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REVIEW ARTICLE

Tramadol as a local anaesthetic agent in dentistry: A systematic review of local and systemic adverse effects

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Abstract Tramadol is an effective alternative local anaesthetic (LA) agent available in dentistry. This review aims to help guide practice by providing clinicians with relevant data regarding adverse effects (AE) associated with locally administered tramadol in the oral environment. A systematic search of three electronic databases was performed to identify relevant studies reporting AE associated with locally administered tramadol in the oral setting. Selected studies were reviewed and included based on inclusion and exclusion criteria. Data collected included: publication year, study design, participant numbers, adverse effects and follow-up duration. Fifteen articles were included comprising of 547 tramadol participants across eight exodontia and seven non-exodontia studies. Thirty-eight associated AE were reported. Nausea was the most commonly reported (4.6%), followed by dizziness (1.3%), vomiting (0.7%) and local erythema (0.4%). No other AE were reported. The prevalence of total AE was similar in $\geq$ 50 mg tramadol doses (7.2–7.3%); however the total affected number is not dose dependent. The prevalence of AE and affected participants was less when tramadol was used as a sole LA rather than as an adjunct (5.6% vs. 7.9% and 3.4–5.6% vs. 6.3%, respectively). Thus, tramadol is a safe LA agent with a low prevalence of AE when administered in the dental setting.

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1. Introduction

Local anaesthesia is a standard and essential component in most routine dental procedures. The primary pharmacological method of obtaining local anaesthesia suitable for dental and oral surgery procedures is via local administration of an amide- (e.g. lidocaine/lignocaine, articaine or mepivacaine) or ester-based (e.g. procaine) local anaesthetic agent through infiltration or nerve blocking techniques. Amide-based local anaesthetics are the most utilised medication in dentistry, with practitioners preferring their use over ester-based local anaes-

Table 1 Potential clinical situations where locally administered tramadol can be considered in the oral setting.

Clinical situation where locally administered tramadol can be considered in the oral setting

1. Patient medical histories disallowing conventional local anaesthesia use
   - Allergy to local anaesthetic agents (rare)
   - Allergy to adjuncts of local anaesthetic agents where alternatives are not clinically appropriate e.g., metabisulphite allergy in context of relevant adrenaline-containing local anaesthetic (rare)
2. As an adjunct to conventional local anaesthesia e.g., when performing extensive procedures approaching the upper limit of conventional local anaesthetic whereby alternative anaesthesia is not clinically appropriate (uncommon)
3. Clinical decision attempting to maximise the benefits of locally administered tramadol regarding post-operative pain, analgesic requirements, and time to first analgesia

thetics due to their rapid onset, reliability and safety profile (Hawkins and Moore, 2002).

Local anaesthetic agents are considered the safest and most effective means to prevent and manage pain (Singh, 2012). Although conventional (amide- and ester-based) local anaesthetics are considered safe, some contraindications exist. Allergies to conventional local anaesthetic is extremely rare and has been associated more with ester-based agents than with amide-based agents owing to the production of *para*-aminobenzoic acid metabolites (Eggleston and Lush, 1996). Patients may have an allergy to previous local anaesthetic adjuncts such as antioxidants (e.g. metabisulfite) and preservatives (e.g. methyl-paraben), or the previous dental cartridge latex diaphragms. Sometimes, intravascular injection of vasoconstrictor-accompanied local anaesthetic may be mistaken as an "allergy" to local anaesthetic rather than recognised as the usually avoidable and inadvertent delivery of an intravascular vasoconstrictor (Rood, 2000). The incidence of complications associated with conventional dental local anaesthetic agents has been reported to be 4.5%, with the most common being dizziness, tachycardia and agitation (Daubländer et al., 1997), whereas others have reported a prevalence of up to 26% (Kaufman et al., 2000).

Alternative pharmacological agents exist for the case when a patient is unable to receive a conventional local anaesthetic. Tramadol is a locally administered analgesic agent (Raffa 1996), which later in 1998, was found to have anaesthetic properties (Pang et al.,1998). However, it is not clinically indicated for this reason. Table 1 identifies some clinical scenarios in which tramadol may be considered as a local anaesthetic.

Since it was first reported as displaying local anaesthetic properties in 1998 (Pang et al., 1998), tramadol has been established in

the literature as an effective local anaesthetic agent in medicine and dentistry including: as a perioperative wound infiltration agent for post-operative pain management in caesarean section surgery (Behdad et al., 2013; Demiraran et al., 2013; (Jabalameli et al., 2012) Sahmeddini et al., 2017), lumbar discectomy surgery (Mitra et al., 2017; Ozyilmaz et al., 2012), and paediatric tonsillectomy surgery (Akkaya et al., 2009; Heiba et al., 2012; Honarmand et al., 2013; Ugur et al., 2013), for infraorbital nerve blocks following nasal surgery (Cekic et al., 2013), as an axillary plexus blockade adjunct (Kapral et al., 1999; Robaux et al., 2004), for use in paediatric circumcision (Kargi et al., 2010), tendon repair surgery (Kargi et al., 2008), plastic skin lesion excision surgery (Altunkaya et al., 2003; Altunkaya et al., 2004; Kakagia et al., 2012) and oral surgery (Al-Haideri, 2013; Ceccheti et al., 2014; Ege et al., 2020; Gönül et al., 2015; Iqbal and Shetty, 2019; Isiordia-Espinoza et al., 2011; Jendi et al., 2019; Khan et al., 2016).

Tramadol was first synthesised in 1962 by Grünenthal GmbH in Germany before becoming commercially available in 1977. It is available as a racemic mixture of (+) and (-) tramadol enantiomers in capsule and liquid formations, and it is primarily used as an analgesic that acts on opioid, serotonergic and noradrenergic pathways. It is inexpensive and has a shelf life of 60 months. Tramadol's mechanism of action as a local anaesthetic is not clearly understood however multiple mechanisms have been proposed (Đanić et al., 2017). Notably, the local anaesthetic effect of tramadol is thought to be unrelated to its opioid-mechanisms and is not influenced by the opioid reversal agent naloxone (Tsai et al., 2001) (Raffa et al., 1992).

The lack of widespread adoption of tramadol as an alternative local anaesthetic agent in clinical practice is likely due to the excellent safety, efficacy and established history of use of traditional amide-based local anaesthetics. Tramadol has however been associated with requiring less post-operative analgesia requirement (Altunkaya et al., 2004; Cekic et al., 2013; Demiraran et al., 2013; Heiba et al., 2012; (Jabalameli et al., 2012) Kakagia et al., 2012; Kargi et al., 2008; Kargi et al., 2010; Mitra et al., 2017; Ozyilmaz et al., 2012; Robaux et al., 2004; Ugur et al., 2013; Vahabi et al., 2011), lower post-operative pain scores (Cekic et al., 2013; Demiraran et al., 2013; Heiba et al., 2012; (Jabalameli et al., 2012) Kakagia et al., 2012; Sahmeddini et al., 2017; Ugur et al., 2013), prolonged analgesic and anaesthetic effects (Behdad et al., 2013; Cekic et al., 2013; Kapral et al., 1999; Robaux et al., 2004), and delaying the time to the first analgesia post-surgery (Altunkaya et al., 2004; Mitra et al., 2017; Ozyilmaz et al., 2012) when compared to conventional local anaesthetics. To date, no study has primarily reviewed the prevalence of local and systemic adverse effects of tramadol when used as a local anaesthetic in the oral environment.

The purpose of this study was to systematically review the literature to provide clinicians and surgeons with the relevant data regarding the prevalence of adverse effects associated with locally administered tramadol in the oral environment to help guide clinical practice.

2. Material and methods

Studies were identified from electronic databases (ScienceDirect, Google Scholar and PubMed) using Medical Subject Heading (MeSH) keywords "tramadol AND submucosal OR local OR anaesthetic [anaesthetic] OR surgery OR dental" and subsequently the reference lists of relevant articles reviewed to ensure relevant studies were captured. The final article search was performed in January 2021, and duplicates were removed.

Studies were initially assessed by our lead author based upon their title and abstract with the following pre-determined inclusion criteria: 1) use of tramadol as a local anaesthetic and/or adjunct, 2) pertaining to the dentoalveolar field, 3) tramadol administration via infiltration, submucosal deposition, or the dental block technique, 4) randomised clinical trial, 5) full-text available article and 6) use of the English language. The full article texts were reviewed by the authors (R.M. and J.J.E.C), and a decision was made if the article inclusion was unclear. A reference list review was performed to capture relevant articles.

A second full-text review process of all articles occurred to assess eligibility according to the inclusion criteria of 1) reported adverse effects data. Articles were excluded if they: 1) did not disclose adverse event numbers for the study cases/-participants, or 2) reported adverse systemic effects in a split-mouth designed study in which control and comparison trials occurred simultaneously. Fig. 1 shows the process for selection of articles with reasons for exclusion at each step.

The authors used the CONSORT guideline for assessing risk of bias within and across included trials. The assessing criteria were sequence generation, allocation concealment, incomplete outcome data, selective outcome reporting, and blinding of participants, personnel, and outcome assessors. Two independent reviewers (R.M and J.C) assessed the risk of bias in duplicate.

Data collected by the authors included: publication year, study design and methodology, control and comparison of participant numbers, adverse effects, and available follow-up duration. Collected data was analysed to evaluate the adverse effects of locally administered tramadol in the oral setting. Study procedure, dose, and clinical use of tramadol was compared among the studies.

3. Results

3.1. Study selection

A database search of ScienceDirect (53), Google Scholar (549) and PubMed (4) identified 606 citations. No further references were identified following the reference list review. Nineteen studies were identified for second full-text review, of which 15 were included in this review (Fig. 1, Table 2).

3.2. Study specialty

Eight studies investigated local tramadol use in the context of oral surgery. Five studies were related to third molar surgery (Ceccheti et al., 2014; Gönül et al., 2015; Iqbal and Shetty, 2019; Isiordia-Espinoza et al., 2011; Khan et al., 2016). Two studies related to premolar exodontia for orthodontic purposes (Ege et al., 2020; Jendi et al., 2019). One study was related to upper molar exodontia (Al-Haideri, 2013). Four studies investigated local tramadol use in endodontics relating to inferior alveolar nerve success in mandibular molars with symptomatic irreversible pulpitis (Aksoy and Ege, 2020a, 2020b; De Pedro-Muñoz and Mena-Álvarez, 2017; Rodríguez-Wong et al.,
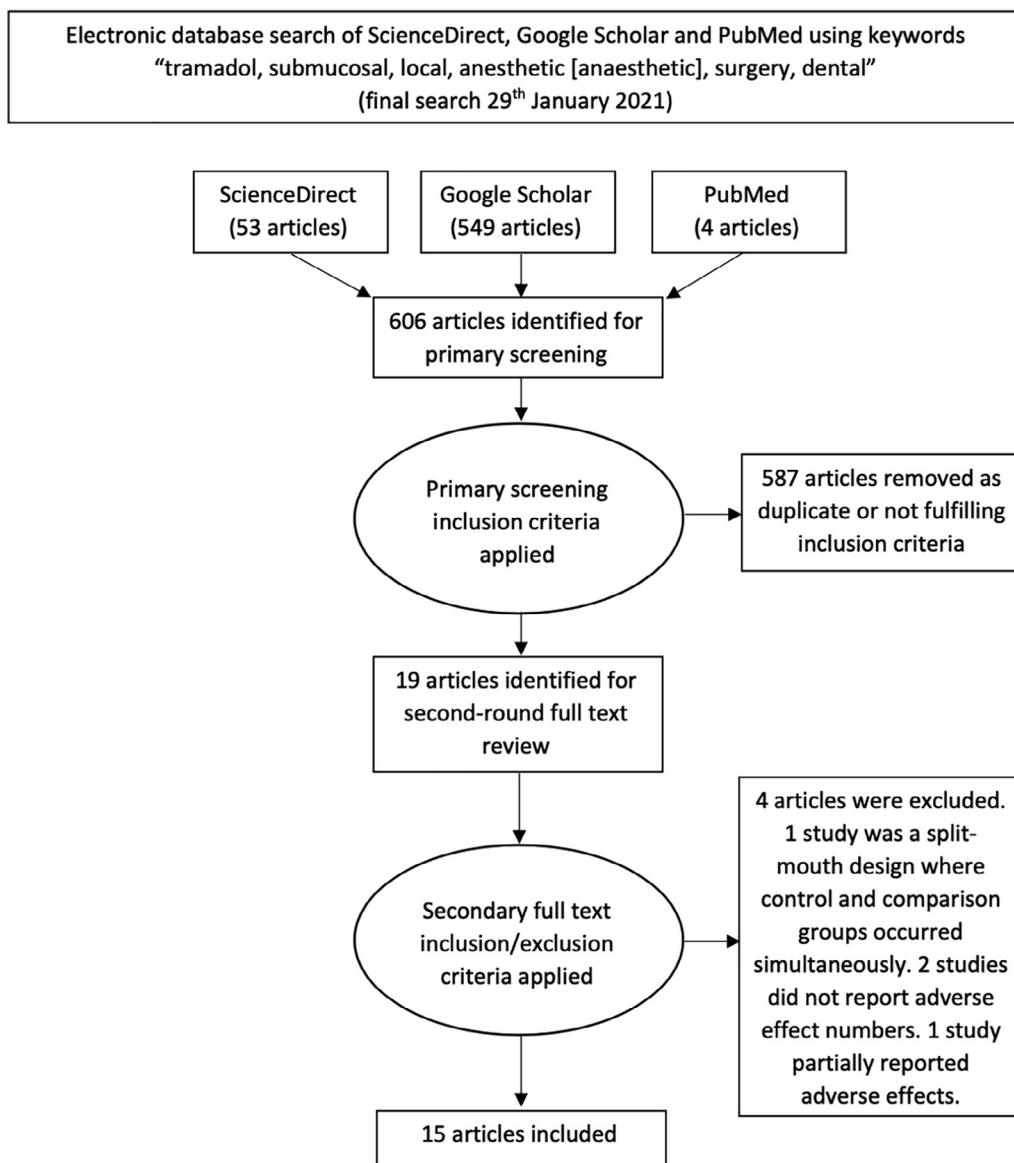
Fig. 1 PRISMA Flow Chart for Included Studies.

2016). Three studies reviewed local tramadol use, including duration and efficacy in a non-operative context (Isiordia-Espinoza et al., 2012; Jendi and Talathi, 2019; Pozos-Guillen et al., 2006).

3.3. Study control and comparisons groups

Four studies investigated tramadol as the sole local anaesthetic agent; one compared tramadol with a tramadol/adrenaline combination (Al-Haideri, 2013), two compared tramadol with lignocaine (Jendi et al., 2019; Jendi and Talathi, 2019), and compared one comparing a tramadol/adrenaline combination with a lignocaine/adrenaline combination (Ege et al., 2020).

One study compared a combination of lidocaine/adrenaline with tramadol against lidocaine/adrenaline as a combined local anaesthetic agent (Rodríguez-Wong et al., 2016).

Eight studies investigated tramadol against placebo/saline as a local anaesthetic adjunct agent when anaesthesia was obtained via conventional local anaesthetic/vasoconstrictor combinations: including articaine/adrenaline[epinephrine] (De Pedro-Muñoz and Mena-Álvarez, 2017; Gönül et al., 2015; Isiordia-Espinoza et al., 2011; Pozos-Guillen et al., 2006), lignocaine/adrenaline[epinephrine] (Iqbal and Shetty, 2019; Khan et al., 2016), mepivacaine/adrenaline (Isiordia-Espinoza et al., 2012) and mepivacaine/levonorfedrin (Ceccheti et al., 2014).

One study compared tramadol against lidocaine/adrenaline with a placebo/saline control group as a local anaesthetic adjunct when anaesthesia was obtained via lidocaine/adrenaline (Aksoy and Ege, 2020b). Another study compared tramadol against dexamethasone with a placebo/saline control group as a local anaesthetic adjunct when anaesthesia was obtained via articaine/adrenaline (Aksoy and Ege, 2020a).

Table 2 Summary of included studies.

Study year; design	Procedure (n = participants)	Follow-up	Reporting Method	Adverse Effects (n = participants) and Statistically Significant Difference Between Groups
Aksoy and Ege 2020a; RCT	Evaluation of post-operative pain following single-visit root canal treatment of mandibular molars with SIP comparing pre-operative buccal submucosal administration of 100 mg tramadol (n = 30) vs 8 mg dexamethasone (n = 30) vs saline (n = 30), following IANB with 4% articaine/1:200,000 adrenaline.	Post-injection	Self-reported, questioned about systemic and local side effects	Group A: 100 mg Tramadol - Nausea (n = 1)No side effects reported in dexamethasone or saline groups.No statistically significant difference (p = 0.364). Total AE Tramadol: nausea (n = 1, 3%)
Aksoy and Ege 2020b; RCT	Evaluation of the IANB success rate in mandibular molars with SIP comparing buccal submucosal administration of 100 mg tramadol (n = 35) vs 40 mg lidocaine (n = 35) vs saline (n = 35) administered 5 min after the IANB was performed with 1.8 mL of 2% lidocaine/1:80,000 adrenaline.	Not stated	Not stated	Group A: 100 mg Tramadol - Nausea (n = 3)Group B: 40 mg Lidocaine - Nausea (n = 1)Group C: Saline - Nausea (n = 0)No statistically significant difference (p = 0.218). Total AE Tramadol: nausea (n = 3, 8.6%)
Al-Haideri 2013; RCT	Supraperiosteal (including palatal) infiltration of 50 mg tramadol (n = 50) vs 50 mg tramadol/0.225 mg adrenaline (n = 50) for elective maxillary molar exodontia.	24 h	Self-reported, 3-point ordinal scale	Group A: Tramadol 50 mg - Nausea (n = 1)Group B: Tramadol 50 mg/Adrenaline 0.225 mg - Nausea (n = 2), vomit (n = 1)No statistically significant difference (p = 0.305). Total AE Tramadol: nausea (n = 3, 3%), vomit (n = 1, 1%)
Ceccheti et al. 2014; RCT/SM	Evaluation of analgesic and adjuvant anaesthetic effect comparing buccal submucosal infiltration of 100 mg tramadol (n = 52) vs saline (n = 52) following surgical removal of bone-impacted mandibular 3rd molars, with local anaesthesia achieved via maximum 5.4 mL of 2% mepivacaine/1:20,000 levonorfedrin, performed at least 1 week apart.	Not stated	Not stated, adverse effects recorded when present	Group A: Tramadol 100 mg - Nausea and vomit (n = 3)Group B: Saline - Nausea and vomit (n = 1)No p-value reported. Total AE Tramadol: nausea (n = 3, 5.7%) and vomit (n = 3, 5.7%)
De Pedro-Muñoz and Mena-Álvarez 2017; RCT	Evaluation of the IANB success rate in mandibular molars with SIP comparing buccal submucosal administration of 50 mg tramadol (n = 21) vs saline (n = 21) 10 min prior to IANB with 4% articaine/1:100,000 adrenaline.	Not stated	Not stated	No side effects reported in both groups.
Ege et al. 2020; RCT/SM	Buccal submucosal infiltration of 36 mg lidocaine/0.0225 mg epinephrine (n = 32) vs 50 mg tramadol/0.0225 mg epinephrine (n = 32) for orthodontically indicated bilateral 1st premolar exodontia performed 2 weeks apart.	After procedure	Self-reported	Group A: 50 mg Tramadol/0.0225 mg epinephrine - Dizziness (n = 3), nausea (n = 2), site erythema (n = 2)Group B: 36 mg lidocaine/0.0225 mg epinephrine - Dizziness (n = 2), nausea (n = 2), site erythema (n = 5)No p-value reported. Total AE Tramadol: dizziness (n = 3, 9.3%), nausea (n = 2, 6.2%), site erythema (n = 2, 6.2%)
Gönül et al. 2015; RCT	Evaluation of analgesic effect of locally applied 1 mg/kg tramadol (n = 30) vs saline (n = 30) drops to exodontia socket and bone surface following elective surgical removal of unilateral, mesially-angulated and completely impacted mandibular 3rd molars, with IANB achieved via 4% articaine/1:100,000 epinephrine.	Post-op	Self-reported, 5-points	Group A: Tramadol 1 mg/kg - Nausea (n = 5)Group B: Saline - Nausea (n = 2), vomit (n = 2), burning (n = 3)No statistically significant difference (nausea p = 0.228, vomit p = 0.15, burning p = 0.076). Total AE Tramadol: nausea (n = 5, 16.6%)
Iqbal and Shetty 2019; RCT	Evaluation of post-operative pain following surgical removal of impacted mandibular 3rd molars comparing post-operative buccal submucosal administration of 1 mg/kg tramadol (n = 30) vs saline (n = 30) with pre-operative lingual, long buccal and IANB via 2% lignocaine/1:200,000	Not stated	Not stated	No signs of tramadol overdose noted (including nausea, vomiting, tachycardia or seizure).No p-value reported.

Table 2 (*continued*)

Study year; design	Procedure (n = participants)	Follow-up	Reporting Method	Adverse Effects (n = participants) and Statistically Significant Difference Between Groups
Isiordia-Espinoza et al. 2012; RCT	epinephrine. Evaluation of soft tissue anaesthetic efficacy of submucosal 50 mg tramadol (n = 20) vs saline (n = 20) when administered following IANB with 2% mepivacaine/1:100,000 adrenaline.	Not stated	Not stated	Group A: 50 mg Tramadol - Dizziness (n = 2), nausea (n = 1), dizziness and nausea (n = 2)Group B: Saline - Dizziness (n = 1), dizziness and nausea (n = 1)No statistically significant difference (p = 0.23). Total AE Tramadol: dizziness (n = 4, 20%), nausea (n = 3, 15%)
Isiordia-Espinoza et al. 2011; RCT	Evaluation of pre-emptive oral 10 mg ketorolac 30 min pre-operatively/pre-dental block submucosal 50 mg tramadol (n = 15) vs oral 10 mg ketorolac 30 min pre-operatively/pre-dental block submucosal saline (n = 15) followed by lingual, buccal and IANB with 3.6 mL of 4% articaine/1:100,000 adrenaline prior to surgical removal of a non-painful impacted mandibular 3rd molar.	Evening of surgery	Self-reported, phone consult	No side effects reported in both groups.
Jendi et al. 2019; RCT	Supraperiosteal infiltration of maximum 50 mg tramadol (n = 50) vs maximum 40 mg lignocaine (n = 50) for orthodontically indicated maxillary premolar exodontia.	24 h	Self-reported, 3-point scale	Group A: Tramadol maximum 50 mg - Nausea (n = 2)Group B: Lignocaine maximum 40 mg - Nausea (n = 1)No statistically significant difference (p = 0.245). Total AE Tramadol: nausea (n = 2, 4%)
Jendi and Talathi 2019; RCT/SM	Infiltration of 50 mg tramadol (n = 50) vs 20 mg lignocaine (n = 50) over maxillary canines for soft tissue anaesthesia assessment.	24 h	Self-reported	No side effects reported in both groups.
Khan et al. 2016; RCT	Evaluation of analgesic and adjuvant anaesthetic effect of post-operative submucosal application of 100 mg tramadol (n = 30) vs saline (n = 30) following surgical removal of bone impacted mandibular 3rd molars with surgical anaesthesia achieved via lignocaine/adrenaline.	Not stated	Self-reported, tramadol specific	No major adverse effects reported.
Pozos-Guillen et al. 2006; RCT	Evaluation on anaesthetic duration comparing buccal mucosal infiltration of 50 mg tramadol (n = 24) vs saline (n = 24) immediately following IANB with 2.7 mL of 4% articaine/1:100,000 adrenaline prior to the surgical removal of a painful impacted mandibular 3rd molar.	Not stated	Self-reported, not stated in methods	Group A: Tramadol - Nausea (n = 3)Group B: Saline - Nausea (n = 2)No p-value reported. Total AE Tramadol: nausea (n = 3, 12.5%)
Rodríguez-Wong et al. 2016; RCT	Evaluation of the IANB success rate in mandibular molars with SIP comparing 1.3 mL 2% mepivacaine/1:100,000 adrenaline/0.5 mL 50 mg tramadol (n = 28) vs 1.8 mL 2% mepivacaine/1:100,000 adrenaline (n = 28).	Not stated	Self-reported, not stated in methods	No side effects reported in both groups.

*IANB = inferior alveolar nerve block **SIP = symptomatic irreversible pulpitis ***RCT = randomised control trial ****SM = split mouth

Table 3 Adverse effects of locally administered tramadol in the oral setting – study procedure, dose, and clinical use of tramadol.

	Participants, n	Total Adverse Effects, n (%)	Total Number (range if applicable) of Participants Affected by Adverse Effect/s, n (%)*	Nausea, n (%)	Vomit, n (%)	Dizziness, n (%)	Erythema, n (%)
Total Studies							
Total Studies (n = 15)	547	38	28–33 (5.1–6.0%)	25 (4.6%)	4 (0.7%)	7 (1.3%)	2 (0.4%)
Study Procedure Type							
Exodontia (n = 8)	339	24 (7.1%)	16–21 (4.7–6.2%)	15 (4.4%)	4 (1.2%)	3 (0.9%)	2 (0.6%)
Non-Exodontia (7)	208	14 (6.7%)	12 (5.8%)	10 (4.8%)	0 (0%)	4 (1.9%)	0 (0%)
Study Dose							
Max 50 mg Tramadol (n = 1)	50	2 (4%)	2 (4%)	2 (4.0%)	0 (0%)	0 (0%)	0 (0%)
50 mg Tramadol (n = 8)	290	21 (7.2%)	14–19 (4.8–6.6%)	11 (3.8%)	1 (0.3%)	7 (2.4%)	2 (0.7%)
1 mg/kg Tramadol (n = 4)	125	9 (7.2%)	9 (7.2%)	9 (7.2%)	0 (0%)	0 (0%)	0 (0%)
100 mg Tramadol (n = 2)	82	6 (7.3%)	3 (3.7%)	3 (3.7%)	3 (3.7%)	0 (0%)	0 (0%)
Clinical Use of Tramadol							
Tramadol as sole local anaesthetic agent (n = 4)	232	13 (5.6%)	8–13 (3.4–5.6%)	7 (3.0%)	1 (0.4%)	3 (1.3%)	2 (0.9%)
Tramadol as adjunct or combination with another local anaesthetic agent (n = 11)	315	25 (7.9%)	20 (6.3%)	18 (5.7%)	3 (1.0%)	4 (1.3%)	0 (0%)

* The "Total Number of Participants Affected by Adverse Effects" number and percentage values are a range as two studies (Ceccheti et al., 2014; Isiordia-Espinoza et al. 2012; RCT) reported 2 simultaneous side effects whilst all other studies did not specify if > 1 adverse effects affected single or multiple participants.

3.4. Study tramadol dose

Most studies utilised either fixed tramadol doses of 50 mg (Al-Haideri, 2013; De Pedro-Muñoz and Mena-Álvarez, 2017; Ege et al., 2020; Isiordia-Espinoza et al., 2012; Isiordia-Espinoza et al., 2011; Jendi and Talathi, 2019; Pozos-Guillen et al., 2006; Rodríguez-Wong et al., 2016) or 100 mg (Ceccheti et al., 2014; Khan et al., 2016), a fixed maximum doses of 50 mg (Jendi et al., 2019) or utilised a 1 mg/kg dose (Aksoy and Ege, 2020a, 2020b; Gönül et al., 2015; Iqbal and Shetty, 2019).

3.5. Study adverse effects reporting periods for adverse effects

Monitoring timeframes for reporting adverse effects varied including following injection (Aksoy and Ege, 2020a), postoperatively or after the procedure (Ege et al., 2020; Gönül et al., 2015), on the evening of the procedure (Isiordia-Espinoza et al., 2011) or 24 h post-operatively (Al-Haideri, 2013; Jendi et al., 2019; Jendi and Talathi, 2019). Most studies did not specify this timeframe (Aksoy and Ege, 2020b; Ceccheti et al., 2014; De Pedro-Muñoz and Mena-Álvarez, 2017; Iqbal and Shetty, 2019; Isiordia-Espinoza et al., 2012; Khan et al., 2016; Pozos-Guillen et al., 2006; Rodríguez-Wong et al., 2016).

3.6. Study participant numbers

The total number of participants among the studies was 547.

3.7. Reported adverse effects

The overall adverse effects are presented in Table 3.

Thirty-eight associated adverse effects were reported in a maximum of 33 (6.0%) and minimum of 28 (5.1%) participants (Table 3). Nausea was the most common (n = 25, 4.6%) followed by dizziness (n = 7, 1.3%), vomiting (n = 4, 0.7%) and local erythema (n = 2, 0.4%). No other associated adverse effects were recorded.

Both affected participants (4.7–6.2% vs 5.8%) and overall adverse effects (7.1% vs 6.7%) were similar among exodontia and non-exodontia studies, respectively (Table 3). Of the 8 studies that performed exodontia (n = 339), nausea was the most common adverse effect (n = 15, 4.4%) followed by vomiting (n = 4, 1.2%), dizziness (n = 3, 0.9%) and erythema (n = 2, 0.6%). Of the 7 non-exodontia studies (n = 208), nausea was the most common adverse effect (n = 10, 4.8%) followed by dizziness (n = 4, 1.9%). No vomiting or erythema was reported in the non-exodontia studies.

Fewer participants were affected in studies that had administered 100 mg of tramadol (3.7%) and a maximum of 50 mg tramadol (4%) compared to 1 mg/kg tramadol (7.2%) and 50-mg tramadol doses (4.8–6.6%) (Table 3). Total adverse effects were lower in the 50 mg maximum tramadol dose study (4%).

Studies that utilised tramadol as a sole local anaesthetic agent reported less overall adverse effects (5.6% vs 7.9%) and fewer affected participants (3.4–5.6% vs 6.3%) compared to tramadol use as an adjunct or combination agent (Table 3).
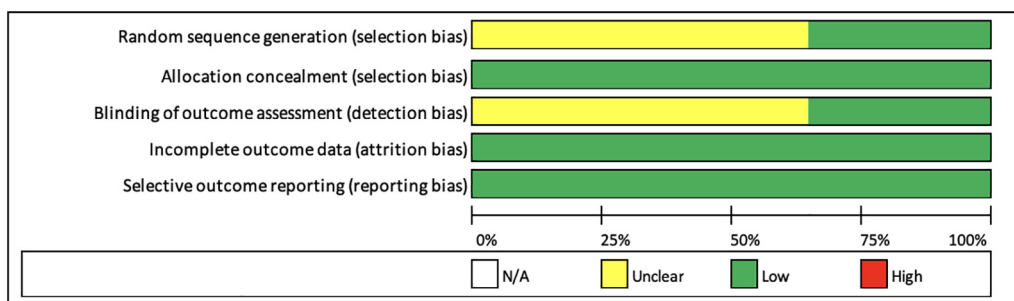
Fig. 2 Summary of the Risk of Bias of Included Studies.

No studies reported a statistically significant difference among control and comparison groups regarding adverse effects or local wound site healing.

3.8. Risk of bias

Based on the evaluation of the 15 included studies according to the CONSORT checklist for risk of bias; all studies had a low risk of bias in terms of their study design and reporting of data (Fig. 2). In two-thirds of studies (10 out of 15) it was unclear how the authors controlled the randomisation process and how blinding of the outcome was controlled (Fig. 2) (Aksoy and Ege, 2020b; Al-Haideri, 2013; Ceccheti et al., 2014; Gönül et al., 2015; Iqbal and Shetty, 2019; Isiordia-Espinoza et al., 2012; Jendi et al., 2019; Jendi and Talathi, 2019; Khan et al., 2016; Pozos-Guillen et al., 2006).

4. Discussion

4.1. Prevalence of adverse effects

The true frequency of adverse reactions to conventional local anaesthetic agents in dentistry is unknown because most data is limited to a few studies (Kaufman et al., 2000) which makes comparison among other agents difficult. The general incidence of complications related to dental local anaesthesia has been reported to be 4.5% (Daubländer et al., 1997), whereas others have reported a prevalence of up to 26% (Kaufman et al., 2000). However most reactions are likely low risk and transient. These adverse reactions can be classified into drug toxicity, drug allergy, local anaesthetic adjunct allergy, vasoconstrictor adjunct response and drug-specific responses (e.g. methemoglobinemia) (Finder and Moore, 2002).

The prevalence of adverse effects of tramadol ranges from 1 to 7% with nausea predominantly reported, followed by dizziness, drowsiness, fatigue, sweating, vomiting and postural hypotension (Cossman and Kohnen, 1995). Tramadol's adverse effects profile is associated with different administration routes, and is more common with intravenous compared to oral routes (Cossman and Kohnen, 1995). However, a comprehensive review of locally administered tramadol effects has not yet been published. A review article on the use of tramadol in oral surgery published in 2017 reported that "few studies had investigated the local effects of tramadol in oral surgery"(Đanić et al., 2017). They presented a limited table

of seven studies which included adverse effects of locally administered tramadol in oral surgery, however, they incorrectly reported some adverse effects (Đanić et al., 2017).

Consistent with the literature (Cossman and Kohnen, 1995), this study reported the prevalence of participants that have experiences an adverse event to be 5.1–6.0% (Table 3) when tramadol was administered locally, and nausea was the most common effect (4.3%), followed by dizziness (1.1%) and vomiting (0.8%); however, local erythema has also been reported (0.3%). Based on these results nausea and dizziness are common side effects (occurring in 1 in 10–100 people), whereas vomiting and local erythema are comparatively uncommon (occurring in 1 in 100–1,000 people) side effects of locally administered tramadol. No study reported a statistically significant difference between control and comparison groups regarding adverse reactions (Table 2). The prevalence and order of occurrence of adverse effects compared to non-locally administered routes is likely explained by eventual systemic distribution following absorption of locally administered tramadol. Although unknown, naloxone co-administration may reduce the prevalence of adverse effects of locally administered tramadol in the oral environment, but also may reduce the efficacy of post-operative opioid analgesia (Raffa et al., 1992). Rat studies have reported local analgesic effects from tramadol that are opioid-mediated in late post-operative pain (de Oliveira Junior et al., 2016), but not early on (Sousa and Ashmawi, 2015). This suggests that naloxone co-administration may reduce tramadol's benefits of lower pain scores, longer time to first analgesia occurrence and lower total analgesic requirements.

4.2. Specific adverse effects

There are no known documented cases of locally administered tramadol in the dental setting that were associated with anaphylaxis, serotonin syndrome, respiratory depression, facial nerve palsy/paresis, permanent paraesthesia, ocular disruption, auditory disruption, methemoglobinemia or substance addiction.

Anaphylaxis has not been reported in any of the studies due to study exclusion criteria. Tramadol should not replace appropriate investigation, referral, or education in the context of an alleged allergy to conventional local anaesthetic agents. Serotonin syndrome and respiratory depression are rare but life-threatening medically significant events associated with tramadol. None of the included studies reported either condi-

tion. This is likely explained by both the conditions' infrequent occurrence, low study numbers, exclusion of medically unwell participants, and the overall tramadol dose administered being low and would have had a delayed systemic absorption following local administration.

None of the included studies (Aksoy and Ege, 2020a, 2020b; Al-Haideri, 2013; Ceccheti et al., 2014; De Pedro-Muñoz and Mena-Álvarez, 2017; Ege et al., 2020; Gönül et al., 2015; Iqbal and Shetty, 2019; Isiordia-Espinoza et al., 2012; Isiordia-Espinoza et al., 2011; Khan et al., 2016; Pozos-Guillen et al., 2006; Rodríguez-Wong et al., 2016) that used a vasoconstrictor reported a reaction consistent with iatrogenic intravascular injection. Intravascular injection may occur clinically however techniques and equipment have been designed to minimise this occurrence. It is likely that intravascular delivery of tramadol at the doses reported in the studies would be trivial. The clinical consequence of accidental intravascular injection would likely be: 1) failure to achieve suitable local anaesthesia and 2) potential analgesic activity.

Unlike conventional local anaesthetics, there are no reports in the literature of locally administered tramadol in the dental setting being associated with anatomical complications such as facial nerve palsy/paresis, permanent paraesthesia of the inferior alveolar nerve or iatrogenic retrograde flow. This is likely due to tramadol's limited incorporation in general clinical practice as a local anaesthetic and small study numbers rather than a pharmacological effect of tramadol. As naloxone does not reverse the local anaesthetic effect of tramadol (Tsai et al., 2001), it likely has no benefit in the context of a potential tramadol-induced facial nerve palsy that is secondary to incorrect anatomical drug deposition.

4.3. Adverse effects are not influenced by procedure type

Surprisingly, the reported total adverse effects and affected participants do not appear to have been influenced by procedure type and have occurred similarly in both exodontia and non-exodontia studies (7.1% vs 6.7% and 4.7–6.2% vs 5.8%, respectively).

4.4. Adverse effects are independent of dose

A dose-dependent adverse effects relationship has been reported in a fixed dose tramadol study (Langley et al., 2010). This study reported that the number of participants who experienced adverse effects was independent of dose (Table 3).

The reported total adverse effects are similar when the administered tramadol dose is ≥ 50 mg. Although studies (n = 125) (Aksoy and Ege, 2020a, 2020b; Gönül et al., 2015; Iqbal and Shetty, 2019) using a 1 mg/kg tramadol protocol did not report participant weights, it was likely based upon the selection criteria that the administered dose was between 50 and 100 mg. One study (n = 50) (Jendi et al., 2019), which reported a 4% prevalence of adverse effects used a maximum of 50 mg dose without reporting an actual dose given.

Included studies utilised considerably lower tramadol doses compared to the maximum tramadol daily dose. The clinical significance of this may become more relevant in more extensive procedures requiring doses above those reported in the studies; however, this would require alternative consideration.

4.5. Adverse effects of tramadol when used as a sole local anaesthetic agent compared to as an adjunct/combination

Adverse effects were 41% more common in studies in which tramadol was used in combination with other local anaesthetics or as an adjunct (7.9%) compared to those in which tramadol was used as the sole anaesthetic agent (5.1%) (Table 3), suggesting a compounded adverse effect profile. This difference however is unlikely to be clinically relevant.

4.6. Adverse effects relevant to specific population groups

No studies included pregnant or paediatric participants however locally administered tramadol has been safely demonstrated in these population groups (Akkaya et al., 2009; Behdad et al., 2013; Demiraran et al., 2013; Heiba et al., 2012; Honarmand et al., 2013; Jabalameli et al., 2012; Kargi et al., 2010; Sahmeddini et al., 2017; Ugur et al., 2013). The use of locally administered tramadol has not been reported among medically compromised patients in dentistry. Appropriate medical consultation would be required prior to using tramadol locally among these population groups.

4.7. Study limitations

The limitations of this review include the following:

1. Reviewed studies were limited to healthy (non-medically compromised) participants and did not include paediatric, pregnant, or lactating patients.
2. The methodology and time period of reporting adverse effects varied significantly or were not stated in the studies (Table 2). Under reporting may have occurred because adverse effects are not always immediate, systemic distribution of locally applied tramadol is not immediate, atypical or uncommon adverse effects may remain unreported with participant bias.
3. Obtaining data on adverse effects was not the primary outcome among the studies.
4. With the exception of two studies (Ceccheti et al., 2014; Isiordia-Espinoza et al., 2012) that reported multiple adverse effects among the same participants, it is unknown if multiple adverse effects occurred among the same participants or were distributed among different participants in the studies we reviewed.
5. The reviewed studies were relevant to dentistry and minor oral surgery. This was relevant for two reasons. Firstly, this is directly applicable to the dentoalveolar field, which primarily occurs in the outpatient setting. Secondly, other studies utilising locally administered tramadol included obstetric surgery, otorhinolaryngology, paediatric orthopaedic and plastic surgery, which would usually occur in an inpatient setting with comprehensive analgesic methods readily available. This may influence the generalisation to inpatient settings and other specialties.

Conventional local anaesthetic agents have an excellent track record. Rather than a replacement for conventional local anaesthetics, tramadol is an alternative agent available to operators in specific clinical scenarios.

5. Conclusion

According to this systematic review, it appears that tramadol is a safe local anaesthetic agent with a low prevalence of adverse effects (5.1–6.0%) including localised erythema (0.3%) when administered in the dental setting.

Ethical approval statement

This article was a systematic review article of the literature, not involving any participants or animals.

CRediT authorship contribution statement

Robert Jonathon Mane: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Joanne Jung Eun Choi:** Methodology, Software, Validation, Formal analysis, Data curation, Writing – review & editing, Visualization. **William Fox Sharpe-Davidson:** Methodology, Validation, Investigation, Writing – review & editing, Visualization.

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