Is the injection of tramadol effective at control of pain after impacted mandibular third molar extractions? A systematic review and meta-analysis

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Abstract

Background: Third molar extraction is among the most common surgical procedures performed by oral-maxillofacial surgeons. Postoperative pain, swelling and trismus are common, especially in wisdom teeth, due to trauma to local tissues and the duration of the surgical procedure, among other factors.

Material and Methods: This systematic review was conducted in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' in order to answer the focused question: 'Is the local submucosal injection of tramadol effective at the control of postoperative pain in patients submitted to impacted mandibular third molar extractions?'. We analyzed papers published until March 30, 2021 in the MEDLINE|PubMed, Web of Science and Cochrane Library databases. Gray literature was also consulted. Standard pairwise meta-analyses of direct comparisons were performed using a fixed-effect model; I2 ≥ 50 % or ≥ 75 % indicated moderate or high heterogeneity, respectively. Risk of bias was assessed by Cochrane Collaboration's tool.

Results: In total, 172 participants (98 males and 74 females, aged 18 or over) from three randomized placebo-controlled trials were considered for analysis. The submucosal injection of 2 ml of tramadol adjacent to the impacted mandibular third molar was effective in controlling pain up to 6-hours after surgery, in increasing the onset of consumption of rescue analgesic and in reducing the total number of rescue analgesics used.

Conclusions: The submucosal injection of tramadol can be considered a safe and effective procedure for pain control after impacted mandibular third molar extractions.

Key words: *Tramadol, impacted teeth, third molars, postoperative pain, adverse effects.*

Introduction

Third molar extraction is among the most common surgical procedures performed by oral-maxillofacial surgeons (1,2). Postoperative pain, swelling and trismus are common, especially in wisdom teeth, due to trauma to local tissues and the duration of the surgical procedure, among other factors (3,4).

After the extraction of third molar teeth, monotherapies or combined therapies of analgesics and/or non-steroidal anti-inflammatories are used for pain control. Despite the benefits of these drugs, many patients do not tolerate their use due to adverse effects, such as gastric or duodenal ulcers, platelet disorders, renal failure and bronchospasm (5,6). Moreover, caution is required regarding the use of these drugs on pregnant women, nursing mothers, diabetics, immunosuppressed individuals and those with vascular diseases (1). The therapeutic individualization strategy for analgesic and anti-inflammatory drugs usage and their route of administration must occurs (7,8).

Opiates are a viable medicinal alternative for the control of moderate to intense acute pain following third molar extraction (9). Tramadol [(1R,2R)-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexan-1-ol)] is classified as a weak, central action opiate that is clinically effective for the control of moderate to intense pain (10). It is an agonist of the μ-opioid receptor that reduces the transmission of pain impulses by inhibiting the reuptake of serotonin and norepinephrine (11,12).

Tramadol can be administered through enteral (oral and rectal) or parenteral (intravenous, intramuscular and submucosal) routes. The local submucosal injection of tramadol after third molar extraction has been studied due to the proximity to the surgical site and low systemic absorption; moreover, this procedure is simple to perform and there is a low frequency of adverse effects (13). The efficacy, posology and route of administration of tramadol after third molar extractions have not yet been established, which compromise the decision-making process in clinical practice. Therefore, this systematic review aims to answer the focal question developed in accordance with the recognized Patient, Intervention, Comparison, and Outcome (PICO) format: 'Is the local submucosal injection of tramadol effective at the control of postoperative pain in patients submitted to impacted mandibular third molar extractions?'.

Material and Methods

- Protocol and registration

This systematic review was conducted in compliance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) (14,15). PROSPERO registration protocol #CRD42020150445.

- Literature search strategy

Searches were performed in the MEDLINE|PubMed, Web of Science and Cochrane Library databases for articles published up to March 30, 2021, using MeSH terms and other free terms, combined by the Boolean operators "OR" and "AND": "tramadol AND third molar" OR "tramadol AND impacted tooth" OR "tramadol AND tooth extraction" OR "analgesics, opioid AND third molar" OR "analgesics, opioid AND impacted tooth" OR "analgesics, opioid AND tooth extraction" OR "tramadol hydrochloride AND third molar" OR "tramadol hydrochloride AND impacted tooth" OR "tramadol hydrochloride AND tooth extraction" OR "opioids AND third molar" OR "opioids AND impacted tooth" OR "opioids AND tooth extraction". The gray literature was accessed by consulting the Brazilian Digital Library of Theses and Dissertations (BDTD) and www.ensaiosclinicos.gov.br databases. Hand-searches were also performed in specialized periodicals (British Journal of Oral and Maxillofacial Surgery; International Journal of Oral and Maxillofacial Surgery; Journal of Dentistry; Medicine and Medical Sciences; Journal of Cranio-Maxillo-Facial Surgery; Journal of Oral and Maxillofacial Surgery; and Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology), and in reference lists of selected articles.

- Selection and eligibility criteria

The controlled vocabulary (MeSH terms) and free keywords in the search strategy were defined to identify clinical trials based on the elements of the PICO question:

1) Participants (P) = patients undergoing impacted mandibular third molar extraction

2) Intervention (I) = use of local submucosal injection of tramadol

3) Comparison (C) = placebo, oral tramadol, intravenous tramadol, or intramuscular tramadol

4) Outcomes (O) = postoperative pain

Secondary outcomes: use of rescue analgesics and adverse effects.

Inclusion criteria: i- randomized controlled trials; ii-studies in which intervention group received local submucosal injection of tramadol, and the control group received a placebo, oral tramadol, intravenous tramadol or intramuscular tramadol out of the operation site; iii- studies that evaluated postoperative pain using a subjective measure, such as the visual analog scale; and iv- studies published in English, Spanish or Portuguese.

Exclusion criteria: i- studies that did not evaluate the primary or secondary outcomes of interest; ii- lack of information on dose or administration route of tramadol; iii- studies that used systemic tramadol (e.g., intramuscular) or other analgesics or anti-inflammatories in the pre or postoperative period (except rescue analgesics), in addition to submucous injection of tramadol adjacent to the third molar; iv- pain assessment presented only in the form of graphs and not provided by the authors; v- studies not related to the subject; and vi- inability

to access the full text. No time or language restrictions was applied.

The selection process was conducted in two phases: Phase 1, two researchers (K.K.N.G. and M.S.S.) independently examined the titles and abstracts of all identified references, applying the including process (blind process); and Phase 2, the same two reviewers independently applied the exclusion criteria to the other studies, based on reading the full text (blind process). Inter-reviewer reliability in the study selection process was determined by the Cohen κ test, assuming an acceptable threshold value of 0.80 (16). The disagreement at any stage was resolved by discussion and mutual decision (consensus meeting) with a third reviewer (B.C.E.V.). The final decision/selection was always based on the full text of the publication.

- Data extraction

The full texts were evaluated and judged in the entire document. Authors were contacted when necessary to obtain details on study design and data clarification. Data were extracted by two independent reviewers (K.K.N.G. and M.S.S.) from the included studies and described in the paper at a consensus meeting with the third reviewer.

- Summary measures and synthesis of the results

Qualitative data were analyzed and presented in the form of text and tables. Standard pairwise meta-analyses of direct comparisons were performed using a fixed-effect model, and results were expressed as mean difference and relative 95 % CI (confidence interval). Heterogeneity was assessed by using the Chi-square-based Q-statistic method and Higgins inconsistency measurement (I2), with significance indicated by $P \leq 0.05$. The I^2 test ≥ 50 % indicates moderate heterogeneity and values ≥ 75 % indicate high heterogeneity (17-19). The effect estimate was calculated through the mean differences, adopting the statistical method of inverse variance.

- Risk of bias

Within studies: Once a detailed appraisal of the methods and results was performed independently by two researchers (K.K.N.G. and M.S.S.), the studies were analyzed to determine the possibility of biased results, using 'Cochrane Collaboration's Tool for assessing risk of bias in randomized trials' from seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (20,21).

Across studies: The presence of publication bias was investigated for the outcome of interest based on visual detection/analysis of the funnel plot (22,23), using the RevMan 5.4 software (Review Manager, version 5.4, Nordic Cochrane Centre, Cochrane Collaboration, September 2020).

Results

- Study selection

The searches of the databases led to the retrieval of 819 records (MEDLINE|PubMed), n = 450; Web of Science, n = 138; and Cochrane Library, n = 231). The studies were imported to the reference manager (EndNote® Online), which led to the removal of 219 duplicates. The analysis of the titles and abstracts, followed by the full text, resulted in the exclusion of 597 papers (Fig. 1). Inter-evaluator agreement in this step was calculated using kappa correlation coefficient (MEDLINE|PubMed, κ = 0.92; Web of Science, κ = 1.0; and Cochrane Library, κ = 0.89), confirming a high level of agreement between the reviewers. No additional publications were found in the gray literature, the specialized periodicals or reference lists of the studies included.

- Characteristics of Included Studies

In total, 172 participants (98 males and 74 females, aged 18 or over) from three randomized placebo-controlled trials were considered for analysis (10,24,25). The submucosal injection of 2 ml of tramadol adjacent to the impacted mandibular third molar was administered at doses of 1 mg/kg, 50 mg and 100 mg, after surgery. The placebo group received a submucosal injection of 2 ml of sterile saline solution injection. Postoperative pain was assessed between 0.5 hours and 72 hours after surgery, using the pain score [10 points visual analogue scale (VAS)]. Local anesthetics and rescue analgesic drugs differed between studies (Table 1).

- Risk of Bias

For the quality assessment, the articles were classified according to the seven domains of risk of bias (20,21): random sequence generation, allocation concealment and selective reporting showed low risk of bias, while the blinding of participants and personnel and blinding of outcome assessment were not clear, representing the main risk of bias. There were incomplete outcome data in the result section of studies, and there was no standardization in the classification of third molars (other risks of bias), both interpreted as uncertain risk of bias (Supplement 1).

- Synthesis of the Results

Iqbal *et al.* (2019) (10) reported the lowest postoperative pain scores and onset of consumption of rescue analgesic, highest number of rescue analgesics used. Ceccheti *et al.* (2014) (24) used tramadol 100 mg, followed by 1 mg/kg and 50 mg used by Gönül *et al.* (2015) (25) and Iqbal *et al.* (2019) (10), respectively. At all doses of tramadol, the postoperative pain score, onset of consumption of rescue analgesic and total number of rescue analgesics were significantly lower in the tramadol group (TG), compared with the placebo group (PG) (Fig. 2, Supplement 2). No adverse effects were seen in TG 50 mg. Nausea, vomiting, dizziness and burning were reported in the other two doses of tramadol (1 mg/kg and 100 mg) (Table 2).
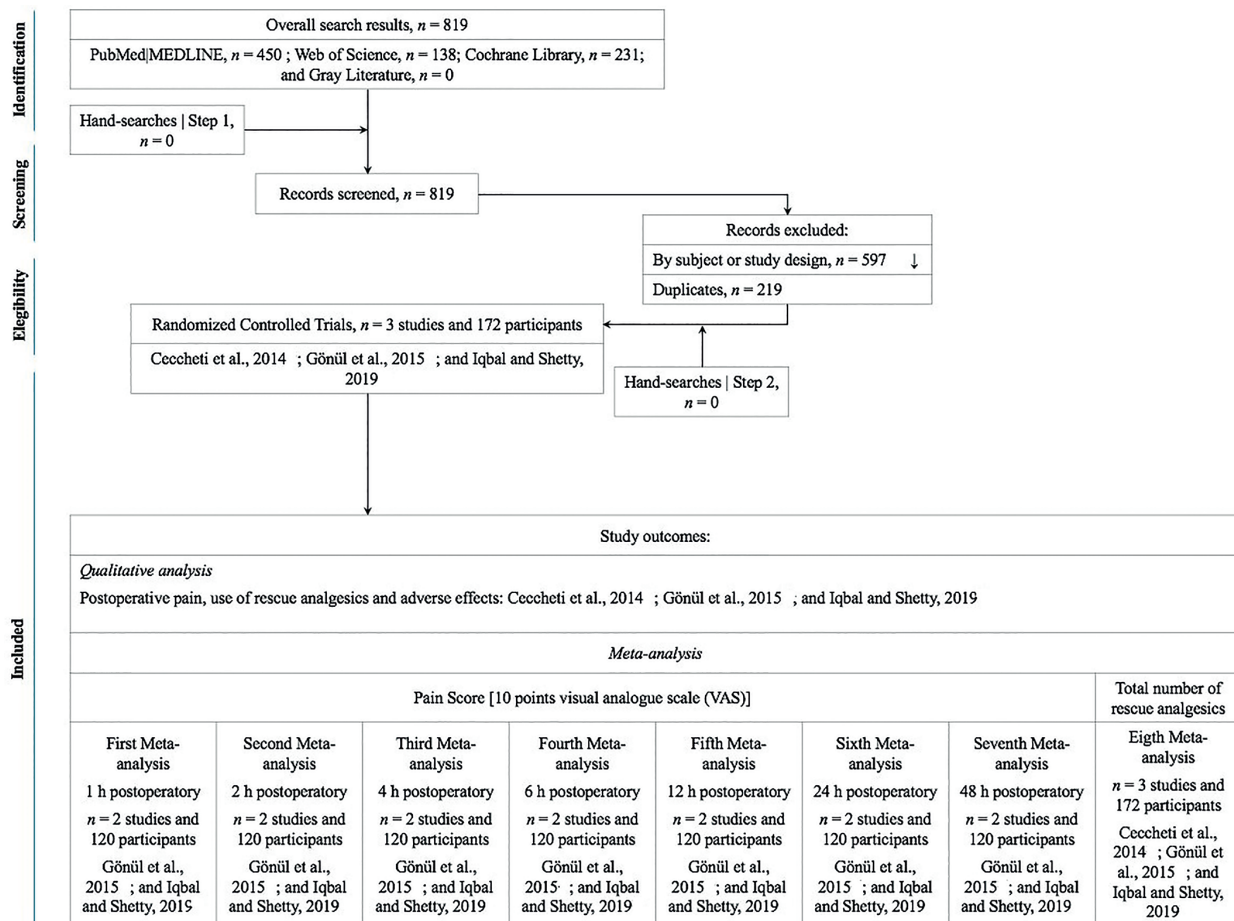
Fig. 1: Screening and enrolment. Legend: PRISMA flow diagram showing selection of articles for overview; n, absolute frequency.
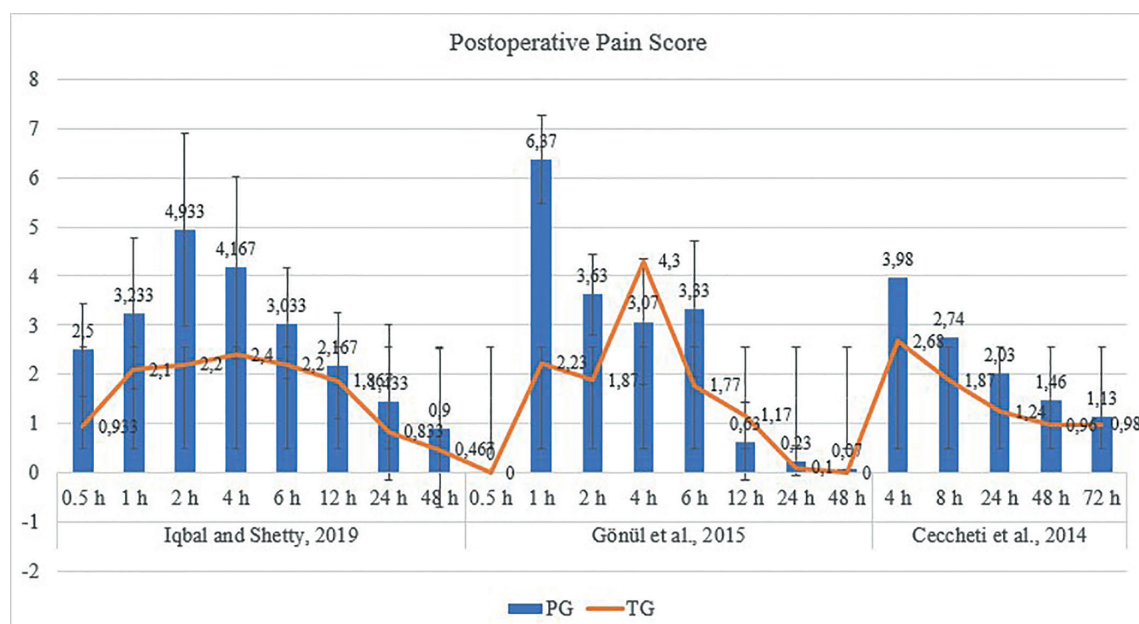

Fig. 2: Clustered column graph of mean pain score in the postoperative period. Legend: PG, placebo group; and TG, tramadol group. Data: mean and standard deviation values.

Table 1: Descriptive data on study design and qualitative results.

Author, year Study design	Participants	Groups	Intervention	Local anesthetic used	Efficacy in controlling postoperative pain	Rescue analgesics	Adverse effect
Iqbal and Shetty, 2019 Parallel-arm Randomized Controlled Trial	$n = 60$ 28 females and 32 males Age range, 19 to 45 years (mean = 22.78 years)	Placebo, $n = 30$ Tramadol, $n = 30$	Submucosal injection of tramadol 50 mg in the immediate postoperative period	Lidocaine 2 % with epinephrine 1:200,000	In favor of submucosal injection of tramadol $P \leq 0.05$	Diclofenac 50 mg	No adverse effect
Gönül et al., 2015 Parallel-arm Randomized Controlled Trial	$n = 60$ 34 females and 26 males > 18 years	Placebo, $n = 30$ Tramadol, $n = 30$	Submucosal injection of tramadol 1 mg/kg in the immediate postoperative period	Articaine 4 % with epinephrine 1:100,000	In favor of submucosal injection of tramadol $P \leq 0.05$	NR	Nausea PG, $n = 2$ | TG, $n = 5$ Vomiting PG, $n = 2$ | TG, $n = 0$ Burning PG, $n = 3$ | TG, $n = 0$ Dizziness PG, $n = 0$ | TG, $n = 0$
Ceccheti et al., 2014 Split-mouth Randomized Controlled Trial	$n = 52$ 36 females and 16 males Age range, 18 to 33 years (mean = 22.1 years)	Placebo, $n = 52$ Tramadol, $n = 52$	Submucosal injection of tramadol 100 mg in the immediate postoperative period	Mepivacaine 2 % with levonordefrin 1:20,000	In favor of submucosal injection of tramadol $P \leq 0.05$	Dipyrone 500 mg	Nausea and Vomiting PG, $n = 2$ | TG, $n = 4$

Legend: n, absolute frequency; Placebo group, submucosal injection of 2 ml sterile saline solution; Tramadol group, submucosal injection of 2 ml tramadol; ml, milliliter; mg, milligram; mg/kg, milligram per kilogram; %, percentage; P, statistical significance level to determine whether the average difference between two sets of observations was zero (probability of type I error = 5 %); PG, placebo group; and TG, tramadol group.

Table 2: Quantitative data on outcomes of interest.

Author, year Study design	Postoperative times	Pain Score [10 points visual analogue scale (VAS)]		Onset of consumption of rescue analgesics		Total number of rescue analgesics	
		PG	TG	PG	TG	PG	TG
Iqbal and Shetty, 2019 Parallel-arm Randomized Controlled Trial	0.5 h	2.5 ± 1.943	0.933 ± 0.944	1.966 ± 0.865 h	3.233 ± 0.679 h	8.2 ± 0.997	6.667 ± 1.061
	1 h	3.233 ± 1.547	2.1 ± 1.539				
	2 h	4.933 ± 1.721	2.2 ± 1.955				
	4 h	4.167 ± 1.51	2.4 ± 1.85				
	6 h	3.033 ± 0.809	2.2 ± 1.126				
	12 h	2.167 ± 1.367	1.867 ± 1.074				
	24 h	1.433 ± 1.501	0.833 ± 1.577				
	48 h	0.9 ± 0.481	0.467 ± 1.613				
Gönül et al., 2015. Parallel-arm Randomized Controlled Trial	0.5 h	0	0	1.87 ± 0.681 h	4.97 ± 0.809 h	3.6 ± 0.814	1.67 ± 0.547
	1 h	6.37 ± 0.850	2.23 ± 0.898				
	2 h	3.63 ± 0.615	1.87 ± 0.819				
	4 h	3.07 ± 0.691	4.3 ± 1.264				
	6 h	3.33 ± 1.446	1.77 ± 1.382				
	12 h	0.63 ± 0.765	1.17 ± 0.791				
	24 h	0.23 ± 0.43	0.1 ± 0.305				
	48 h	0.07 ± 0.254	0				
Ceccheti et al., 2014. Split-mouth Randomized Controlled Trial	4 h	3.98	2.68	185.4 ± 59.4 min	303.72 ± 416.01min	4.4 ± 3.71	3.37 ± 4.65
	8 h	2.74	1.87				
	24 h	2.03	1.24				
	48 h	1.46	0.96				
	72 h	1.13	0.98				

Legend: PG, placebo group (submucosal injection of 2 ml sterile saline solution); TG, tramadol group (submucosal injection of 2 ml tramadol); *, average difference between two sets of observations was zero at a statistical significance level of 5 % (statistically significant result if $P \leq 0.05$). Data: mean ± standard deviation values.

- Meta-analysis for postoperative pain
Submucosal injection of tramadol significantly reduced pain 2-hours [χ^2, $P > 0.05$; $I^2 = 72$ %; mean difference -2.15 (95 % CI = -3.08 to -1.21)] and 6-hours after surgery [χ^2, $P > 0.05$; $I2 = 63$ %; mean difference -1.15 (95 % CI = -1.86 to -0.44)]. Although not statistically sig-

nificant, the 1-hour, 24-hours and 48-hours postoperative meta-analyzes suggest better pain control in favor of tramadol (Fig. 3).
The total number of rescue analgesics consumed was significantly lower in TG [χ^2, $P > 0.05$; $I^2 = 16$ %; mean difference -1.78 (95 % CI = -2.07 to -1.50)], compared to PG (Fig. 4).
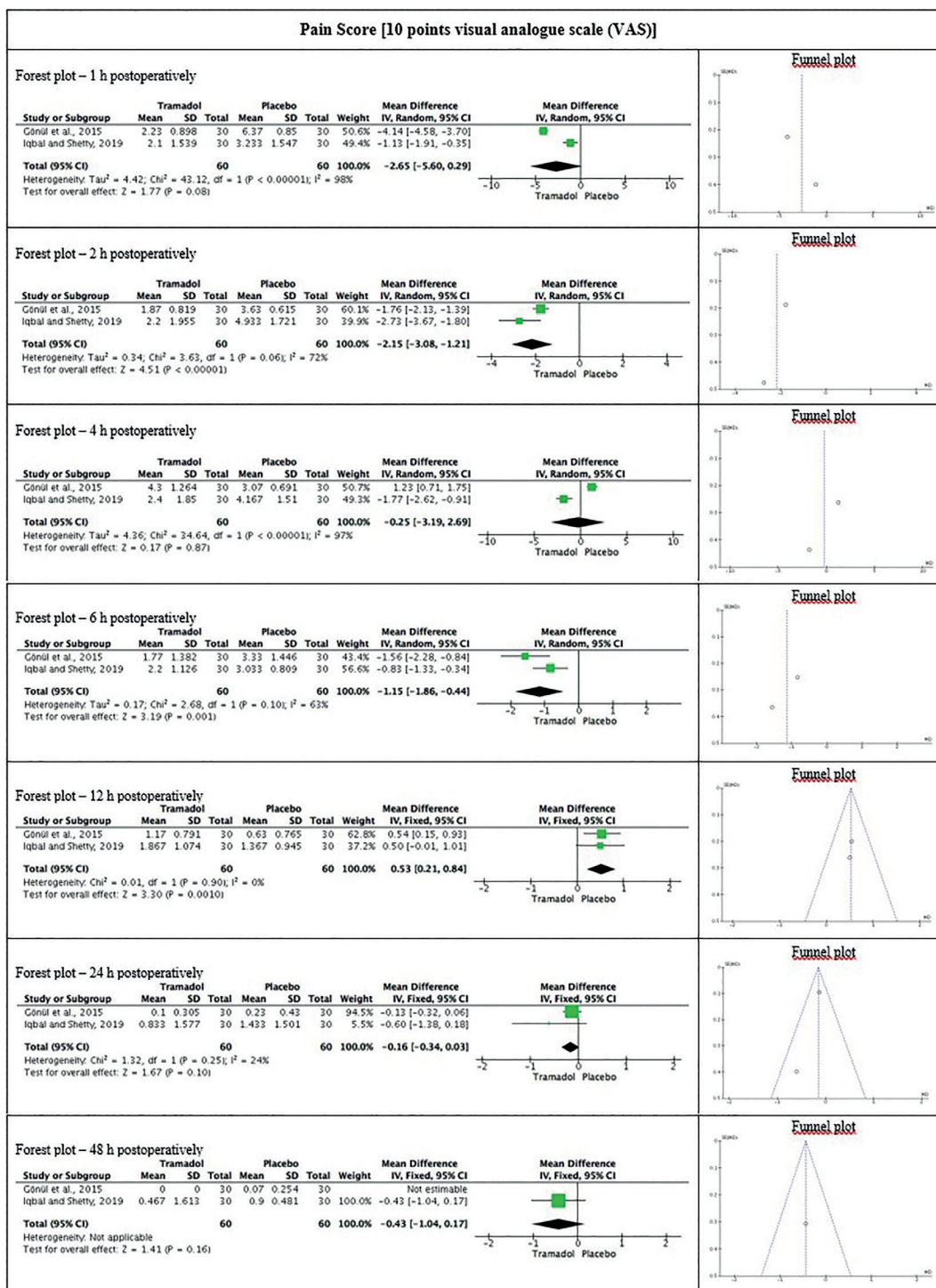

Fig. 3: Meta-analysis on the efficacy of submucosal injection of tramadol for postoperative pain after third molar extraction, compared to placebo group.
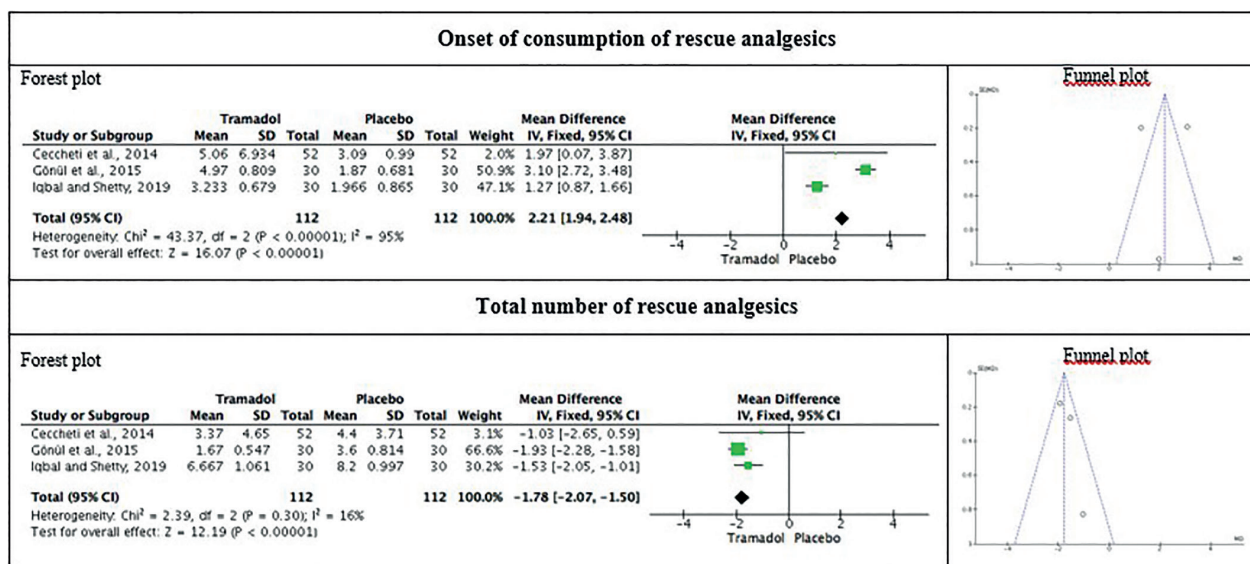
Fig. 4: Meta-analysis on the 'Onset of consumption of rescue analgesics' and 'Total number of rescue analgesics' used after third molar extraction, comparing the submucosal injection of tramadol with the placebo group.

Discussion

The submucosal injection of 2 ml of tramadol adjacent to the impacted mandibular third molar was effective in controlling pain up to 6-hours after surgery, with benefits observed up to 48-hours postoperatively. Consequently, the total number of rescue analgesics used was significantly lower in the TG compared to the PG. In addition, the onset of consumption of rescue analgesic in the TG was approximately twice that observed in the PG. Tramadol is an atypical opioid analgesic, with opioidergic, noradrenergic and serotonergic actions, well tolerated and effective in controlling moderate pain due to its opioidergic and monoaminergic activities. Tramadol modulates the cellular response to pain through voltage-gated sodium ion channels, V1 channels of transient receptor potential, glutamate receptors, α2 adrenoceptor receptors, adenosine receptors and mechanisms involving the substance P, related peptide to the calcitonin gene, prostaglandin E2 and pro-inflammatory cytokines downregulation. It also modifies the crosstalk between neuronal and non-neuronal cells in peripheral and central tissues and modulates neuronal hyperexcitability in these regions. Due to the wide spectrum of molecular targets, tramadol monotherapy relieves several types of pain, such as post-operative, lumbar and neuropathic, and is associated with childbirth, osteoarthritis, fibromyalgia and cancer, being used as a well-tolerated alternative to other drugs (26,27).

Like lidocaine, tramadol's blocking activity not only suppresses nerve conduction, but also inhibits ectopic activities in sensitized neurons. Both have high affinity to fast inactivated sodium ion channels than to resting channels and exhibit usage-dependent blockage. Tramadol 50 mg leads to membrane-stabilizing with a higher local concentration (IC50 = 21 µM) than in plasma (1 µM) (27,28). According to Pozos-Guillén *et al.* (2005) (29), tramadol prolongs the anesthetic effect and postoperative analgesic effectiveness, prolonging the onset of the need for rescue analgesics and reducing the number of these drugs in the postoperative period. Then, the postoperative benefit of submucosal injection of tramadol immediately after impacted mandibular third molar extraction can be perceived by the patient as a significant extension of local anesthesia.

Furthermore, tramadol it acts on opioid receptors and seems to modify the transmission of pain, inhibiting the reuptake of monoamines. It has been described that µ-opioid receptor agonists act to inhibit activation of adenylyl cyclase and tetrodotoxin-resistant Na+ channels on peripheral afferent neurons produced by inflammatory mediators such as prostaglandin E2 and serotonin. There is also evidence pointing that opioids inhibit release of substance P and calcitonin gene-related peptide from primary afferent neurons, and open ATP-sensitive K+ channels via Gi proteins resulting in hyperpolarization, reduction in firing of the primary afferent neuron and antinociception. Action mechanism of tramadol blocks noradrenaline uptake with selectivity, serotonin uptake, nonspecific voltage-dependent K+ channels and the nitrergic system. It has been demonstrated that tramadol not only inhibits 5-HT reuptake, but also induces 5-HT release in the raphe dorsal nucleus. However, explanations for the local action of tramadol remain unclear. One possible explanation is that the local effect of tramadol is mediated locally in peripheral nerve fibers (30). Tramadol 50–100 mg intramuscularly showed an effec-

tive and well-tolerated postoperative analgesic effect, comparable to morphine, pentazocine and ketorolac. Although tramadol 75 mg was also associated with sedation, adverse effects such as nausea and vomiting were more frequent (26). Even at the injectable dose of 50 mg of tramadol, burning sensation, pain and local pre-anesthetic erythema may occur (27).

Oral non-steroidal anti-inflammatory drugs are the most used to control postoperative pain in teeth extractions, although they are not always effective alone (28). The combined therapy of ibuprofen 400 mg and oxycodone hydrochloride 5 mg produced the best postoperative analgesia for impacted mandibular third molar extractions. However, adverse effects such as nausea, dizziness and headache have been associated with this therapy (31). The same adverse effects have been reported in two studies included in this systematic review (24,25); Iqbal and Shetty (2019) (10) used the lowest dose of submucosal tramadol (50 mg) and reported no adverse effects among the participants, even with the highest consumption of rescue analgesics among the studies analyzed. However, the tolerability of patients to submucosal injection of tramadol was similar or less than PG, confirming the low occurrence of adverse effects to tramadol (24,25), and suggesting a nocebo effect. According to Agrawal *et al.* (2019) (32), therapeutic doses of tramadol do not cause the depression of the circulatory or respiratory systems, being considered even safer with local application.

Beyond third molar surgery, local tramadol injections were reported by Demiraran *et al.* (2006) (33) and Alemanno *et al.* (2012) (34), for inguinal herniotomy and arthroscopic surgery for rotator cuff tears, respectively. Local tramadol injection prolonged the duration of anesthesia and reduced the requirement for total analgesics after surgery. These results were also observed in the submucosal injection for impacted mandibular third molar extractions (10,24,25).

The present meta-analysis demonstrated that the submucosal injection of tramadol achieved superior results with statistical significance in terms of pain control compared to the placebo six hours after third molar surgery. This finding may be explained by the fact that the plasma half-life of tramadol is six hours, independently of the administration route, demonstrating that this drug has a beneficial effect, especially with regards to early pain control.

In contrast, the placebo was superior to submucosal tramadol regarding pain control 12 hours after surgery, likely due to the fact that the effect of tramadol had been reduced by half, losing its analgesic effect over time. Moreover, the local application of the drug was progressively absorbed by systemic circulation. At 24 hours, no statistically significant difference was found between the two groups, offering no evidence of a late effect of submucosal injected tramadol. The three randomized placebo-controlled studies evaluated showed mild methodological heterogeneity, and statistical heterogeneity in the 1-hour and 4-hours postoperative pain score meta-analyzes. The summary measures of pain 2-hours and 6-hours after surgery represented a significant difference of approximately two points in the 10-points VAS, in favor of TG. Descriptive data suggest at least twice as much pain in the PG compared to the TG, for almost all postoperative follow-up. Some limitations must be considered when interpreting our findings. We believe that the number of clinical trials analyzed and the lack of standardization regarding the classification method for third molar impaction, the degree of surgical difficulty, the duration of surgery and the experience of the surgeon limit the evidence for clinical decision making. There was also no consensus among the studies included in this review regarding the local anesthetic and dose of tramadol used. Besides that, the risk of bias assessment revealed the need for further studies with more precise and clearer methodologies; many domains of the 'Cochrane Collaboration's Tool for assessing risk of bias in randomized trials' have not been clearly described in the papers.

Despite these limitations, the three randomized placebo-controlled trials included in this systematic review represent suggest the clinical efficacy of local submucosal injection of tramadol to control postoperative pain and reduce consumption of other drugs after surgery, in impacted mandibular third molar extractions.

In conclusion, results of the present systematic review and meta-analysis revealed that submucosal injection of tramadol adjacent to the impacted mandibular third molar is a safe procedure with important analgesics potential, especially in the first 6-hours after surgery. Reducing the demand for rescue analgesics or combination therapies represents an additional benefit of submucosal tramadol for patients. However, caution should be exercised when interpreting these results due to the heterogeneity among studies. We strongly recommend that new RCTs be performed using well-defined methodologies to improve the quality of evidence regarding this topic.

References

1. Almeida RAC, Lemos CAA, de Moraes SLD, Pellizzer EP, Vasconcelos BC. Efficacy of corticosteroids versus placebo in impacted third molar surgery: systematic review and meta-analysis of randomized controlled trials. Int J Oral Maxillofac Surg. 2019;48:118-31.
2. Sánchez-Torres A, Soler-Capdevila J, Ustrell-Barral M, Gay-Escoda C. Patient, radiological, and operative factors associated with surgical difficulty in the extraction of third molars: a systematic review. Int J Oral Maxillofac Surg. 2020;49:655-65.
3. Majid OW. Submucosal dexamethasone injection improves quality of life measures after third molar surgery: a comparative study. J Oral Maxillofac Surg. 2011;69:2289-97.
4. De Souza GM, Fernandes IA, Dos Santos CRR, Falci SGM. Is bro-

melain effective in controlling the inflammatory parameters of pain, edema, and trismus after lower third molar surgery? A systematic review and meta-analysis. Phytother Res. 2019;33:473-81.

5. Cetira Filho EL, Carvalho FSR, de Barros Silva PG, Barbosa DAF, Alves Pereira KM, Ribeiro TR, *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.

6. González-Barnadas A, Camps-Font O, Martín-Fatás P, Figueiredo R, Gay-Escoda C, Valmaseda-Castellón E. Efficacy and safety of selective COX-2 inhibitors for pain management after third molar removal: a meta-analysis of randomized clinical trials. Clin Oral Investig. 2020;24:79-96.

7. Shipton EA, Roelofse JA, Blignaut RJ. An evaluation of analgesic efficacy and clinical acceptability of intravenous tramadol as an adjunct to propofol sedation for third molar surgery. Anesth Prog. 2003;50:121-8.

8. Đanić P, Salarić I, Macan D. New Findings on Local Tramadol Use in Oral Surgery. Acta Stomatol Croat. 2017;51:336-44.

9. Wang TT, Tong J, Hersh EV, Chuang SK, Panchal N. Does prescription drug monitoring program usage affect opioid analgesic prescriptions by oral and maxillofacial surgeons after third molar surgery?. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;132:26-31.

10. Iqbal AM, Shetty P. Effect of Submucosal Injection of Tramadol on Postoperative Pain After Third Molar Surgery. J Oral Maxillofac Surg. 2019;77:1752-9.

11. Akinbade AO, Ndukwe KC, Owotade FJ. Comparative analgesic efficacy and tolerability of celecoxib and tramadol on postoperative pain after mandibular third molar extraction: A double blind randomized controlled trial. Niger J Clin Pract. 2019;22:796-800.

12. Gay-Escoda C, Hanna M, Montero A, Dietrich T, Milleri S, Giergiel E, *et al*. Tramadol/dexketoprofen (TRAM/DKP) compared with tramadol/paracetamol in moderate to severe acute pain: results of a randomized, double-blind, placebo and active-controlled, parallel group trial in the impacted third molar extraction pain model (DAVID study). BMJ Open. 2019;9:e023715.

13. Freda NM, Keenan AV. Moderate evidence to recommend submucosal injection of dexamethasone in reducing post-operative oedema and pain after third molar extraction. Evid Based Dent. 2016;17:58-9.

14. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.

15. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

16. Landis JR, Koch GG. The measurement of observer agreement for categorial data. Biometrics. 1977;33:159-74.

17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.

18. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. J Health Serv Res Policy. 2002;7:51-61.

19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.

20. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ. 2011;343:d5928.

21. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:ED000142.

22. Oxman AD, Guyatt GH. The science of reviewing research. Ann N Y Acad Sci. 1993;703:125-33.

23. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol. 2001;54:1046-55.

24. Cecchetti MM, Negrato GV, Peres MP, Deboni MC, Naclério-Homem Mda G. Analgesic and adjuvant anesthetic effect of submucosal tramadol after mandibular third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;117:e249-54.

25. Gönül O, Satılmış T, Bayram F, Göçmen G, Sipahi A, Göker K. Effect of submucosal application of tramadol on postoperative pain after third molar surgery. Head Face Med. 2015;11:35.

26. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet. 2004;43:879-923.

27. Haeseler G, Foadi N, Ahrens J, Dengler R, Hecker H, Leuwer M. Tramadol, fentanyl and sufentanil but not morphine block voltage-operated sodium channels. Pain. 2006;126:234-44.

28. Barakat A. Revisiting Tramadol: A Multi-Modal Agent for Pain Management. CNS Drugs. 2019;33:481-501.

29. Pozos-Guillén Ade J, Martínez-Rider R, Aguirre-Bañuelos P, Arellano-Guerrero A, Hoyo-Vadillo C, Pérez-Urizar J. Analgesic efficacy of tramadol by route of administration in a clinical model of pain. Proc West Pharmacol Soc. 2005;48:61-4.

30. Isiordia-Espinoza MA, Orozco-Solis M, Tobías-Azúa FJ, Méndez-Gutiérrez EP. Submucous tramadol increases the anesthetic efficacy of mepivacaine with epinephrine in inferior alveolar nerve block. Br J Oral Maxillofac Surg. 2012;50:157-60.

31. Au AH, Choi SW, Cheung CW, Leung YY. The Efficacy and Clinical Safety of Various Analgesic Combinations for Post-Operative Pain after Third Molar Surgery: A Systematic Review and Meta-Analysis. PLoS One. 2015;10:e0127611.

32. Agrawal S, Patel PR, Gundloori RVN. Proteins as Nanocarriers To Regulate Parenteral Delivery of Tramadol. ACS Omega. 2019;4:6301-10.

33. Demiraran Y, Ilce Z, Kocaman B, Bozkurt P. Does tramadol wound infiltration offer an advantage over bupivacaine for postoperative analgesia in children following herniotomy?. Paediatr Anaesth. 2006;16:1047-50.

34. Alemanno F, Ghisi D, Fanelli A, Faliva A, Pergolotti B, Bizzarri F, *et al*. Tramadol and 0.5% levobupivacaine for single-shot interscalene block: effects on postoperative analgesia in patients undergoing shoulder arthroplasty. Minerva Anestesiol. 2012;78:291-6.

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(K.K.N.G) - Conception and design of study; (M.S.S.) - Conception and design of study and acquisition of data: laboratory or clinical; (D.S.B.) - Acquisition of data: laboratory or clinical; (C.C.G.S.) - Analysis of data; (A.M.V.B.) - Analysis of data; (E.S.M.A.) - Analysis of data; (R.A.C.A.) - Drafting of article and/or critical revision; (B.C.E.V.) - Drafting of article and/or critical revision and final approval of manuscript.