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Review Article

The effects of continuous intravenous infusion of dexmedetomidine and remifentanil on postoperative pain: a systematic review and meta-analysis

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Abstract: Background: Intraoperative infusion of remifentanil is widely used for analgesia; however, remifentanil administration has been associated with hyperalgesia, respiratory depression, nausea and vomiting, emergence agitation, and delirium. Intraoperative infusion of dexmedetomidine may be an effective alternative for pain control. Method: We conducted a comprehensive literature review of the PubMed, Embase, and Cochrane Library databases for relevant randomized controlled trials (RCTs) comparing intraoperative infusion of dexmedetomidine and remifentanil. Outcome measures included: requirement for rescue analgesia, evaluation of postoperative analgesia by pain scores, intraoperative and postoperative blood pressure and heart rate, and incidence of postoperative vomiting and shivering. Results: Twelve RCTs were included in the meta-analysis. Results demonstrated significant decreases in the requirement for rescue analgesia (OR: 0.42, 95% CI: 0.22, 0.80, P = 0.008, I^2 = 0%), postoperative pain score (mean difference (MD): -1.60, 95% CI: -2.24, -0.96, P < 0.00001, I^2 = 62%), and incidence of postoperative vomiting (OR: 0.42, 95% CI: 0.21, 0.85, P = 0.02, I^2 = 14%) in patients administered intraoperative dexmedetomidine versus remifentanil. There were no differences in incidence of intraoperative and postoperative hypotension (odds ratio (OR): 0.72, 95% confidence interval (CI): 0.24, 2.17, P = 0.56, I^2 = 72%), incidence of intraoperative and postoperative bradycardia (OR: 1.06, 95% CI: 0.48, 2.34, P = 0.89, I^2 = 63%), or incidence of postoperative shivering (OR: 0.61, 95% CI: 0.29, 1.30, P = 0.20, I^2 = 24%). Conclusions: Intraoperative infusion of dexmedetomidine can alleviate postoperative pain in patients undergoing general anesthesia compared to remifentanil.

Keywords: Dexmedetomidine, remifentanil, postoperative pain, meta-analysis

Introduction

Postoperative pain is a common clinical problem, with approximately 80% of patients experiencing pain after surgery [1]. Postoperative pain can adversely affect a patient's comfort, ability to exercise, and therefore recovery. Remifentanil is an opioid that is widely used for intraoperative analgesia. It has a rapid onset and a short half-life [2, 3] and can be given in high doses; however, remifentanil administration has been associated with hyperalgesia [2], which aggravates postoperative pain. Remifentanil can also lead to other complications, such as nausea and vomiting, and emergence agitation. Commonly accepted current practice utilizes intraoperative infusions of remifentanil ranging from 0.1 μg/kg/to 0.5 μg/kg/min. Although up to 2 μg/kg/min remifentanil has been recommended, in clinical practice, doses above 0.2 μg/kg/min are unlikely to confer any additional benefit and are more likely to be associated with hemodynamic instability [4, 5].

Dexmedetomidine is a highly selective α2-adrenoreceptor agonist with an α2:α1 receptor affinity of 1620:1 [6]. Dexmedetomidine produces sedation similar to natural sleep [7, 8] without respiratory depression and has a protective effect on certain organs, including the heart, kidney, and brain [9-12]. The mean onset time of analgesia/sedation is 15 minutes after

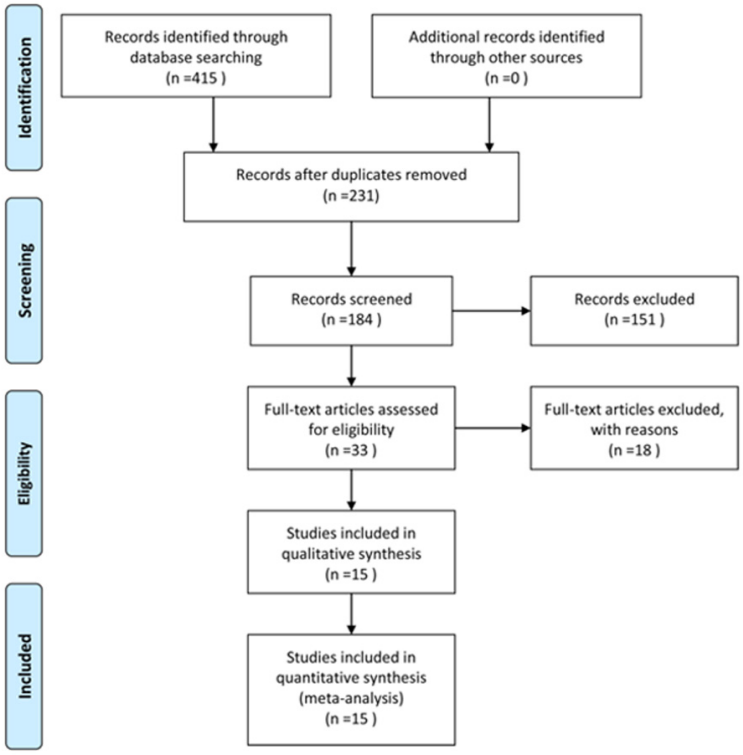

Figure 1. Flow diagram of study search and selection.

intravenous administration of dexmedetomidine [13]. Pharmacokinetic studies show a distribution half-life of approximately 6 minutes and a terminal elimination half-life of 2 hours after intravenous administration [14]. A loading dose of 1 μg/kg dexmedetomidine in 10 min followed by a maintenance infusion of 0.6 μg/kg/h, titrated to the desired clinical effect with doses ranging from 0.2 to 1 μg/kg/h, is recommended. Consistent with its pharmacological effects, dexmedetomidine decreases heart rate and blood pressure. These haemodynamic changes are associated with a reduction in noradrenaline and adrenaline levels [15]. At higher doses, dexmedetomidine has been associated with hypotension, bradycardia, and xerostomia [16], especially in elderly patients (> 65 years of age) [6].

Recent reports suggest that intraoperative dexmedetomidine can provide satisfactory analgesia with limited side effects, and studies have shown that dexmedetomidine can be used as a substitute for remifentanil [17-19]. However, the impact of dexmedetomidine on postoperative pain remains controversial. The objectives of this meta-analysis were to 1) compare the effect of dexmedetomidine and remifentanil on postoperative pain in patients undergoing general anesthesia, and 2) evaluate the feasibility of intraoperative infusion of dexmedetomidine for pain management in this patient population.

Methods

This meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews [20].

Searches

Two review authors (C-Y J, Y-Y C) independently searched the Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases in May 2017 using subject headings and keywords: dexmedetomidine and remifentanil. Methodology filters recommended by the Countway Library of Medicine were used to limit searches to randomized controlled trials (RCTs) in Medline and Embase. ClinicalTrials.gov was searched for ongoing trials (http://clinicaltrials.gov/). A manual search of the reference lists from relevant articles was also carried out; this process was performed iteratively until no additional articles could be identified. Study authors were contacted for information on missing data or conference proceedings. The search strategy is summarized in the **Appendix**.

Inclusion and exclusion criteria

Inclusion criteria were: 1) RCTs comparing intraoperative infusion of dexmedetomidine and remifentanil; 2) patients > 18 years of age; and 3) patients undergoing general anesthesia.

Exclusion criteria were: 1) quasi- or pseudo-randomized trials; 2) reviews, letters, or editorials; or 3) studies that reported insufficient data.

Study selection

Two review authors (C-Y J, Y-Y C) independently examined titles and abstracts to select eligible RCTs. Where datasets were duplicated, only the

Table 1. Dosage of dexmedetomidine and remifentanil

Reference	Dexmedetomidine*	Remifentanil**
Chaves 2003 [25]	1 μg/kg + 0.7 μg/kg/h	1 μg/kg + 0.5 μg/kg/h
Hwang 2015 [22]	0.01-0.02 μg/kg/min	0.01-0.2 μg/kg/min
Jung 2011 [27]	1 μg/kg + 0.2-0.7 μg/kg/h	0.8-1.2 μg/kg + 0.05-0.1 μg/kg/min
Karabayirli 2017 [24]	1 μg/kg + 0.7 μg/kg/h	1 μg/kg + 0.25-0.5 μg/kg/min
Kim 2015 [23]	0.5 μg/kg + 0.5 μg/kg/h	Remifentanil TCI to achieve a HR and MBP with 20% of the preoperative baseline values.
Lee 2017 [17]	0.3-0.4 μg/kg + 0.2-1 μg/kg/h	1-5 μg/kg/h
Murari Sudré 2004 [29]	0.5 μg/kg/h	0.1 μg/kg/min
Polat 2015 [26]	0.4 μg/kg/h	0.05 μg/kg/min
Rajan 2015 [18]	0.5-1 μg/kg + 0.2-0.7 μg/kg/h	0.08-0.15 μg/kg/min
Richa 2008 [28]	1 μg/kg + 0.4-0.8 μg/kg/h	1 μg/kg + 0.2-0.4 μg/kg/min
Salman 2009 [19]	1 μg/kg + 0.2 μg/kg/h	1 μg/kg + 0.2 μg/kg/min
Turgut 2009 [21]	1 μg/kg + 0.2-1 μg/kg/h	1 μg/kg + 0.05-1 μg/kg/min

*Loading dose and/or maintenance dose of dexmedetomidine. **Loading dose and/or maintenance dose of remifentanil. ASA, American Society of Anesthesiologists HR, heart rate; MBP, mean blood pressure; TCI, targeted controlled infusion.

most recent information was included. The full text of potentially relevant RCTs was retrieved. Two review authors (C-Y J, Y-Y C) independently examined the full text records to determine which RCTs met the inclusion criteria. Disagreements about study selection were resolved by discussion and consensus with a third author (Y S).

Outcomes

Two review authors (C-Y J, Y-Y C) independently extracted data from eligible RCTs including details describing study population, interventions, and outcome measures.

The primary outcome measures were: postoperative pain, evaluated by the requirement for rescue analgesia and postoperative pain scores (visual analogue scale [VAS]; 0 [no pain]-10 [severe pain]). Secondary outcome measures were blood pressure, quantitatively evaluated by the incidence of hypotension; heart rate, quantitatively evaluated by the incidence of bradycardia; incidence of postoperative vomiting; and incidence of postoperative shivering.

Disagreements about data extraction were resolved by discussion and consensus with a third author (Y S).

Assessment of quality of evidence in included studies

Two review authors (C-Y J, Y-Y C) independently assessed the risk of bias in each included RCT using tools provided by the Cochrane Collaboration. Six domains, including random sequence generation (selection bias), allocation concealment (selection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias, and blinding (performance bias and detection bias) were assessed for each trial. Risk of bias was categorized as low (all domains were considered adequate), high (presence of information that could cause bias), or unclear (inadequate information available to assess risk of bias).

Disagreements about risk of bias were resolved by discussion and consensus with a third author (Y S).

Statistical analysis

Statistical analyses were performed using RevMan (v. 5.3; The Cochrane Collaboration, Oxford, UK). Mean differences (MDs) were calculated for continuous variables, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous variables.

Methodological and clinical heterogeneity were investigated by comparing interventions, participants, and study endpoints. Reasons for methodological and clinical heterogeneity were discussed. Statistical heterogeneity was investigated with the inconsistency index. A random-effects model was used to pool studies with significant heterogeneity, defined as $I^2 \geq 50\%$. Studies with substantial heterogeneity ($I^2 \geq 75\%$) that could not be explained by data extraction or clinical and methodological heterogeneity (e.g., race, dose, design) were excluded from the meta-analysis.

Table 2. Characteristics of included studies

Reference	Dexmedetomidine			Remifentanil		
	Number	Age (Y)	Gender (M/F)	Number	Age (Y)	Gender (M/F)
Chaves 2003 [25]	21	41.76 ± 12.08	4/17	21	41.76 ± 12.08	7/14
Hwang 2015 [22]	19	65.9 ± 5.8	8/11	18	65.1 ± 5.3	8/10
Jung 2011 [27]	25	46.3 ± 3.7	/	25	45.4 ± 4.2	/
Karabayirli 2017 [24]	24	37 (27-46)	11/13	24	36 (28-46)	13/11
Kim 2015 [23]	21	39.2 ± 12.5	14/7	18	36.2 ± 15.1	9/9
Lee 2017 [17]	38	75.4 ± 6.4	4/34	37	77.1 ± 7.4	2/35
Murari Sudré 2004 [29]	44	43 ± 4	11/33	44	42 ± 5	11/33
Polat 2015 [26]	30	36 (23-53)	22/8	30	37 (17-48)	18/12
Rajan 2015 [18]	68	56 ± 14	35/33	71	55 ± 14	34/37
Richa 2008 [28]	12	34.2 6 9.6	5/7	12	36.6 6 9.9	6/6
Salman 2009 [19]	30	34 ± 7	22/8	30	34 ± 8	21/9
Turgut 2009 [21]	25	56.52 ± 12.54	/	25	53.56 ± 10.14	/

Y: years; M: male; F: female.

Table 3. Study protocols

Reference	Inhaled anesthetics^	Muscle relaxant**	Sedatives‡	Other analgesics†
Chaves 2003 [25]	2% sevoflurane	0.2 mg/kg cisatracurium*	2.5 mg/kg propofol*	-
Hwang 2015 [22]	-	1 mg/kg rocuronium*	1-2 mg/kg propofol* 3-12 mg/kg/h propofol	-
Jung 2011 [27]	2 L/min O_2, 3 L/min N_2O, 6-7% desflurane	0.6 mg/kg rocuronium*	2 mg/kg propofol*	-
Karabayirli 2017 [24]	2% sevoflurane in 50% O_2, and 50% N_2O	0.6 mg/kg rocuronium*	2.5 mg/kg propofol*	1 μg/kg fentanyl (when BIS > 60)
Kim 2015 [23]	-	0.6 mg/kg rocuronium*	Using a propofol TCI*	1 μg/kg fentanyl*
Lee 2017 [17]	-	-	0.3 mg/kg propofol*	-
Murari Sudré 2004 [29]	0.5-1% sevoflurane	1 mg/kg succinylcholine* 0.15 mg/kg/h rocuronium	2 mg/kg propofol*	150 μg fentanyl*
Polat 2015 [26]	Desflurane in 50% O_2/N_2O	0.6-0.8 mg/kg rocuronium*	1.5-2 mg/kg propofol*	1 μg/kg fentanyl*
Rajan 2015 [18]	Sevoflurane	1 mg/kg rocuronium* maintained during surgery	1-3 mg/kg propofol*	1-3 μg/kg fentanyl* 50 μg fentanyl during clousure
Richa 2008 [28]	1-1.5 MAC isoflurane in 50% O_2/N_2O	0.15 mg/kg cisatracurium* 2 μg/kg/min Cisatracurium	2.5 mg/kg propofol*	15 mg/kg paracetamol during clousure
Salman 2009 [19]	6% desflurane in 50% O_2, and 50% N_2O	0.1 mg/kg vecuronium*	2 mg/kg propofol*	-
Turgut 2009 [21]	-	0.2 mg/kg cisatracurium* Maintained during surgeries	1-2.5 propofol* maintained during surgeries (150 μg/kg/min)	1 mg/kg Tramadol during clousure

^Type and maintenance dose of inhaled anesthetics. **Loading dose and/or maintenance dose of muscle relaxant. ‡Loading dose and/or maintenance dose of sedatives. †Dose of other analgesics. *Drugs were used during induction periods. TCI, targeted controlled infusion.

Subgroup analyses stratified by anesthesia protocol were conducted to further compare and validate the impact of intraoperative dexmedetomidine and remifentanil on postoperative pain.

Results

Study selection

The searches identified 326 articles; of these, 30 studies were considered potentially eligible for inclusion. After analyzing the full text articles, 18 studies were excluded (14 studies did not fulfill the inclusion criteria; four studies had no extractable data), and 12 RCTs were found eligible for inclusion according to our criteria for considering studies in this review (**Figure 1**).

Characteristics of included studies

The characteristics of the included RCTs are shown in **Tables 1** and **2**, and the study protocols for anesthesia and analgesia used in the

Table 4. Methodological quality of the included studies

Reference	Random sequence generation	Allocation	Blinding	Incomplete data	Selective reporting	Other bias
Chaves 2003 [25]	No details	No details	Double blind	No dropouts	Not all expected outcomes reported	Small sample size
Hwang 2015 [22]	A computer-generated program	No details	Double blind	No loss to follow-up	Not all expected outcomes reported	Small sample size
Jung 2011 [27]	A computer-generated program	Sealed envelops	Double blind	No dropouts	Not all expected outcomes reported	Small sample size
Karabayirli 2017 [24]	No details	No details	Double blind	No dropouts	Never report a pre-design result	Small sample size
Kim 2015 [23]	A computer-generated program	No details	Double blind	No loss to follow-up	Not all expected outcomes reported	Small sample size
Lee 2017 [17]	A computer-generated program	No details	Double blind	No loss to follow-up	Not all expecte d outcomes reported	Small sample size
Murari Sudré 2004 [29]	No details	No details	Double blind	No loss to follow-up	Not all expected outcomes reported	Small sample size
Polat 2015 [26]	A computer-generated program	No details	Double blind	No dropouts	Not all expected outcomes reported	Small sample size
Rajan 2015 [18]	A computer-generated program	Sealed envelops	Double blind	No loss to follow-up	Not all expected outcomes reported	Large sample size
Richa 2008[28]	A computer-generated program	No details	Double blind	No dropouts	Not all expected outcomes reported	Small sample size
Salman 2009 [19]	A computer-generated program	No details	Double blind	No loss to follow-up	Not all expected outcomes reported	Small sample size
Turgut 2009 [21]	A computer-generated program	Sealed envelops	Double blind	No loss to follow-up	Not all expected outcomes reported	Small sample size

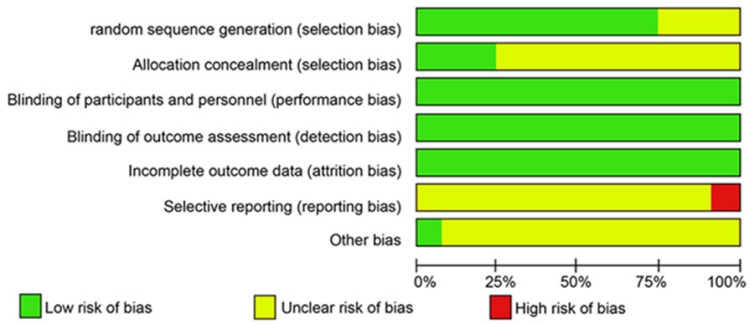

Figure 2. Methodological quality of included studies: Each domain is presented as a percentage across the included studies.

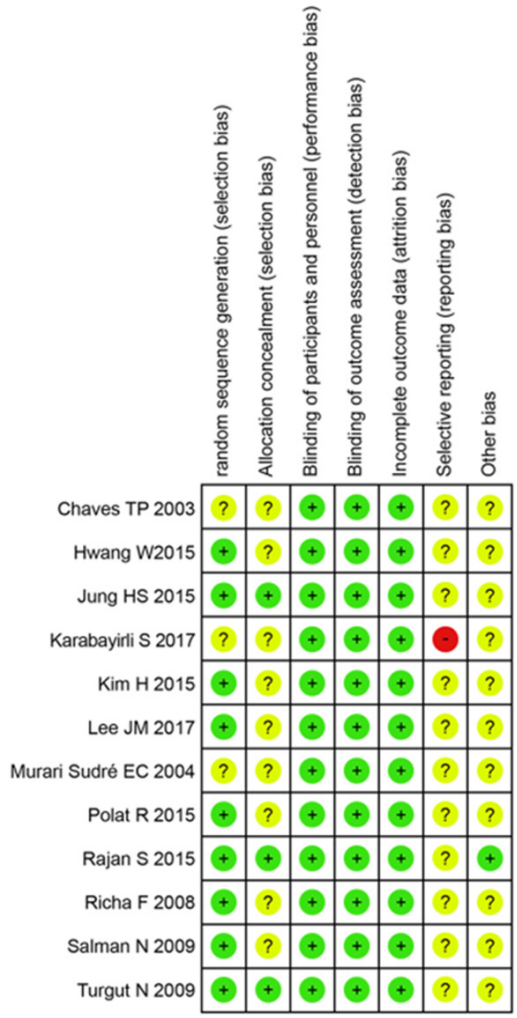

Figure 3. Methodological quality of included studies: "+" low risk of bias; "?" unclear risk of bias; "-" high risk of bias.

RCTs are shown in **Table 3**. The 12 included RCTs incorporated 353 patients treated with intraoperative dexmedetomidine and 358 treated with intraoperative remifentanil; all were classified as American Society of Anesthesiologists I-III. Dexmedetomidine was administered with a loading dose ranging from 0.3 μg/kg to 1 μg/kg and a maintenance dose ranging from 0.2 μg/kg/hr to 1 μg/kg/h. Remifentanil was administered with a loading dose of 1 μg/kg and a maintenance dose ranging from 0.01 μg/kg/min to 1 μg/kg/min. Protocols for anesthesia included total intravenous anesthesia without inhaled anesthetics, administered in four RCTs [17, 21-23], and balanced anesthesia, administered in seven RCTs. Other analgesics were fentanyl, administered in five RCTs, paracetamol, administered in one RCT, and tramadol, administered in one RCT.

Quality of the studies

Assessment of quality of evidence in the included RCTs is shown in **Table 4**; **Figures 2** and **3**. Eleven RCTs showed low or unclear risk of bias in all six domains. One RCT [24] showed high risk of bias on selective reporting, as it did not report a pre-specified primary outcome.

Outcomes

Primary outcomes

Postoperative Pain evaluation: Requirement for rescue analgesia is described in five RCTs [19, 22, 24-26] (dexmedetomidine, n = 123; remifentanil, n = 123). The meta-analysis demonstrated a significant decrease in the requirement for rescue analgesia in patients undergoing general anesthesia with intraoperative administration of dexmedetomidine compared to those with intraoperative administration of remifentanil (OR: 0.42, 95% CI: 0.22, 0.80, P = 0.008, I^2 = 0%; **Figure 4**).

Overall VAS score is described in three RCTs [18, 19, 23] (dexmedetomidine, n = 122; remifentanil, n = 116). The meta-analysis demonstrated a significant decrease in the postoperative VAS score in patients undergoing general anesthesia with intraoperative administration of dexmedetomidine compared to those with intraoperative administration of remifentanil

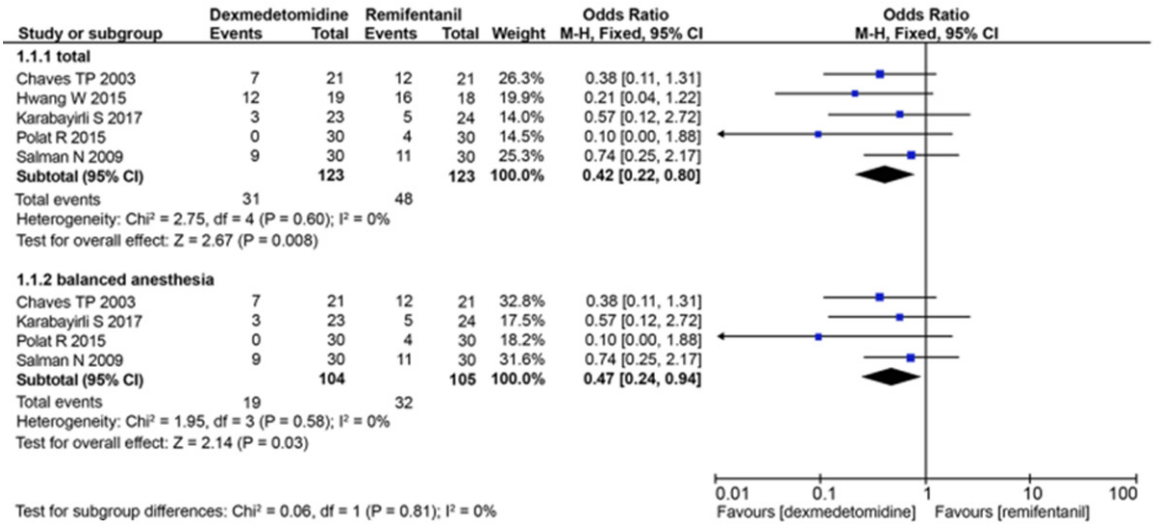

Figure 4. Postoperative pain: Requirement for rescue analgesics.

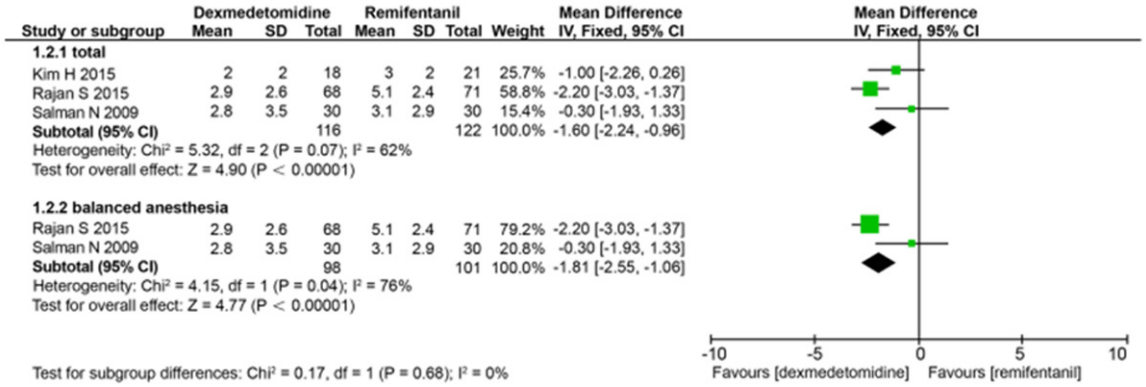

Figure 5. Postoperative pain: Overall VAS score.

(MD: -1.60, 95% CI: -2.24, 0.96, P < 0.00001, I^2 = 62%; **Figure 5**).

Secondary outcomes

Blood pressure: Intraoperative blood pressure is described in eight RCTs. Five [21, 23-26] RCTs demonstrated no significant difference in intraoperative blood pressure, two RCTs [17, 27] demonstrated a significant decrease in intraoperative blood pressure, and one RCT [28] demonstrated a significant increase in intraoperative blood pressure in patients undergoing general anesthesia with intraoperative administration of dexmedetomidine compared to those with intraoperative administration of remifentanil.

Incidence of intraoperative and postoperative hypotension is described in four RCTs [17, 19, 27, 28] (dexmedetomidine, n = 105; remifentanil, n = 104). The meta-analysis demonstrated no significant difference in incidence of intraoperative and postoperative hypotension in patients undergoing general anesthesia with intraoperative administration of dexmedetomidine compared to those with intraoperative administration of remifentanil (OR: 0.72, 95% CI: 0.24, 2.17, P = 0.56, I^2 = 72%; **Figure 6**).

Heart rate: Intraoperative heart rate is described in eight RCTs. Five [21, 23-26] RCTs demonstrated no significant difference in intraoperative heart rate, two RCTs [17, 27] demonstrated a significant decrease in intraoperative heart rate, and, one RCT [28] demonstrated a significant increase in intraoperative heart rate in patients undergoing general anesthesia with intraoperative administration of dexmedetomi-

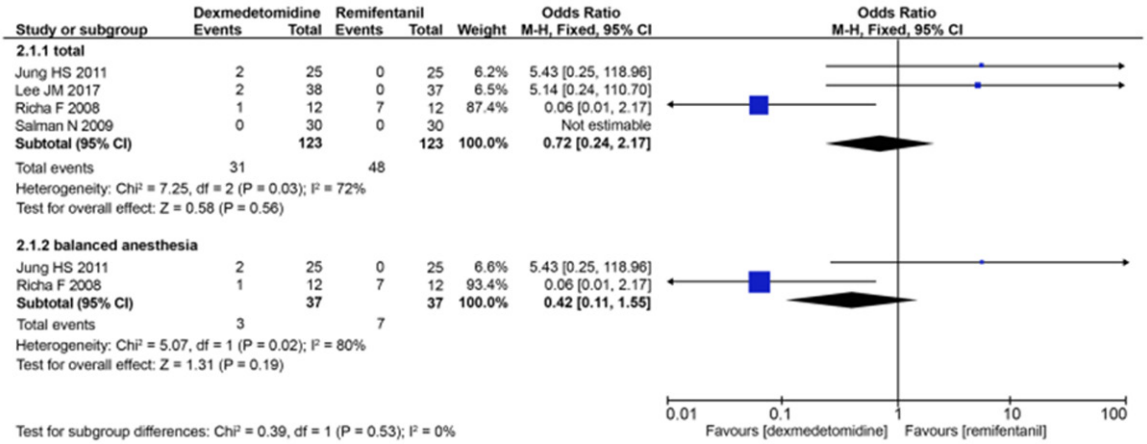

Figure 6. Incidence of postoperative and intraoperative hypotension.

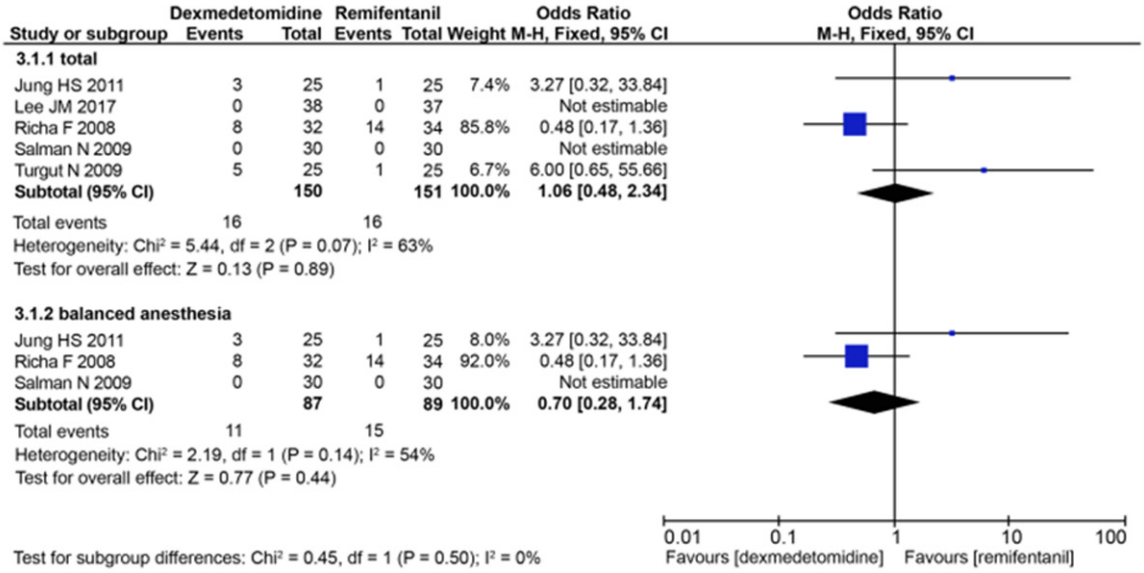

Figure 7. Incidence of postoperative and intraoperative bradycardia.

dine compared to those with intraoperative administration of remifentanil.

Incidence of intraoperative and postoperative bradycardia is described in five RCTs [17, 19, 21, 27, 28] (dexmedetomidine, n = 150; remifentanil, n = 151). The meta-analysis demonstrated no significant difference in incidence of intraoperative and postoperative bradycardia in patients undergoing general anesthesia with intraoperative administration of dexmedetomidine compared to those with intraoperative administration of remifentanil (OR: 1.06, 95% CI: 0.48, 2.34, P = 0.89, I^2 = 63%; **Figure 7**).

Incidence of postoperative vomiting: Incidence of postoperative vomiting is described in six RCTs [18, 19, 21, 24, 27, 29] (dexmedetomidine, n = 215; remifentanil, n = 219). The meta-analysis demonstrated a significantly decreased incidence of postoperative vomiting in patients undergoing general anesthesia with intraoperative administration of dexmedetomidine compared to those with intraoperative administration of remifentanil (OR: 0.42, 95% CI: 0.21, 0.85, P = 0.02, I^2 = 14%; **Figure 8**).

Incidence of postoperative shivering: Incidence of postoperative shivering is described in four RCTs [17, 19, 27, 28] (dexmedetomidine, n = 141; remifentanil, n = 145). The meta-analysis demonstrated no significant difference in incidence of postoperative shivering in patients

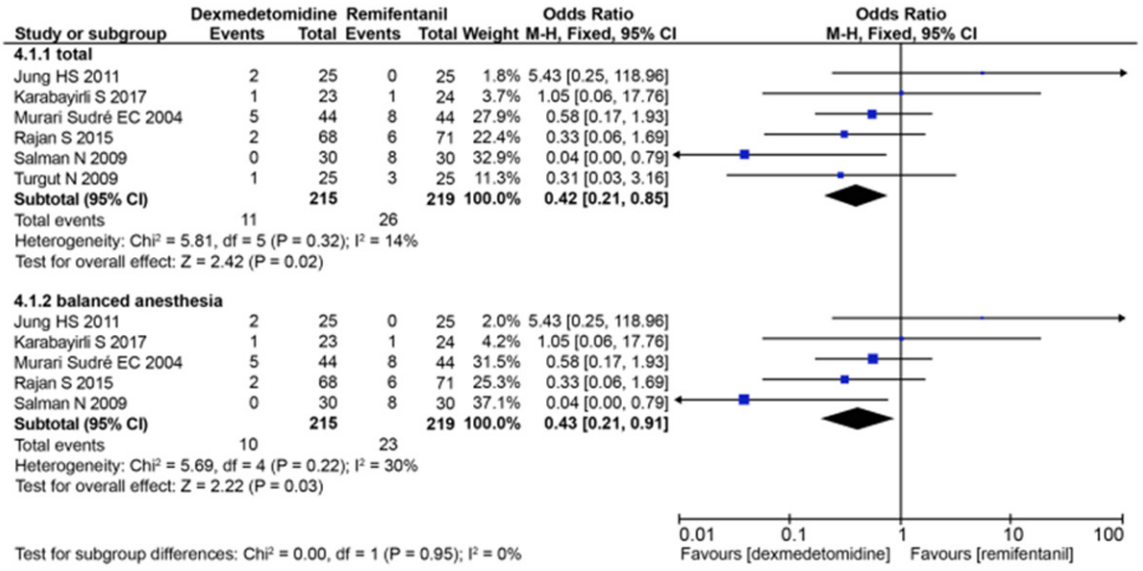

Figure 8. Incidence of postoperative vomiting.

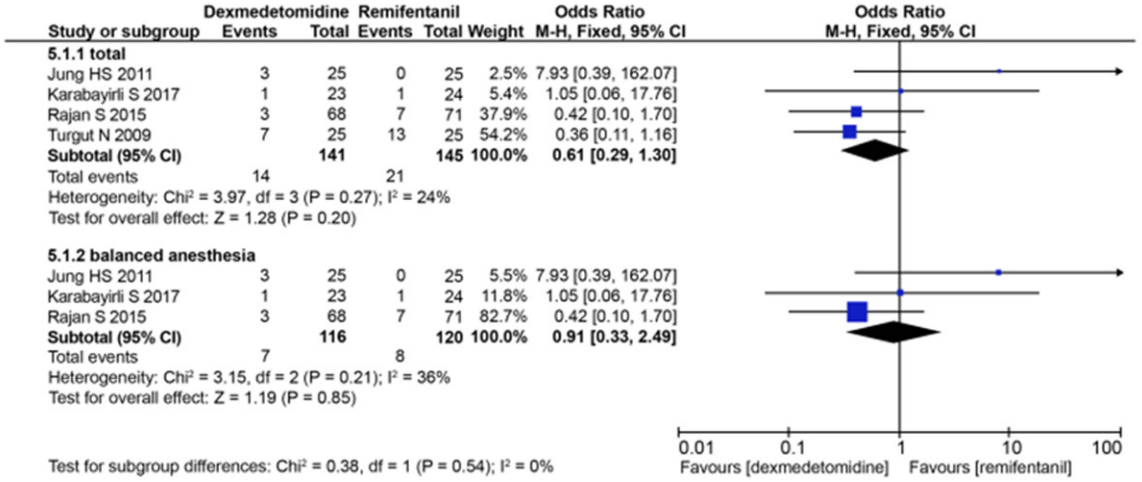

Figure 9. Incidence of postoperative shivering.

undergoing general anesthesia with intraoperative administration of dexmedetomidine compared to those with intraoperative administration of remifentanil (OR: 0.61, 95% CI: 0.29, 1.30, P = 0.20, I^2 = 24%; **Figure 9**).

Subgroup analysis

Subgroup analyses were stratified by protocol for anesthesia; the four RCTs that administered total intravenous anesthesia without inhaled anesthetics [17, 21-23] were excluded, and the meta-analyses were repeated in patients administered balanced anesthesia only. Intraoperative dexmedetomidine administration decreased the requirement for rescue analgesics (OR: 0.47, 95% CI: 0.24, 0.94, P = 0.03, I^2 = 0%), postoperative VAS score (MD: -1.81, 95% CI: -2.55, -1.06, P < 0.00001, I^2 = 76%), and incidence of postoperative vomiting (OR: 0.43 95% CI: 0.21, 0.91, P = 0.03, I^2 = 30%) compared to intraoperative remifentanil administration in patients undergoing balanced anesthesia. There were no significant differences in incidence of intraoperative and postoperative hypotension (OR: 0.42, 95% CI: 0.11, 1.55, P = 0.19, I^2 = 80%), incidence of intraoperative and postoperative bradycardia (OR: 0.70, 95% CI: 0.28,

1.74, P = 0.44, I^2 =54%), or incidence of postoperative shivering (OR: 0.91, 95% CI: 0.33, 2.49, P = 0.85, I^2 = 36%) in these patients.

Discussion

The use of intraoperative remifentanil causes postoperative discomfort in patients due to opioid-induced hyperalgesia [4]. Suppressed reuptake or increased release of excitatory neurotransmitters including glutamate, aspartate, and substance P [30], and the N-methyl-D-aspartate (NMDA) receptor and its ligands glutamate and aspartate are important in opioid-induced hyperalgesia [31]. Dexmedetomidine prevents hyperalgesia by modulating the expression, membrane trafficking, and function of NMDA receptors [32-34], provides an analgesic effect by acting on α2 adrenergic receptors in the spinal cord, and maintains normal nociceptive responses.

Some studies indicate that dexmedetomidine lacks analgesic efficacy [35, 36]. In particular, a plasma concentration of 1.23 ng/ml dexmedetomidine did not provide adequate analgesia to heat or electrical stimuli in healthy volunteers [35], suggesting that additional analgesic drugs may be needed during the intraoperative period to enhance analgesia in surgical patients administered intraoperative dexmedetomidine. One study reported that patients scheduled for vertebroplasty or kyphoplasty who received intraoperative dexmedetomidine required additional fentanyl during surgery compared to those who received intraoperative remifentanil [17]. Despite these reports, our study demonstrated a significant decrease in the requirement for rescue analgesia in patients that received intraoperative administration of dexmedetomidine versus remifentanil.

The most common side effects of intraoperative dexmedetomidine are hypotension and bradycardia due to its impact on hemodynamic stability. In the current study, most studies reported no significant difference in intraoperative blood pressure and heart rate in patients undergoing general anesthesia with intraoperative administration of dexmedetomidine compared to those with intraoperative administration of remifentanil. However, some studies [17, 27] indicated that intraoperative dexmedetomidine lowered blood pressure and heart rate compared to intraoperative remifentanil. In two studies, the maintenance dose of remifentanil was less than 0.1 μg/kg/min, which may minimize hemodynamic effects. In another study, remifentanil lowered mean arterial pressure and heart rate during tympanoplasty. The authors proposed that remifentanil induces a consistent and sustained controlled hypotension, potent analgesia and decreased middle-ear blood flow.

Dexmedetomidine has a biphasic hemodynamic effect [15, 16]. A loading dose of dexmedetomidine causes a peak concentration, leading to stimulating α2-receptors in vascular smooth muscle, reducing heart rate and causing reflexive vasoconstriction and hypertension [16]. At lower concentrations, dexmedetomidine stimulates α2-receptors in vascular endothelial cells, and increases vagal activity, causing vasodilatation [37]. Our study demonstrated no significant difference in the incidence of intraoperative or postoperative hypotension in patients that received intraoperative administration of dexmedetomidine versus remifentanil. Since the majority of the adverse events associated with dexmedetomidine administration occur during or shortly after the loading dose, a lower loading infusion rate during the first hour or eliminating the loading dose may reduce the incidence of hypotension [38].

Dexmedetomidine leads to reduced cardiac output because it decreases heart rate [39]; specifically, heart rate decreases 16-30% from baseline at plasma drug concentrations > 1-3 ng/ml [16, 40, 41]. Several studies suggested that intraoperative dexmedetomidine should be used with caution in elderly patients > 65 years of age because of the risk of bradycardia and hypotension [42-45]. The studies included in this review excluded patients with congestive heart failure, bradycardia (heart rate < 50 bpm), or atrioventricular block. As our findings are only relevant to surgical patients with good cardiac function, who have a lower incidence of bradycardia and milder impairment of cardiac function as a result of dexmedetomidine or remifentanil administration, our data should be interpreted with caution.

The current study revealed a significantly lower incidence of postoperative vomiting in patients that received intraoperative administration of dexmedetomidine versus remifentanil. Our pooled analysis only included RCTs that reported

incidence of postoperative vomiting in order to reduce heterogeneity; however, data may have been confounded as postoperative nausea and vomiting (PONV) was ambiguously defined in individual trials. Opioids can stimulate opioid receptors in gastrointestinal smooth muscle, act on opioid receptors in the brain stem, and lead to PONV. Dexmedetomidine antiemetic effects may result from inhibition of the sympathetic nervous system and catecholamine release by its actions on α2-adrenoreceptors. In accordance with our findings, a previous review reported that dexmedetomidine prevented PONV in patients undergoing general anesthesia [46].

The current study showed no significant difference in the incidence of postoperative shivering in patients that received intraoperative administration of dexmedetomidine versus remi-0fentanil. In contrast, some studies suggest that intraoperative dexmedetomidine has good efficacy in the prevention of postoperative shivering [47, 48]. Shivering is caused by systemic vasodilation and dysfunction in thermotaxic centers, leading to increased heat exchange and decreased core temperature. The role of dexmedetomidine in postoperative shivering remains controversial, as dexmedetomidine can activate α2B-receptors in the hypothalamus, which mediate anti-shivering and suppress the spontaneous firing of neurons.

Anesthesia protocol may impact postoperative pain. In the current study, subgroup analyses suggested that intraoperative dexmedetomidine is comparable or superior to intraoperative remifentanil for alleviating postoperative pain in balanced anesthesia.

Limitations

This study has several limitations. First, we only assessed the effect of intraoperative dexmedetomidine on blood pressure and heart rate using descriptive analyses due to the missing data. However, hypotension and bradycardia were used as surrogate variables for quantitative analyses. Second, there was evidence of heterogeneity between the included RCTs, which may have been caused by different types of surgery, demographic and clinical characteristics of the patients, timing of administration of rescue analgesics, concentrations of dexmedetomidine and remifentanil, and small sample size. However, subgroup analyses that stratified RCTs by protocol for anesthesia demonstrated results that were similar to the overall findings, suggesting that the methodology and outcomes of this meta-analysis are robust.

Conclusion

Data from this meta-analysis, which included a limited number of RCTs, indicate that dexmedetomidine has superior safety and efficacy for alleviating postoperative pain compared to remifentanil in patients undergoing general anesthesia. Dexmedetomidine administration was associated with less postoperative vomiting and therefore may improve recovery after surgery in this patient population. Additional high-quality studies with a large sample size are required to confirm these findings.

Disclosure of conflict of interest

None.

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Appendix

Search strategy

#1 dexmedetomidine
#2 MPV-1440
#3 MPV 1440
#4 MPV1440
#5 Precedex
#6 Hospira Brand of Dexmedetomidine Hydrochloride
#7 Dexmedetomidine Hydrochloride
#8 Hydrochloride, Dexmedetomidine
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 remifentanil [Supplementary Concept]
#11 3-(4-methoxycarbonyl-4-((1-oxopropyl)phenylamino)-1-piperidine)propanoic acid methyl ester
#12 remifentanil monohydrochloride
#13 GI 87084B
#14 GI87084B
#15 GI-87084B
#16 remifentanil hydrochloride
#17 Ultiva
#18 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#19 random*[tw]
#20 #9 AND #18 AND #19