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Effect of combining tramadol and morphine in adult surgical patients: a systematic review and meta-analysis of randomized trials

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Editor's key points

- Adjunctive analgesics offer the possibility of reducing opioid-related side-effects.
- Results of small trials conducted in a specific study population may not be generalizable.
- Small trials are unlikely to identify adverse effects of medications.
- Tramadol can reduce opioid requirements after surgery, but this may not be clinically important.

The role for tramadol in multimodal postsurgical analgesic strategies remains unclear. We undertook a systematic review to evaluate the utility of combining tramadol with morphine after surgery. We searched the MEDLINE, EMBASE, LILAC, Cochrane, and Clinical Trial Register databases for randomized, controlled studies comparing tramadol with placebo or active control in patients undergoing surgery. Fourteen studies (713 patients) were included. There was a limited but significant postoperative morphine-sparing effect, with a weighted mean difference (WMD) of −6.9 (95% confidence interval −11.3 to −2.5) mg. This effect was not associated with a decrease in morphine-related adverse effects. No difference in the incidence of nausea, vomiting, sedation, or shivering was observed. There was no decrease in pain intensity at 24 h; the WMD was −0.9 (−7.2; 5.2) on a 100 mm visual analogue scale at 24 h. We found no significant clinical benefit from the combination of i.v. tramadol and morphine after surgery.

Keywords: balanced analgesia; meta-analysis; postoperative pain; surgery; tramadol

Multimodal analgesic regimens use combinations of different analgesic drugs, methods to reduce pain after operation, or both while decreasing morphine use and its associated adverse effects.[1] This approach is recommended by national guidelines and publications.[2 3] Non-opioid analgesics are generally used for this purpose after major surgery. Tramadol is a unique analgesic with two modes of action.[4] It activates the opioid and non-opioid systems involved in pain inhibition. The non-opioid effect of tramadol is mediated through α-2-agonistic and serotoninergic activities.[5] Tramadol is also a weak opioid, acting on μ-receptors.

Tramadol, administered parenterally or orally, has proven to be an effective and well-tolerated analgesic for the management of moderate to severe acute postoperative pain in adults.[6] However, the value of tramadol–morphine combinations remains uncertain. The first randomized controlled trial (RCT) investigating the efficacy of tramadol in combination with potent opioids in 1995 reported negative results,[7] but several additional trials have since reported conflicting results,[8–18] including one study suggesting tramadol and morphine could be infra-additive.[19] However, other authors reported that the monoaminergic modulation induced by tramadol made this drug valuable for combination with morphine.[17] It is currently unclear to what extent perioperative tramadol decreases postoperative opioid consumption, opioid-related side-effects, and pain intensity.

We thus undertook a systematic review of RCTs comparing the efficacy and safety of tramadol *vs* placebo or active controls for the treatment of post-surgical pain.

Methods

This systematic review was performed in accordance with the criteria of the PRISMA statement and the current recommendations of the Cochrane Collaboration.[20 21] The protocol was registered with PROSPERO, under number CDR 42013006285, on November 13, 2013.

Search strategy

We attempted to identify all relevant studies, regardless of language or publication status (published, unpublished). We searched for RCTs indexed in the following databases: CENTRAL, PUBMED, and EMBASE. We applied the highly sensitive search strategy of the Cochrane Collaboration, to identify trials.[22] This search strategy combined free text words and controlled vocabulary MeSH terms, with no limitation on the search period. Full details of the search strategy are provided in the Appendix. The search equation for PUBMED was adapted for each database. The date of the last search was June 1, 2014. We searched the Cochrane database of systematic reviews and the DARE meta-register. We also searched the proceedings of the two

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major annual meetings of two major anaesthesiology societies; the ASA and the European Society of Anaesthesiology, over the last 5 yr (from June 2008 to December 2013). In addition to the preplanned literature search, we also searched for randomized trials that had already been completed in the clinicaltrials.gov (http://www.clinicaltrial.gov) and international clinical trials registry platform (http://apps.who.int/trialsearch) databases. We then searched the reference lists of the relevant review articles and selected articles, for the identification of additional, potentially relevant trials. Authors were contacted, as necessary, to obtain additional information if the published reports were incomplete or to collect data for unpublished studies.

Inclusion and exclusion criteria

We included all RCTs, with no restriction as to date of publication, language, or number of participants. The study populations included were (i) adults and children (able to perform an auto-evaluation of pain), (ii) undergoing all types of surgery, and (iii) receiving rescue morphine over a period of at least 24 h, regardless of the route of administration (p.o., i.v., subcutaneous, or patient-controlled analgesia) and the opioid used (e.g. meperidine, alfentanil, fentanyl, hydromorphone, oxycodone). The interventions considered were the addition of tramadol to the regimen, whatever the route of administration (parenteral or p.o.), the timing (pre-, post-incision), and the mode of administration (single bolus, continuous, or repetitive). Comparisons were made with placebo or any other non-opioid analgesic drug. Studies were excluded if: (i) analgesia techniques or the drugs used were not equivalent or comparable between groups during the intervention, and (ii) the duration of the study was limited to the stay in the postoperative anaesthesia care unit (PACU).

Definition of primary and secondary outcome parameters

The primary outcomes were cumulative morphine consumption in the 24 h after surgery, expressed in milligrams of morphine equivalent, and pain at rest at 24 h, expressed on a visual analogue scale (VAS: 0: no pain to 100: worst possible pain). Intensity scores reported on a numerical rating scale (NRS: 0: no pain to 10: worst possible pain) were converted to the equivalent values for a 0-to-100 VAS scale. The following outcomes were considered as secondary outcomes: morphine titration in the PACU; pain at rest at other time points (PACU, 4 h, 12 h); opioid-related adverse effects, such as nausea, vomiting, sedation, dizziness, dry mouth, or any other adverse effect reported at 24 h. If another shorter or longer time interval was reported, we used the time interval closest to the defined time of 24 h. The original papers often did not distinguish between nausea and vomiting[23] and reported both outcomes together. We therefore used the classification defined in the article by Apfel and colleagues[24] to determine the incidence of nausea. When an adverse effect was assessed with a score, we considered only the presence of the adverse effect, regardless of its severity.

Study selection

Two authors (L.G. and D.F.) independently screened titles, abstracts, and full texts according to the inclusion criteria. Any disagreement between these two authors was settled by discussion with the third author (V.M.), until a consensus was reached. The reasons for exclusion were noted, for each publication, at the full-text review stage.

Data extraction

One author (V.M.) designed a standard data extraction form in Excel, and the other authors (L.G. and D.F.) amended and validated the design of this form before its use for data extraction. Data were extracted by one author (L.G.) and were cross-checked by the other authors (V.M. and D.F.). The authors of the study were contacted (by V.M.) and asked to provide missing data or to add to the data when possible. If necessary, means and measures of dispersion were approximated from figures generated with dedicated software (ref: http://www.datathief.org/). We extracted information about the general characteristics of the study (first author, number of arms, country), participants (characteristics of the populations, population randomized and analysed, type of surgery), experimental intervention (administration route, timing of administration, and doses), and outcomes. Dichotomous outcomes were extracted as the presence or absence of an effect. For continuous data, we extracted means and standard deviations (SDs). If not reported, the SDs were obtained from confidence intervals (CIs) or *P*-values for the differences between the means of two groups.[22 25] If medians with ranges were reported, we obtained the mean and SD as described by Hozo and colleagues.[26] If only means were reported, we contacted the authors. If no response could be obtained, we took the respective median SDs of each group.

Assessment of methodological quality

We used the Cochrane Collaboration tool to evaluate the risk of bias in the randomized studies selected. We documented the methods used for the generation of allocation sequences, allocation concealment, the blinding of investigators and participants, the blinding of outcome assessors, and for dealing with incomplete outcome data. Each item was classified as having a low, unclear, or high risk of bias. The overall risk of bias corresponds to the lowest risk of bias documented.

Data synthesis and analysis

Pain intensity scores were assumed to have been obtained at rest, unless otherwise stated. Pain scores reported within 2 h of our time points were included in the analysis. Doses of opioids other than morphine were converted to morphine equivalents with standard conversion factors (1 mg of i.v. morphine was considered to be equivalent to 7.5 mg of i.v. meperidine or 1 mg of i.v. nalbuphine).[27] Nausea and vomiting were analysed separately. We calculated risk ratios (RRs) with 95% CI for dichotomous data and mean differences (MD) with 95% CI for continuous data. We expected there to be heterogeneity (because of the diverse populations included), and

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we therefore used the Dersimonian and Lairs random effects meta-analysis modules. We assessed heterogeneity with the I^2 statistic ($I^2>50\%$ indicates substantial heterogeneity). Sources of heterogeneity were investigated by the analysis of prespecified subgroups. The subgroups included were defined as follows: high/low doses were defined for each intervention (low <1 defined daily dose, high ≥ 1 defined daily dose), type of administration (single bolus or multiple doses), timing of administration (pre/post-surgical incision). The World Health Organization defined daily dose for tramadol as 300 mg 24 h^{-1}, regardless of the route of administration (http://www.whocc.no/atc_ddd_index/). Finally, we evaluated publication bias by assessing funnel plot asymmetry. All statistical analyses were performed with Review Manager (RevMan version 5.2.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

The systematic literature search identified 1477 relevant publications. After a review of titles and abstracts, 54 studies were selected as potentially eligible for inclusion in this systematic review. After reading the full-text articles, we selected 14 RCTs (published between 1995 and 2013) including a total of 713 patients in the meta-analysis (Fig. 1). None of the trials in the clinicaltrial.gov register satisfied our eligibility criteria. Two trials of potential interest were identified in the ESA symposium, but with too little information for their inclusion. We requested additional information from the authors, but this information was not forthcoming.

Characteristics of the studies included

All of the studies included were carried out at single sites. The median target sample size was 60 (16–120) [median (min–max)] patients. The participants were adults or children with an ASA physical status of class I or II. The studies investigated patients undergoing surgery in various specialities: gynaecology,[10 15 28] abdominal surgery,[12 14 16 17] Caesarean section,[18 29] cardiac surgery,[9] orthopaedic surgery,[7] tonsillectomy,[8] and various types of major surgery.[11] General anaesthesia was used in 11 trials,[8–13 15–17 28 29] spinal anaesthesia in two trials,[7 18] and the type of anaesthesia was not reported in one trial.[14] Most of the RCTs (n =12) investigated tramadol

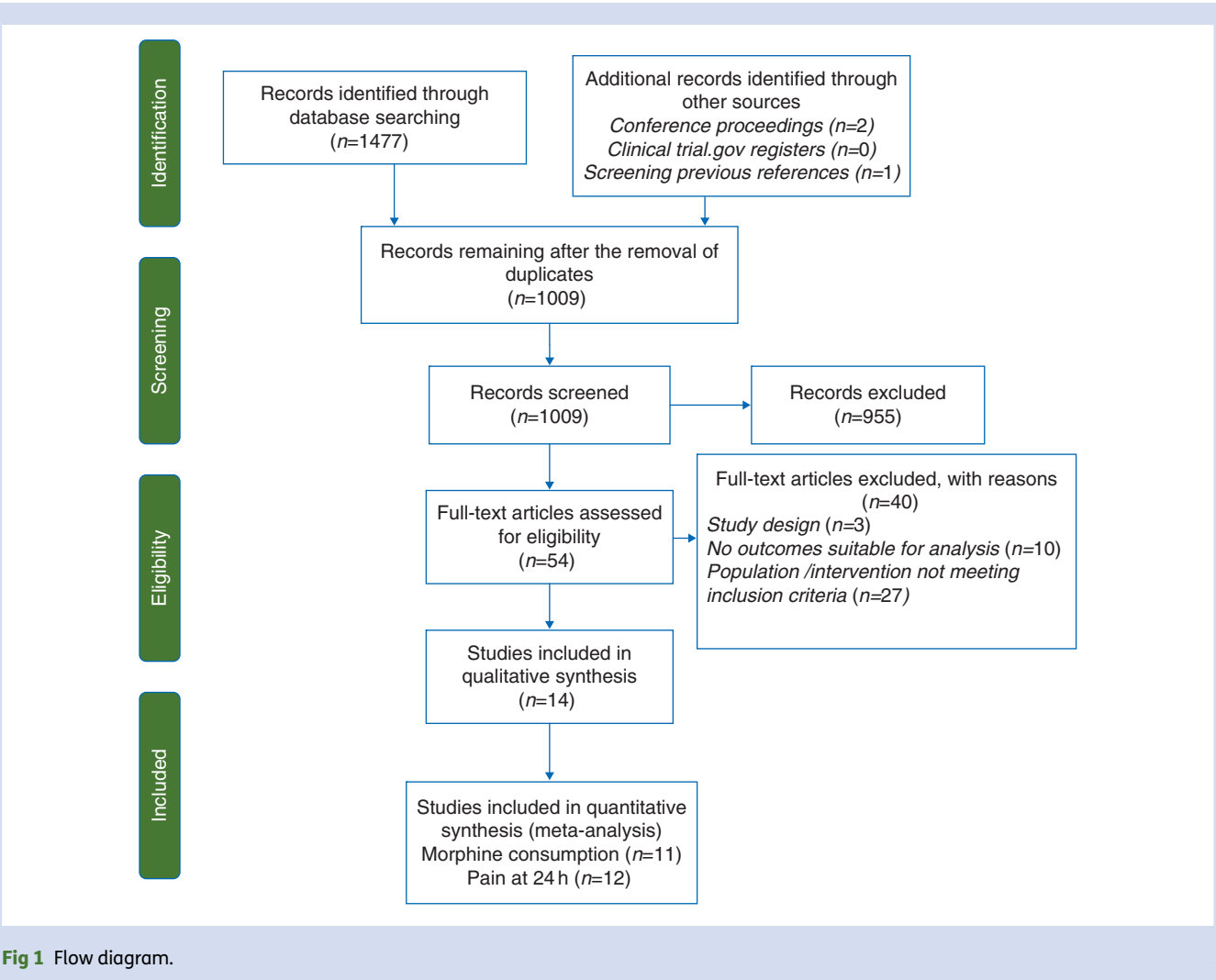

Fig 1 Flow diagram.

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Table 1 Characteristics of the studies included

Study	Country	Number of patients	Surgery	Intervention	Duration of tramadol treatment	Analgesia	Outcomes	Adverse effects evaluated
Antila and colleagues[8]	Finland	45	Tonsillectomy	Tramadol (i.v. 1 mg kg^{-1}) *vs* placebo preincision and then 1 mg h^{-1}	6 h	PCA fentanyl	Pain VAS at 4 and 24 h	Nausea/vomiting (N/V), no treatment
But and colleagues[9]	Turkey	60	Cardiothoracic surgery	Tramadol (i.v. 1 mg kg^{-1}) *vs* placebo post-incision	Single dose	PCA morphine	Pain VAS at PACU, 4, 12, and 24 h	Nausea, vomiting, pruritus, no treatment
Elhakim and colleagues[29]	Egypt	60	Caesarean section	Tramadol (i.v. 100 mg) *vs* 20 mg famotidine preincision	Single dose	PCA nalbuphine	Pain VAS at 6, 12, and 24 h	Nausea, vomiting, sedation, treatment
Guler and colleagues[28]	Turkey	40	Hysterectomy	Tramadol (i.v. 100 mg) *vs* placebo preincision	Single dose	PCA morphine	Pain VAS at 4, 12, and 24 h	No treatment
Kocabas and colleagues[10]	Turkey	60	Hysterectomy	Tramadol (i.v. 1 mg kg^{-1}) *vs* placebo post-incision, and then 0.2 mg kg^{-1} h^{-1}	24 h	PCA morphine	Pain VAS at 4, 12, and 24 h	Nausea, sedation, treatment
Ozbakis Akkurt and colleagues[11]	Turkey	40	Major surgery	Tramadol (i.v. 1 mg kg^{-1}) *vs* placebo preincision	Single dose	PCA morphine	Pain VAS at 4, 6, 12, and 24 h	No treatment
Spacek and colleagues[12]	Poland	60	Abdominal surgery	Tramadol (i.v. 600 mg) *vs* placebo PACU and then continuous	24 h	PCA morphine	Pain VAS at 24 h	Nausea, vomiting, treatment
Stiller and colleagues[13]	Sweden	63	TKA	Tramadol (i.v. 100 mg) *vs* placebo post-incision and then/6 h	24 h	PCA morphine	Pain VAS at 24 h	Nausea, vomiting, sedation, confusion, shivering, headache, tachycardia, no treatment
Stratigopoulou and colleagues[14]	Greece	16	Abdominal surgery	Tramadol (i.v. 50 mg) *vs* placebo post-incision and then/8 h	24 h	PCA morphine	Pain VAS at 24 h	No treatment
Stubhaug and colleagues[7]	Norway	71	Orthopaedic surgery	Tramadol (p.o. 100 and 50 mg) *vs* placebo post-incision	Single dose	Morphine bolus		Vomiting, sedation, sweating, vertigo, dry mouth, treatment
Thienthong and colleagues[15]	Thailand	50	Mastectomy	Tramadol (i.v. 100 mg) *vs* placebo preincision and then/12 h	24 h	PCA morphine	Pain VAS at PACU, 4, 12, and 24 h	Nausea, vomiting, vertigo, rash, treatment
Unlugenc and colleagues[16]	Turkey	60	Abdominal surgery	Tramadol (i.v. 1 mg kg^{-1}) *vs* placebo preincision	Single dose	PCA morphine	Pain VAS at 4, 12, and 24 h	Nausea, vomiting, treatment
Webb and colleagues[17]	Australia	69	Abdominal surgery	Tramadol (i.v. 1 mg kg^{-1}) *vs* placebo post-incision, and then 0.2 mg kg^{-1} h^{-1}	48 h	PCA morphine	Pain VAS at 24 h	Nausea, treatment
Wilder-Smith and colleagues[18]	South Africa	60	Caesarean section	Tramadol (i.m. 100 mg) *vs* placebo post-incision	Single dose	Morphine bolus	Pain VAS at 4, 12, and 24 h	Nausea, vomiting, sedation, vertigo, shivering, headache, prevention

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administered i.v.[7–11 14–18 28 29] One RCT explored oral administration[7] and one used i.m. administration.[13] In most studies, the comparison was with placebo (n =13).[7–18] In one trial, the control was a histamine receptor subtype 2 antagonist.[29] One trial compared two doses of tramadol.[7] Tramadol were given before (n =6)[8 11 15 16 28 29] or after (n =8) surgical incision.[7 9 10 12–14 17 18] It was administered as a single bolus in seven RCTs,[7 9 11 16 18 28 29] and repetitively or continuously in seven trials.[8 10 12–15 17] The total dose of tramadol administered during the first 24 h was 50–600 mg, with a median value of 100 mg (Table 1).

Assessment of the risk of bias for the studies included

One trial was classified as being at low risk of bias, 12 at unclear risk of bias, and one at high risk of bias. The randomization procedure was adequately described in seven trials (50%), and the concealment of treatment allocation was described in five trials (36%). Nine studies (64%) were double-blind, whereas blinding status was unclear for all the others. Eight studies (57%) had an unclear or high risk of incomplete data outcomes (Fig. 2). For the eight trials published after 2005, no registered protocols were retrieved from clinicaltrial.gov, so it was not possible to evaluate selective reporting.

Postoperative morphine use

No RCTs reported morphine titration. Ten RCTs, including 562 patients, reported data for cumulative morphine use at 24 h. The median value for the mean cumulative morphine consumption at 24 h in the control groups was 38.4 mg (range: 12.6–57.4). Slightly but significantly lower cumulative morphine consumption values at 24 h were reported with tramadol (6.9 mg less morphine used; Fig. 3). No difference was found at 4 and 12 h. These pooled data analyses were influenced by heterogeneity (Fig. 3).

Pain intensity

Twelve trials, including 639 patients, reported data for postoperative pain intensity at rest, at 24 h. In the control groups, the median value for postoperative pain intensity at rest, at 24 h, was 16.5 (range: 7–52). Analysis of the combined data showed that postoperative pain intensity at 24 h was not lower in the tramadol group than in the control group. A small, but significant difference was reported in the early postoperative phase in the PACU and at 4 and 12 h. These pooled data analyses were influenced by heterogeneity (Fig. 4). No studies evaluated pain on movement.

Opioid-related adverse events

The numbers of patients with nausea, vomiting, sedation, or shivering in the postoperative period were reported in 10, six, five, and two trials, respectively (Table 1). Seven studies have some form of treatment of PONV, six studies have no treatment, and one study a preventive approach. Important heterogeneity precludes any common analysis (Table 1). No significant differences were found between the tramadol and control groups, for any of these adverse events (Table 2).

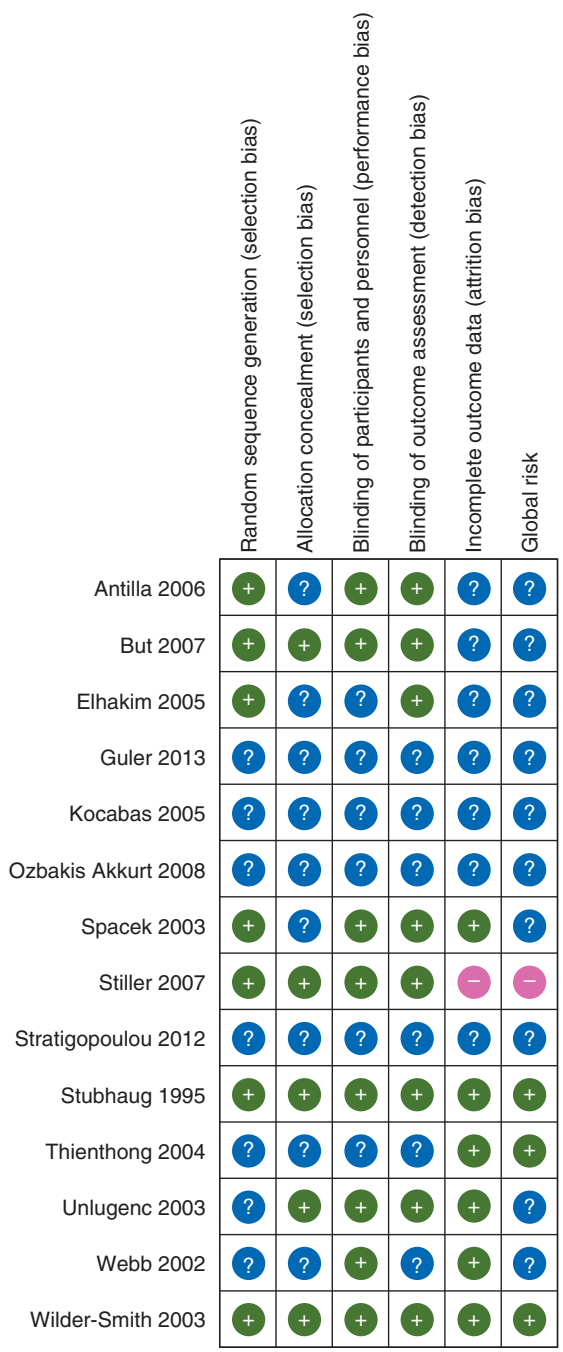

Fig 2 Risk of bias summary.

Other adverse events

The numbers of patients with dizziness, headache, dry mouth, tachycardia, and rash in the postoperative period were reported in three, two, one, one, and one trial, respectively. No significant differences were found between the tramadol and control groups, for any of these adverse events. However, in the three trials assessing dizziness, this adverse effect tended to have a higher incidence in the tramadol groups, but the RR was not significant.

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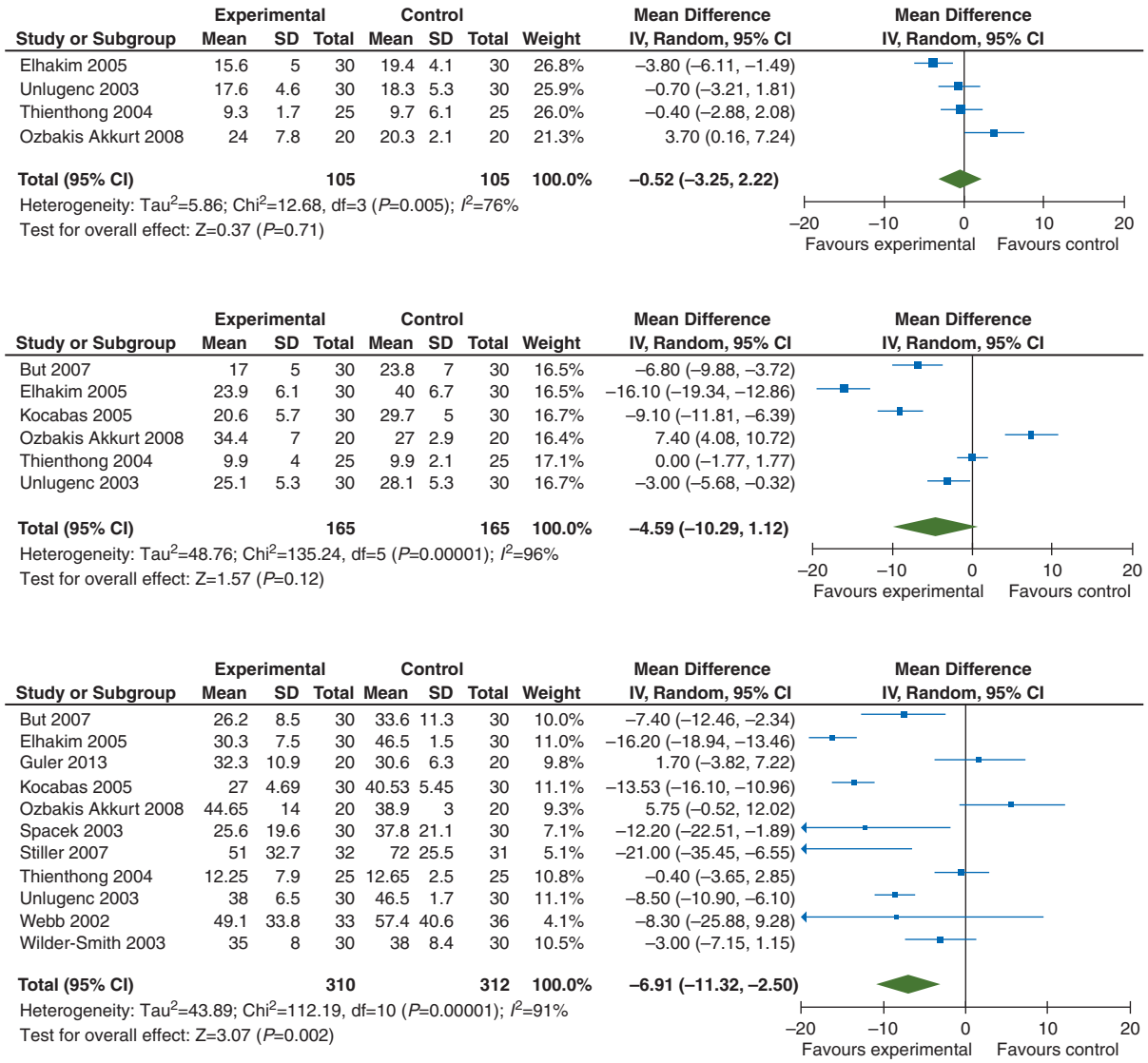

Fig 3 Forest plot for morphine consumption at 4, 12, and 24 h after surgery.

Heterogeneity, subgroup analysis, and reporting bias

For both primary outcomes, the I^2 statistic was 95%, indicating high levels of heterogeneity. Several characteristics of studies may be responsible for heterogeneity, and we explored five of these characteristics in subgroup analysis (Table 3). This analysis clearly showed that high doses of tramadol (>300 mg) were associated with a greater mean difference in morphine consumption at 24 h. However, this difference was not associated with any impact on pain intensity (Table 3), or the incidence of nausea [RR 1 (0.7, 1.4)] or vomiting [RR 0.9 (0.54, 1.53) not shown]. Too few data were available for the oral administration of tramadol for explorations of the effect of administration route.

The sensitivity analysis of trial quality showed that the standardized mean difference (SMD) in morphine consumption at 24 h was lower in trials at low risk of bias [−3 (−8, 2), P =0.26] than in trials with unclear or high risks of bias [−7.38 (−12.1, −2.63), P=0.002]. The mean difference in pain at rest at 24 h was smaller in trials at low risk of bias [0.08 (−6.5, −6.6), P=0.9] than in trials with unclear or high risks of bias [−12.5 (−19.6, −5.36), P=0.006]. Visual inspection of the funnel plots of morphine consumption highlighted asymmetry in the distribution of trials that could be accounted for by both a small study effect and the possibility of publication bias. No such asymmetry was found in the funnel plot for pain (Fig. 5).

Discussion

This is the first systematic quantitative review to evaluate the potential benefits of combining tramadol with morphine after surgery. We found that tramadol slightly decreases morphine consumption at 24 h but has no impact on

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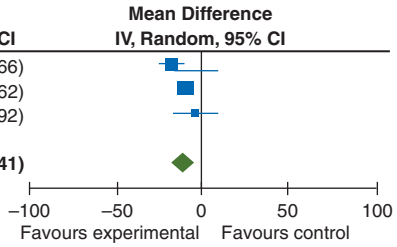
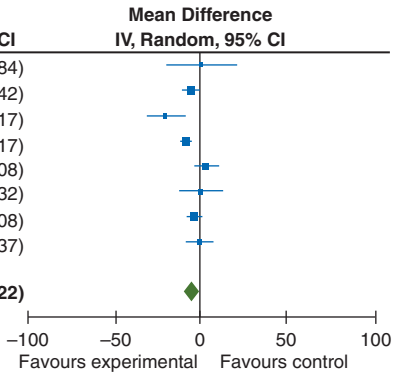
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
But 2007	36.5	13	30	54	14	30	34.7%	−17.50 (−24.34, −10.66)
Kocabas 2005	29	6.6	30	38.3	7.9	30	46.7%	−9.30 (−12.98, −5.62)
Thienthong 2004	48.8	19	25	52.5	26	25	18.6%	−3.70 (−16.32, 8.92)
Total (95% CI)			**85**			**85**	**100.0%**	**−11.11 (−17.81, −4.41)**

Heterogeneity: Tau^2=21.47; Chi^2=5.54, df=2 (*P*=0.06); I^2=64%
Test for overall effect: Z=3.25 (*P*=0.001)



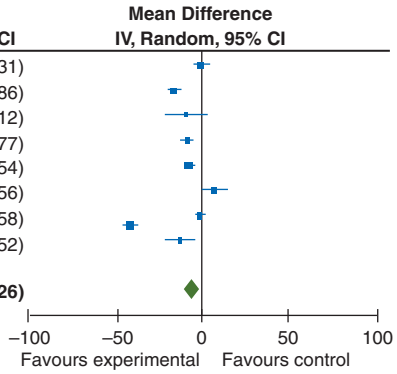
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Antilla 2006	43.8	28	15	43	28	15	3.3%	0.80 (−19.24, 20.84)
But 2007	23	8	30	28	10	30	17.0%	−5.00 (−9.58, −0.42)
Guler 2013	30	20	30	49.5	17	20	8.7%	−19.50 (−29.83, −9.17)
Kocabas 2005	16	6.2	30	24	4.9	30	19.8%	−8.00 (−10.83, −5.17)
Ozbakis 2008	22.5	13.8	20	19	5.9	20	13.6%	3.50 (−3.08, 10.08)
Thienthong 2004	9.5	21	25	9.1	22	25	7.3%	0.40 (−11.52, 12.32)
Unlugenc 2003	16	7	30	19	9	30	17.8%	−3.00 (−7.08, 1.08)
Wilder-Smith 2003	25	18	30	25	10	30	12.4%	0.00 (−7.37, 7.37)
Total (95% CI)			**210**			**200**	**100.0%**	**−4.14 (−8.07, −0.22)**

Heterogeneity: Tau^2 = 18.14; Chi^2=22.08, df=7 (*P*=0.002); I^2=68%
Test for overall effect: Z=2.07 (*P*=0.04)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
But 2007	21	8	30	21	9	30	13.4%	0.00 (−4.31, 4.31)
Elhakim 2005	23.9	6.1	30	40	6.7	30	14.2%	−16.10 (−19.34, −12.86)
Guler 2013	30	18	20	39	21	20	7.4%	−9.00 (−21.12, 3.12)
Kocabas 2005	13	7	30	21.6	3.7	30	14.4%	−8.60 (−11.43, −5.77)
Ozbakis 2008	12	3.5	20	19	4.4	20	14.6%	−7.00 (−9.46, −4.54)
Thienthong 2004	8.5	18	25	1.3	5.3	25	11.0%	7.20 (−0.16, 14.56)
Unlugenc 2003	12	4	30	13	6	30	14.5%	−1.00 (−3.58, 1.58)
Wilder-Smith 2003	12.5	7.5	30	25	21	30	10.5%	−12.50 (−20.48, −4.52)
Total (95% CI)			**215**			**215**	**100.0%**	**−5.87 (−10.49, −1.26)**

Heterogeneity: Tau^2 = 36.42; Chi^2=77.78, df =7 (*P*=0.002); I^2=91%
Test for overall effect: Z=2.49 (*P*=0.01)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Antilla 2006	46.3	23.2	15	29.1	23.2	15	5.7%	17.20 (0.60, 33.80)
But 2007	17	11	30	18	10	30	9.0%	−1.00 (−6.32, 4.32)
Elhakim 2005	15.1	5.9	30	33.1	8.9	30	9.3%	−18.00 (−21.82, −14.18)
Guler 2013	10	11	20	18	14	20	8.4%	−8.00 (−15.80, −0.20)
Kocabas 2005	26	4.4	30	12.6	6.3	30	9.5%	13.40 (10.65, 16.15)
Ozbakis 2008	10.5	15	20	7	6.5	20	8.5%	3.50 (−3.66, 10.66)
Spacek 2003	17	11	30	15	16	30	8.6%	2.00 (−4.95, 8.95)
Stiller 2007	50	16.5	22	52	11.1	28	8.3%	−2.00 (−10.03, 6.03)
Thienthong 2004	14	15	25	9	21	25	7.6%	5.00 (−5.12, 15.12)
Unlugenc 2003	10	2	30	12	4	30	9.6%	−2.00 (−3.60, −0.40)
Webb 2002	30	35.1	36	31.5	19.17	33	6.7%	−1.50 (−14.70, 11.70)
Wilder-Smith 2003	0	11	30	12.5	12.5	30	8.9%	−12.50 (−18.46, −6.54)
Total (95% CI)			**318**			**321**	**100.0%**	**−0.90 (−7.04, 5.23)**

Heterogeneity: Tau^2=101.32; Chi^2=208.41, df=11 (*P*=0.00001); I^2=95%
Test for overall effect: Z=29 (*P*=0.77)

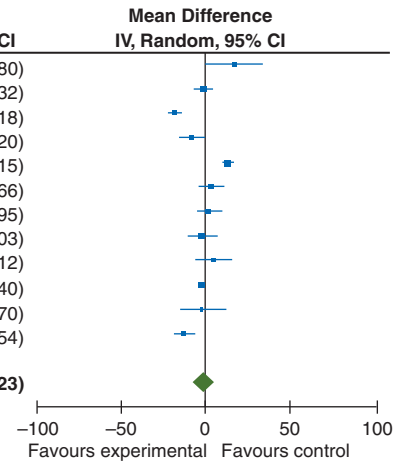


Fig 4 Forest plot for pain in PACU, at 4, 12, and 24 h after surgery.

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Table 2 Adverse effects in patients allocated to the experimental and control groups. CI, confidence interval

Comparison	Number of studies	Experimental	Control	Risk ratio	95% CI	*P*-value	Heterogeneity (I^2) with random effect estimate (%)
Nausea	10	83/278	76/283	1.17	0.85–1.61	0.24	5
Vomiting	6	31/177	26/183	1.15	0.76–1.75	0.46	0
Sedation	4	51/118	60/123	0.89	0.60–1.32	0.69	39
Dizziness	3	19/91	11/90	1.35	0.28–6.60	0.29	0
Shivering	2	4/52	6/58	0.81	0.24–2.67	0.96	0

Table 3 Subgroup analysis. MD, mean difference

Outcomes	Number of trials	Number of participants	Random effect (95% CI)	*P*-value	Heterogeneity (I^2) with random effect estimate (%)	Heterogeneity (I^2) test for subgroup differences (%)
Morphine consumption (MD)						
Type of tramadol administration						2.6
Single bolus	6	320	−4.9 (−10.8, 0.9)	0.1	93	
Repetitive bolus or continuous /24 h	5	299	−8.29 (−14, −2.5)	0.005	90	
Timing of administration						42
Before surgical incision	5	150	−3.8 (−11, 3.4)	0.3	95	
After surgical incision	6	372	−9.87 (−15.6, −4.6)	0.0003	71	
Defined daily dose(DDD) of tramadol						89
<1 DDD	7	370	−4.3 (−9.7, 1.1)	0.3	93	
≥1 DDD	4	252	−13.57 (−16.00, −11.13)	<0.0001	0	
Pain at rest at 24 h (MD)						
Type of tramadol administration						0
Single bolus	6	380	−6.43 (−13.1, 0.32)	0.23	93	
Repetitive bolus or continuous /24 h	5	319	−5.48 (−1.6, 12.6)	0.13	79	
Timing of administration						0
Before surgical incision	6	280	−1.94 (−10.1, 6.3)	0.65	93	
After surgical incision	6	259	−0.01 (−9.5, 93)	0.99	94	
Defined daily dose (DDD) of tramadol						40
<1 DDD	8	400	−3.43 (−9.7, 2.7)	0.28	91	
≥1 DDD	4	239	3.75 (−5.5, 13)	0.43	87	

morphine-related adverse effects and no persistent effect on pain intensity at rest during the first 24 h after surgery.

This meta-analysis revealed a morphine-sparing effect of tramadol, estimated at almost 6 mg over 24 h. The sensitivity analysis of trial quality showed that the SMD in morphine consumption at 24 h was lower in trials at low risk of bias than in trials with unclear or high risks of bias. Visual inspection of the funnel plots of morphine consumption highlighted asymmetry in the distribution of trials that could be accounted for by both a small study effect and the possibility of publication

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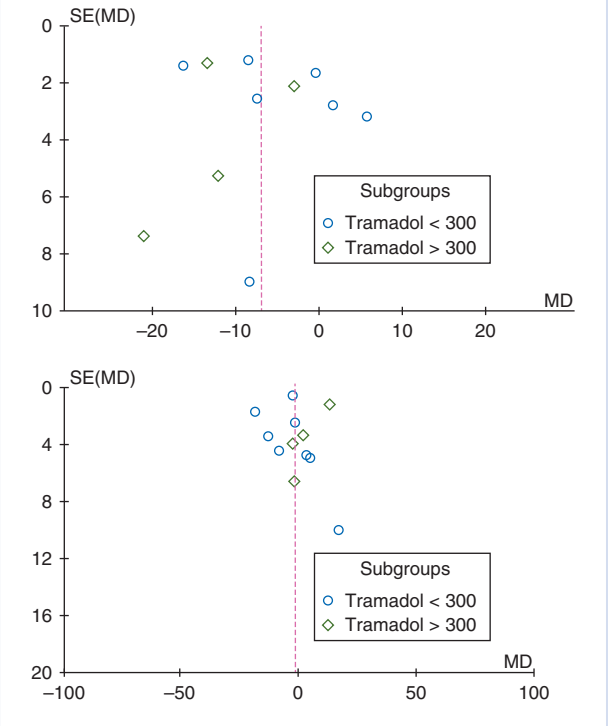

Fig 5 Funnel plot for morphine consumption and pain at 24 h after surgery.

bias. As the analgesic potency of i.v. tramadol is 1/10th that of morphine, this decrease in morphine dose is equianalgesic to 60 mg of tramadol.[30] Interestingly, it is lower than the median dose of tramadol used in the trials included in this meta-analysis. The morphine-sparing effect of tramadol may, therefore, be considered negligible. Indeed, it is the smallest 24 h morphine-sparing effect reported, smaller than those for non-steroidal anti-inflammatory drugs (from 10.2 to 19.7),[31–33] acupan (13 mg),[34] and paracetamol (9 mg),[35] when these co-analgesics are combined with morphine after surgery. We were unable to analyse morphine use in the PACU due to lack of sufficient data. Early morphine consumption at 4 and 12 h appeared not to vary, although some studies used only intraoperative tramadol bolus. This may be related to smaller sample size available at 4 and 12 h

The tramadol dose was directly correlated with the morphine-sparing effect. The most favourable morphine-sparing effect, with a decrease in morphine intake of 13 mg, was reported for patients treated with a high dose of tramadol (>300 mg). Repetitive or continuous administration, which would logically have resulted in the administration of higher doses of tramadol, also resulted in a greater morphine-sparing effect. Preoperative tramadol administration was not associated with a stronger morphine-sparing effect.

This limited morphine-sparing effect was not associated with a decrease in the incidence of the most frequent adverse effects of opioids (i.e. nausea and vomiting, and sedation). This is not surprising, because it has already been shown that morphine consumption is positively correlated with the incidence of nausea and vomiting, and the morphine-sparing effect of tramadol was small.[36] Paracetamol and acupan, which also have limited morphine-sparing effects, were also unable to decrease the frequency of these opioid-related adverse effects.[34 35] In contrast, non-steroidal anti-inflammatory drugs, which have a larger morphine-sparing effect,[33] are associated with a significant decrease in the incidence of nausea, vomiting, and sedation.[36 37] Another possible reason for the lack of decrease in the incidence of adverse effects relates to the intrinsic opioid action of tramadol. Indeed, tramadol may itself cause nausea, vomiting, and sedation.[38] We were unable to differentiate between the various mechanisms involved in the incidence of these adverse effects in the studies included in our meta-analysis.

Approaches involving the combination of analgesics are designed to limit the adverse effects of morphine, but they may themselves lead to additional side-effects. Only limited data are available to address this issue, as tramadol-related adverse effects, such as dry mouth, headache, shivering, and dizziness, are rarely assessed.[38] We were unable to detect differences in the incidence of dizziness and shivering. However, the three studies investigating dizziness showed that this adverse effect tended to be more frequent in the tramadol groups.[7 15 18] The absence of detectable differences may also reflect limited power and we cannot rule out the possibility that tramadol was responsible for adverse effects, particularly when used at higher doses.

The second primary outcome was pain intensity at rest, 24 h after surgery. Our meta-analysis suggests that the addition of tramadol to the analgesic regimen has no effect on pain intensity 24 h after surgery. This is a key point, because the secondary objective of balanced analgesia is to reduce the intensity of postoperative pain. The low pain score observed in the control group may have limited the possibility to reveal the benefit of multimodal analgesia. The combination treatment resulted in slightly lower levels of pain in the PACU (−11 mm mean difference), but this decrease gradually disappeared over the course of the next 24 h, becoming non-significant. This early significant pain intensity reduction may in part be related to the studies including intraoperative single doses of tramadol. This decrease in pain intensity is thus essentially limited to the immediate postoperative period and is not clinically significant. Indeed, the largest decrease in pain observed was smaller than the minimal significant decrease in cases of moderate baseline pain (13 on the VAS 0–100).[39] In the subgroup analysis, the timing, dose, and mode of administration of tramadol had no effect on the impact on pain intensity at 24 h after surgery. Thus, the administration of tramadol in combination with morphine does not reduce pain intensity 24 h after surgery. Limited pain reduction, of no clinical relevance, was observed only in the immediate postoperative period.

Most of the studies included in this meta-analysis involved the i.v. administration of tramadol. This drug is metabolized in the liver, to generate principally *O*-demethyltramadol (metabolite denoted M1) and mono-*N*-demethyltramadol

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(metabolite denoted M2). Its mode of action is not completely understood, but there seem to be at least two complementary mechanisms at work: weak binding of the parent compound and stronger binding of mono-*O*-desmethyltramadol (M1) to μ-opioid receptors, and the weak inhibition of norepinephrine and serotonin uptake. In volunteers, the analgesic concentration of M1 seemed to be maintained for longer periods, resulting in more sustained analgesia, after i.v. administration than after oral administration.[40] In our meta-analysis, this would have made the detection of an analgesic efficacy of tramadol combined with morphine more likely.

The dose used in most of the studies (11/14; 78%) was lower than the defined daily dose (median dose: 100 mg), even for the continuous administration of tramadol. These low doses are related to the studies using single tramadol dose administration. The use of such low doses may contribute to the lack of significance of the effect of combining tramadol with morphine. Indeed, in our subgroup analysis, higher doses (>300 mg) were associated with significantly lower levels of pain, at least in the early postoperative period, and subgroup analysis revealed a significant morphine-sparing effect in the early stages, when tramadol doses exceeded the daily dose (>300 mg). However, the maximum recommended dose of tramadol is 400 mg day^{-1}, and there is no logical reason to exceed this dose.

The evidence available for this meta-analysis was weak, as most of the studies were academic in nature and were carried out on small samples at a single centre. The global risk of bias was unclear in most of the studies. The high levels of data heterogeneity, reflected by an $I^2 > 50\%$, probably reflected differences between the surgical models, tramadol administration protocols, and different modes of morphine administration. Furthermore, it was frequently necessary to extract data from graphs, we did not assess the value of tramadol alone and it is not possible to extrapolate our results to assess the value of tramadol after the first 24 h. All of these issues are outside the scope of our review.

Conclusion

The clinical impact of combining tramadol with morphine in the immediate postoperative period appears to be limited to slightly lower levels of morphine use after surgery than for patients treated with placebo or non-opioid analgesic, with no detectable benefit on the incidence of opioid-related adverse effects and no decrease in pain intensity at rest at 24 h.

Authors' contributions

The protocol was developed by V.M., L.G., and D.F. The search strategy was developed by V.M., and L.G. and D.F. searched for and procured studies. The studies to be included were selected by L.G. and D.F., with V.M. as the arbiter, and data were extracted by V.M., L.G., and D.F. Analyses were done by V.M. and D.F. The analysis was interpreted by V.M., L.G., and D.F. The final review was drafted by V.M., L.G., and D.F. Both V.M. and D.F. will be responsible for the update of the final review.

Declaration of interest

None declared.

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Appendix: PUBMED search equation

The following search strategy was developed for PUBMED and was adapted for the other databases to be searched.

Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format

(1) Randomized controlled trial[Publication Type]
(2) Controlled clinical trial[Publication Type].
(3) Randomized[Title/Abstract]
(4) Placebo[Title/Abstract]
(5) Drug therapy[sh]
(6) Clinical trials as topic[sh]
(7) Randomly[Title/Abstract]
(8) Trial [Title/Abstract]
(9) Groups[Title/Abstract])
(10) 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
(11) 9. Animals[mh] not (humans)[mh]
(12) 10 not 11
(13) "Analgesic rescue" or "morphine"[MeSH Terms] OR "morphine"[All Fields]) OR "opioid consumption "[All Fields] OR ("meperidine"[MeSH Terms] OR "meperidine"[All Fields]) OR ("alfentanil"[MeSH Terms] OR "alfentanil"[All Fields]) OR ("fentanyl"[MeSH Terms] OR "fentanyl"[All Fields]) OR ("hydromorphone"[MeSH Terms] OR "hydromorphone"[All Fields]) OR ("oxycodone"[MeSH Terms] OR "oxycodone"[All Fields])) OR "morphine"[MeSH Terms]
(14) Postoperative pain[MeSH Terms]) OR postoperative pain[Title/Abstract] OR post operative pain[Title/

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Abstract] OR post-operative pain[Title/Abstract] OR post surgical pain[Title/Abstract] OR post-surgical pain[Title/Abstract] OR pain after surgery[Title/Abstract] OR pain after surgical[Title/Abstract] OR pain after operation[Title/Abstract]

(15) Surgery[Title/Abstract]) OR surgical[Title/Abstract]) OR operation[Title/Abstract] OR operations[Title/Abstract] OR surgeries[Title/Abstract]) OR "Surgical Procedures, Operative"[Mesh]

(16) Postoperative pain[MeSH Terms] OR pain[MeSH Terms]) OR pain[Title/Abstract]

(17) 16 AND 15

(18) 17 OR 14

(19) 18 AND 13

(20) "Tramadol"[MeSH Terms] OR "tramadol"[Title/Abstract] OR "zaldiar"[Title/Abstract] OR "contramal"[Title/Abstract] OR "topalgic"[Title/Abstract] OR "dolzam"[Title/Abstract] OR "ixprim"[Title/Abstract] OR "monocrixo"[Title/Abstract] OR "ultram"[Title/Abstract] OR "ultram"[Title/Abstract] OR "tramacet"[Title/Abstract] OR "zaldiar"[Title/Abstract]

(21) 12 AND 19 AND 20.

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