Editorial Commentary

The injection of tramadol after impacted third molar extractions appears to control acute post-operative pain in systemic reviews and meta-analysis

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Comment on: Gonçalves KK, Santos MS, Barbirato DD, *et al*. Is the injection of tramadol effective at control of pain after impacted mandibular third molar extractions? A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal 2022;27:e560-8.

Keywords: Third molar extraction; third molar pain; acute post-operative pain; tramadol; systematic review; meta-analysis

Received: 20 April 2023; Accepted: 19 May 2023; Published online: 02 June 2023.

doi: 10.21037/joma-23-14

View this article at: https://dx.doi.org/10.21037/joma-23-14

Is the injection of tramadol effective at control of pain after impacted mandibular third molar extractions?

The research question this study aimed to answer was proposed as a PICO (patient/population, intervention, comparison, and outcomes): Is the local submucosal injection of tramadol effective at controlling postoperative pain in patients submitted to impacted mandibular third molar extractions? (1). To answer the question, a comprehensive literature search identified 819 records, of which three met the inclusion criteria and were selected for meta-analysis, comprising 172 participants (98 males and 74 females aged 18 or over). Three randomized placebo-control trials were selected and consisted of an intervention group that received a submucosal injection of either 1 mg/kg, 50 mg, or 100 mg of tramadol after surgery and a control group of patients who received a placebo injection of 2 mL sterile saline solution. Studies in which combination therapies and use of pre/postoperative analgesics or anti-inflammatories were excluded except for the measurement of rescue analgesic onset. Standard pairwise meta-analyses of direct comparisons were performed using a fixed-effect model to assess the effectiveness of submucosal injection of tramadol following mandibular third molar extractions. Pain scores were measured by the visual analog scale (VAS) as the primary outcome measure. Pain scores at post-operative intervals were expressed as mean difference and relative 95% confidence interval (CI). Heterogeneity was assessed using the Chi-square-based Q-statistic method and Higgins inconsistency measurement (I^2), with statistical significance indicated by a P value ≤ 0.05. This analysis reported that the submucosal injection of tramadol, compared to the placebo, effectively reduced post-operative pain, with a statistically significant reduction in pain at 2 and 6 hours. Pain scores at 1, 24, and 48 hours post-operative were not statistically significant. Statistical data analysis showed moderate heterogeneity, suggesting that results should be interpreted cautiously.

Clinical pharmacology of tramadol and its use in dentistry

Tramadol was first introduced for clinical use in 1977 and has remained an efficacious treatment for pain and, notably, a significantly less potent opioid drug when compared to other narcotics (2). Like other opioid drugs, tramadol acts on the central nervous system but is unique in inhibiting serotonin and norepinephrine reuptake, specifically on

nociceptive receptors (3). Tramadol is also convenient because it can be administered orally or parenterally. As such, the pharmacokinetics of tramadol and its various routes of administration have been extensively studied. Most relevant to the dental practitioner would be oral bioavailability, which has been shown to be up to 70% (4). Effective local anesthesia and pre/post-operative analgesic support are of the utmost importance when performing procedures in the oral cavity. Though tramadol is not common in one's armamentarium, the application of tramadol for dental and oral surgery procedures has been researched. Considering the use of submucosal tramadol injection for mandibular third molar surgery described by Gonçalves *et al.*, a selected literature search was done to explore additional alternative uses of tramadol to characterize its use in dentistry further.

Gómez-Sánchez *et al.* (5) conducted a meta-analysis to determine the effect of tramadol on pre-treatment as well as pain control for patients with symptomatic irreversible pulpitis. In an analysis of six randomized, double-blinded, parallel clinical studies, a local submucosal injection of tramadol increased the anesthetic rate when compared to a placebo in patients with symptomatic irreversible pulpitis (P<0.004). Of note, there was also a statistically significant increase in adverse events, defined as nausea and vomiting, in 9/144 patients in the tramadol group. Although this meta-analysis was limited due to the small sample size and dosage variation, which ranged from 12.5 to 100 mg, it provides insight into an alternative anesthetic method for the provider when faced with the proverbial "hot" tooth. The properties of 5% tramadol and 2% lidocaine were compared in a double-blinded study by Jendi *et al.* (6), including the onset of action, duration of action, intra-operative pain, and post-operative pain analgesic effect, and adverse events in patients undergoing maxillary premolar extraction with supra-periosteal infiltration. In a sample of 100 patients, the only statistically significant finding (P=0.04) was a difference in mean intra-operative pain, which, as measured by the VAS, was minimal for both groups. Another novel use for the local application of tramadol, described by Gönül *et al.*, is applying a resorbable gelatin sponge to the extraction socket (7). In a study of 90 patients undergoing molar extraction, it was found that VAS scores were statistically higher in a placebo group than tramadol, though interestingly, they found the application of ketamine to have the lowest pain intensity. Although rare, some social or heritable factors can make a patient resistant to local anesthesia, requiring alternative methods for pain control (8,9). In summary, the majority of literature on tramadol use in dentistry is limited by sample size. Still, the above studies offer a representative finding of why one might consider tramadol use in their practice. In dental practice, injecting tramadol as an effective acute post-operative pain control protocol has been shown in this article to be a viable option for relieving mild, moderate, and severe pain ranges. Single application at the time of surgery has the advantage of being patient-independent with few adverse events. Combined with local anesthetics and other oral analgesics, it may offer clinicians and patients a safe and effective modality to provide reliable and reproducible acute pain control.

Commentary regarding the Gonçalves *et al.* publication on the effectiveness of tramadol injection on pain control after impacted third molar extractions

Strengths in study design

The meta-analysis by Gonçalves *et al.* provides a relevant finding due to a comprehensive literature search and thorough statistical analysis. Using a fixed-effect model for analysis helps account for the variability in data. Likewise, using the univariate outcome of pain measured by the VAS decreases the risk of random effects. Though the findings showed moderate heterogeneity, the subjective sensation of pain and difference in pain thresholds could contribute to the variability. The clear, focused PICO question decreases the risk of potential bias and aids in the reproducibility of the study.

Weakness in study design

Fig. 2 in the study demonstrates a nonlinear relationship between pain scores and different groups of patients. This could be due to variations in study design or different cause factors such as the difficulty of extraction, the placebo effect, or subjective pain value among patients, which are intrinsic weaknesses when comparing multiple studies with multiple study designs. The inability to account for these factors can lead to meaningless estimates of pain relief. Though the included studies were high-level evidence, using only three studies decreases the power of the study. Finally, as all three

studies were conducted in different countries, the results are at risk for prevalence bias, given the population difference. For example, there has been an ongoing effort in the USA to reduce opioid use in acute postoperative pain conditions, including third molar surgery. There are now many dental and oral and maxillofacial offices advertising opioid-free environments and care.

Areas of further study

Future studies on the effect of submucosal tramadol on postoperative pain will require larger sample sizes. Further studies could investigate the efficacy of submucosal tramadol injections after other oral and maxillofacial surgery procedures with varying postoperative courses, such as dental implants and orthognathic surgery. While several studies compare tramadol to various combination therapies, none have compared the efficacy of tramadol injection to a more commonly used injection such as liposomal bupivacaine for postoperative pain control (10).

Conclusions

This was a well-done meta-analysis of a focused research question on an important clinical issue. The only weakness would be those inherent weaknesses related to meta-analysis studies. Overall, the meta-analysis presented by Gonçalves *et al.* introduces a novel treatment that should be considered in our practices.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Oral and Maxillofacial Anesthesia*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://joma.amegroups.org/article/view/10.21037/joma-23-14/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/joma-23-14
Cite this article as: Wahidi J, Zuniga JR. The injection of tramadol after impacted third molar extractions appears to control acute post-operative pain in systemic reviews and meta-analysis. J Oral Maxillofac Anesth 2023;2:11.