventing and treating preoperative, intraoperative, and postoperative patient pain. This paper aims to review the various pain management modalities and factors influencing the choice of treatment in current practice of oral and maxillofacial surgery.

Keywords: maxillofacial surgery, opioids, post-operative analgesia, preventive analgesia, pre-emptive analgesia, multimodal analgesia, review

Introduction

Pain is an essential task of the nervous system as it alerts the body of actual or potential damage. Monheims defined pain as "an unpleasant emotional experience

usually initiated by a noxious stimulus and transmitted over a specialized neural network to the central nervous system where it is interpreted as such". [1] Dental anxiety is an aversive state of apprehension in anticipation of stimulus resulting from the treatment of which pain is the most common, but often avoidable.

Maxillofacial pain is distinct in its presentation due to the multiplex structure of the head and neck and its specialized sensory innervation with the trigeminal pathway being responsible for the perception of pain. [2] The Somatic input does not reach the spinal cord by the way of spinal nerves; it is carried by the V cranial nerve. Cell bodies are located in the large Gasserian ganglion. The brainstem, in the region of the pons, receives the impulses directly to synapse in the trigeminal spinal tract nucleus. [3]

Acute pain is a frequent complaint for reporting to an emergency room, and acute postoperative pain is often associated with surgical procedures. [2,3] The surgical stress response is activated by the noxious stimuli. This commences a series of pathophysiological changes that negatively alter the body's homeostasis and are deleterious to surgical outcomes. [4]

Methods of management are multimodal, yet individualized and involve the application of physical, chemical, and psychologic methods aimed at preventing and treating preoperative, intraoperative, and postoperative patient pain. This paper aims to review the various pain management modalities and factors influencing the choice of treatment in the current practice of oral and maxillofacial surgery.

Concepts in Acute Pain Management

The World Health Organisation has acknowledged pain as a problem on a global scale. [1] Post-operative pain is repeatedly seen in clinical practice and undertreatment of this is still a major concern globally. A study conducted by the Royal College of Surgeons in Britain highlighted pain management as a significant problem since they found that among the 3000 patients surveyed, 87% of them complained of moderate to severe pain postoperatively. [3] A questionnaire survey by Vijayan et al revealed that, in India, only 30% of the patients received satisfactory pain management. [4] Poor pain control postoperatively not only causes discomfort but also paves way for poor wound healing, extended hospital stays, psychological distress, and the likelihood of chronic persistent pain.

To prevent these deleterious outcomes of undertreated postoperative pain, several concepts have evolved, including pre-emptive, preventive, and multimodal analgesia.

Pre-Emptive Analgesia

Pre-emptive analgesia as a treatment modality prevents altered processing of afferent input and thereby controls the postoperative pain. [5,6] This concept was first formulated by Crile when he discussed a correlation between tissue injury caused intraoperatively and accentuation of postoperative pain, a process now known as central sensitization. It ensues following the hyperexcitability of the neurons to the afferent impulses at the injury site, which in turn results in an exaggerated response. [7] Central sensitization occurs following peripheral sensitization, which refers to the lowered threshold of peripheral nociceptors (A and C fibers,) to intense stimuli resulting in enhanced stimulus-dependent pain or hyperalgesia. Crile elaborated the advantage of regional blocks along with general anesthesia to obstruct intraoperative nociception and resultant painful scars. [5,6]

Pre-emptive analgesia can be instituted by preventing nociceptive impulses through administration of local anesthetics, inhibiting inflammation and peripheral

sensitization by nonsteroidal anti-inflammatory drugs, or prevention of central sensitization by opioids. [8,9]

Pre-emptive analgesia has found its application in dentoalveolar surgery, especially before the removal of third molars. 0.5% Bupivacaine administered preoperatively showed a statistically significant cutback in perceived pain after 4 and 48 hours post-operatively. This was observed in comparison to lidocaine and saline placebo injections. [10] Literature has also shown that preoperative NSAIDs along with administration of long-acting anesthetic before incisions, showed significant pain control postoperatively. [8] Preoperative administration of opioids has also shown reduced postoperative pain. The efficacy (absolute relief of pain) of pre-emptive Tramadol was found to be 86% at 24 hours when compared with postoperative administration of Tramadol which showed 70% analgesic efficacy, thus reducing the consumption of postoperative analgesics. [11]

The specialties of Orthopaedics and General surgery have vastly experimented with pre-emptive analgesia, however, there are only sparse studies that elaborate their benefits in oral surgery, excluding teeth removal.

A study compared pre-surgical and post-operative flurbiprofen in patients undergoing open reduction and fixation of facial fractures and ablation of tumors under general anesthesia. The study did not report significant variance in the postoperative pain intensity among the two groups. [8]

In contrast, Cillo et al proclaimed that a pre-operative dose of both pregabalin and celecoxib before orthognathic procedures reduced the overall intravenous morphine requirement, opioid consumption, and the mean of pain scores as reported by the patients.[9] Krishnan et al studied the efficacy of 0.25% bupivacaine in patients undergoing elective orthognathic surgery and found that the number of rescue analgesics administered and the incidence of complications attributed was less in the study group.

Abe et al collated three groups: local anesthesia; preoperative ketamine; and preoperative flurbiprofen, for maxillary sinus procedures under general anesthesia. The depth of postoperative pain and time for first rescue medication were assessed. All the groups exhibited significantly lessened postoperative pain in contrast to the control group. Subsequently, they deduced that pre-emptive analgesia effects were advantageous.[8]

Therefore, the current literature, although mixed, shows an inclination towards pre-emptive analgesia in prolonging the onset of postoperative pain and subsequent narcotic consumption. The premise for this includes diminution of noxious stimulation by neurogenic or inflammatory mediators at the site of injury which will, in turn, inhibit channeling to the brain and therefore control pain perception postoperatively.[9]

Preventive Analgesia

Pre-emptive analgesia can be demonstrated by comparing and proving that intervention before surgery is more effectual when contrasted with the treatment provided at the end of surgery. [12]

Moiniche et al investigated the effect of pre and postoperative analgesia (Pre vs. Post) on pain scores within 24 h after surgery in 3761 patients of which 1964 patients received pre-emptive analgesia. The study inferred that the timing of treatment approaches did not alter the quality of pain control, indicating that pre-emptive analgesia is not superior to post-incisional treatment. [13]

This conclusion is largely based on the hypothesis that Pre-emptive analgesia prevents central sensitization to nociception produced at the site of injury by initial incision alone. However, with recent evidence-based

clinical research, other factors such as pre-operative pain, added noxious intraoperative inputs like retraction, and post-operative inflammatory processes are known to cause intensification of acute postoperative pain.[5] Hence, a more comprehensive approach would be to reduce the detrimental short and long-term results of noxious perioperative afferent input, at present, termed as Preventive Analgesia (Figure 1).

The perioperative period comprises three separate phases: preoperative, intraoperative, and postoperative. Factors of these phases are important in causing acute postoperative pain. These include

- Preoperative pain, genetic predisposition, and psychological vulnerability
- Intraoperative nociceptive unmyelinated and afferents carrying injury discharge brought about by incision, retraction, and manipulation of tissues
- postoperative afferent inputs, such as the inflammatory response and neuropathic ectopic neural activity from regenerating afferents nerve.[14]

Preventive analgesia, therefore, aims at preventing central and peripheral sensitization that can be caused by any of these agents.

Rosero & Joshi elucidated the requirements to attain preventive analgesia. One is to reduce the mean analgesic consumption in comparison to the control. Two, is to increase the duration of the intervention beyond the clinical duration of action of the target drug.[7]

In oral surgery, for cases where no inflammation is present preoperatively, preventive analgesia may provide a pain-free postoperative period, decrease likelihood of chronic central sensitization, and decrease analgesic use. When procedures are of longer duration, preventive analgesia is advantageous and may prevent the undesirable sequelae from the procedure. For cases with associated preoperative pain such as trauma, preventive analgesia may be beneficial in controlling intraoperative pain and to increase the potency of anesthetic blockade.[15]

Incisions induce central sensitization and hyperalgesia, which may be impaired by different agents in the perioperative period, including N-methyl-D-aspartic acid (NMDA) receptor antagonists such as dextromethorphan and ketamine.[5] Other agents include non-steroidal anti-inflammatory agents and opioids.

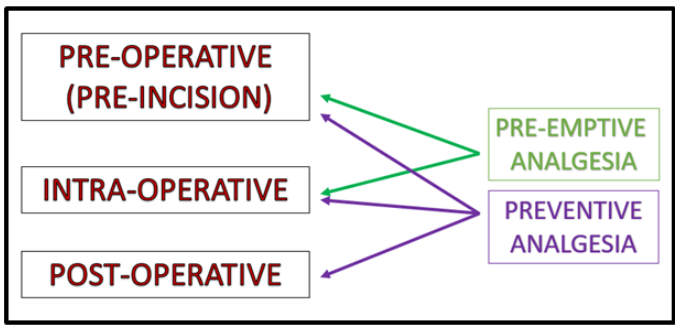

Figure 1: The targets for pre-emptive and preventive analgesia

Multimodal Analgesia

Post-operative pain is a complex and multiform process and hence it is warranted to combine analgesics belonging to different classes with individual target sites to achieve adequate pain control. This concept forms the basis of multimodal analgesia. It involves using two or more drugs acting at separate sites in the central and peripheral nervous systems to yield postoperative analgesia. The drugs may also be administered via separate routes. Therefore, the objective of multimodal or balanced analgesia is to refine analgesia while decreasing opioid consumption and its adverse effects.[7,16]

Opioids are key in post-operative pain control, however, in addition to these, agents used for multimodal analgesia include NSAIDs, especially selective COX-2

inhibitors, ketamine, dexmedetomidine, dextromethorphan, alpha2agonists, beta-blockers, local anesthetics, and acetaminophen.

Bisgaard et al evaluated a regimen in patients post laparoscopic cholecystectomy with successful clinical outcomes. The regimen consisted of one preoperative dose of dexamethasone, incisional local anesthetics and NSAIDs during the first 3–4 postoperative days. A similar regimen may be used in the case of ambulatory maxillofacial procedures.[17]

Perioperative multimodal analgesia with oral oxycodone, gabapentin, and acetaminophen yielded excellent postoperative pain control following major orthopedic surgery.[16]

Local infiltration and other topical and parenteral routes of local anesthetics have been mentioned in the literature. Intranasal lidocaine complemented with naphazoline reduced both intraoperative and postoperative pain, thereby reducing rescue analgesic requirements in the postoperative period following septorhinoplasty.[18]

Caitlin et al retrospectively evaluated a multimodal analgesic protocol for patients undergoing third molar surgery, post-operatively. The protocol included a dose of 8 mg dexamethasone and 30 mg ketorolac intravenously at the start of the procedure. Local anesthesia was achieved with 2% lidocaine and 0.5% bupivacaine both with epinephrine. At the end of the procedure, topical 1 mg minocycline was placed in each of the mandibular extraction sites along with cold therapy. Following this, a significant proportion of patients filled no opioid Rx, hence proving the efficacy of the protocol.[19]

The use Multimodal analgesia in oral and maxillofacial surgery is limited and still, at its nascent stages, it requires further studies to increase its application in the field. A multimodal analgesic regimen should be individualized to each patient based on their pre-existing medical conditions, type of surgery, and previous experiences related to pain management (figure 2).

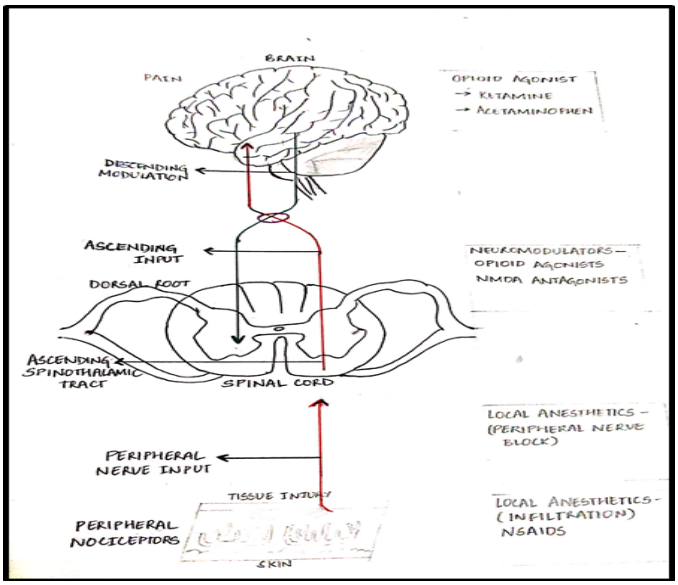

Figure 2: Representation of multimodal analgesia: Examples of analgesic agents and their action at different levels of the pain pathway

Advances in Pain Management

A leap in the knowledge of molecular operations have led to the invent of multimodal analgesia and development of advanced agents to treat postoperative pain.

Patient Controlled Analgesia

Postoperative pain is usually effectively managed using intravenous (IV) and intramuscular (IM) opioid analgesics. However, literature reports that approximately 75% of hospitalized patients remain in moderate to severe pain. Patient-controlled analgesia (PCA) provides a specific dose of opioids in par with the patient's needs, controlled by an infusion pump.[20] Sechzer reported a decrease in postoperative pain from 20% to 40% to less than 5% with the use of PCA when compared with IM injections.[21] The use of PCA has been mainly documented in specialties such as

cardiothoracic, orthopedic, and general surgery, however, there is scant literature on its application in maxillofacial surgery.

Similarly, Precious et al observed in a comparative study that, patients administered with intravenous opioid PCA were significantly more comfortable than fixed schedule and dosage of opioid administration, intramuscularly/orally, following orthognathic surgery. [22]

More recent routes include incisional patient-controlled regional analgesia (PCRA), intraarticular PCRA, perineural PCRA, and intranasal PCA. While these routes are being continuously investigated in other surgical fields, it is still a long way from being applied in maxillofacial surgery.

Transdermal Drug Delivery

Fentanyl, which is a potent, synthetic and short-acting opiate can be administered via the transdermal route, referred to as the Fentanyl Transdermal System (FTS). It is available as a rectangular adhesive patch, including a gel matrix containing a high concentration of fentanyl and a release membrane that ensures time and surface-limited absorption of the drug. This system allows a continuous systemic delivery of Fentanyl for 72 hours, commonly used following third molar removal, minor surgical procedures, and also in head and neck surgery.[23]

The transdermal system is useful in delivering drugs with a relatively smaller molecular size and lipophilic nature, which poses a challenge with highly hydrophilic drugs. This limitation is resolved by the use of iontophoresis, the electrically driven permeation of ionized drug molecules across biological membranes.[24]

Iontophoretic drug delivery can be used for both local and systemic drug administration. Local anesthetics can be applied to the oral mucosal tissues using iontophoresis before the oral procedure. Fentanyl Iontophoretic transdermal system has been gaining popularity in the management of acute postoperative pain.[24,25]

Panchal et al. compared the incidence of interruptions in analgesic delivery (alternatively, analgesic gaps) for patients using the fentanyl ITS and morphine IV PCA for postoperative pain management. It was noted that Fentanyl ITS was associated with a significantly lower incidence of analgesic gaps than morphine IV PCA.[26]

Analgesic Adjuvants

Ketamine: Ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, is being commonly used in perioperative pain management. At low subanesthetic doses (0.15–1 mg/kg), ketamine exerts an inhibitory action on NMDA receptors, hence, modulates central sensitization induced both by the incision and tissue damage.[27] The local administration of ketamine can reduce the incidence and severity of postoperative pain after the surgical extraction of the third molar.[28] Hadhimane et al evaluated the efficacy of pre-emptive sub-mucosal injection of ketamine at low doses on postoperative pain in patients who underwent surgical extraction of mandibular third molars. They reported a significant reduction of postoperative pain for the first 24 hours.[29] Dubey et al compared a combination of articaine and ketamine with articaine alone for surgical extractions of mandibular third molars. The results revealed that the combination with ketamine produced good local anesthesia and adequate postoperative analgesia with reduced swelling and trismus.[30] Topical application of Ketamine has also been known to postoperative pain in third molar surgeries.[31] Low dose ketamine infusion can significantly reduce

postoperative pain in patients undergoing orthognathic surgery and head and neck surgery. [32,33]

Gabapentinoids

Gabapentin and pregabalin are both antiepileptics which also demonstrate analgesic properties. They act by inhibiting calcium influx at the presynaptic voltage-gated calcium channels, thereby preventing the release of excitatory neurotransmitters involved in pain pathways.

Four RCTs assessed the effectiveness of pregabalin as pre-emptive analgesia before or following third molar surgery and orthognathic surgery. All of them reported the superiority of gabapentinoids in reducing postoperative pain and opioid consumption.[34]

However, two metanalyses assessing the perioperative use of gabapentin and pregabalin showed only a marginal reduction in postoperative pain with an increased risk of adverse effects. Literature reports a low quality of evidence for the use of gabapentin and pregabalin for perioperative pain control, although they may be considered when the benefit seems to outweigh the risk.[35]

Dexmedetomidine

Dexmedetomidine is a selective agonist of alpha 2 adrenergic receptor, it binds to the presynaptic alpha 2 adrenergic receptors, hampering the norepinephrine release, thereby reducing postsynaptic adrenergic activity.[36] It is an effective sedative agent that also offers analgesic, anxiolytic and sympatholytic effects while having minimal impact on respiratory physiology. It can be given orally, intravenously, intramuscularly, or intranasally.[37] In a case-control study using intranasal dexmedetomidine (1 μg/kg) preoperatively, 45 minutes before administration of local anesthesia in patients undergoing unilateral third molar surgery, it was found that patients were more deeply sedated with better post-operative pain control.[38] According to another multicentre trial, dexmedetomidine proved an effective baseline anesthetic adjuvant for procedures under local anesthesia, ensuring better patient satisfaction, reduced opioid intake, and lesser respiratory depression in comparison to placebo rescued with midazolam and fentanyl. However, the reported adverse effects of this agent include bradycardia and hypotension, although mild to moderate in severity.[39]

Conclusion

Acute postoperative pain has a substantial impact on patients and the healthcare system on a wider scale. Hence, it is of utmost importance for healthcare practitioners to heed adequate pain control and not just the surgical procedures alone. The most promising approach to the management of post-operative pain favors multimodal analgesia which includes the use of a combination of two or more analgesics, differing in their modes of action either through the same or different route of delivery. The prompt management of pain will thus reduce the burden of surgical stress, postoperative complications, duration of stay, and the risk of developing chronic pain.

References

1. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. JAMA. 1998 Jul 8;280(2):147-51. doi: 10.1001/jama.280.2.147. Erratum in: JAMA 1998 Oct 7;280(13):1142. PMID: 9669787.
2. Stephens J, Laskin B, Pashos C, Peña B, Wong J. The burden of acute postoperative pain and the potential role of the COX-2-specific inhibitors. Rheumatology (Oxford). 2003 Nov;42 Suppl 3:iii40-52. doi: 10.1093/rheumatology/keg497. PMID: 14585917.

3. Coulthard P, Haywood D, Tai MA, Jackson-Leech D, Pleuvry BJ, Macfarlane TV. Treatment of postoperative pain in oral and maxillofacial surgery. Br J Oral Maxillofac Surg. 2000 Dec;38(6):588-592. doi: 10.1054/bjom.2000.0536. PMID: 11092771.
4. Khatib SK, Kulkarni SS, Razvi SS. Acute pain services in India: A long and challenging journey ahead. Indian J Pain 2016;30:83-9
5. Vadivelu N, Mitra S, Schermer E, Kodumudi V, Kaye AD, Urman RD. Preventive analgesia for postoperative pain control: a broader concept. Local Reg Anesth. 2014 May 29;7:17-22. doi: 10.2147/LRA.S62160. PMID: 24872720; PMCID: PMC4012350.
6. Kissin I. Preemptive analgesia. Anesthesiology. 2000 Oct;93(4):1138-43. doi: 10.1097/00000542-200010000-00040. PMID: 11020772.
7. Rosero EB, Joshi GP. Preemptive, preventive, multimodal analgesia: what do they really mean? Plast Reconstr Surg. 2014 Oct;134(4 Suppl 2):85S-93S. doi: 10.1097/PRS.0000000000000671. PMID: 25255012.
8. Yamaguchi A, Sano K. Effectiveness of preemptive analgesia on postoperative pain following third molar surgery: Review of literatures. Jpn Dent Sci Rev [Internet]. 2013;49(4):131–8. Available from: http://dx.doi.org/10.1016/j.jdsr.2013.07.002
9. Cillo JE Jr, Dattilo DJ. Pre-emptive analgesia with pregabalin and celecoxib decreases postsurgical pain following maxillomandibular advancement surgery: a randomized controlled clinical trial. J Oral Maxillofac Surg. 2014 Oct;72(10):1909-14. doi: 10.1016/j.joms.2014.05.014. Epub 2014 May 27. PMID: 25234526.
10. Fletcher MC, Spera JF. Pre-emptive and postoperative analgesia for dentoalveolar surgery. Oral Maxillofac Surg Clin North Am. 2002 May;14(2):137-51. doi: 10.1016/s1042-3699(02)00007-9. PMID: 18088617.
11. Pozos-Guillen A, Martinez-Rider R, Aguirre-Banuelos P, Perez-Urizar J. Pre-emptive analgesic effect of tramadol after mandibular third molar extraction: a pilot study. J Oral Maxillofac Surg. 2007 Jul;65(7):1315-20. doi: 10.1016/j.joms.2006.10.079. PMID: 17577495.
12. Kissin I. Preemptive analgesia at the crossroad. Anesth Analg. 2005 Mar;100(3):754-756. doi: 10.1213/01.ANE.0000144429.39988.9B. PMID: 15728065.
13. Pogatzki-Zahn EM, Zahn PK. From preemptive to preventive analgesia. Curr Opin Anaesthesiol. 2006 Oct;19(5):551-5. doi: 10.1097/01.aco.0000245283.45529.f9. PMID: 16960490.
14. 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.
15. Chavarría-Bolaños D, Esparza-Villalpando V. Preventive Analgesia: An Evidence-Based Alternative for Dentistry. Odovtos - Int J Dent Sci. 2017;19(2):10.
16. Elvir-Lazo OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. Curr Opin Anaesthesiol. 2010 Dec;23(6):697-703. doi: 10.1097/ACO.0b013e32833fad0a. PMID: 20847690.

17. Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. Anesthesiology 2006; 104(4): 835-846.
18. Granier M, Dadure C, Bringuier S, Bonnet-Boyer MC, Ryckwaert Y, Loriaux E, Capdevila X. Intranasal lidocaine plus naphazoline nitrate improves surgical conditions and perioperative analgesia in septorhinoplasty surgery. Can J Anaesth. 2009 Feb;56(2):102-8. doi: 10.1007/s12630-008-9020-7. Epub 2009 Jan 7. PMID: 19247757.
19. Magraw C, Pham M, Neal T, Kendell B, Reside G, Phillips C, White RP Jr. A multimodal analgesic protocol may reduce opioid use after third molar surgery: A pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018 Sep;126(3):214-217. doi: 10.1016/j.oooo.2018.04.007. Epub 2018 May 3. PMID: 29880285.
20. Rosenberg M. Patient-controlled analgesia. J Oral Maxillofac Surg. 1992 Apr;50(4):386-9. doi: 10.1016/0278-2391(92)90404-n. PMID: 1545294.
21. Grass JA. Patient-controlled analgesia. Anesth Analg. 2005 Nov;101(5 Suppl):S44-S61. doi: 10.1213/01.ANE.0000177102.11682.20. PMID: 16334492.
22. Precious DS, Multari J, Finley GA, McGrath P. A comparison of patient-controlled and fixed schedule analgesia after orthognathic surgery. J Oral Maxillofac Surg. 1997 Jan;55(1):33-9; discussion 40. doi: 10.1016/s0278-2391(97)90442-0. PMID: 8994466.
23. Todorovic VS, Vasovic M, Andric M, Todorovic L, Kokovic V. Efficacy of fentanyl transdermal patch in pain control after lower third molar surgery: A preliminary study. Med Oral Patol Oral Cir Bucal. 2016 Sep 1;21(5):e621-5. doi: 10.4317/medoral.21161. PMID: 27475691; PMCID: PMC5005101.
24. Dhote V, Bhatnagar P, Mishra PK, Mahajan SC, Mishra DK. Iontophoresis: a potential emergence of a transdermal drug delivery system. Sci Pharm. 2012 Jan-Mar;80(1):1-28. doi: 10.3797/scipharm.1108-20. Epub 2011 Dec 13. PMID: 22396901; PMCID: PMC3293348.
25. Wanasathop A, Li SK. Iontophoretic Drug Delivery in the Oral Cavity. Pharmaceutics. 2018 Aug 7;10(3):121. doi: 10.3390/pharmaceutics10030121. PMID: 30087247; PMCID: PMC6161066.
26. Panchal SJ, Damaraju CV, Nelson WW, Hewitt DJ, Schein JR. System-related events and analgesic gaps during postoperative pain management with the fentanyl iontophoretic transdermal system and morphine intravenous patient-controlled analgesia. Anesth Analg. 2007 Nov;105(5):1437-41, table of contents. doi: 10.1213/01.ane.0000281442.36582.81. PMID: 17959979.
27. De Kock MF, Lavand'homme PM. The clinical role of NMDA receptor antagonists for the treatment of postoperative pain. Best Pract Res Clin Anaesthesiol. 2007 Mar;21(1):85-98. doi: 10.1016/j.bpa.2006.12.006. PMID: 17489221.
28. Esparza-Villalpando V, Ascencio-Padilla R, Pozos-Guillen A, Pozos-Guillen F, Hidalgo-Hurtado JA, Chavarria-Bolaños D. Local Ketamine Improves Postoperative Analgesia After Third Molar Surgery. J Oral Maxillofac Surg. 2019 Dec;77(12):2386-2400. doi: 10.1016/j.joms.2019.07.002. Epub 2019 Jul 16. PMID: 31404519.
29. Hadhimane A, Shankariah M, Neswi KV. Pre-Emptive Analgesia with Ketamine for Relief of Postoperative Pain After Surgical Removal of

Impacted Mandibular Third Molars. J Maxillofac Oral Surg. 2016 Jun;15(2):156-63. doi: 10.1007/s12663-015-0813-2. Epub 2015 Jul 5. PMID: 27298538; PMCID: PMC4871823.

30. Dubey T, Singh M, Sharma A, Laskar S, Vashistha A. Combination of Articaine and Ketamine V/S Articaine Alone After Surgical Extraction of Impacted Third Molars. Ann Maxillofac Surg. 2020 Jan-Jun;10(1):42-46. doi: 10.4103/ams.ams_143_19. Epub 2020 Jun 8. PMID: 32855913; PMCID: PMC7433971.
31. Gönül O, Satilmiş T, Ciftci A, Sipahi A, Garip H, Göker K. Comparison of the Effects of Topical Ketamine and Tramadol on Postoperative Pain After Mandibular Molar Extraction. J Oral Maxillofac Surg. 2015 Nov;73(11):2103-7. doi: 10.1016/j.joms.2015.05.012. Epub 2015 May 21. PMID: 26044602.
32. Pota V, Passavanti MB, Aurilio C, Barbarisi M, Giaccari LG, Colella U, et al. Ketamine Infusion in Post-Surgical Pain Management after Head and Neck Surgery: A Retrospective Observational Study. Open Anesth J. 2019;13(1):132–8 (2019).
33. Kido K, Toda S, Shindo Y, Miyashita H, Sugino S, Masaki E. Effects of low-dose ketamine infusion on remifentanil-induced acute opioid tolerance and the inflammatory response in patients undergoing orthognathic surgery. *J Pain Res*. 2019;12:377-385 https://doi.org/10.2147/JPR.S177098
34. Sulukdjian A, Homme RL, Chanlon A, Moreau N. Gabapentinoid prescription in Oral Medicine and Oral Surgery practice. Part II - a systematic scoping review of the literature. Journal of Oral Medicine and Oral Surgery 2020;26(4):1–12.
35. Evans SW, McCahon RA. Management of postoperative pain in maxillofacial surgery. Br J Oral Maxillofac Surg. 2019 Jan;57(1):4-11. doi: 10.1016/j.bjoms.2018.11.010. Epub 2018 Dec 27. PMID: 30595335.
36. Li S, Yang Y, Yu C, Yao Y, Wu Y, Qian L, Cheung CW. Dexmedetomidine Analgesia Effects in Patients Undergoing Dental Implant Surgery and Its Impact on Postoperative Inflammatory and Oxidative Stress. Oxid Med Cell Longev. 2015;2015:186736. doi: 10.1155/2015/186736. Epub 2015 Jun 15. PMID: 26171113; PMCID: PMC4485522.
37. Tang C, Xia Z. Dexmedetomidine in perioperative acute pain management: a non-opioid adjuvant analgesic. J Pain Res. 2017 Aug 11;10:1899-1904. doi: 10.2147/JPR.S139387. PMID: 28860845; PMCID: PMC5565238.
38. Cheung CW, Ng KF, Liu J, Yuen MY, Ho MH, Irwin MG. Analgesic and sedative effects of intranasal dexmedetomidine in third molar surgery under local anaesthesia. Br J Anaesth. 2011 Sep;107(3):430-7. doi: 10.1093/bja/aer164. Epub 2011 Jun 16. PMID: 21685111.
39. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY; MAC Study Group. Monitored anesthesia care with dexmedetomidine: a prospective, randomized, double-blind, multicenter trial. Anesth Analg. 2010 Jan 1;110(1):47-56. doi: 10.1213/ane.0b013e3181ae0856. Epub 2009 Aug 27. PMID: 19713256.