Review Article

Intra-operative analgesia with remifentanil vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis

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Summary

Intra-operative remifentanil is associated with increased postoperative analgesic requirements and opioid consumption. Dexmedetomidine has characteristics suggesting it may substitute for intra-operative remifentanil during general anaesthesia, but existing literature has reported conflicting results. We undertook this meta-analysis to investigate whether general anaesthesia including dexmedetomidine would result in less postoperative pain than general anaesthesia including remifentanil. The MEDLINE and PubMed electronic databases were searched up to October 2018. Only randomised trials including patients receiving general anaesthesia and comparing dexmedetomidine with remifentanil administration were included. Meta-analyses were performed mostly employing a random effects model. The primary outcome was pain score at rest (visual analogue scale, 0–10) at two postoperative hours. The secondary outcomes included: pain score at rest at 24 postoperative hours; opioid consumption at 2 and 24 postoperative hours; and rates of hypotension, bradycardia, shivering and postoperative nausea and vomiting. Twenty-one randomised trials, including 1309 patients, were identified. Pain scores at rest at two postoperative hours were lower in the dexmedetomidine group, with a mean difference (95%CI) of −0.7 (−1.2 to −0.2), I^2 = 85%, p = 0.004, and a moderate quality of evidence. Secondary pain outcomes were also significantly better in the dexmedetomidine group. Rates of hypotension, shivering and postoperative nausea and vomiting were at least twice as frequent in patients who received remifentanil. Time to analgesia request was longer, and use of postoperative morphine and rescue analgesia were less, with dexmedetomidine, whereas episodes of bradycardia were similar between groups. There is moderate evidence that intra-operative dexmedetomidine during general anaesthesia improves pain outcomes during the first 24 postoperative hours, when compared with remifentanil, with fewer side effects.

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Introduction

Remifentanil is a potent synthetic opioid with an ultra-short–acting pharmacokinetic profile. These characteristics allow for rapid and accurate titration, making the drug attractive during management of a broad range of surgical procedures [1]. The quick onset and offset of effect, allowing

remifentanil administration to control the intra-operative response to changing noxious stimuli, and permitting rapid recovery after general anaesthesia [1]. However, patients who receive intra-operative remifentanil may experience hypotension, bradycardia and postoperative secondary hyperalgesia, with associated need for increased opioid consumption [1, 2].

Dexmedetomidine is a highly, potent, selective α_2-adrenergic agonist with intrinsic analgesic properties as well as sedative, anxiolytic and sympatholytic effects [3, 4]. In the last decade, many researchers have investigated whether dexmedetomidine could be substituted for the intra-operative administration of remifentanil during general anaesthesia, but these studies have come to conflicting conclusions. With recent increased attention on the administration of intra-operative and postoperative opioids, quantifying the impact of anaesthetic strategies on this outcome is highly relevant [5–7]. We, therefore, undertook this meta-analysis to investigate whether general anaesthesia including dexmedetomidine would result in less postoperative pain, when compared with general anaesthesia including remifentanil.

Methods

This investigation followed the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement recommended process [8]. The authors searched electronic databases MEDLINE and PUBMED up to October 2018, and the following population search terms were applied: Pain OR Pain measurement OR Pain perception OR Nociception OR Hyperalgesia OR Analgesia OR Remifentanil OR Dexmedetomidine. The results of this search were combined with Surgery OR Surgical procedures OR Perioperative period OR Perioperative care. The limits of Clinical trials OR Random allocation OR Therapeutic use were then applied to the results. The following words were searched as keywords: Allodynia*, Pain*, Analgesi*, Nociception*, Surger*, Surgical*, Operation*, Operative*, Perioperati*, Anesthe*, Anaesthe*, Incisi*, Invasive*, Remif* and dexmedeto*. The results of this search strategy were limited to randomised controlled trials and humans. No age or language limits were placed on the search. Finally, the references of all articles retrieved from the search were manually reviewed and Google Scholar™ was queried for any relevant trials not already identified using the strategy described above.

The meta-analysis addresses women and men undergoing any surgical operation under general anaesthesia. Only trials that included patients under general anaesthesia and investigated pain outcomes, comparing dexmedetomidine with remifentanil administration were included in the present meta-analysis. Trials that examined these medications for the primary outcome of sedation were excluded. We selected our extracted outcomes following the standard approach described in our previous meta-analyses on acute postoperative pain [9–11]. The primary outcome was pain score at rest at two postoperative hours. Secondary pain-related outcomes included: pain score at rest at 12 and 24 postoperative hours; intravenous (i.v.) morphine consumption equivalents at 2, 12 and 24 postoperative hours; time to first analgesic request; and need for rescue analgesics. Other secondary outcomes sought were rates of hypotension and bradycardia during surgery and rates of shivering and postoperative nausea and vomiting within the first 24 postoperative hours. We also aimed to capture hospital resource-related outcomes including time to extubation and length of stay in the recovery area. Extracted trial characteristics included surgical procedure, intra-operative opioid regimen, medication used for anaesthetic maintenance and type of postoperative analgesia.

We then employed the same methodology as described in a recent article [12]. Briefly, the Cochrane Collaboration's Risk of Bias Tool for randomised controlled trials was used to assess the methodological quality of each randomised trial [13]. Two authors (SG and JF) independently scored the items for each trial using this method and extracted the relevant data for the analyses. Disagreements with scoring or extracted data were resolved through discussion with a third author (KK). If data were missing, authors were contacted, or median and interquartile range were used for mean and standard deviation approximations [14]. All opioids were converted into equianalgesic doses of i.v. morphine [15]. Finally, the quality of evidence for each outcome was rated according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system [16].

Meta-analyses were conducted using the Review Manager software (RevMan version 5.3.5; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration 2014). The coefficient I^2 was calculated to evaluate heterogeneity [17]. If moderate or high heterogeneity was present, a random effects model was applied; otherwise a fixed effect model was used [18]. Sub-group analyses were performed for our primary outcome according to the type of surgery (laparoscopic surgery vs. ear, nose and throat surgery vs. other operations), or the type of medication used for anaesthetic maintenance (volatile anaesthetic vs. propofol) as propofol might reduce pain outcomes [19], in an attempt to explain anticipated heterogeneity [18]. The

likelihood of publication bias for our primary outcome was evaluated by drawing a funnel plot of the mean difference standard error of pain score at rest on postoperative day one (y-axis) as a function of the mean difference of pain score at rest on postoperative day one (x-axis) [20] and confirmed with Duval and Tweedie's trim and fill test [21]. This assessment was performed using Comprehensive Meta-analysis Version 2 software (Biostat, Englewood, NJ, USA). Finally, trial sequential analysis was performed on the primary outcome (pain score at rest at two postoperative hours), to confirm whether firm evidence was reached or not (TSA software version 0.9.5.10 Beta; Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark) [22]. Results are presented as the mean difference or relative risk with 95%CI. A two-sided value of $p < 0.05$ was considered significant.

Results

Of the 4548 trials identified from the literature search strategy, 21 met the inclusion criteria [23–43], representing a total of 1309 patients (Fig. 1). According to our assessment following the Cochrane Collaboration Risk of

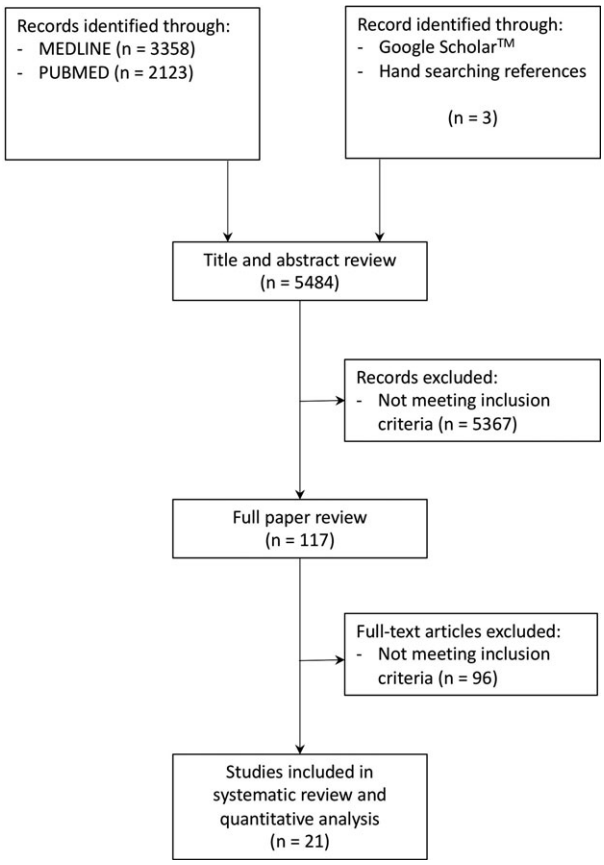

Figure 1 PRISMA flow diagram showing literature search results.

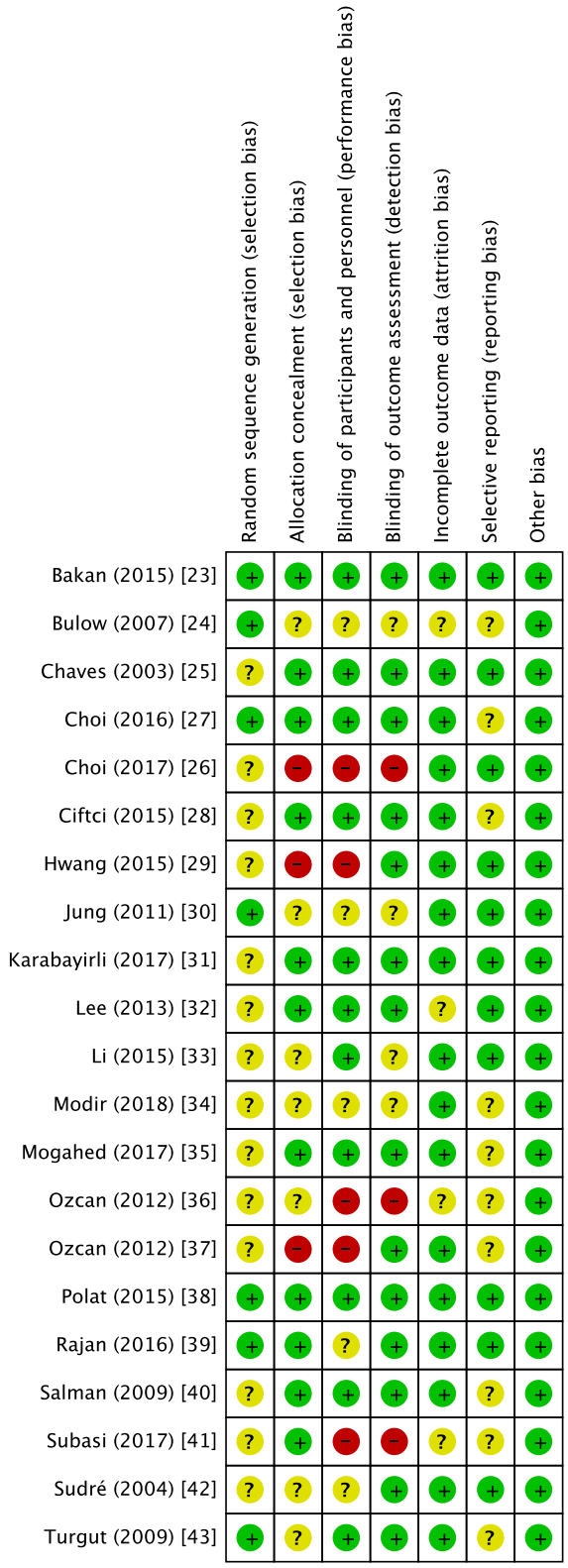

Figure 2 Cochrane Collaboration risk of bias summary: evaluation of bias risk items for each included study. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear risk of bias.

Bias tool (Fig. 2), the majority of trials had a low risk of bias. Attempts were made to contact seven authors [23, 27, 31, 34, 37–39], but none provided the additional data requested.

Table S1 in the online Supplementary Material presents the trial characteristics. All studies included a total of patients ranging from 30 to 88, with the exception of one study that included a total of 139 patients [39]. Nine trials included patients scheduled for laparoscopic surgery [23–25, 27, 30, 35, 40–42], seven for ear, nose and throat surgery [26, 28, 31, 32, 34, 37, 38], and five for different types of elective operations [29, 33, 36, 39, 43]. Fourteen (66%) included trials used volatile anaesthetic to maintain anaesthesia and seven that administered propofol [23, 24, 29, 33, 34, 41, 43]. Authors investigated doses of remifentanil with boluses ranging from 0.01 to 2 $\mu g.kg^{-1}$, followed by intra-operative infusions of 0.01–1 $\mu g.kg.min^{-1}$ [29, 33, 43]; boluses of dexmedetomidine used varied from 0.1 to 1 $mcg.kg^{-1}$, with infusions from 0.2 to 1.2 $\mu g.kg.h^{-1}$ [29, 30]. In nine trials [23, 24, 33, 34, 36, 37, 39, 41, 42], another analgesic modality was used in addition to remifentanil or dexmedetomidine. These included: a mean bolus of 1 $\mu g.kg^{-1}$ of fentanyl administered at the induction of general anaesthesia in seven trials [23, 24, 34, 36, 37, 39, 41, 42]; in one trial, a bolus of 0.3 $\mu g.kg^{-1}$ sufentanil injected after umibilical cord clamping [33]; and an epidural catheter used during surgery in one trial [42].

Mean pain scores (95%CI) at rest at two postoperative hours were 3.3 (2.7–3.9) and 4.0 (3.2–4.8) in the dexmedetomidine and remifentanil groups, respectively, with a mean difference of −0.7 (−1.2 to −0.2, p = 0.004), without sub-group differences between types of surgery, p = 0.28 (Fig. 3). Sub-group analyses according to the type of medication used for anaesthetic maintenance suggested a similar effect in both the volatile anaesthetic [26, 27, 30, 32, 35, 38–40] (mean difference (95%CI): 0.6 (0.0–1.1); I^2 = 87%; p = 0.05) and propofol sub-groups [29, 41] (mean difference (95%CI): 1.3 (0.7, 1.8); I^2 = 85%; p < 0.0001), with no difference between sub-groups (p = 0.05). With regard to the funnel plots for our primary outcome, the Duval and Tweedie's trim and fill test revealed the point estimates (95%CI) for the combined studies to be −0.48 (−0.64 to −0.32); using trim and fill, these values are unchanged, suggesting that no trials are missing from the meta-analysis. The trial sequential analysis indicated that firm evidence was reached and that dexmedetomidine was superior to remifentanil (see also Supporting Information, Figure S1). The quality of evidence for our primary outcome was moderate according to the GRADE system.

All other secondary pain-related outcomes were significantly improved in the dexmedetomidine group compared with the remifentanil group, except pain scores at rest measured at 12 postoperative hours, which were sought by two trials and were equivalent in both groups (see

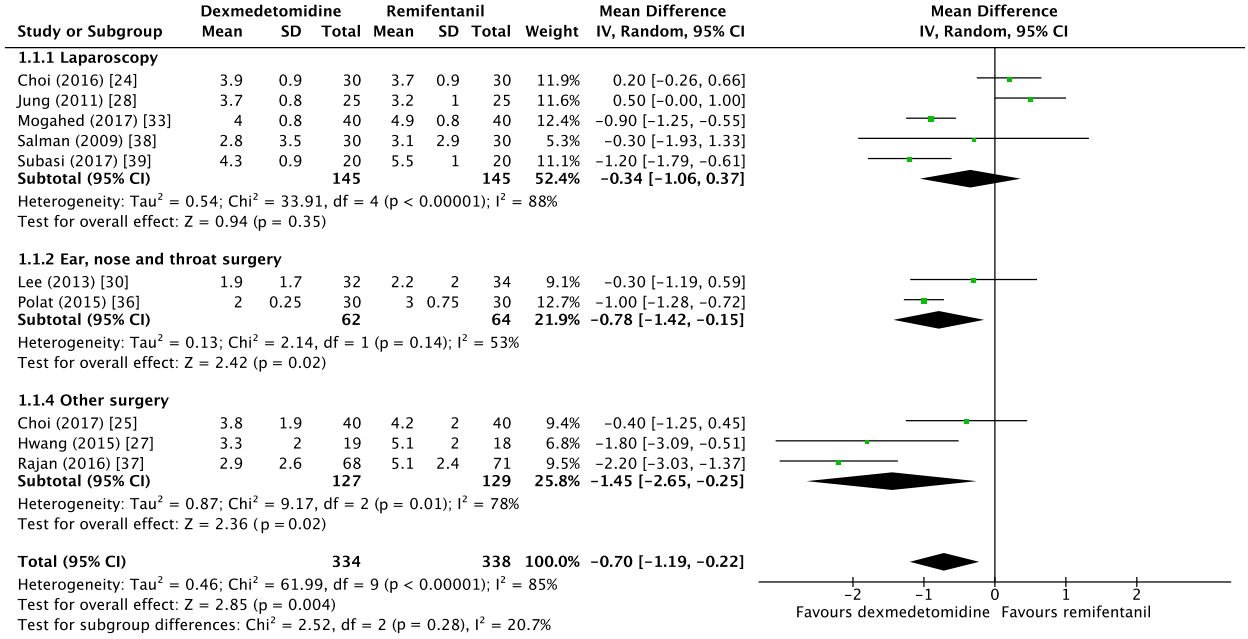

Figure 3 Forest plot of pain score at rest at two postoperative hours according to the type of surgery (laparoscopy vs. ear, nose and throat surgery vs. other types of operation).

Table 1 Summary of findings.

Quality assessment								
Outcome	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Total number of participants**	**Conclusion**	**Quality of evidence (GRADE)**
Rest pain score at two postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	672	Reduced pain scores in dexmedetomidine group	Moderate quality (⊕⊕⊕O)[e]
Rest pain score at 12 postoperative hours (analogue scale, 0–10)	Outcome reported by two trials	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	77	Reduced pain scores in dexmedetomidine group	Very low quality (⊕OOO)[f]
Rest pain score at 24 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	237	Reduced pain scores in dexmedetomidine group	Moderate quality (⊕⊕⊕O)[e]
Intravenous morphine consumption equivalents at two postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	297	Equivalent consumption in both groups	Moderate quality (⊕⊕⊕O)[e]
Intravenous morphine consumption equivalents at 12 posto perative hours	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	77	Reduced consumption in dexmedetomidine group	High quality (⊕⊕⊕⊕)
Intravenous morphine consumption equivalents at 24 postoperative hours	Outcome reported by two trials	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	77	Reduced consumption in dexmedetomidine groups	Low quality (⊕⊕OO)[g]
Time to first analgesic request	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	217	Longer time in dexmedetomidine group	Moderate quality (⊕⊕⊕O)[e]
Need for rescue analgesics	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	532	Less rescue analgesics in dexmedetomidine group	High quality (⊕⊕⊕⊕)
Rate of hypotension	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	390	Reduced rate in dexmedetomidine group	High quality (⊕⊕⊕⊕)
Rate of bradycardia	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	477	Equivalent rates in both groups	High quality (⊕⊕⊕⊕)
Rate of shivering	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	480	Reduced rate in dexmedetomidine group	High quality (⊕⊕⊕⊕)
Rate of postoperative nausea and vomiting	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	953	Reduced rate in dexmedetomidine group	High quality (⊕⊕⊕⊕)

(continued)

Table 1 (*continued*)

Quality assessment								
Outcome	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Total number of participants**	**Conclusion**	**Quality of evidence (GRADE)**
Time to extubation	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	807	Reduced time to extubation in remifentanil group	Moderate quality (⊕⊕⊖⊖)[e]
Length of stay in recovery area	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	861	Reduced length of stay in remifentanil group	Moderate quality (⊕⊕⊖⊖)[e]

[a]Even if allocation concealment was not clear in a majority of studies, we estimate that this does not represent a major limitation after reviewing the global risks of bias.
[b]I^2 above 50% or not applicable as only one trial reported this outcome.
[c]Consistent definition of the reported outcome.
[d]No serious imprecision as the clinical decision would not be modified whether the upper or lower boundary limit of the confidence interval represented the truth.
[e]As there was a concern about inconsistency, we rated down the quality of evidence even if the trial sequential analysis on the primary outcome showed that firm evidence was reached.
[f]We rated down by two levels for limitations, as two trials gathering less than 100 patients reported this outcome, and for inconsistency,
[g]We rated down for limitations, as two trials gathering less than 100 patients reported this outcome.

also Supporting Information, Table S2). For example, mean difference (95%CI) in pain scores at rest and i.v. morphine consumption equivalents at 24 postoperative hours were −0.9 (−1.7 to −0.2), p = 0.01 and −4.6 (−7.7 to −1.4) mg, p = 0.004, respectively. Rates of hypotension, shivering and postoperative nausea and vomiting were at least twice as frequent in patients who received remifentanil than dexmedetomidine, whereas episodes of bradycardia were similar between groups (see also Supporting Information, Table S2).

Time to extubation [23, 24, 32–35, 38–43] and length of stay in the recovery area [23, 24, 26, 29, 31, 34, 35, 38–43] were significantly longer in the dexmedetomidine group by a mean difference (95%CI) of 4.9 (0.8–9.1) min, I^2 = 99%, p = 0.02, and 8.9 (4.4–13.4) min, I^2 = 97%, p < 0.0001, respectively.

Table 1 summarises our findings according to the GRADE system.

Discussion

This systematic review and meta-analysis investigated the effect of intra-operative dexmedetomidine on postoperative pain when compared with intra-operative remifentanil. Based on 21 randomised controlled trials, which included a total of 1309 patients, we demonstrated that dexmedetomidine was superior to remifentanil with improved pain outcomes in the immediate postoperative period, and for up to 24 postoperative hours. Furthermore, dexmedetomidine was associated with significantly fewer episodes of hypotension, shivering and postoperative nausea and vomiting. Although no difference for pain at rest 2 h after surgery was identified between medications in the laparoscopy sub-group, this particular finding may represent a type-2 error. Indeed, a post-hoc analysis revealed that a total of 386 patients would be required in this sub-group to detect a difference, with alpha- and beta-values of 0.05 and 0.2. The longer extubation time and length of stay in the recovery room in patients receiving dexmedetomidine are statistically significant but, in our view, clinically negligible.

With current clinical trends moving strongly towards reduction in peri-operative opioid administration, and indeed even opioid-free anaesthesia [5, 44, 45], the findings of this meta-analysis represent a two-fold benefit. Although avoiding remifentanil reduces intra-operative opioid consumption, its impact must be balanced against later postoperative outcomes. Our finding that substituting dexmedetomidine also reduces postoperative pain, with the potential for further opioid reduction, represents significant support for moving towards a reduction in intra-operative opioid use [5, 44–47].

There are notable limitations to this meta-analysis. Despite our attempt to group trials according to the type of surgery and by medication used for anaesthetic maintenance (volatile anaesthetic vs. propofol), the coefficient of heterogeneity remained high. The degree to which this heterogeneity affects the generalisability of the underlying conclusion is unclear, but the effect was similar across all sub-groups analysed, suggesting a consistent clinical impact. Laparoscopic surgery and head and neck surgery were well represented in this meta-analysis, however, other types of surgical procedures where remifentanil is commonly used, such as craniotomy and spinal procedures, were represented by only a single study each. Although the primary outcome effect was strongest in this group, secondary outcomes such as a delay in extubation may be more clinically-relevant and deserve consideration when applying the findings of this study.

In conclusion, there is moderate evidence that intra-operative dexmedetomidine during general anaesthesia results in lower pain outcomes during the first 24 postoperative hours when compared with remifentanil, with fewer episodes of hypotension, shivering and postoperative nausea and vomiting.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Trial characteristics.

Table S2. Secondary pain-related outcomes and side-effects.

Figure S1. Trial sequential analysis for pain scores at rest at two postoperative hours. The cumulative Z-curve (blue) crosses the monitoring boundary curve (red) and reaches the required information size, indicating firm evidence that dexmedetomidine is superior to remifentanil for this outcome.