REVIEW ARTICLE

Efficacy of tramadol for postoperative pain management in dogs: systematic review and meta-analysis

Pablo A Donati[a], Lisa Tarragona[a], Juan VA Franco[b], Veronica Kreil[a], Rodrigo Fravega[c], Alfredo Diaz[a], Natali Verdier[a,d] & Pablo E Otero[a]

[a]Department of Anesthesiology and Pain Management, Facultad de Ciencias Veterinarias, Universidad de Buenos Aires, Buenos Aires, Argentina

[b]Argentine Cochrane Centre, Instituto Universitario Hospital Italiano, Buenos Aires, Argentina

[c]Hospital Veterinario de Santiago, Santiago, Chile

[d]Department of Anesthesiology and Perioperative Intensive Care, University of Veterinary Medicine, Vienna, Austria

Correspondence: Pablo E Otero, Universidad de Buenos Aires, Facultad de Ciencias Veterinarias, Cátedra de Anestesiología y Algiología, Avenida Chorroarín 280, C1427CWO, Buenos Aires, Argentina. E-mail: potero@fvet.uba.ar

Abstract

Objective To evaluate the evidence of analgesic efficacy of tramadol for the management of postoperative pain and the presence of associated adverse events in dogs.

Databases used A comprehensive search using PubMed/MEDLINE, LILACS, Google Scholar and CAB databases with no restrictions on language and following a prespecified protocol was performed from June 2019 to July 2020. Included were randomized controlled trials (RCTs) performed in dogs that had undergone general anesthesia for any type of surgery. Two authors independently classified the studies, extracted data and assessed their risk of bias using Cochrane's tool. RevMan and GRADE methods were used to rate the certainty of evidence (CoE).

Conclusions Overall 26 RCTs involving 848 dogs were included. Tramadol administration probably results in a lower need for rescue analgesia *versus* no treatment or placebo [moderate CoE; relative risk (RR): 0.47; 95% confidence interval (CI): 0.26–0.85; $I^2 = 0\%$], and may result in a lower need for rescue analgesia *versus* buprenorphine (low CoE; RR: 0.50; 95% CI: 0.20–1.24), codeine (low CoE; RR: 0.75; 95% CI: 0.16–3.41) and nalbuphine (low CoE; RR: 0.05; 95% CI: 0.00–0.72). However, tramadol administration may result in an increased requirement for rescue analgesia *versus* methadone (low CoE; RR: 3.45; 95% CI: 0.66–18.08; $I^2 = 43\%$) and COX inhibitors (low CoE; RR: 2.27; 95% CI: 0.68–7.60; $I^2 = 45\%$). Compared with multimodal therapy, tramadol administration may make minimal to no difference in the requirement for rescue analgesia (low CoE; RR: 1.12; 95% CI: 0.48–2.60; $I^2 = 0\%$). Adverse events were inconsistently reported and the CoE was very low. The overall CoE of the analgesic efficacy of tramadol for postoperative pain management in dogs was low or very low, and the main reasons for downgrading the evidence were risk of bias and imprecision.

Keywords analgesia, COX inhibitors, meloxicam, multimodal therapy, opioids.

Introduction

Systemic administration of opioids is a commonly used treatment for pain and has been associated with decreased perioperative morbidity and mortality in dogs. This is most likely resulting from the general anesthetics-sparing effect of opioids in dogs undergoing surgical and anesthetic procedures (Gil & Redondo 2013). Tramadol is a synthetic analgesic drug that exerts its effects through interaction with opioid, noradrenergic and serotoninergic receptors (Halfpenny et al. 1999; Sagata et al. 2002; Ogata et al. 2004; Ide et al. 2006). It is a racemic mixture of two enantiomers with a different ability to rotate light: a positive enantiomer that has low opioid and α_2-adrenergic receptor affinity and inhibits serotonin neuronal reuptake, and a negative enantiomer that binds to α_2-receptors and inhibits norepinephrine neuronal reuptake (Raffa et al. 1992; Driessen et al. 1993; Sevcik et al. 1993). One of the main metabolites of tramadol is the O-desmethyltramadol (metabolite M1), which has little intrinsic activity on the μ-receptor (Ide et al. 2006; Berrocoso et al. 2007), but is reported to have an affinity 200 times higher than tramadol (Hennies et al. 1988).

Although tramadol is widely used in veterinary medicine to provide analgesia (Clarke et al. 2019), its efficacy in dogs is questionable. Pharmacokinetic studies have reported a variable ability of dogs to metabolize tramadol compared with

other species and indeed, variable quantities of M1 have been detected in mixed breed and Beagle dogs (KuKanich & Papich 2004; McMillan et al. 2008). In addition, the lack of conclusive studies and consensus on its beneficial clinical effect and the evidence of associated gastrointestinal adverse events (KuKanich & Papich 2004) call for a further assessment of the effectiveness and side-effect profile of tramadol in dogs.

To date, there is no systematic review and meta-analysis evaluating the analgesic efficacy of tramadol and the occurrence of associated adverse events in dogs. The objectives of this study were to evaluate the evidence of analgesic efficacy of tramadol and the presence of associated adverse events for 24 hour postoperative pain treatment in dogs undergoing surgery.

Materials and methods

A systematic literature search of randomized clinical trials (RCTs) investigating tramadol for treatment of postoperative pain in dogs was performed in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (Moher et al. 2015). A protocol for review was conducted following the Cochrane Handbook (Higgins & Green 2011) and the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) guidelines (Hooijmans et al. 2014), and is detailed in Appendix SA.

Criteria for considering studies

All RCTs evaluating tramadol for postoperative pain in dogs were included and all dogs that underwent general anesthesia irrespective of type of surgery. All RCTs were included that investigated tramadol administered intravenously, subcutaneously, intramuscularly and orally, as well as comparisons of tramadol *versus* no treatment or any other analgesic drug.

Types of outcome measures

Primary outcome included number of dogs requiring analgesic rescue in the postoperative period. Secondary outcomes included the highest pain score obtained during postoperative evaluation (using a pain scale) and the occurrence of adverse events.

Search methods

Between June 2019 and July 2020, an electronic literature search was performed using PubMed/MEDLINE, LILACS, Google Scholar and CAB abstracts databases. No restrictions on language or publication status were applied. Additionally, reference lists of included trials were also examined.

The search strategy consisted of a combination of terms that included 'tramadol' AND 'pain' AND ('post-operative' OR 'surgery') AND ('canine' OR 'dogs') for all databases used except PubMed/MEDLINE. The search strategy used for PubMed/MEDLINE is outlined in Appendix SA.

Data collection and analysis

Review authors (PAD, LT) independently scanned the studies retrieved by the initial search using Rayyan software (Rayyan QCRI, Qatar; Ouzzani et al. 2016) to decide inclusion. In case of disagreement, a third investigator (PEO) was consulted. After preselection based on title and abstract, two review authors (PAD, LT) independently read studies in full to decide final inclusion. Again, in case of disagreement, a third investigator (PEO) was consulted.

Review authors (PAD, LT) independently performed data extraction. Information was extracted from the following variables: demographic characteristics of the dogs studied, pain scale used, number of analgesic rescues per treatment or group, highest pain scale value obtained during postoperative evaluation, type of surgery, drugs administered, occurrence of adverse events, funding and conflicts of interest. In studies where multiple comparison groups were evaluated, the information for each comparison was extracted, avoiding double-counting. In cases where more than one dose of tramadol or comparators were administered, only the data from the highest dose was used. In the presence of relevant missing data, corresponding authors were contacted.

Studies comparing tramadol with tramadol plus another drug were excluded. Studies using tramadol as premedication were also excluded if another analgesic drug was used postoperatively.

Studies using the following pain scales were included: Glasgow composite measure pain scale (GCMPS), University of Melbourne pain scale (UMPS), Colorado State University canine acute pain scale (CSU-CAP), numerical rating scale (NRS) or variations thereof, visual analog scale (VAS) and dynamic interactive visual analog scale (DIVAS). If information was provided by more than one pain scale, a descending order of priority based on objectivity was established as follows: GCMPS, UMPS, CSU-CAP, NRS, DIVAS and VAS. Adverse events such as sedation, salivation, dysphoria, loss of appetite, constipation, regurgitation or vomiting were categorized as minor if they were self-limiting and did not require treatment and as major when medical intervention was required. In addition, vomiting and regurgitation were classified as minor or major when occurred less or more than twice in a 12 hour period, respectively.

Assessment of risk of bias

The risk of bias was assessed using Review Manager (RevMan) Version 5.4 2020 (Cochrane Collaboration, Denmark) and the strategy proposed by SYRCLE (Hooijmans et al. 2014) (Appendix SB).

Data synthesis

The Mantel–Haenszel random models and the inverse variance random models were used for dichotomous and continuous data, respectively. The results of the relative risk (RR) and standardized mean difference (SMD) are reported with a 95% confidence interval (95% CI). We considered RR with the range of the lower and upper bounds of the 95% CI not crossing 1, and SMD with the range of the lower and upper bounds of the 95% CI not crossing 0, to be statistically significant.

Subgroup analysis and investigation of heterogeneity

Sensitivity analysis was performed on studies with differences in the risk of bias (high and low risk of bias studies). Heterogeneity between trials was assessed by means of I^2 and assumed significant heterogeneity when I^2 was $\geq$ 50% (Deeks et al. 2011). Furthermore, a *post hoc* subgroup analysis was performed for the type of surgery (ovariohysterectomy and orchiectomy), route of administration (oral) and dose administered ($\leq$3 mg kg^{-1}) based on the reviewers' assessment. A fixed-effect model chi-square test of heterogeneity was used to compare subgroups.

Certainty of evidence

The certainty of evidence (CoE) was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (https://gradepro.org). Fundamental aspects of the CoE, the magnitude of the effect of the evaluated interventions and the sum of data on the primary outcomes were included.

Results

A total of 9008 articles were retrieved in the literature search and 26 RCTs met inclusion criteria (Fig. 1 & Table 1). All of the included studies, except one (Meunier et al. 2019), had a superiority design, out of which 11 were performed as multi-arm trials (Mondal et al. 2005; Martins et al. 2010; Fajardo et al. 2012; Kongara et al. 2012; Rialland et al. 2012; Davila et al. 2013; Morgaz et al. 2013; Cardozo et al. 2014; Marques 2015; Zhang et al. 2017; Ugwu et al. 2020) and 14 as parallel trials (Mastrocinque & Fantoni 2003; Carareto et al. 2007; Gupta et al. 2009; Schuszler et al. 2010; Kongara et al. 2013; Stănescu et al. 2013; Centonze et al. 2014; Delgado et al. 2014; Benitez et al. 2015; Oliveira et al. 2016; Giudice et al. 2017; Saberi Afshar et al. 2017; Uscategui et al. 2017; Read et al. 2019). The mean sample size of the included studies was 33 ± 24 dogs. Sample size was calculated in three of the 26 included studies (Delgado et al. 2014; Uscategui et al. 2017; Meunier et al. 2019).

In total, 848 dogs were included in this meta-analysis, aged 0.5–19 years and weighing 2.5–45.0 kg. A total of 642 dogs were included in the studies that reported sex, and 478 (74.4%) were female.

The surgeries performed were ovariohysterectomy (Mastrocinque & Fantoni 2003; Mondal et al. 2005; Carareto et al. 2007; Gupta et al. 2009; Fajardo et al. 2012; Kongara et al. 2012; Morgaz et al. 2013; Stănescu et al. 2013; Oliveira et al. 2016; Saberi Afshar et al. 2017; Uscategui et al. 2017; Zhang et al. 2017; Meunier et al. 2019; Ugwu et al. 2020), orchiectomy (Kongara et al. 2013), cruciate ligament repair and other orthopedic surgeries (Schuszler et al. 2010; Rialland et al. 2012; Davila et al. 2013; Cardozo et al. 2014; Benitez et al. 2015; Marques 2015), eye enucleation (Delgado et al. 2014), hemilaminectomy (Giudice et al. 2017), thoracic surgery (Read et al. 2019), maxillectomy and mandibulectomy (Martins et al. 2010) and mastectomy (Uscategui et al. 2017).

Excluded studies

A total of 10 studies were excluded from this review—three studies because outcome data were not evaluated or reported in detail (Yasbek & Fantoni 2005; Sandoval et al. 2010; Santos & Herrera 2014), two studies because the analgesic effect of tramadol was compared against tramadol combined with another analgesic drug (Teixeira et al. 2013; Kaka et al. 2018) and one study for each of the following reasons: because it was not randomized (Tudor et al. 2018), pain was not assessed during the first 24 hours after surgery (Vullo et al. 2004), the pre-emptive effect of tramadol *versus* carprofen was compared, but all animals were administered hydromorphone (Karrasch et al. 2015), analgesia was evaluated only during the intra-operative period (Ospina-Argüelles et al. 2017) and because a

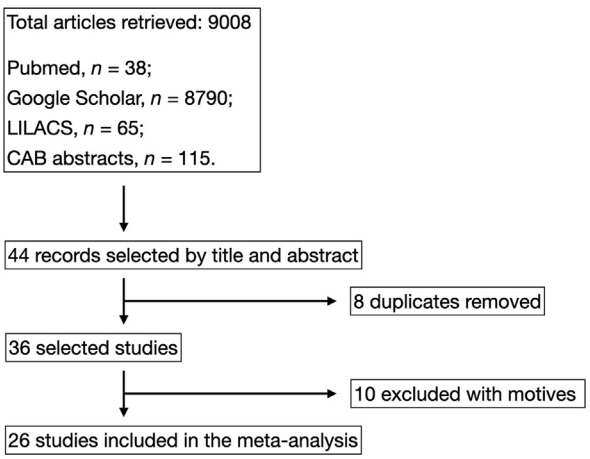

Figure 1 Study flow diagram. CAB, Commonwealth Agricultural Bureaux; LILACS, Latin American and Caribbean Health Sciences Literature.

Table 1 Characteristics of the included trials

Author/year	Country	Sex (*n*)	Surgical procedure	Intervention *versus* comparator	Co-interventions	Outcomes
Davila et al. 2013	USA	Female (22); male (8)	TPLO	Tramadol *versus* COX inh or tramadol + COX inh (firocoxib)	Premedicated with morphine IM Postoperative hydromorphone SC	GCMPS; serum cortisol; limb function
Benitez et al. 2015	USA	ND (48)	TPLO	Tramadol *versus* hydrocodone + acetaminophen	Postoperative intra-articular bupivacaine + morphine	GCMPS
Carareto et al. 2007	Brazil	Female (20)	OVH	Tramadol *versus* COX inh (tepoxalin)	Premedicated with acepromazine IV	Melbourne pain scale
Cardozo et al. 2014	Brazil	ND (28)	Cruciate ligament repair	Tramadol *versus* methadone	Bolus of fentanyl IV before starting osteotomy	GMPS; VAS; Colorado State University canine acute scale; serum IL-6
Centonze et al. 2014	Italy	ND (20)	Orthopedic surgery	Tramadol *versus* placebo	Premedicated with acepromazine + morphine	Short Form-GMPS; VAS
Delgado et al. 2014	USA	ND (43)	Eye enucleation	Tramadol *versus* COX inh (carprofen)	Premedicated with hydromorphone IM	Pain scoring system modified from previously published studies; VAS
Fajardo et al. 2012	Colombia	Female (30)	OVH	Tramadol *versus* tramadol + lidocaine + ketamine or morphine + ketamine + lidocaine	None	Melbourne pain scale
Giudice et al. 2017	Italy	Male (34); female (16)	Hemilaminectomy	Tramadol *versus* buprenorphine	Fentanyl CRI	GCMPS
Gupta et al. 2009	India	Female (12)	OVH	Tramadol *versus* buprenorphine	None	Multifactorial numerical rating scale
Kongara et al. 2012	New Zealand	Female (24)	OVH	Tramadol *versus* morphine	None	GCMPS
Kongara et al. 2013	New Zealand	Male (16)	Orchiectomy	Tramadol *versus* morphine	None	GCMPS
Marques 2015	Brazil	Female (15); male (13)	TPLO	Tramadol *versus* nalbuphine	Premedicated with acepromazine Fentanyl CRI	Colorado State University canine acute scale; GCMPS; VAS
Martins et al. 2010	Brazil	Male and female (42)	Maxillectomy and mandibulectomy	Tramadol *versus* codeine or ketoprofen or tramadol + ketoprofen or codeine + ketoprofen	None	NRS; descriptive scale; glycemia; serum cortisol; serum IL-6
Mastrocinque & Fantoni 2003	Brazil	Female (30)	OVH	Tramadol *versus* morphine	None	Descriptive scale; VAS; glycemia; cortisol; serum catecholamines
Meunier et al. 2019	India	Male (62); female (63)	Orchiectomy and OVH	Tramadol *versus* placebo	Premedicated with xylazine + butorphanol IM Postoperative meloxicam	Colorado State University canine acute pain scale; VAS; modified Short Form-GMPS

Table 1 (*continued*)

Author/year	Country	Sex (*n*)	Surgical procedure	Intervention *versus* comparator	Co-interventions	Outcomes
Mondal et al. 2005	India	Female (18)	OVH	Tramadol *versus* COX inh (ketoprofen or meloxicam)	Xylazine IM	Standard scoring system
Morgaz et al. 2013	Spain	Female (75)	OVH	Tramadol *versus* buprenorphine	Premedicated with medetomidine IM	DIVAS; GCMPS
Oliveira et al. 2016	Brazil	Female (14)	OVH	Tramadol + meloxicam *versus* meloxicam	Premedicated with acepromazine Fentanyl CRI	Melbourne; VAS
Read et al. 2019	UK	Male (8); female (8)	Thoracotomy	Tramadol *versus* transdermal fentanyl	Premedicated with methadone, medetomidine IM + carprofen SC Intercostal bupivacaine + remifentanil CRI Postoperative methadone + carprofen orally	GCMPS
Rialland et al. 2012	Canada	ND (25)	Trochleoplasty	Tramadol *versus* placebo	None	VAS; 4A-VET pain scale
Saberi Afshar et al. 2017	Iran	Female (10)	OVH	Tramadol *versus* placebo	Premedicated with acepromazine IM (None)	Simple descriptive scale; VAS; Melbourne pain scale
Schuszler et al. 2010	Romania	Male (11); female (6)	Osteosynthesis	Tramadol *versus* butorphanol	None	DIVAS
Stănescu et al. 2013	Romania	Male (12); female (28)	Genital surgery	Tramadol *versus* COX inh (robenacoxib)	None	GCMPS
Ugwu et al. 2020	Nigeria	Female (15)	OVH	Tramadol *versus* placebo	Ketoprofen SC	Melbourne pain scale
Uscategui et al. 2017	Brazil	Female (48)	Mastectomy	Tramadol *versus* methadone	None	Melbourne pain scale
Zhang et al. 2017	China	Female (24)	OVH	Tramadol *versus* nefopam	None	GCMPS

COX inh, cyclooxygenase inhibitors; CRI, continuous rate infusion; DIVAS, dynamic interactive visual analog scale; GCMPS and GMPS, Glasgow composite measure pain scale; IL-6, interleukin-6; IM, intramuscular; IV, intravenous; ND, not described; NRS, numerical rating scale; OVH, ovariohysterectomy; SC, subcutaneously; TPLO, tibial plateau levelling osteotomy; VAS, visual analog scale; 4A-VET pain scale, composite pain scale.

pain scale was not used (Mondal et al. 2006). All included RCTs were assessed for risk of bias (Fig. 2).

Effects of interventions

Tramadol versus no treatment

Tramadol administration probably results in a reduction in the number of dogs requiring analgesic rescue *versus* no treatment or placebo (moderate CoE; RR: 0.47; 95% CI: 0.26–0.85; $I^2 = 0\%$, studies = 5, $n = 189$; Fig. 3). No statistically significant differences were observed in the subgroup analysis for ovariectomies and orchiectomies (Oliveira et al. 2016; Saberi Afshar et al. 2017; Meunier et al. 2019) *versus* other type of surgeries (Rialland et al. 2012; Centonze et al. 2014; $p = 0.59$), in those administered tramadol orally (Rialland et al. 2012) *versus* intravenously, subcutaneously or intramuscularly (Centonze et al. 2014; Oliveira et al. 2016; Saberi Afshar et al. 2017; Meunier et al. 2019; $p = 0.82$), or in those administered a dose ≤ 3 mg kg^{-1} (Centonze et al. 2014; Saberi Afshar et al. 2017) *versus* those administered higher doses (Oliveira et al. 2016; Saberi Afshar et al. 2017; Meunier et al. 2019; $p = 0.95$).

Tramadol administration may reduce the highest pain score obtained, but the evidence for this outcome is very uncertain (very low CoE; SMD: −1.09; 95% CI: −2.34 to 0.16; $I^2 = 77\%$; studies = 4, $n = 159$; Fig. 4).

Tramadol versus methadone

Tramadol may result in an increased number of dogs requiring analgesic rescue *versus* methadone. However, the range in which the actual effect may be, the 'margin of error', indicates

Figure 2 Risk of bias assessment of included trials using the Cochrane's Collaboration tool. ?, unclear risk; −, high risk; +, low risk.

that tramadol may make minimal or no difference (low CoE; RR: 3.45; 95% CI: 0.66−18.08; $I^2 = 43\%$; studies = 2, $n = 66$; Fig. 5).

Only one study (Cardozo et al. 2014) reported the highest pain scores obtained with each treatment and concluded that higher pain scores may be obtained with tramadol *versus* methadone, but the evidence is very uncertain (very low CoE; SMD: 0.51; 95% CI: −0.44 to 1.45, studies = 1, $n = 18$).

Tramadol versus morphine

Tramadol administration may result in minimal to no difference in the number of dogs requiring analgesic rescue *versus* morphine, but the evidence is very uncertain (very low CoE; RR: 1.11; 95% CI: 0.45−2.74; $I^2 = 0\%$'; studies = 3, $n = 62$; Fig. 5). None of the studies reported the highest pain scores obtained.

Tramadol versus butorphanol

Tramadol may decrease the number of dogs requiring analgesic rescue *versus* butorphanol, but the evidence is very uncertain (very low CoE; RR: 0.42; 95% CI: 0.17−1.06; studies = 1, $n = 17$; Fig. 5). The analgesic efficacy of tramadol resulted in lower pain scores than butorphanol, but the evidence is very uncertain (very low CoE; SMD: −0.32; 95% CI: −1.28 to 0.64).

Tramadol versus buprenorphine

Tramadol administration may result in a lower number of dogs requiring analgesic rescue *versus* buprenorphine. However, the range in which the actual effect may be, the margin of error, indicates that tramadol may make minimal or no difference (low CoE; RR: 0.50; 95% CI: 0.20−1.24; studies = 1, $n = 43$; Fig. 5). The evidence is very uncertain on the analgesic efficacy of tramadol *versus* buprenorphine on the highest pain score obtained (very low CoE; RR: 0.42; 95% CI: −1.04 to 1.89; $I^2 = 91\%$; studies = 3, $n = 108$).

Tramadol versus codeine

One study reported that tramadol may result in a lower number of dogs requiring analgesic rescue *versus* codeine. However, the range in which the actual effect may be, the margin of error, indicates that tramadol may make minimal or no difference (low CoE; RR: 0.75; 95% CI: 0.16−3.41; studies = 1, $n = 17$; Fig. 5). This study did not report the highest pain score obtained.

Tramadol versus transdermal fentanyl

It is not certain whether tramadol results in a lower number of dogs requiring analgesic rescue *versus* transdermal fentanyl patch. No analgesic rescue was required in any of the groups,

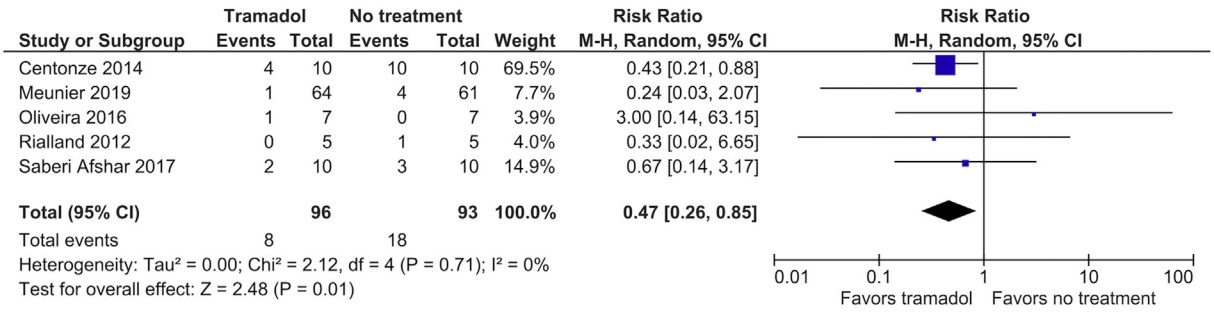

Figure 3 Forest plot showing the number of dogs treated with tramadol *versus* no treatment requiring rescue analgesia in the postoperative period. A Mantel-Haenszel (M-H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown.

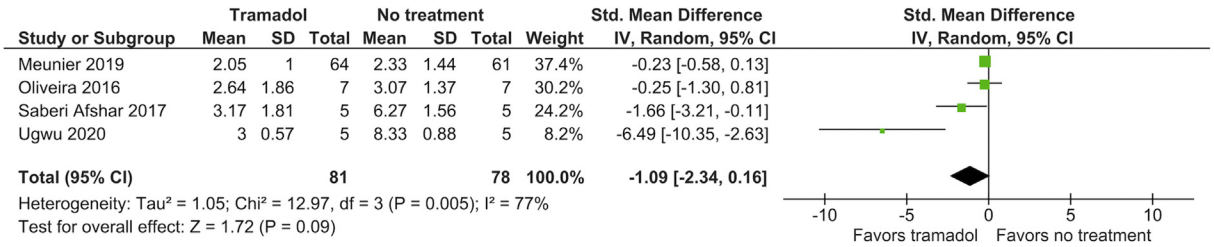

Figure 4 Forest plot showing the highest pain score obtained in dogs treated with tramadol *versus* no treatment, in the postoperative period. An inverse variance (IV) random effects model was used for this meta-analysis. The results of the standardized mean difference (Std. Mean Difference) with a 95% confidence interval (95% CI) are shown. SD, standard deviation.

so the RR could not be calculated (Fig. 5). No data on the highest pain score obtained were reported.

Tramadol versus nalbuphine

Tramadol administration may result in a significant decrease in the number of dogs requiring analgesic rescue *versus* nalbuphine (low CoE; RR: 0.05; 95% CI: 0.00−0.72; studies = 1, $n = 19$; Fig. 5). Tramadol may also decrease the highest pain score obtained (low CoE; SMD: −0.50; 95% CI: −1.42 to 0.41; studies = 1, $n = 19$). However, the range in which the actual effect for this outcome may be, the margin of error, indicates that tramadol may make minimal or no difference.

Tramadol versus nefopam

Tramadol administration may result in an increase in the number of dogs requiring analgesic rescue *versus* nefopam (very low CoE; RR: 3; 95% CI: 0.14−64.26; studies = 1, $n = 16$). However, the range in which the actual effect may be, the margin of error, indicates that tramadol may make minimal or no difference. The evidence is very uncertain on the analgesic efficacy of tramadol *versus* nefopam on the highest pain score obtained (very low CoE; SMD: 0.94; 95% CI: −0.11 to 1.99).

Tramadol versus COX inhibitors

Tramadol may result in an increased number of dogs requiring analgesic rescue *versus* COX inhibitors. However, the range where the actual effect may be, the margin of error, indicates that tramadol may make minimal or no difference (low CoE; RR: 2.27; 95% CI: 0.68−7.60; $I^2 = 45\%$; studies = 5, $n = 163$; Fig. 6). When analyzing the different surgery subgroups, no statistically significant differences were observed ($p = 0.53$; Fig. 7).

A *post hoc* analysis was performed to evaluate the results in the group of dogs who underwent maxillectomy or mandibulectomy for oncological reasons. In this group, tramadol reduced the RR to require analgesic rescue (RR: 0.45; 95% CI: 0.12−1.71). However, the difference among subgroups was also not statistically significant ($p = 0.07$), and there was an overlap between the CIs.

No statistically significant differences were observed in the subgroup analysis for ovariohysterectomies and orchiectomies (Morgaz et al. 2013; Stănescu et al. 2013) *versus* other types of surgeries (Martins et al. 2010; Davila et al. 2013; Delgado et al. 2014; $p = 0.59$), in those administered tramadol orally (Davila et al. 2013; Delgado et al. 2014) *versus* intravenously, subcutaneously or intramuscularly (Martins et al. 2010; Morgaz et al. 2013; $p = 0.33$), or in those

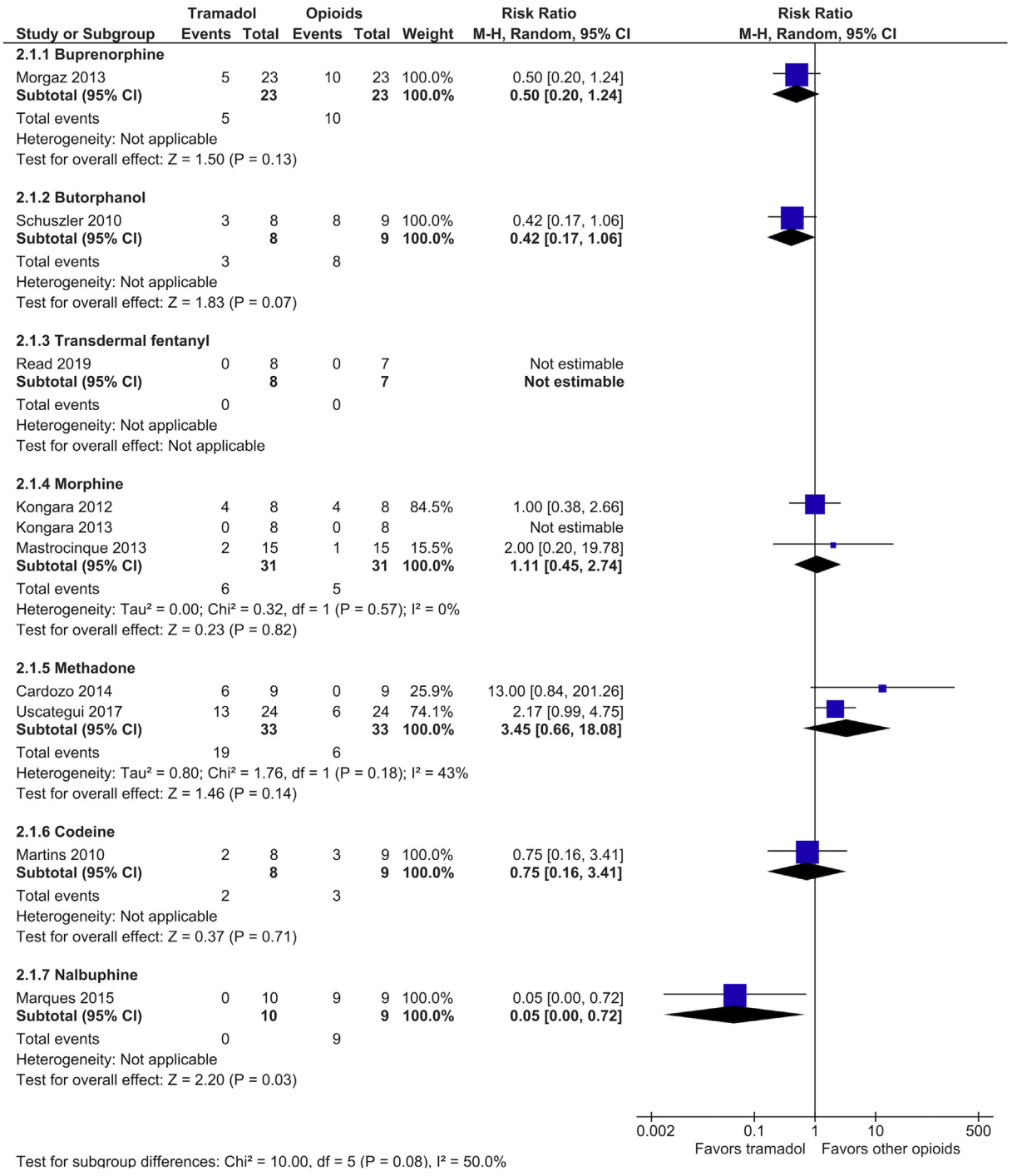

Figure 5 Forest plot showing the number of dogs treated with tramadol *versus* opioids requiring rescue analgesia in the postoperative period. A Mantel-Haenszel (M-H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown.

administered a dose $\leq$ 3 mg kg^{-1} (Martins et al. 2010; Morgaz et al. 2013; Stănescu et al. 2013) *versus* those administered higher doses (Davila et al. 2013; Delgado et al. 2014; $p = 0.95$).

The highest pain scores obtained were reported in three studies (Mondal et al. 2005; Carareto et al. 2007; Morgaz et al. 2013). The administration of tramadol may result in higher pain scores *versus* COX inhibitors, but the evidence is very

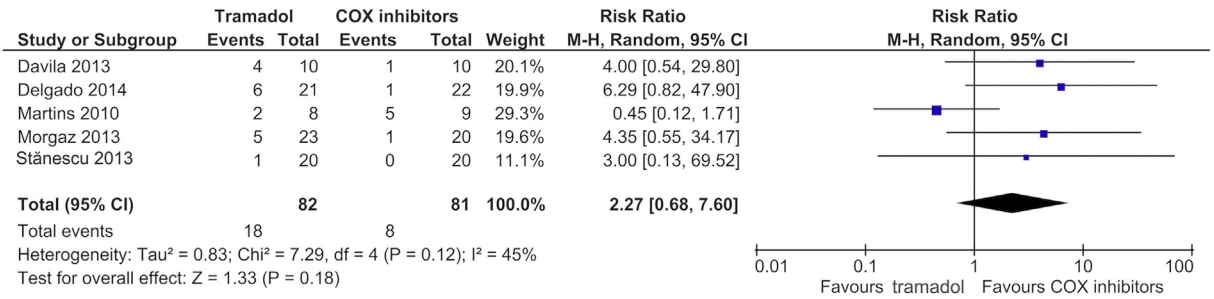

Figure 6 Forest plot showing the number of dogs treated with tramadol *versus* COX inhibitors requiring rescue analgesia in the postoperative period. An inverse variance (IV) random effects model was used for this meta-analysis. The results of the standardized mean difference (Std. Mean Difference) with a 95% confidence interval (95% CI) are shown. SD, standard deviation.

uncertain (very low CoE; SMD: 0.97; 95% CI: −0.63 to 2.58: $I^2 = 86\%$; studies = 3, $n = 84$).

Tramadol versus multimodal therapy

All studies evaluated the number of animals that required analgesic rescue in each group. Tramadol administration may result in minimal to no difference in the number of dogs requiring analgesic rescue *versus* multimodal therapy (low CoE; RR: 1.12; 95% CI: 0.48−2.60; $I^2 = 0\%$; studies = 3, $n = 78$; Fig. 8). None of the studies reported the highest pain scores obtained.

Adverse events

Adverse events associated with drug administration were described in seven studies (Gupta et al. 2009; Davila et al. 2013; Morgaz et al. 2013; Stănescu et al. 2013; Cardozo et al. 2014; Benitez et al. 2015; Read et al. 2019). In three studies, the number of adverse events associated with tramadol administration were compared against those associated with administration of COX inhibitors (Davila et al. 2013; Morgaz et al. 2013; Stănescu et al. 2013). Excessive salivation was observed in three of 20 dogs treated with

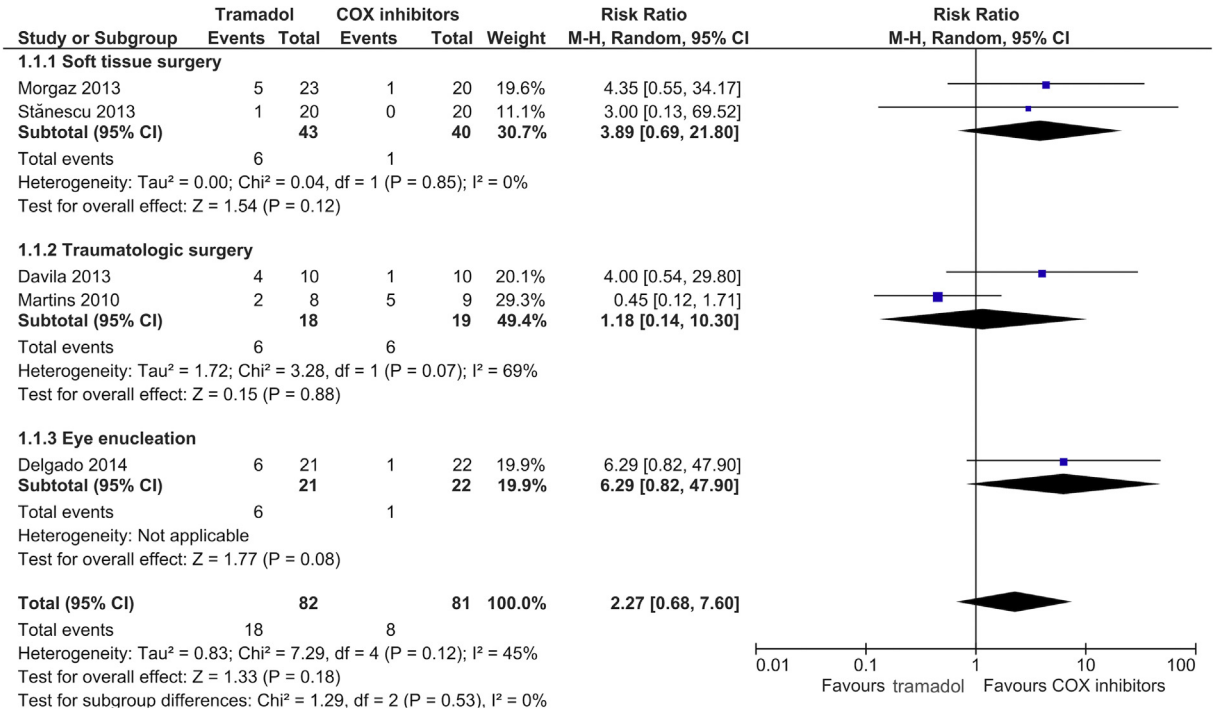

Figure 7 Forest plot showing the subgroup type of surgery, for the number of dogs treated with tramadol *versus* opioids requiring rescue analgesia in the postoperative period. A Mantel-Haenszel (M-H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown.

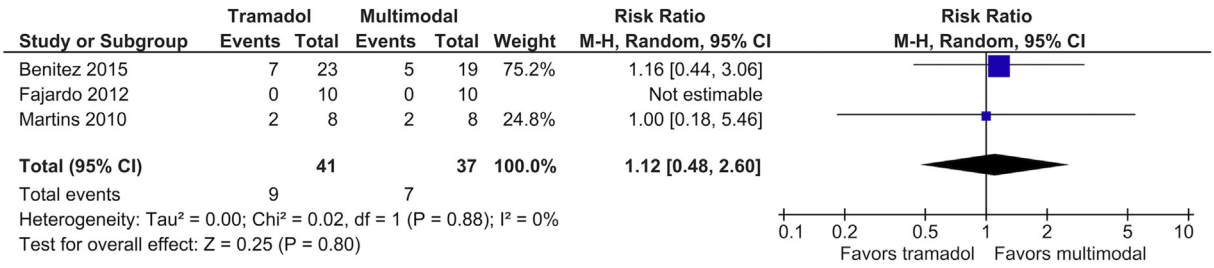

Figure 8 Forest plot showing the number of dogs treated with tramadol *versus* multimodal therapy requiring rescue analgesia in the postoperative period. A Mantel-Haenszel (M-H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown.

tramadol *versus* none treated with robenacoxib (Stănescu et al. 2013). Mild head tremors were observed in one dog treated with tramadol (Davila et al. 2013) and mild dysphoria in another dog (Morgaz et al. 2013); both effects were self-limiting and did not require treatment. The evidence is very uncertain about the number of adverse events in dogs treated with tramadol *versus* the number of adverse events in dogs treated with COX inhibitors (RR: 1.74; 95% CI: 0.34−8.86; $I^2 = 7\%$).

The number of adverse events observed in dogs treated with tramadol was compared with other opioids in four studies (Gupta et al. 2009; Morgaz et al. 2013; Cardozo et al. 2014; Read et al. 2019). Excessive salivation was observed in five of seven animals treated with fentanyl *versus* two of eight animals treated with tramadol (Read et al. 2019). No salivation was recorded in a group of 23 dogs treated with tramadol *versus* one of 23 dogs treated with buprenorphine (Morgaz et al. 2013), but in a different study, salivation was recorded in eight of nine animals treated with tramadol (Cardozo et al. 2014). Mild dysphoria was recorded in one dog in each of two groups of 23 dogs administered tramadol or buprenorphine, respectively, that required no treatment (Morgaz et al. 2013). Nausea was observed in one of six dogs administered tramadol and in one of six dogs administered buprenorphine (Gupta et al. 2009). The evidence is very uncertain about the number of adverse events in dogs treated with tramadol *versus* the number of adverse events in dogs treated with other opioids (RR: 1.08; 95% CI: 0.18−6.59; studies = 4, $n = 91$; $I^2 = 65\%$).

When occurrence of adverse events associated with tramadol was compared with multimodal treatment (hydrocodone−acetaminophen), five of 23 dogs treated with tramadol regurgitated *versus* three of 19 dogs administered hydrocodone−acetaminophen (Benitez et al. 2015). Excessive salivation occurred in one dog administered hydrocodone−acetaminophen, and one dog administered tramadol regurgitated and required treatment (major adverse event).

Certainty of evidence

The overall CoE was low to very low and the main reasons for downgrading were risk of bias and imprecision (Appendix SC).

A summary of findings for the main comparisons for the primary and secondary outcomes are presented in Tables 2 and 3.

Discussion

No systematic review and meta-analysis on the efficacy of tramadol for management of postsurgical pain in dogs was found in the literature. This systematic review included 26 RCTs investigating the efficacy of tramadol *versus* no treatment or other analgesics for the treatment of postoperative pain and the occurrence of associated adverse events in dogs. A total of 848 dogs undergoing different surgeries were included. The majority of the included studies had a low sample size and none of them performed a power calculation. The general quality of the evidence was low; therefore, the results of the present meta-analysis must be interpreted with caution.

Compared with no treatment, the use of tramadol probably results in a reduction in the number of dogs requiring analgesic rescue. Tramadol was compared with other opioids by evaluating each drug individually and not pooling all the opioids together because of the high statistical heterogeneity observed when pooling the data. The information obtained for the number of dogs requiring rescue analgesia from the comparison of tramadol *versus* nalbuphine, butorphanol, buprenorphine, codeine and fentanyl (patch presentation) comprised a small number of participants and a low number of studies. A comparison of tramadol with morphine did not show superiority of either of the drugs. However, this study included only 31 animals per study group and had a very low CoE. The use of methadone showed a decrease in the number of analgesic rescues along with a decrease in the resulting highest pain scores obtained. However, these results did not reach statistical significance and the CoE was low. The results of the comparison of tramadol *versus* nefopam are inconclusive because pooling the data was not possible and because of very low CoE. COX inhibitors may decrease the number of pain rescues in the

Table 2 Summary of findings. Number of dogs included, relative risk (RR) with a 95% confidence interval (95% CI) and certainty of evidence (CoE) of the comparison between tramadol and other analgesic drugs administration, for the outcome number of dogs requiring analgesic rescue

Comparison	Number of dogs (number of studies)	RR (95% CI)	CoE (⊕⊕⊕⊕−⊕)
Placebo	189 (5)	0.47 (0.26−0.85)	⊕⊕⊕◯
Methadone	66 (2)	3.45 (0.66−18.08)	⊕⊕◯◯
Morphine	62 (3)	1.11 (0.45−2.74)	⊕◯◯◯
Butorphanol	17 (1)	0.42 (0.17−1.06)	⊕◯◯◯
Buprenorphine	46 (1)	0.50 (0.20−1.24)	⊕⊕◯◯
Codeine	17 (1)	0.75 (0.16−3.41)	⊕⊕◯◯
Transdermal fentanyl	15 (1)	not estimated	⊕◯◯◯
Nalbuphine	19 (1)	0.05 (0.00−0.72)	⊕⊕◯◯
Nefopam	16 (1)	3.00 (0.14−64.26)	⊕◯◯◯
COX inhibitors	163 (5)	2.27 (0.68−7.60)	⊕⊕◯◯
Multimodal	78 (3)	1.12 (0.48−2.60)	⊕⊕◯◯

CoE: ⊕⊕⊕⊕, high, new research is unlikely to change our confidence in the estimated effects; ⊕⊕⊕, moderate, further investigation is likely to change our confidence in the estimated effect and could change the estimate; ⊕⊕, low, further investigation is very likely to change our confidence in the estimated effect and could change the estimate; ⊕, very low, there is a lot of uncertainty about the effect estimates.

postoperative period *versus* tramadol. However, the results did not reach statistical significance either and the CoE was low. The results of comparing tramadol with multimodal therapy should be interpreted with caution. Although no significant differences were found among groups, the CoE was poor and these studies only evaluated as comparators the combinations of hydrocodone−acetaminophen, morphine−ketamine−lidocaine and codeine−ketoprofen. Currently, the American Society of Anesthesiologists Task Force on Acute Pain Management (2012) considers multimodal therapy or combination therapy as the most effective strategy for the treatment of postoperative pain. However, the limited number of studies and combination therapies evaluated in this meta-analysis prevent definitive conclusions. Although the CoE was low, tramadol resulted in

Table 3 Summary of findings. Number of dogs included, standardized mean difference (SMD) with a 95% confidence interval (95% CI), relative risk (RR) with a 95% CI and certainties of evidence (CoE) of the comparisons between tramadol and other analgesic drugs administration in dogs, for the outcomes highest pain score obtained and observation of adverse effects

Comparison	Outcome highest pain score obtained			Outcome observation of adverse effects		
	Number of dogs (number of studies)	SMD (95% CI)	CoE (⊕⊕⊕⊕−⊕)	Number of dogs (number of studies)	RR (95% CI)	CoE (⊕⊕⊕⊕−⊕)
Placebo	159 (4)	−1.09 (−2.34 to 0.16)	⊕◯◯◯	na	na	na
Methadone	18 (1)	0.51 (−0.44 to 1.45)	⊕◯◯◯	18 (1)	17.00 (1.13 −256.56)	⊕◯◯◯
Morphine	na	na	na	na	na	na
Butorphanol	17 (1)	−0.32 (−1.28 to −0.64)	⊕◯◯◯	na	na	na
Buprenorphine	108 (3)	0.42 (−1.04 to 1.89)	⊕◯◯◯	46 (1)	0.50 (0.05− 5.14)	⊕◯◯◯
Codeine	na	na	na	na	na	na
Transdermal fentanyl	na	na	na	15 (1)	0.35 (0.10− 1.27)	⊕◯◯◯
Nefopam	16 (1)	0.94 (−0.11 to 1.99)	⊕◯◯◯	na	na	na
COX inhibitors	84 (3)	0.97 (−0.63 to 2.58)	⊕◯◯◯	106 (3)	1.74 (0.34− 8.86)	⊕◯◯◯
Multimodal	na	na	na	na	na	na

⊕, very low, there is a lot of uncertainty about the effect estimates; na, not available.

inferior efficacy to COX inhibitors for the management of postsurgical pain in the included studies. By contrast, in one study of maxillectomy or mandibulectomy, dogs treated with tramadol required fewer analgesic rescues than those treated with ketoprofen (Martins et al. 2010). Additional studies are required to draw a conclusion on the efficacy of tramadol compared with COX inhibitors. Adverse events were poorly reported, and the CoE was very low.

This study has some limitations. First, studies using several types of pain scales with inconsistent cut-off values were included for analysis. Although a recent study showed low intra- and interobserver variability for the VAS, NRS and GCMPS pain scales (Hofmeister et al. 2018), the subjectivity and variability of the scales used are a potential source of error that should be considered when evaluating the results of this meta-analysis. Second, although several methods to construct the main outcome variable (i.e., number of dogs requiring rescue analgesia) could have been employed in this type of analysis, the included studies lack sufficient information to allow another strategy to be applied for a homogeneous operationalization of this variable. Third, because of the low number of included studies, subgroup analysis was not possible for all comparisons. Further well-designed multicenter studies and clinical trials using standardized evaluating tools are necessary for future meta-analysis to obtain results with a higher level of evidence.

Conclusions

The overall CoE regarding the efficacy of tramadol on postoperative analgesia in dogs compared with other analgesic agents or no treatment is currently low or very low. In comparison with no treatment, tramadol administration probably results in a reduced number of dogs requiring analgesic rescue. Additional studies are warranted to draw definitive conclusions on the efficacy of tramadol for the management of postsurgical pain and the occurrence of adverse events in dogs.

Authors' contributions

PAD and LT: study design, data collection and interpretation, statistical analysis, writing of manuscript. JVAF: study design, statistical analysis, revision of manuscript. VR, RF and AD: data interpretation, statistical analysis, initial drafting of tables and manuscript. NV: data interpretation, writing of manuscript. PEO: study design, data collection and interpretation, writing of manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

References

American Society of Anesthesiologists Task Force on Acute Pain Management (2012) Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 116, 248–273.

Benitez ME, Roush JK, McMurphy R et al. (2015) Clinical efficacy of hydrocodone-acetaminophen and tramadol for control of postoperative pain in dogs following tibial plateau leveling osteotomy. Am J Vet Res 76, 755–762.

Berrocoso E, De Benito MD, Mico JA (2007) Role of serotonin 5-HT1A and opioid receptors in the antiallodynic effect of tramadol in the chronic constriction injury model of neuropathic pain in rats. Psychopharmacology 193, 97–105.

Carareto R, Gering AP, Kunz Adams F, Sousa MG (2007) Estudo comparativo dos efeitos analgesicos do Zubrin® versus tramadol no pos-operatorio de cadelas submetidas a ovario-salpingo-histerectomia eletiva. Vet News 88, 11–15 (In Portuguese).

Cardozo LB, Cotes LC, Kahvegian MAP et al. (2014) Evaluation of the effects of methadone and tramadol on postoperative analgesia and serum interleukin-6 in dogs undergoing orthopaedic surgery. BMC Vet Res 10, 1–7.

Centonze P, Cagnardi PP, Bianchi G et al. (2014) Postoperative analgesic effects and pharmacokinetic profile of a constant rate infusion of tramadol in dogs undergoing orthopaedic surgery. In: Proceedings of the LXVIII Convegno Sisvet, XI Convegno Aipvet e XII Convegno Sira (abstract).

Clarke DL, Drobatz KJ, Korzekwa C et al. (2019) Trends in opioid prescribing and dispensing by veterinarians in Pennsylvania. JAMA Netw Open 2, e186950.

Davila D, Keeshen TP, Evans RB, Conzemius MG (2013) Comparison of the analgesic efficacy of perioperative firocoxib and tramadol administration in dogs undergoing tibial plateau leveling osteotomy. J Am Vet Med Assoc 243, 225–231.

Deeks J.J., Higgins J.P.T. and Altman D.G., Analysing data and undertaking meta-analyses, In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, 2011, The Cochrane Collaboration, (updated March 2019) , Accessed 12 February 2021.

Delgado C, Bentley E, Hetzel S, Smith LJ (2014) Comparison of carprofen and tramadol for postoperative analgesia in dogs undergoing enucleation. J Am Vet Med Assoc 245, 1375–1381.

Driessen B, Reimann W, Giertz H (1993) Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine in vitro. Br J Pharmacol 108, 806–811.

Fajardo MA, Lesmes MA, Cardona LA (2012) Evaluación del efecto analgésico postoperatorio de infusiones intraoperatorias de tramadol y tramadol/lidocaína/ketamina en comparación con morfina/lidocaína/ketamina en hembras caninas sometidas a ovariohisterectomía. Arch Med Vet 44, 145–153 (In Spanish).

Gil L, Redondo JI (2013) Canine anaesthetic death in Spain: a multicentre prospective cohort study of 2012 cases. Vet Anaesth Analg 40, e57–e67.

Giudice E, Barillaro G, Crinò C et al. (2017) Postoperative pain in dogs undergoing hemilaminectomy: comparison of the analgesic activity of buprenorphine and tramadol. J Vet Behavior 19, 45–49.

Gupta AK, Bisla RS, Singh K, Kumar A (2009) Evaluation of buprenorphine and tramadol as pre-emptive analgesics following ovariohysterectomy in female dogs. Indian J Vet Surg 30, 22–26.

Halfpenny DM, Callado LF, Hopwood SE et al. (1999) Effects of tramadol stereoisomers on norepinephrine efflux and uptake in the rat locus coeruleus measured by real time voltammetry. Br J Anaesth 83, 909–915.

Hennies HH, Friderichs ESJ, Schneider J (1988) Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. Arzneimittelforschung 38, 877–880.

Higgins JPT, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. p. 2011 (updated March 2019). http://handbook.cochrane.org. (Accessed 12 February 2021).

Hofmeister EH, Barletta M, Shepard M et al. (2018) Agreement among anesthesiologists regarding postoperative pain assessment in dogs. Vet Anaesth Analg 45, 695–702.

Hooijmans CR, Rovers MM, de Vries RV et al. (2014) SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 26, 43.

Ide S, Minami M, Ishihara K et al. (2006) Mu opioid receptor-dependent and independent components in effects of tramadol. Neuropharmacology 51, 651–658.

Kaka U, Rahman NA, Abubakar AA et al. (2018) Pre-emptive multimodal analgesia with tramadol and ketamine–lidocaine infusion for suppression of central sensitization in a dog model of ovariohysterectomy. J Pain Res 11, 743–752.

Karrasch NM, Lerche P, Aarnes TK et al. (2015) The effects of preoperative oral administration of carprofen or tramadol on postoperative analgesia in dogs undergoing cutaneous tumor removal. Can Vet J 56, 817–822.

Kongara K, Chambers JP, Johnson CB (2012) Effects of tramadol, morphine or their combination in dogs undergoing ovariohysterectomy on peri-operative electroencephalographic responses and post-operative pain. N Z Vet J 60, 129–135.

Kongara K, Chambers JP, Johnson CB, Dukkipati VSR (2013) Effects of tramadol or morphine in dogs undergoing castration on intra-operative electroencephalogram responses and post-operative pain. N Z Vet J 61, 349–353.

KuKanich B, Papich MG (2004) Pharmacokinetics of tramadol and the metabolite O-desmethyltramadol in dogs. J Vet Pharmacol Ther 27, 239–246.

Marques JdeS (2015) Efeitos da nalbufina e do tramadol após infusão contínua com fentanil em cães submetidos a osteotomia de nivelamento de platô tibial (TPLO). In: Thesis for Mestrado em Clínica Cirúrgica Veterinária, Universidade de São Paulo, Brazil (In Portuguese).

Martins TL, Kahvegian MA, Noel-Morgan J et al. (2010) Comparison of the effects of tramadol, codeine, and ketoprofen alone or in combination on postoperative pain and on concentrations of blood glucose, serum cortisol, and serum interleukin-6 in dogs undergoing maxillectomy or mandibulectomy. Am J Vet Res 71, 1019–1026.

Mastrocinque S, Fantoni DT (2003) A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. Vet Anaesth Analg 30, 220–228.

McMillan CJ, Livingston A, Clark CR et al. (2008) Pharmacokinetics of intravenous tramadol in dogs. Can J Vet Res 72, 325–331.

Meunier NV, Panti A, Mazeri S et al. (2019) Randomised trial of perioperative tramadol for canine sterilisation pain management. Vet Rec 185, 406.

Moher D, Shamseer L, Clarke M et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4, 1.

Mondal P, Nandi SK, Ghosh D (2005) Evaluation of post-operative analgesia of ketoprofen, meloxicam and tramadol in bitches undergoing ovariohysterectomy. Indian J Anim Sci 75, 513–515.

Mondal P, Nandi SK, Ghosh D (2006) Postoperative analgesic effects of ketoprofen, meloxicam and tramadol in bitches. Indian Vet J 83, 165–167.

Morgaz J, Navarrete R, Muñoz-Rascón P et al. (2013) Postoperative analgesic effects of dexketoprofen, buprenorphine and tramadol in dogs undergoing ovariohysterectomy. Res Vet Sci 95, 278–282.

Ogata J, Minami K, Uezono Y et al. (2004) The inhibitory effects of tramadol on 5-hydroxytryptamine Type 2C receptors expressed in Xenopus oocytes. Anesth Analg 98, 1401–1406.

Oliveira MT, França RT, Feranti JPS et al. (2016) Meloxicam associado ou não ao tramadol no controle da dor após ovário-histerectomia videoassistida em cadelas. Arq Bras Med Vet Zoo 68, 10–16 (In Portuguese).

Ospina-Argüelles DA, Ramírez Sierra CA, Buriticá Gaviria E, Bonilla DF (2017) Infusiones analgésicas de lidocaína o tramadol en perras sometidas a ovariohisterectomía lateral bajo un protocolo de anestesia disociativa. REDVET 18, 1–13 (In Spanish).

Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan—a web and mobile app for systematic reviews. Syst Rev 5, 210.

Raffa RB, Friderichs E, Reimann W et al. (1992) Opioid and non-opioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 260, 275–285.

Read K, Khatun M, Murphy H (2019) Comparison of transdermal fentanyl and oral tramadol for lateral thoracotomy in dogs: cardiovascular and behavioural data. Vet Anaesth Analg 46, 116–125.

Rialland P, Authier S, Guillot M et al. (2012) Validation of orthopedic postoperative pain assessment methods for dogs: a prospective, blinded, randomized, placebo-controlled study. PLoS ONE 7, e49480.

Saberi Afshar AF, Shekarian M, Baniadam A et al. (2017) Comparison of different tools for pain assessment following ovariohysterectomy in bitches. Iran J Vet Med 11, 255–265.

Sagata K, Minami K, Yanagihara N et al. (2002) Tramadol inhibits norepinephrine transporter function at desipramine-binding sites in cultured bovine adrenal medullary cells. Anesth Analg 94, 901–906.

Sandoval O, Herzberg D, Galecio Sebastián et al. (2010) Analgesia preventiva en hembras caninas sometidas a ovariohisterectomía: comparación del efecto analgésico de morfina y tramadol asociados a xilazina. Rev Cient (Maracaibo) 20, 138–143 (In Spanish).

Santos MS, Herrera DA (2014) Evaluación intraoperatoria y postoperatoria del efecto analgésico de infusiones intravenosas de tramadol, ketamina, lidocaína y su combinación, en hembras caninas sometidas a ovariohisterectomía'. https://ciencia.lasalle.edu.co/medicina_veterinaria/43. (Accessed 12 February 2021) (In Spanish).

Schuszler L, Sala IA, Dasălu R et al. (2010) Analgesic effect of premedication with tramadol or butorphanol in dogs undergoing osteosynthesis. Lucrări Ştiinłifice Medicină Veterinară 43, 104–108.

Sevcik J, Nieber K, Driessen B, Illes P (1993) Effects of the central analgesic tramadol and its main metabolite, O-desmethyltramadol, on rat locus coeruleus neurones. Br J Pharmacol 110, 169–176.

Stănescu M, Burac ME, Diaconescu A et al. (2013) Comparison of tramadol and robenacoxib postoperative analgesic efficacy in dogs. Scientific Works Series C. Veterinary Medicine LIX 1, 72–75.

Teixeira RC, Monteiro ER, Campagnol D et al. (2013) Effects of tramadol alone, in combination with meloxicam or dipyrone, on postoperative pain and the analgesic requirement in dogs undergoing unilateral mastectomy with or without ovariohysterectomy. Vet Anaesth Analg 40, 641–649.

Tudor R, Degan A, Costea R, Predoi G (2018) Postoperative analgesic management of geriatric dogs that underwent soft tissue surgery. Scientific Works Series C. Veterinary Medicine LXIV 2, 82–87.

Ugwu NE, Eze CA, Udegbunam RI, Nnaji TO (2020) Perioperative analgesic efficacy of constant rate infused tramadol hydrochloride as an adjunct to postoperative ketoprofen in ovariohysterectomized bitches. Indian J Anim Res 54, 627–630.

Uscategui R, Tiosso C, Moro J et al. (2017) Pre-emptive methadone or tramadol analgesia for mastectomy and ovariohysterectomy in bitches. Rev Colomb Cienc Pecu 30, 39–47.

Vullo C, Tambella AM, Scrollavezza P (2004) Studio comparativo sull'efficacia del tramadolo verso il meloxicam nel controllo del dolore ortopedico. Veterinaria Anno 18, 43–48 (In Italian).

Yasbek K, Fantoni DT (2005) Evaluation of tramadol, an "atypical" opioid analgesic in the control of immediate postoperative pain in dogs submitted to orthopedic surgical procedures. Braz J Vet Res Anim Sci 42, 250–258.

Zhang S, Li JN, Luan L et al. (2017) Comparison of the effects of nefopam and tramadol on postoperative analgesia in dogs undergoing ovariohysterectomy. Veterinarni Medicina 62, 131–137.

Received 17 June 2020; accepted 22 January 2021.

Available online 10 February 2021

Supporting Information

Additional supporting information may be found in the online version of this article at: https://doi.org/10.1016/j.vaa.2021.01.003.

Appendix SA GRADE methodology.

Appendix SB Risk of bias assessment.

Appendix SC Downgrading the certainty of evidence.