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Comparison of efficacy and safety profiles of perioperative sufentanil and remifentanil: a systematic review and meta-analysis with trial sequential analysis

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Abstract

Background Sufentanil and remifentanil are commonly used during general anesthesia. This systematic review and meta-analysis with trial sequential analysis of randomized controlled trials (RCTs) aims to comprehensively evaluate and compare the efficacy and safety profiles of perioperative sufentanil and remifentanil administration in patients undergoing surgery under general anesthesia.

Methods This study was registered in INPLASY (INPLASY202270070). A comprehensive search was performed using MEDLINE, EMBASE, CENTRAL, Web of Science, and Google Scholar to identify all RCTs comparing the efficacy of the intraoperative use of sufentanil to that of remifentanil. The primary outcome were the postoperative pain scores measured using visual analogue scale (VAS) or numerical rating scales (NRS). The secondary outcomes were the postoperative analgesic use, time to first analgesic need, intraoperative hemodynamic profiles, postoperative nausea and vomiting (PONV), incidence of respiratory depression, and recovery characteristics.

Results A total of 31 studies were included in the final analysis. Postoperative pain score was significantly higher in remifentanil group than that in sufentanil group, with a small effect size (standardized mean difference [SMD] = -0.47; 95% confidence interval [CI] = 0.24 to 0.70). Postoperative analgesic amount used was lower in sufentanil group than that in remifentanil group, with a medium effect size (SMD = 0.55; 95% CI = 0.12 to 0.99). In terms of hemodynamic profiles, intraoperative systolic blood pressure (mean difference [MD] = -6.30; 95% CI = -10.76 to -1.85), mean arterial pressure (MD = -6.38; 95% CI = -10.25 to -2.51), and heart rate (MD = -4.16; 95% CI = -6.65 to -1.68) were lower in remifentanil group than in sufentanil group. Incidence of postoperative nausea (relative risk = 1.39; 95% CI = 1.13 to 1.71) was higher in remifentanil group than in sufentanil group. The remifentanil group showed a faster recovery profile than the sufentanil group.

Conclusions Compared with remifentanil, sufentanil demonstrated superior efficacy in postoperative pain management and superior safety profiles with respect to postoperative nausea and hemodynamic stability; however, remifentanil showed a faster recovery profile.

Systematic review registration International Prospective Register of Systematic Reviews (INPLASY), NPLASY202270070.

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Keywords Anesthesia, General, Sufentanil, Systematic review, Randomized controlled trial, Remifentanil

Introduction

Intravenous opioids are commonly used for pain relief during general anesthesia and are crucial for perioperative acute pain management. These opioids facilitate intraoperative patient comfort and influence the overall postoperative experience [1]. Among them, remifentanil and sufentanil have gained significant attention due to their distinct pharmacological properties. Remifentanil, a μ -opioid receptor agonist, is characterized by rapid onset and a very short duration of action given its rapid degradation by non-specific plasma and tissue esterases [2, 3]. For remifentanil, the time for a 50% decrease in blood concentration after discontinuation of a steady-state infusion is consistently 4 min, regardless of the infusion duration [4]. This distinctive pharmacokinetic profile allows precise titration, minimizing the risk of residual sedation and delayed recovery [5]. Sufentanil, a fentanyl derivative, offers rapid onset and unique pharmacological properties [6, 7]. Its high lipophilicity and μ -opioid receptor affinity facilitate achievement of potent analgesia at lower doses, which may reduce side effects such as respiratory depression and nausea [8–10].

Effective perioperative pain management is crucial for facilitating patient comfort and early mobilization, reducing postoperative complications, and optimizing overall surgical outcomes. This systematic review and meta-analysis with trial sequential analysis of randomized controlled trials (RCTs) aimed to evaluate and compare the efficacy and safety profiles of perioperative sufentanil and remifentanil administration in patients undergoing surgery under general anesthesia.

Methods

The protocol of this study was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) and registered in the International Prospective Register of Systematic Reviews (INPLASY; registration number: INPLASY202270070). Furthermore, this study was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [11].

Inclusion and exclusion criteria

The inclusion and exclusion criteria were determined prior to this study being conducted. We included RCTs comparing the efficacy and safety profiles of sufentanil and remifentanil. The study details were as follows:

1. Patients (P): All patients receiving elective surgery under general anesthesia.
2. Intervention (I): Intraoperative administration of sufentanil.
3. Comparison (C): Intraoperative administration of remifentanil.
4. Outcome measurements (O): The primary outcomes were the postoperative pain score measured using a visual analogue scale (VAS), numerical rating scale (NRS), pain relief score (PRS), or ICU pain score. The secondary outcomes were the postoperative analgesic usage; time to first analgesic requirement; and perioperative hemodynamic variables including systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Furthermore, we evaluated the incidence of postoperative nausea (PON), postoperative vomiting (POV), postoperative nausea and vomiting (PONV), and recovery time. Recovery time was delineated by time to extubation, time to eye opening, time to spontaneous respiration, time to emergence, and time to orientation.
5. Study design (SD): RCTs.

We excluded data from conference abstracts, posters, case reports, case series, editorials or letters to the editor, reviews, and animal or laboratory studies.

Systematic search

A comprehensive, systematic search for RCTs comparing the efficacy and safety of perioperative sufentanil and remifentanil in patients undergoing elective surgery under general anesthesia was performed by two independent investigators (HJK and CGJ). Furthermore, we included studies comparing the use of four opioids: sufentanil, remifentanil, alfentanil, and fentanyl. Ovid-MEDLINE, Ovid-EMBASE, CENTRAL, Web of Science, and Google Scholar were searched for relevant articles published from inception to August 31, 2023 (inclusive), and updated on November 15, 2023.

Search terms comprised a combination of free text; Medical Subject Headings; and Emtree terms for “sufentanil,” “remifentanil,” and “randomized controlled trial.” Clinical trial registries were implemented to identify completed but unpublished RCTs, while Open SIGLE was used to search the gray literature. Additionally, a manual search through the reference lists of the retrieved articles was performed. The search strategy is described in the Supplementary file.

Study selection

Supplementary Figure 1 presents a schematic flow diagram of the study selection. Two investigators (KHJ and CGJ) separately scanned the titles and abstracts of the retrieved reports via the aforementioned search algorithms. Subsequently, the full text of articles considered to be eligible after the initial screening was independently evaluated by the same investigators, with disagreements being settled through discussion. If consensus could not be achieved, a third investigator (KH) was consulted.

Data extraction

Using a predefined, standardized data collection form, two researchers (KHJ and CGJ) independently retrieved relevant data from the included studies, followed by cross-checking the findings. In case of disagreements, a consensus was reached through discussion between the two investigators. In case a consensus could not be reached, a third investigator (KH) was consulted. The data extraction form included the following items: (1) title; (2) name of first author; (3) journal name; (4) year of publication; (5) study design; (6) clinical trial registration; (7) country; (8) language; (9) risk of bias; (10) conflicts of interests; (11) number of patients included; (12) sex; (13) age; (14) height of patients; (15) weight of patients; (16) duration of anesthesia; (17) physical status according to the American Society of Anesthesiologists classification; (18) inclusion criteria; (19) exclusion criteria; (20) anesthesia type; (21) surgery type; (22) agent of anesthesia induction; (23) agent of anesthesia maintenance; (24) dose or experimental drug (sufentanil or remifentanil); (25) administration methods of the experimental drug (bolus administration, continuous infusion, or target-controlled infusion [TCI]); (26) postoperative pain score; (27) postoperative analgesic amount; (28) incidence of need for postoperative analgesics; (29) time to first analgesic requirement; (30) perioperative hemodynamic variables such as SBP, DBP, mean arterial pressure (MAP), and HR; (31) incidence of PON, POV, and PONV; (32) number of patients requiring rescue anti-emetics; (33) cases of respiratory depression; (34) SpO₂ level; and (35) time to extubation, eye opening, spontaneous respiration, orientation, and emergence.

Data were initially extracted from tables, figures, or text or were calculated from the available data, if possible. Data presented only in a graphical format were derived from the open-source software Plot Digitizer (version 2.6.8; <http://plotdigitizer.sourceforge.net>). The corresponding authors were contacted via email to obtain pertinent information in case of missing or insufficient data.

Statistical analysis

Conventional meta-analysis

Meta-analyses were conducted using Comprehensive Meta-Analysis version 2.0 (Englewood, NJ, USA, 2008). Two authors (HJK, HK) independently performed data entry into the software. The pooled risk ratio (RR) for binary variables and mean difference (MD) or standardized mean difference (SMD) for quantitative data and their 95% confidence intervals (CIs) were calculated for each outcome. Heterogeneity was assessed using the chi-squared test, Higgins' I^2 , τ using the DerSimonian-Laird estimator, and prediction interval (PI). If τ was 0.0, PI was not calculated [12]. We regarded heterogeneity as substantial if I^2 was greater than 50% or P -value for the chi-square test (P_{chi^2}) was less than 0.10 [13]. We used random-effects meta-analysis for combining data as we expected clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials. To explore heterogeneity, we performed sensitivity analysis with removal of one study each time to determine whether it altered our results. Furthermore, we also conducted sensitivity analysis with respect to heterogeneous outcomes. We conducted meta-regression analysis age, duration of operation or anesthesia, and ratio of sufentanil and remifentanil dose (sufentanil dose/remifentanil dose used) as independent variables and each outcomes as dependent variables. If studies per outcome was less than 10, meta-regression was not performed.

If the reported data were median (P_{25} – P_{75}), median (range), or mean (standard error of mean), mean and standard deviation were calculated from these values [14, 15]. Since data measured at multiple time points were dependent on each other and multiple comparisons at each time point would increase the possibility of type I error, we combined outcomes at multiple time points and performed analysis using the pooled combined outcomes.

We calculated the number needed to treat (NNT) based on the absolute risk reduction, as an estimate of the overall clinical impact of the intervention.

Publication bias was evaluated using funnel plots and Egger's linear regression test. Publication bias was indicated by an asymmetrical funnel plot or a P value < 0.100 in Egger's test, in which case trim and fill analysis was performed. In case of < 10 included studies, publication bias was not evaluated [16].

Trial sequential analysis

Conventional meta-analysis runs the risk of random errors due to sparse data. Trial sequential analysis (TSA) is a methodology that comprises calculation of the required information size (RIS) for a meta-analysis

with a threshold for statistical significance, which controls the risk of potential false-positive and false-negative findings. Therefore, we performed TSA of the outcomes to calculate the RIS and assess whether our results were conclusive. We used a random effects model to construct the cumulative z -curve. TSA was performed to maintain an overall 5% risk of a type I error.

When the cumulative z -curve crossed the trial sequential monitoring boundary or entered the futility area, it suggested a sufficient evidence level for accepting or rejecting the anticipated intervention effect, with no further studies being required. If the z -curve did not cross any boundaries and the RIS was not reached, the evidence was considered inconclusive, indicating the requirement of more studies.

For dichotomous outcomes, we estimated the RIS based on the observed proportion of patients with an outcome in the remifentanyl group (the cumulative proportion of patients with an event relative to the number of patients in the remifentanyl groups), an RR reduction of 30% in the sufentanyl group, an alpha of 5% for all outcomes, a beta of 20%, and the observed diversity as suggested by the included trials. For quantitative outcomes, we used the observed standard deviation (SD) in the trial sequential analysis, a mean difference of the observed SD/3, an alpha of 5% for all outcomes, a beta of 10%, and the observed diversity as suggested by the included trials.

Validity scoring

Using the revised Cochrane risk of bias tool for randomized trials (RoB 2.0 version), the quality of each study was critically appraised by two separate investigators (GJC and KHJ) [17]. Primarily, each domain was evaluated and rated as follows: (D1) bias derived from the randomization process, (D2) bias due to deviations from the intended interventions, (D3) bias resulting from missing data regarding outcomes, (D4) bias due to outcome measurements, and (D5) bias due to the selection of the reported result. Next, the overall risk of bias was assessed as follows: (1) low risk, which occurs when the risk of bias for all domains was low; (2) high risk, which occurs when the risk of bias for at least one domain was high or the risk of bias for multiple domains was of some concern; and (3) some concern, which occurs when the overall judgment was neither low nor high.

When consensus could not be established, disputes were resolved through discussions with a third investigator (KH). The risk of bias for each outcome was visualized using traffic light plots generated through the ROBVIS tool (<https://www.riskofbias.info/welcome/robvis-visualization-tool>).

Quality of evidence

The guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system were applied to evaluate the quality of evidence. The guidelines involve the sequential assessment of the evidence quality, evaluation of the risk–benefit balance, and subsequent appraisal of the strength of the recommendations [18]. The evidence quality was graded as follows: (1) high, indicating that the confidence in the effect estimate was unlikely to alter with further research; (2) moderate, indicating that further research was likely to significantly alter confidence in the effect estimate and might alter the estimate; (3) low, indicating that further research was likely to significantly change confidence in the effect estimate and alter the estimate; and (4) very low, indicating that no effect estimate was certain.

Results

Literature search and study selection

The initial search of the databases yielded 417 articles; moreover, 13 additional articles were identified after a manual search of the reference lists. After removing duplicates ($n=66$), 364 studies were retained. Among them, 303 studies were excluded after reviewing the titles and abstracts. The kappa value for literature selection between the two investigators at this stage of study selection was 0.938.

After a full-text review of the 61 remaining articles, 30 articles were excluded for the following reasons: non-RCTs ($n=8$) [19–26], animal studies ($n=6$) [27–32], no outcome of interest ($n=9$) [33–41], non-general anesthesia ($n=6$) [42–47], and missing data ($n=1$) [48]. The kappa value for selecting articles between the two investigators was 0.902. Finally, 31 studies (1684 patients) were included in the final analysis (Fig. 1).

Study characteristics

Table 1 describes the characteristics of the 31 eligible studies. The surgery types included abdominal surgery [49–57], neurosurgery [58–63], cardiac surgery [64–68], breast surgery [69, 70], dental surgery [71, 72], retinal surgery [73], carotid surgery [74], thyroid surgery [75], spinal surgery [76], plastic surgery [77], colectomy or pedicle screw inter-fixation [78], and not reported [79]. Apart from two studies involving pediatric patients [77, 79], the remaining studies focused on adults. Nineteen studies utilized total intravenous anesthesia [52, 54, 57–60, 62, 63, 65–70, 72, 73, 75, 76, 78, 79], while the remaining studies employed volatile anesthetics. Among the volatile anesthetics used, four studies each used sevoflurane [49, 50, 55, 78], desflurane [51, 53, 56, 71], and iso-flurane [61, 64, 74, 77]. The administration methods for

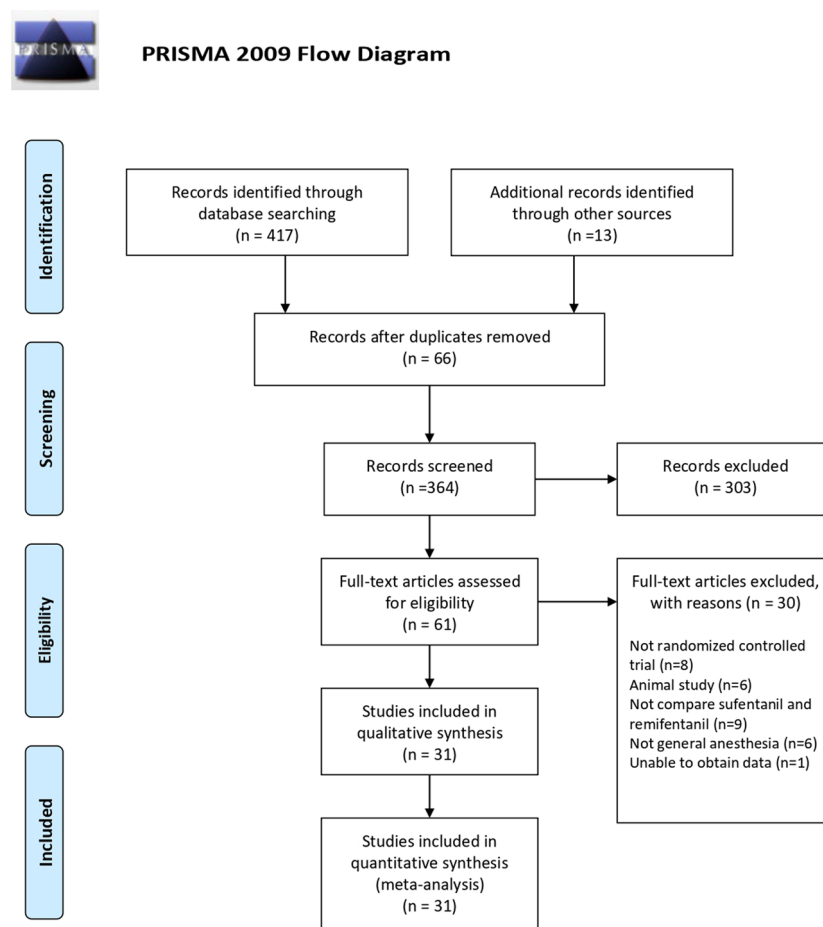


Fig. 1 PRISMA flow diagram of the search for randomized controlled trials as well as the inclusion and exclusion criteria

remifentanil and sufentanil varied across studies. Eleven studies performed continuous intravenous (IV) infusion of both remifentanil and sufentanil [49, 50, 54, 55, 59–62, 65, 70, 75], while nine studies performed TCI of both drugs [51, 53, 56, 57, 63, 68, 72, 78, 79]. In another nine studies, remifentanil was administered via continuous IV infusion, while sufentanil was initially administered as a loading dose followed by additional bolus administrations, as required [52, 58, 64, 66, 67, 69, 73, 74, 76]. Both remifentanil and sufentanil were administered as bolus loading doses in two studies [71, 77].

Postoperative pain score

Eighteen studies (914 patients) reported the postoperative pain scores, with their characteristics being described in Supplementary Table 1. Among them, 16 studies (795 patients) measured postoperative pain scores using quantitative variables such as VAS [51, 53, 56, 60, 65, 74, 79], NRS [58, 63, 64], verbal rating scale [49, 52, 73], PRS [76], simple numerical scale [72], or ICU

pain score [66]. The remaining two studies (119 patients) reported postoperative pain scores using qualitative variables ($\geq$ VAS4 vs. $<$ VAS4 or $\geq$ VAS3 vs. $<$ VAS3) [54, 71]. Accordingly, we separately analyzed quantitatively or qualitatively measured postoperative pain scores.

Quantitative postoperative pain scores were significantly higher in the remifentanil group than in the sufentanil group, with a small effect size (SMD, 0.47; 95% CI, 0.24–0.70; $I^2=59.95$; $P_{\text{chi}^2}=0.001$; $\tau=0.36$; 95% PI, –0.30–1.24) (Fig. 2A). For postoperative pain score reported using qualitative variables, there was no evidence of differences between the two groups (RR, 4.38; 95% CI, 0.28–68.34; $I^2=87.39$; $P_{\text{chi}^2}=0.005$; $\tau=1.87$; 95% PI, 0.68–28.29). However, there was a significant difference with respect to NNT (number needed to treat benefit [NNTB], 2.3; 95% CI, NNTB 1.7 to NNTB 3.8) (Supplementary Figure 2A). In the meta-regression, age, duration of operation or anesthesia, and ratio of sufentanil and remifentanil dose were significantly correlated with quantitative postoperative pain scores (slope, –0.00859; 95% CI, –0.01708 to –0.00010;

Table 1 Study characteristics of included studies

Author, year	Country	Type of Surgery	Group	Age (yrs)	Sex (M/F)	Duration of operation (min)	Duration of anesthesia (min)	ASA-PS	Anesthesia	Dosage	Rescue analgesics	PCA
Brockmann, 2000 [71]	Germany	Retinal surgery	Remifentanyl	64.2 [6.0]	8/3	108 [7.1]	NR	NR	TIVA	0.25ug/kg/min CIV	IV Piritramide	NR
Casati, 2000 [47]	Italy	Elective upper abdominal surgery	Sufentanyl	61.5 [11.2]	6/5	139 [93]				1ug/kg bolus		
			Remifentanyl	55 (27–70)	6/9	210 (90–700)	NR	NR	Sevoflurane	0.15–0.25ug/kg/min CIV	NR	Epi
			Sufentanyl	59 (39–70)	11/4	250 (80–560)				0.01–0.025ug/kg/min CIV		
Casati, 2001 [48]	Italy	Abdominal surgery	Remifentanyl	56 [13]	6/9	NR	NR	NR	Sevoflurane	0.1ug/kg/min CIV	NR	NR
			Sufentanyl	60 [10]	11/4					0.01ug/kg/min CIV		
Engoren, 2001 [62]	USA	Cardiac surgery	Remifentanyl	66 (59–72)	17/12	NR	NR	NR	Isoflurane	0.05–1ug/kg/min CIV	IV Morphine	No
			Sufentanyl	68 (60–74)	17/11					1–4ug/kg bolus		
			Fentanyl	58 (51–66)	23/10					7–10ug/kg bolus		
Mouren, 2001 [72]	France	Carotid surgery	Remifentanyl	66 [13]	21/6	98 [20]	148[25]	NR	Isoflurane	0.5–1ug/kg/min CIV	IV Morphine	No
			Sufentanyl	68 [10]	26/3	92 [18]	137[18]			0.5ug/kg bolus		
Derrode, 2003 [49]	France	Colorectal surgery	Remifentanyl	64 (47–85)	10/5	236 [96]	293[95]	3/11/1	Desflurane	TCI Ce 1–4 ng/mL	IV Morphine	IV
			Sufentanyl	70 (52–83)	9/6	223 [106]	278[105]	3/9/3		TCI Ce 0.25–0.5 ng/mL		
Gerlach, 2003 [56]	France	Craniotomy for supratentorial tumor resection	Remifentanyl	47 [14]	5/13	172 [11]	198[64]	NR	TIVA	0.2–0.35ug/kg/min CIV	IV Morphine	No
			Sufentanyl	53 [13]	6/11	169 [9]	180[66]			0.5ug/kg bolus		
Lentschene, 2003 [73]	Germany	Thyroid surgery	Remifentanyl	50 [15]	8/17	76 [22]	110[26]	NR	TIVA	0.2–1.5ug/kg/min CIV	IV Morphine	No
			Sufentanyl	48 [13]	3/22	87 [33]	121[35]			0.2ug/kg/hr CIV		
Damen, 2004 [50]	Netherlands	Laparoscopic cholecystectomy	Remifentanyl	43	10/25	43 [13]	NR	NR	TIVA	12.5–25ug/kg/hr CIV	NR	No
			Sufentanyl	44	8/27	48 [13]				0.5ug/kg bolus		
Grottke, 2004 [74]	Germany	Spinal surgery	Remifentanyl	54 [15]	6/12	4.1 [1.8]	5.6[1.9]	NR	TIVA	0.2–0.5ug/kg/min CIV	NR	IV
			Sufentanyl	60 [11]	6/12	4.4 [2.3]	6[2.3]			0.1–1ug/kg bolus		
			Desflurane + Remifentanyl	45 [15]	5/13	4.1 [1.8]	5.8[2.1]			0.2–0.5ug/kg/min CIV		

Table 1 (continued)

Author, year	Country	Type of Surgery	Group	Age (yrs)	Sex (M/F)	Duration of operation (min)	Duration of anesthesia (min)	ASA-PS	Anesthesia	Dosage	Rescue analgesics	PCA
Djian, 2006 [57]	France	Supratentorial neurosurgical procedure	Remifentanyl	45.7 [11.9]	11/18	4.1 [1.8]	NR	9/10/10	TIVA	0.25ug/kg/min CIV	NR	No
Guggenberger, 2006 [63]	USA	CABG	Sufentanyl	55.3 [8.9]	12/19	4.4 [2.3]		5/15/11		0.0025ug/kg/min CIV		
			Remifentanyl	66.8 [7]	24/1	238 [39.6]	NR	4/21	TIVA	0.5–1.5ug/kg/min CIV	NR	IV
			Sufentanyl	67.5 [7.2]	23/2	234.4 [42.9]		3/22		20–40 ng/kg/min CIV		
Bilotta, 2007 [58]	Italy	Craniotomy for supratentorial expanding lesions resection	Remifentanyl	55 [14]	13/17	244 [50]	259[60]	18/8/4	TIVA	0.1–0.5ug/kg/min CIV	IV Paracetamol	No
			Sufentanyl	54 [11]	14/15	256 [46]	273[58]	16/9/4		0.01–0.05ug/kg/min CIV		
			Remifentanyl	36 (20–57)	4/16	NR	99[17]	NR	Desflurane	TCI Ce 4 ng/mL	IV Paracetamol	IV
Baerdemaeker, 2007 [51]	Belgium	Laparoscopic gastric banding	Sufentanyl	41 (19–57)	2/18		109[19]			TCI Ce 0.2 ng/mL		
Lison, 2007 [59]	Germany	Craniotomy for supratentorial expanding lesions resection	Remifentanyl	57.6 [11.8]	46/10	338 (297–368)	NR	0/54/2	Isoflurane	1ug/kg/min CIV	IV piritramide	No
			Sufentanyl	58.7 [11.3]	44/13	333 (295–370)		1/55/1		0.02–1ug/kg/min CIV		
			Remifentanyl	56.1 [13.48]	20/18	240 [14]	302[15]	NR	TIVA	0.1–2ug/kg/min CIV	IV Tramadol	IV
Martorano, 2008 [60]	Italy	Neurosurgery	Sufentanyl	52.8 [12.78]	15/16	211 [15]	280[17]			0.005–0.04ug/kg/min CIV		
Simoni, 2008 [52]	Brazil	Non-gynecological laparoscopic surgery	Remifentanyl	42 [12]	7/23	NR	95[9]	25/5	TIVA	0.3–0.5ug/kg/min CIV	IV Tramadol	No
			Sufentanyl	46 [12]	15/15		105[26]	26/4		0.5ug/kg/hr CIV		
			Remifentanyl	6.2 [1.5]	35/15	NR	NR	NR	Isoflurane	2ug/kg bolus	NR	No
Liao, 2009 [75]	China	Plastic surgery	Sufentanyl	6.2 [1.4]	32/18	NR				0.2ug/kg bolus		
Zhang, 2009 [53]	China	Major abdominal surgery	Remifentanyl	45 [15]	20/10	NR	NR	22/8	Sevoflurane	0.1ug/kg/min CIV	NR	NR
			Sufentanyl	43 [13]	13/17			23/7		0.01ug/kg/min CIV		
			Fentanyl	44 [12]	16/14			23/7		0.1ug/kg/min CIV		
Bidgoli, 2011 [54]	Netherlands	Laparoscopic adjustable gastric banding	Remifentanyl	40 [10]	9/41	79 [26]	127[31]	NR	Desflurane	TCI Ce 3–4 ng/mL	NR	IV
			Sufentanyl	36 [10]	5/45	79 [35]	128[35]			TCI Ce 0.3–0.4 ng/mL		

Table 1 (continued)

Author, year	Country	Type of Surgery	Group	Age (yrs)	Sex (M/F)	Duration of operation (min)	Duration of anesthesia (min)	ASA-PS	Anesthesia	Dosage	Rescue analgesics	PCA
Yang, 2011 [76]	China	Colectomy or pedicle screw interfix	Remifentanyl	68 [12]	7/13	192 [60]	213[59]	NR	Sevoflurane	TCI Ce 2–4 ng/mL	IV Morphine	NR
Lili, 2012 [77]	China	NR	Sufentanyl	68 [11]	7/13	221 [91]	247[93]			TCI Ce 0.2–0.4 ng/mL		
			Remifentanyl	11 [4]	12/11	41.2 [4.1]	NR	NR	TIVA	TCI Ce 1–2 ng/mL	NR	NR
			Sufentanyl	10 [4]	11/12	40.3 [3.4]				TCI Ce 0.1–0.2 ng/mL		
Yeganeh, 2013 [55]	Iran	Traumatic abdominal surgery	Remifentanyl	31.3 [8.4]	11/9	NR	NR	18/2	TIVA	TCI Ce 2 ng/mL	NR	NR
			Sufentanyl	33.5 [6.3]	12/8			17/3		TCI Ce 0.2 ng/mL		
Macario-Gerard, 2014 [70]	France	Ambulatory multiple third molar avulsion	Remifentanyl	21.5 [5.6]	11/19	NR	NR	25/3/2	TIVA	TCI Ce 2–5 ng/mL	IV Morphine	No
			Sufentanyl	19.8 [3.5]	13/17			24/6/0		TCI Ce 0.15–0.4 ng/mL		
Bhavsar, 2016 [64]	Denmark	GABG with or without aortic valve surgery	Remifentanyl	47.9 [12.8]	0/8	NR	NR	NR	TIVA	0.2–0.6ug/kg/min CIV	IV Morphine, alfentanil	NR
			Sufentanyl	43.9 [13.5]	0/8					1–2ug/kg bolus		
Ohnesorge, 2016 [67]	Germany	Mastectomy	Remifentanyl	47.9 (68–75)	21/9	NR	84.6[24.8]	NR	TIVA	0.4ug/kg/min CIV	IV Paracetamol	NR
			Sufentanyl	68.5 (64–75)	26/4		75.6[22.8]			0.25ug/kg bolus q1hr		
Rasmussen, 2016 [65]	Denmark	CABG with or without AVR	Remifentanyl	NR	NR	NR	NR	NR	TIVA	0.2–0.6ug/kg/min CIV	IV Paracetamol, ketorolac	NR
			Sufentanyl	68.5 (64–75)	26/4					1–2ug/kg bolus		
Ouyang, 2019 [68]	China	Mastectomy	Remifentanyl	NR	NR	120 [18.7]	NR	NR	TIVA	8–10ug/kg/hr CIV	NR	IV
			Sufentanyl			124 [15.2]				0.02–0.04ug/kg/min CIV		
Dolsan, 2020 [69]	France	Tooth extraction	Remifentanyl	24.5 [7.4]	NR	NR	NR	NR	Desflurane	3ug/kg bolus	IV Morphine, tramadol	No
			Sufentanyl	24.8 [6.7]						0.3ug/kg bolus		
Liu, 2020 [61]	China	Supratentorial glioma resection	Remifentanyl	47 [13]	14/8	284 (219–329)	333(285–380)	17/5	TIVA	TCI Ce 3–8 ng/mL	IV Hydromorphone	NR
			Sufentanyl	44 [10]	15/8	225 (200–282)	270(245–350)	20/3		TCI Ce 0.2–0.4 ng/mL		

Table 1 (continued)

Author, year	Country	Type of Surgery	Group	Age (yrs)	Sex (M/F)	Duration of operation (min)	Duration of anesthesia (min)	ASA-PS	Anesthesia	Dosage	Rescue analgesics	PCA
Poterman, 2020 [66]	Netherlands	Off-pump CABG	Remifentanyl Sufentanyl	67 [8] 64 [8]	23/7 23/7	NR NR	NR NR	NR NR	TIVA TIVA	TCI Ce 8 ng/mL TCI Ce 0.48 ng/mL	NR NR	NR NR

Values are expressed as mean [standard deviation], median (interquartile range), or absolute number
yrs Years, M Male, F Female, ASA-PS American Society of Anesthesiologists Physical Status, PCA Patient-controlled analgesia, IV Intravenous, NR Not reported, TIVA Total intravenous anesthesia, CIV Continuous intravenous infusion, TCI Target-controlled infusion, Ce Effect site concentration, ESWL Extracorporeal shock wave lithotripsy, CABG Coronary artery bypass graft, AVR aortic valve replacement

$P=0.04727$: slope, -0.00252 ; 95% CI, -0.00439 to -0.00065 ; $P=0.00817$: slope, 4.76018 ; 95% CI, 0.14402 to 9.37634 ; $P=0.04327$, respectively) (Supplementary Table 2, Supplementary Figure 3).

For quantitative postoperative pain score, TSA indicated that only 67.9% (795 of 1171 patients) of the RIS was accrued. The cumulative z -curve (depicted as the complete blue curve) crossed both the conventional test boundary (represented by the dotted red line) and the trial sequential monitoring boundary (indicated by the complete red curve) (Fig. 2B). For qualitative postoperative pain scores, the cumulative z -curve (depicted as the complete blue curve) did not cross the conventional test boundary (Supplementary Figure 2B).

Amount of postoperative analgesic used

Thirteen studies (738 patients) reported the amount of postoperative analgesic used, which was lower in the sufentanil group than in the remifentanil group, with a medium effect size (SMD, 0.55 ; 95% CI, 0.12 – 0.99 ; $I^2=88.39$; $P_{\text{chi}^2}<0.001$; $\tau=0.82$; 95% PI, -1.25 – 2.35) (Fig. 2C).

In the meta-regression, duration of operation or anesthesia and ratio of sufentanil and remifentanil dose were significantly correlated with amount of postoperative analgesic used (slope, 0.00084 ; 95% CI, 0.00067 to 0.00396 ; $P=0.00591$: slope, -8.11301 ; 95% CI, -12.39657 to -3.82944 ; $P=0.000021$, respectively), but no significant relationship was observed between age and amount of postoperative analgesic used (slope, -0.00038 ; 95% CI, -0.01049 to 0.00973 ; $P=0.94165$) (Supplementary Table 2, Supplementary Figure 4).

TSA indicated that 96.2% (230 of 249 patients) of the RIS was accrued. The cumulative z -curve crossed both the conventional test boundary and the trial sequential monitoring boundary (Fig. 2D).

Incidence of patients who needed postoperative analgesics

Nine studies (513 patients) reported the incidence of patients requiring postoperative analgesics. Aggregate analysis of this incidence revealed no between-group difference (RR, 1.60 ; 95% CI, 0.99 – 2.60 ; $I^2=53.92$; $P_{\text{chi}^2}=0.021$; $\tau=0.53$; 95% PI, 0.94 – 2.72). However, there was a significant between-group difference with respect to NNT (NNTB, 8.2 ; 95% CI, NNTB 5.1 to NNTB 20.4) (Supplementary Figure 5A). TSA indicated that only 23.2% (503 of 2165 patients) of the RIS was accrued. The cumulative z -curve crossed the conventional test boundary but did not cross the trial sequential monitoring boundary (Supplementary Figure 5B).

Time to first analgesic administration

Two studies (70 patients) reported the time to first analgesic administration, which was longer in the sufentanil group than in the remifentanil group (MD, -41.99 ; 95% CI, -60.71 – -23.27 ; $I^2=0.00$; $P_{\text{chi}^2}=0.883$; $\tau=0.00$) (Supplementary Figure 6A). TSA indicated that only 32.9% (70 out of 213 patients) of the RIS was accrued. The cumulative z -curve intersected both the conventional test boundary and the trial sequential monitoring boundary (Supplementary Figure 6B).

Systolic blood pressure (preoperative, intraoperative, and postoperative phase)

Seven studies (348 patients) reported the preoperative SBP, which showed no significant between-group difference (MD, 1.06 ; 95% CI, -1.63 – 3.75 ; $I^2=0.00$; $P_{\text{chi}^2}=0.476$; $\tau=0.00$) (Supplementary Figure 7A). TSA indicated that 94.7% (268 of 283 patients) of the RIS was accrued. The cumulative z -curve crossed the futility boundary (represented by the complete red curve on the right side) (Supplementary Figure 7B).

Nine studies (400 patients) reported the intraoperative SBP, which was higher in the sufentanil group than in the remifentanil group (MD, -6.30 ; 95% CI, -10.76 to -1.85 ; $I^2=74.82$; $P_{\text{chi}^2}<0.001$; $\tau=5.48$; 95% PI, -18.93 – 6.33) (Supplementary Figure 8A). TSA indicated that only 74.7% (360 of 482 patients) of the RIS was accrued. The cumulative z -curve crossed the conventional test boundary but not the trial sequential monitoring boundary (Supplementary Figure 8B).

Three studies (118 patients) reported the postoperative SBP, which showed no between-group difference (MD, 3.83 ; 95% CI, -1.51 to 9.17 ; $I^2=24.05$; $P_{\text{chi}^2}=0.266$; $\tau=2.36$; 95% PI, -6.22 – 14.08) (Supplementary Figure 9A). TSA indicated that only 42.9% (118 of 275 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 9B).

Mean arterial pressure (preoperative, intraoperative, and postoperative phase)

Twelve studies (735 patients) reported the preoperative MAP, which showed no between-group difference (MD, -0.18 ; 95% CI, -1.61 to 1.26 ; $I^2=41.60$; $P_{\text{chi}^2}=0.064$; $\tau=1.37$; 95% PI, -3.19 – 2.83) (Supplementary Figure 10A). In the meta-regression, no significant relationship was observed between age and preoperative MAP, nor between ratio of sufentanil and remifentanil dose and preoperative MAP (slope, 0.00093 ; 95% CI, -0.00725 to 0.00911 ; $P=0.82419$: slope, -4.18159 ; 95% CI, -8.75668 to 0.39349 ; $P=0.07323$, respectively) (Supplementary Table 2, Supplementary Figure 11).

TSA indicated that patients enrolled exceeded the RIS (735 of 446 patients). The cumulative z -curve crossed the futility boundary (Supplementary Figure 10B).

Thirteen studies (745 patients) reported the intraoperative MAP, which was higher in the sufentanil group than in the remifentanil group (MD, -6.38 ; 95% CI, -10.25 to -2.51 ; $I^2=92.82$; $P_{\text{chi}^2}<0.001$; $\tau=6.42$; 95% PI, -20.52 – 7.76) (Fig. 3A). In the meta-regression, duration of operation or anesthesia and ratio of sufentanil and remifentanil dose were significantly correlated with intraoperative MAP (slope, -0.00275 ; 95% CI, -0.00500 to -0.00049 ; $P=0.01690$; slope, 6.04224 ; 95% CI, 1.23623 to 10.84825 ; $P=0.01374$, respectively), but no significant relationship was observed between age and intraoperative MAP (slope, -0.00685 ; 95% CI, -0.01638 to 0.00269 ; $P=0.15920$) (Supplementary Table 2, Supplementary Figure 12).

TSA indicated that the number of included patients exceeded the RIS (72 patients). The cumulative z -curve crossed both the conventional test boundary and the trial sequential monitoring boundary (Fig. 3B).

Two studies (109 patients) reported the postoperative MAP, which showed no between-group difference (MD, -1.53 ; 95% CI, -7.72 – 4.65 ; $I^2=64.04$; $P_{\text{chi}^2}=0.095$; $\tau=3.81$; 95% PI, -49.91 – 46.85) (Supplementary Figure 13A). TSA indicated that only 19.2% (194 of 1006 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 13B).

Diastolic blood pressure (preoperative, intraoperative, and postoperative phase)

Six studies (289 patients) reported the preoperative DBP, which showed no significant between-group difference (MD, 2.13 ; 95% CI, -2.60 – 6.85 ; $I^2=71.13$; $P_{\text{chi}^2}=0.004$; $\tau=4.89$; 95% PI, -10.45 – 14.71) (Supplementary Figure 14A). TSA indicated that only 27.3% (289 of 1059 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 14B).

Seven studies (345 patients) reported the intraoperative DBP, which showed no significant between-group difference (MD, -3.88 ; 95% CI, -8.00 – 0.24 ; $I^2=66.55$; $P_{\text{chi}^2}=0.006$; $\tau=3.81$; 95% PI, -14.61 – 6.85) (Supplementary Figure 15A). TSA indicated that only 14.8% (345 of 2333 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 15B).

Two studies (99 patients) reported postoperative DBP, which was higher in the remifentanil group than in the sufentanil group (MD, 6.14 ; 95% CI, 1.33 – 10.96 ; $I^2=0.00$; $P_{\text{chi}^2}=0.553$; $\tau=0.00$) (Supplementary Figure 16A). TSA indicated that only 35.0% (99 of 283 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary or the trial sequential monitoring boundary (Supplementary Figure 16B).

(See figure on next page.)

Fig. 2 **A** Forest plot for the quantitative postoperative pain scores. The figure depicts individual trials as filled squares with relative sample size and the 95% confidence interval (CI) of the difference as a solid line. The diamond shape indicates the pooled estimate and uncertainty for the combined effect. The overall pooled estimate showed significantly higher quantitative postoperative pain scores in the remifentanil group than in the sufentanil group. **B** Trial sequential analysis plot for the quantitative postoperative pain scores. The uppermost and lowermost complete red curves represent the trial sequential monitoring boundaries for benefit and harm, respectively. The horizontal dotted red line represents the conventional boundaries for statistical significance. Triangular red lines on the right side reflect the futility boundaries. The blue solid line represents the cumulative z -curve. The number on the x -axis indicates the required information size. The cumulative z -curve crosses the alpha spending boundary, which favors sufentanil over remifentanil for lower postoperative pain scores. The alpha spending boundary indicates the required information size to confirm the findings. **C** Forest plot for the amount of postoperative analgesic used. The figure depicts individual trials as filled squares with the relative sample size and the 95% confidence interval (CI) of the difference as a solid line. The diamond shape indicates the pooled estimate and uncertainty for the combined effect. The overall pooled estimate showed significantly higher use of postoperative analgesics in the remifentanil group than in the sufentanil group. **D** Trial sequential analysis plot for the amount of postoperative analgesic used. The uppermost and lowermost complete red curves represent the trial sequential monitoring boundary lines for benefit and harm, respectively. The horizontal dotted red line represents the conventional boundaries for statistical significance. Triangular red lines on the right side reflect the futility boundaries. The blue solid line represents the cumulative z -curve. The number on the x -axis indicates the required information size. The cumulative z -curve surpasses the alpha-spending boundary, indicating a statistically significant difference favoring sufentanil for reduced postoperative analgesic consumption before reaching the required information size

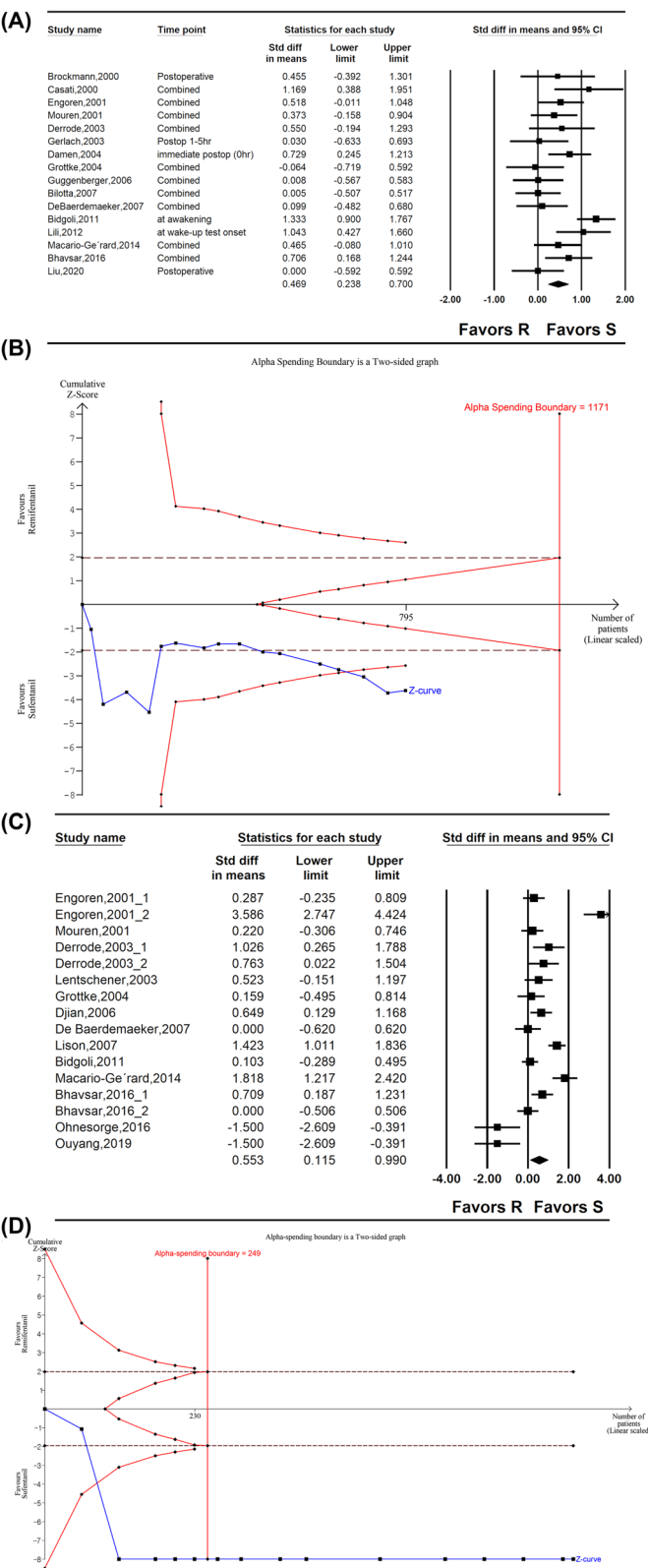


Fig. 2 (See legend on previous page.)

Heart rate (preoperative, intraoperative, and postoperative phase)

Sixteen studies (933 patients) reported the preoperative HR, which showed no significant between-group difference (MD, -0.95 ; 95% CI, -2.80 – 0.90 ; $I^2=63.47$; $P_{\text{chi}^2}<0.001$; $\tau=2.67$; 95% PI, -6.64 – 4.74) (Supplementary Figure 17A). In the meta-regression, no significant relationship was observed between age and preoperative HR, nor between ratio of sufentanil and remifentanil dose and preoperative HR (slope, 0.00435 ; 95% CI, -0.00294 to 0.01164 ; $P=0.24255$; slope, 2.36045 ; 95% CI, -1.73664 to 6.45753 ; $P=0.25882$, respectively) (Supplementary Table 2, Supplementary Figure 18).

TSA indicated that only 50.1% (839 of 1676 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 17B).

Sixteen studies (839 patients) reported the intraoperative HR, which was higher in the sufentanil group than in the remifentanil group (MD, -4.16 ; 95% CI, -6.65 to -1.68 ; $I^2=85.08$; $P_{\text{chi}^2}<0.001$; $\tau=4.33$; 95% PI, -13.38 – 5.06) (Fig. 3C). In the meta-regression, ratio of sufentanil and remifentanil dose was significantly correlated with intraoperative HR (slope, -7.63972 ; 95% CI, -11.70005 to -3.57940 ; $P=0.00023$), but no significant relationship was observed between age and intraoperative HR (slope, 0.00600 ; 95% CI, -0.00218 to 0.01418 ; $P=0.15081$) (Supplementary Table 2, Supplementary Figure 19).

TSA indicated that 98.3% (745 out of 758 patients) of the RIS was accrued. The cumulative z -curve crossed both the conventional test boundary and the trial sequential monitoring boundary (Fig. 3D).

Six studies (287 patients) reported postoperative HR, which showed no significant between-group difference (MD, 1.20 ; 95% CI, -1.54 – 3.94 ; $I^2=88.38$;

$P_{\text{chi}^2}<0.001$; $\tau=2.63$; 95% PI, -5.56 – 7.96) (Supplementary Figure 20A).

TSA indicated that only 15.8% (287 of 1813 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 20B).

Side effects (PON, POV, PONV, use of anti-emetics, respiratory depression, SpO2)

Six studies (351 patients) reported the incidence of PON, which was higher in the remifentanil group than in the sufentanil group (RR, 1.39 ; 95% CI 1.13 to 1.71 ; $I^2=0.00$; $P_{\text{chi}^2}=0.494$, $\tau=0.00$). Moreover, there was a significant between-group difference with respect to NNT (NNTB, 8.9 ; 95% CI, NNTB 4.7 to NNTB 91.4) (Supplementary Figure 21A). TSA indicated that only 46.9% (365 of 779 patients) of the RIS was accrued. The cumulative z -curve crossed the conventional test boundary but not the trial sequential monitoring (Supplementary Figure 21B).

Seven studies (410 patients) reported the incidence of POV, which showed no significant between-group difference (RR, 1.23 ; 95% CI 0.62 – 2.46 ; $I^2=0.00$; $P_{\text{chi}^2}=0.910$; $\tau=0.00$). There was no evidence of difference with respect to NNT (NNTB, 70.7 ; 95% CI, number needed to harm [NNTH] 28.3 to ∞ to NNTB 15.7) (Supplementary Figure 22A). TSA indicated that only 12.6% (434 of 3445 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 22B).

Eleven studies (545 patients) reported the incidence of PONV, which showed no significant between-group difference (RR, 0.87 ; 95% CI 0.57 to 1.34 ; $I^2=6.04$; $P_{\text{chi}^2}=0.386$; $\tau=0.17$; 95% PI, 0.44 – 2.27). There was no evidence of difference with respect to NNT (NNTH,

(See figure on next page.)

Fig. 3 **A** Forest plot for the intraoperative mean arterial pressure. The figure depicts individual trials as filled squares with the relative sample size and the 95% confidence interval (CI) of the difference as a solid line. The diamond shape indicates the pooled estimate and uncertainty for the combined effect. The overall pooled estimate showed a significantly higher intraoperative mean arterial pressure in the sufentanil group than in the remifentanil group. **B** Trial sequential analysis plot for the intraoperative mean arterial pressure. The uppermost and lowermost complete red curves represent the trial sequential monitoring boundary lines for benefit and harm, respectively. The horizontal dotted red line represents the conventional boundaries for statistical significance. Triangular red lines on the right side reflect the futility boundaries. The blue solid line represents the cumulative z -curve. The number on the x -axis indicates the required information size. The z -curve surpasses the alpha-spending boundary, indicating a statistically significant difference favoring sufentanil for maintaining mean arterial pressure, which exceeded the required information size. **C** Forest plot for the intraoperative heart rate. The figure depicts individual trials as filled squares with relative sample size and the 95% confidence interval (CI) of the difference as a solid line. The diamond shape indicates the pooled estimate and uncertainty for the combined effect. The overall pooled estimate showed a significantly higher intraoperative heart rate in the sufentanil group than in the remifentanil group. **D** Trial sequential analysis plot for the intraoperative heart rate. The uppermost and lowermost complete red curves represent trial sequential monitoring boundary lines for benefit and harm, respectively. The horizontal etched red line represents the conventional boundaries for statistical significance. Triangular red lines on the right side reflect the futility boundaries. The blue solid line represents the cumulative z -curve. The number on the x -axis indicates the required information size. The z -curve surpasses the alpha-spending boundary, indicating a statistically significant difference favoring sufentanil for maintaining heart rate before reaching the required information size

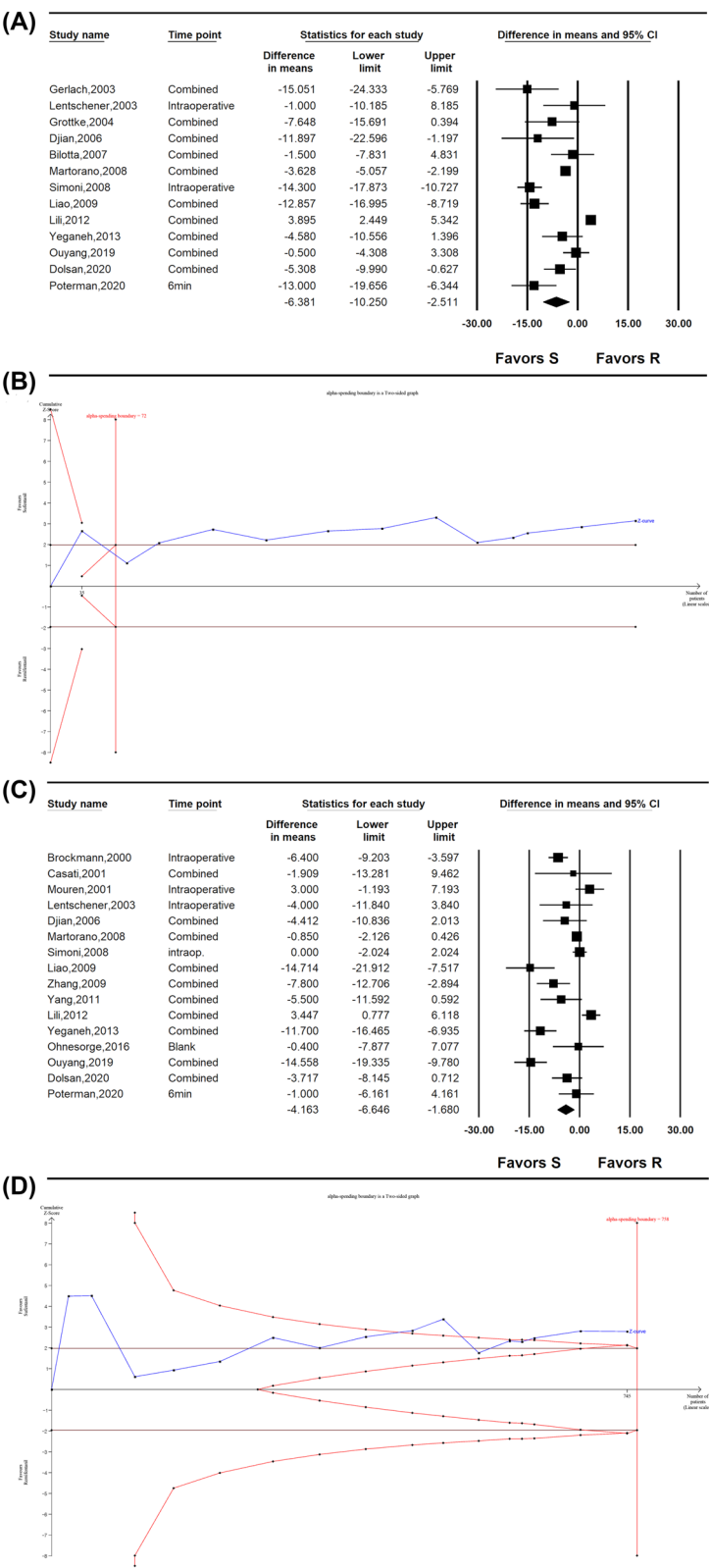


Fig. 3 (See legend on previous page.)

880.9; 95% CI, NNTH 30.9 to ∞ to NNTB 33.2) (Supplementary Figure 23A). In the meta-regression, no significant relationship was observed between age and PONV, nor between ratio of sufentanil and remifentanil dose and PONV (slope, -0.00539 ; 95% CI, -0.04127 to 0.03049 ; $P=0.76846$; slope, 5.74618 ; 95% CI, -18.53772 to 30.03008 ; $P=0.64281$, respectively) (Supplementary Table 2, Supplementary Fig. 24).

TSA indicated that only 16.5% (545 of 3310 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 23B).

Three studies (140 patients) reported the use of rescue anti-emetics, which showed no significant between-group difference (RR, 1.42; 95% CI 0.90–2.22; $I^2=0.00$; $P_{\text{chi}^2}=0.862$; $\tau=0.00$). There was also no evidence of a difference with respect to NNT (NNTB, 10.0; 95% CI, NNTH 0.18.6 to ∞ to NNTB 3.9) (Supplementary Figure 25A). TSA indicated that only 25.5% (140 of 548 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary or the trial sequential monitoring boundary (Supplementary Figure 25B).

Nine studies (726 patients) reported the incidence of respiratory depression, which showed no significant between-group difference (RR, 0.65; 95% CI 0.28–1.52; $I^2=0.00$; $P_{\text{chi}^2}=0.913$; $\tau=0.00$). There was also no evidence of a difference with respect to NNT (NNTH, 44.9; 95% CI, NNTH 22.1 to ∞ to NNTB 1414.1) (Supplementary Figure 26A). TSA indicated that only 5.5% (726 of 13,226 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 26B).

Six studies (555 patients) reported SpO_2 levels, which showed no significant between-group difference (MD, 0; 95% CI, -0.005 – 0.005 ; $I^2=54.09$; $P_{\text{chi}^2}=0.054$; $\tau=0.00$) (Supplementary Figure 27A). TSA indicated that only 10.0% (555 of 5562 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 27B).

Recovery profiles

Seventeen studies (943 patients) reported the time to extubation, which was shorter in the remifentanil group than in the sufentanil group, with a medium effect size (SMD, -0.59 ; 95% CI -0.93 to -0.26 ; $I^2=83.47$; $P_{\text{chi}^2}<0.001$; $\tau=0.64$; 95% PI, -1.95 – 0.77) (Fig. 4A). In the meta-regression, no significant relationship was observed between age and time to extubation, between

duration and time to extubation, nor between ratio of sufentanil and remifentanil dose and time to extubation (slope, 0.00495 ; 95% CI, -0.00504 to 0.01494 ; $P=0.33144$; slope, 0.00079 ; 95% CI, -0.00076 to 0.00234 ; $P=0.31889$; slope, 0.83120 ; 95% CI, -3.28930 to 4.95170 ; $P=0.69257$, respectively) (Supplementary Table 2, Supplementary Figure 28).

TSA exceeded the RIS of 393 patients. The cumulative z -curve crossed both the conventional test boundary and the trial sequential monitoring boundary (Fig. 4B).

Four studies (231 patients) reported the time to eye opening, which was shorter in the remifentanil group than in the sufentanil group, with a medium effect size (SMD, -0.64 ; 95% CI -0.90 to -0.37 ; $I^2=36.65$; $P_{\text{chi}^2}=0.192$; $\tau=0.22$; 95% PI, -1.35 – 0.07) (Supplementary Figure 29A). TSA indicated that only 14.2% (231 of 1623 patients) of the RIS was accrued. The cumulative z -curve crossed the conventional test boundary but not the trial sequential monitoring boundary (Supplementary Figure 29B).

Six studies (267 patients) reported the time to spontaneous respiration, which showed no significant between-group difference (SMD, -0.16 ; 95% CI -0.64 – 0.33 ; $I^2=73.76$; $P_{\text{chi}^2}=0.002$; $\tau=0.52$; 95% PI, -1.50 – 1.18) (Supplementary Figure 30A). TSA indicated that only 23.5% (267 of 1138 patients) of the RIS was accrued. The cumulative z -curve did not cross the conventional test boundary nor the trial sequential monitoring boundary (Supplementary Figure 30B).

Three studies (176 patients) reported the time to orientation, which was shorter in the remifentanil group than in the sufentanil group, with a medium effect size (SMD, -0.77 ; 95% CI -1.08 to -0.46 ; $I^2=85.08$; $P_{\text{chi}^2}=0.001$; $\tau=0.72$; 95% PI, -4.00 – 2.20) (Supplementary Figure 31A). TSA indicated that only 4.3% (176 of 4115 patients) of the RIS was accrued. The cumulative z -curve crossed the conventional test boundary but not the trial sequential monitoring boundary (Supplementary Figure 32B).

Five studies (240 patients) reported the time to emergence, which was shorter in the remifentanil group than in the sufentanil group, with a small effect size (SMD, -0.44 ; 95% CI -0.70 to -0.19 ; $I^2=0.00$; $P_{\text{chi}^2}=0.985$; $\tau=0.00$) (Supplementary Figure 32A). TSA indicated that only 84.8% (240 of 283 patients) of the RIS was accrued. The cumulative z -curve crossed both the conventional test boundary and the trial sequential monitoring boundary (Supplementary Figure 32B).

Publication bias

Egger's linear regression methods were performed for the following outcomes: postoperative pain score

(intercept = -2.47 ; 95% CI = -7.57 – -2.63 ; $p = 0.316$, Supplementary Figure 33A), amount of postoperative analgesic used (intercept = -0.92 ; 95% CI = -7.01 – 5.17 ; $p = 0.750$, Supplementary Figure 33B), incidence of patients who needed postoperative analgesics (intercept = 0.45 ; 95% CI = -1.94 – 2.84 ; $p = 0.675$, Supplementary Figure 33C), PONV (intercept = -0.70 ; 95% CI = -2.48 – 1.09 ; $p = 0.398$, Supplementary Figure 33D), preoperative MAP (intercept = -1.11 ; 95% CI = -2.02 to -0.20 ; $p = 0.022$, Supplementary Figure 33E), preoperative HR (intercept = 1.75 ; 95% CI = 0.83 – 2.66 ; $p = 0.0001$, Supplementary Figure 33F), and time to extubation (intercept = -0.70 ; 95% CI = -2.48 – 1.09 ; $p = 0.398$, Supplementary Figure 33G).

The funnel plot indicated asymmetry for the following outcomes: intraoperative MAP (intercept = -3.11 ; 95% CI = -6.40 – -0.17 ; $p = 0.061$, Supplementary Figure 33H), intraoperative HR (intercept = -2.11 ; 95% CI = -4.41 – 0.19 ; $p = 0.069$, Supplementary Fig. 33I). Therefore, a trim and fill analysis was performed to assess publication bias; however, it did not yield any significant alterations in the findings.

Risk of bias

Supplementary Table 3 presents the risk of bias assessment performed using the Cochrane tool. Studies were judged to have low risk [49, 50, 54–56, 63, 66–68, 70–72, 75, 79], some concerns [51–53, 57–60, 69, 73, 77], or high risk [61, 62, 64, 65, 74, 76, 78]. All studies had a “low risk” of bias due to missing outcome data, bias in measurement of the outcome data, and bias in selection of the reported results. Bias arising from the randomization process was assessed as “some concerns” in 13 studies [51, 53, 57, 60–62, 64, 65, 69, 73, 74, 76, 78]. Furthermore, bias due to deviations from intended interventions was assessed as “some concerns” in 11 studies [52, 58, 59, 61, 62, 64, 65, 74, 76–78]. The results of the RoB assessments are visually summarized in Supplementary Figures 34–37, where each figure presents the risk of bias for different outcome categories, including pain-related outcomes, hemodynamic outcomes, adverse outcomes, and recovery outcomes.

Quality of the evidence

Table 2 presents a summary of the meta-analysis and TSA. Twenty-eight outcomes were evaluated using the GRADE system (Supplementary Table 4). The quality of pooled analysis for patients requiring postoperative analgesics, time to first analgesic administered, preoperative MAP, POV, PONV, and incidence of respiratory depression was rated high. The quality was rated low for the postoperative pain score (qualitative assessments), postoperative MAP, preoperative DBP, postoperative HR, time to spontaneous respiration, and time to orientation. For the remaining outcomes, the quality of pooled analysis was rated as moderate.

Discussion

Sufentanil and remifentanil are opioids frequently administered during general anesthesia. This systematic review and meta-analysis, which includes trial sequential analysis, aimed to compare the perioperative efficacy and safety profiles of sufentanil and remifentanil in patients undergoing surgical procedures under general anesthesia. Our findings indicated that compared with the remifentanil group, the sufentanil group showed lower postoperative pain scores and consumption of postoperative analgesics; higher intraoperative MAP, intraoperative HR, and time to first analgesic administration; and delayed time to extubation and emergence. For these outcomes, the cumulative z-curve crossed the trial sequential monitoring boundary, suggesting that the TSA results reached a sufficient evidence level, and thus were conclusive. Moreover, compared with the remifentanil group, the sufentanil group showed higher intraoperative SBP, delayed time to eye opening and orientation, and lower incidence of PON. However, the cumulative z-curve did not cross the trial sequential monitoring boundary due to sparse data or not reaching significance after adjusting for the risk of potential false-positive findings.

In our study, the sufentanil group showed lower postoperative pain scores, reduced consumption of postoperative analgesics, and delayed time to first analgesic administration compared with the remifentanil group. Additionally, ratio of sufentanil and remifentanil dose was significantly correlated with postoperative pain scores

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Fig. 4 Time to extubation. **A** Forest plot. The figure depicts individual trials as filled squares with the relative sample size and the 95% confidence interval (CI) of the difference as a solid line. The diamond shape indicates the pooled estimate and uncertainty for the combined effect. The overall pooled estimate showed a significantly shorter time to extubation in the remifentanil group than in the sufentanil group. **B** Trial sequential analysis plot. The uppermost and lowermost complete red curves represent trial sequential monitoring boundary lines for benefit and harm, respectively. Horizontal etched red lines represent the conventional boundaries for statistical significance. Triangular red lines on the right side reflect the futility boundaries. The blue solid line represents the cumulative z-curve. The number on the x-axis indicates the required information size. The z-curve surpasses the alpha-spending boundary, indicating a statistically significant difference favoring remifentanil for reduced time to extubation exceeding the required information size

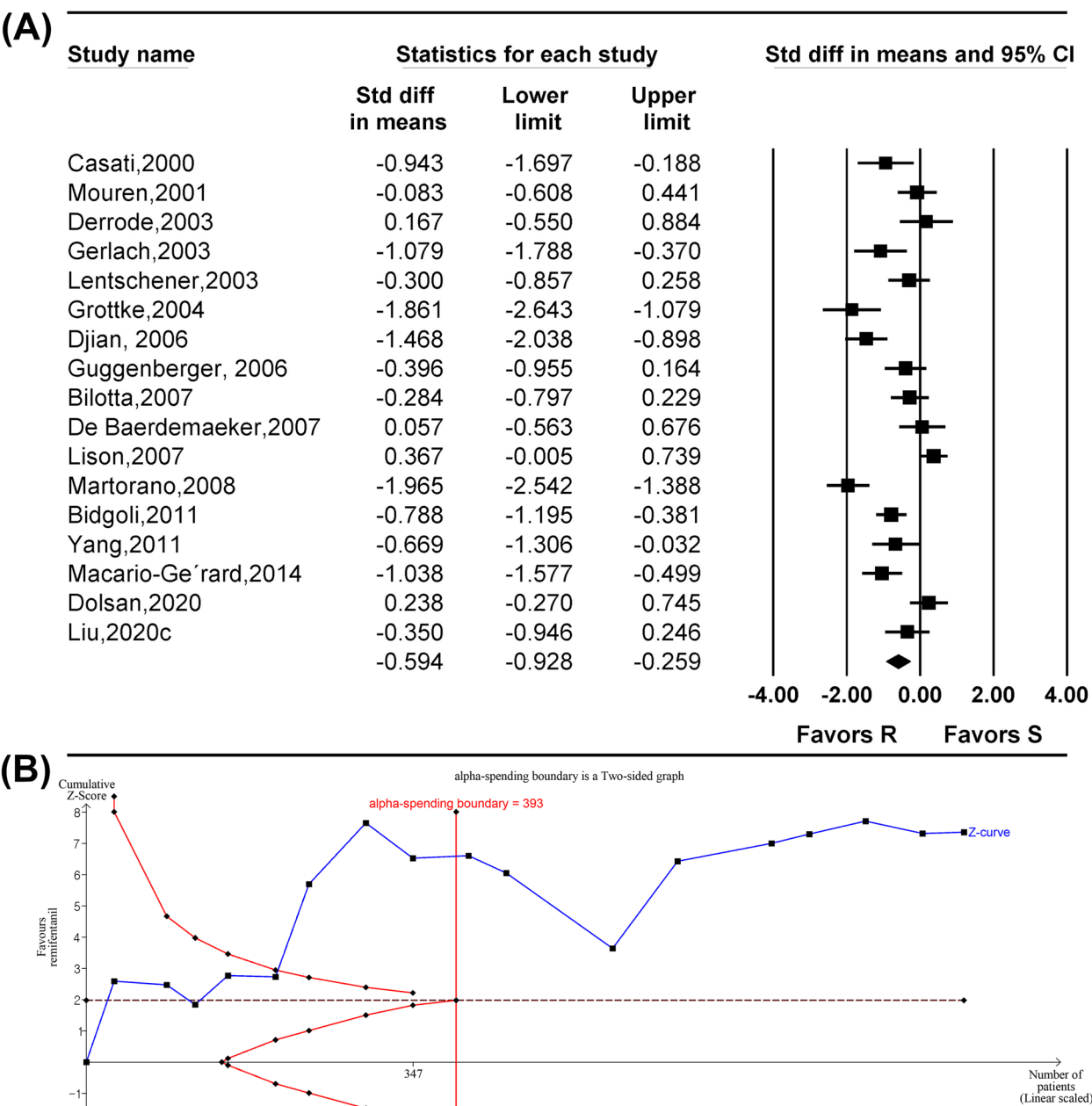


Fig. 4 (See legend on previous page.)

and postoperative analgesic used in meta-regression analysis. These results are consistent with the pharmacological properties of sufentanyl, which exhibits higher potency and longer duration of action than remifentanyl. Remifentanyl is an agonist of the μ -opioid receptor with potency similar to that of fentanyl [4]. Contrastingly,

Table 2 The summary of meta-analysis and trial sequential analysis

	No. of studies	No. of patients	Conventional meta-analysis		Trial sequential analysis			NNT
			RR or MD or SMD with 95% CI	Heterogeneity (I^2 ; P_{chi^2} ; τ ; 95% PI)	Conventional test boundary	Monitoring boundary	Futility boundary	RIS
Postoperative pain score (quantitative)	16	795	Significant (SMD, 0.47; 95% CI, 0.24 to 0.70)	$I^2 = 59.95$; $P_{\text{chi}^2} = 0.001$; $\tau = 0.36$; 95% PI, -0.30 to 1.24	Cross	Cross	Not cross	67.9% (795 of 1171 patients)
Postoperative pain score (qualitative)	2	119	Not significant (RR, 4.38; 95% CI 0.28 to 68.34)	$I^2 = 87.39$; $P_{\text{chi}^2} = 0.005$; $\tau = 1.87$; 95% PI, 0.68 to 28.29	Not cross	Not cross	Not cross	0.6% (119 of 19,986 patients)
Amount of postoperative analgesic used	13	738	Significant (SMD, 0.55; 95% CI, 0.12 to 0.99)	$I^2 = 88.39$; $P_{\text{chi}^2} = 0.001$; $\tau = 0.82$; 95% PI, -1.25 to 2.35	Cross	Cross	Not cross	96.2% (230 of 249 patients)
Patients needed postoperative analgesics	9	513	Not significant (RR, 1.60; 95% CI 0.99 to 2.60)	$I^2 = 53.92$; $P_{\text{chi}^2} = 0.021$; $\tau = 0.53$; 95% PI, 0.94 to 2.72	Cross	Not cross	Not cross	23.2% (503 of 2165 patients)
Time to 1st analgesic	2	70	Significant (MD, -41.99; 95% CI, -60.71 to -23.27)	$I^2 = 0.00$; $P_{\text{chi}^2} = 0.883$; $\tau = 0.00$	Cross	Cross	Not cross	32.9% (70 out of 213 patients)
SBP-Pre	7	348	Not significant (MD, 1.06; 95% CI, -1.63 to 3.75)	$I^2 = 0.00$; $P_{\text{chi}^2} = 0.476$; $\tau = 0.00$	Not cross	Not cross	Cross	94.7% (268 of 283 patients)
SBP -Intra	9	400	Significant (MD, -6.30; 95% CI, -10.76 to -1.85)	$I^2 = 74.82$; $P_{\text{chi}^2} < 0.001$; $\tau = 5.48$; 95% PI, -18.93 to 6.33	Cross	Not cross	Not cross	74.7% (360 of 482 patients)
SBP -Post	3	118	Not significant (MD, 3.83; 95% CI, -1.51 to 9.17)	$I^2 = 24.05$; $P_{\text{chi}^2} = 0.266$; $\tau = 2.36$; 95% PI, -6.22 to 14.08	Not cross	Not cross	Not cross	42.9% (118 of 275 patients)
MAP-Pre	12	735	Not significant (MD, -0.18; 95% CI, -1.61 to 1.26)	$I^2 = 41.60$; $P_{\text{chi}^2} = 0.064$; $\tau = 1.37$; 95% PI, -3.19 to 2.83	Not cross	Not cross	Cross	Exceeds RIS (735 of 446 patients)
MAP -Intra	13	745	Significant (MD, -6.38; 95% CI, -10.25 to -2.51)	$I^2 = 92.82$; $P_{\text{chi}^2} < 0.001$; $\tau = 6.42$; 95% PI, -20.52 to 7.76	Cross	Cross	Not cross	Exceeds RIS (745 of 72 patients)
MAP -Post	2	109	Not significant (MD, -1.53; 95% CI, -7.72 to 4.65)	$I^2 = 64.04$; $P_{\text{chi}^2} = 0.095$; $\tau = 3.81$; 95% PI, -49.91 to 46.85	Not cross	Not cross	Not cross	19.2% (194 of 1006 patients)

Table 2 (continued)

	No. of studies	No. of patients	Conventional meta-analysis		Trial sequential analysis			NNT
			RR or MD or SMD with 95% CI	Heterogeneity (I^2 ; P_{chi^2} , τ ; 95% PI)	Conventional test boundary	Monitoring boundary	Futility boundary	RIS
DBP-Pre	6	289	Not significant (MD, 2.13; 95% CI, -2.60 to 6.85)	$I^2 = 71.13$; $P_{\text{chi}^2} = 0.004$; $\tau = 4.89$; 95% PI, -10.45 to 14.71	Not cross	Not cross	Not cross	27.3% (289 of 1059 patients)
DBP -Intra	7	345	Not significant (MD, -3.88; 95% CI, -8.00 to 0.24)	$I^2 = 66.55$; $P_{\text{chi}^2} = 0.006$; $\tau = 3.81$; 95% PI, -14.61 to 6.85	Not cross	Not cross	Not cross	14.8% (345 of 2333 patients)
DBP -Post	2	99	Not significant (MD, 6.14; 95% CI, 1.33 to 10.96)	$I^2 = 0.00$; $P_{\text{chi}^2} = 0.553$; $\tau = 0.00$	Not cross	Not cross	Not cross	35.0% (99 of 283 patients)
HR-Pre	16	933	Not significant (MD, -0.95; 95% CI, -2.80 to 0.90)	$I^2 = 63.47$; $P_{\text{chi}^2} < 0.001$; $\tau = 2.67$; 95% PI, -6.64 to 4.74	Not cross	Not cross	Not cross	50.1% (839 of 1676 patients)
HR -Intra	16	839	Significant (MD, -4.16; 95% CI, -6.65 to -1.68)	$I^2 = 85.08$; $P_{\text{chi}^2} < 0.001$; $\tau = 4.33$; 95% PI, -13.38 to 5.06	Cross	Cross	Not cross	98.3% (745 out of 758 patients)
HR -Post	6	287	Not significant (MD, 1.20; 95% CI, -1.54 to 3.94)	$I^2 = 88.38$; $P_{\text{chi}^2} < 0.001$; $\tau = 2.63$; 95% PI, -5.56 to 7.96	Not cross	Not cross	Not cross	15.8% (287 of 1813 patients)
PON	6	351	Significant (RR, 1.39; 95% CI, 1.13 to 1.71)	$I^2 = 0.00$; $P_{\text{chi}^2} = 0.494$; $\tau = 0.00$	Cross	Not cross	Not cross	46.9% (365 of 779 patients)
POV	7	410	Not significant (RR, 1.23; 95% CI, 0.61 to 2.46)	$I^2 = 0.00$; $P_{\text{chi}^2} = 0.910$; $\tau = 0.00$	Not cross	Not cross	Not cross	Significant (NNTB, 8.9; 95% CI, NNTB 4.7 to NNTB 91.4)
PONV	11	545	Not significant (RR, 0.87; 95% CI, 0.57 to 1.34)	$I^2 = 6.04$; $P_{\text{chi}^2} = 0.386$; $\tau = 0.17$; 95% PI, 0.44 to 2.27	Not cross	Not cross	Not cross	Not significant (NNTB, 70.7; 95% CI, NNTH 28.3 to ∞ to NNTB 15.7)
Use of rescue anti-emetics	3	140	Not significant (RR, 1.42; 95% CI, 0.90 to 2.22)	$I^2 = 0.00$; $P_{\text{chi}^2} = 0.862$; $\tau = 0.00$	Not cross	Not cross	Not cross	Not significant (NNTB, 880.9; 95% CI, NNTH 30.9 to ∞ to NNTB 33.2)
Respiratory depression	9	726	Not significant (RR, 0.65; 95% CI, 0.28 to 1.52)	$I^2 = 0.00$; $P_{\text{chi}^2} = 0.913$; $\tau = 0.00$	Not cross	Not cross	Not cross	Not significant (NNTB, 10.0; 95% CI, NNTH, 18.6 to ∞ to NNTB 3.9)
								5.5% (726 of 13,226 patients)
								Not significant (NNTB, 44.9; 95% CI, NNTH 22.1 to ∞ to NNTB 1414.1)

Table 2 (continued)

	No. of studies	No. of patients	Conventional meta-analysis			Trial sequential analysis			NNT
			RR or MD or SMD with 95% CI	Heterogeneity (I^2 ; P_{chi^2} ; τ ; 95% PI)		Conventional test boundary	Monitoring boundary	Futility boundary	RIS
SpO ₂	6	555	Not significant (MD, 0; 95% CI, -0.005 to 0.005)	$I^2 = 54.09$; $P_{\text{chi}^2} = 0.054$; $\tau = 0.00$		Not cross	Not cross	Not cross	10.0% (555 of 5562 patients)
Time to extubation	17	943	Significant (SMD, -0.59; 95% CI -0.93 to -0.26)	$I^2 = 83.47$; $P_{\text{chi}^2} < 0.001$; $\tau = 0.64$; 95% PI, -1.95 to 0.77		Cross	Cross	Not cross	Exceeds RIS (943 of 393 patients)
Time to eye opening	4	231	Significant (SMD, -0.64; 95% CI -0.90 to -0.37)	$I^2 = 36.65$; $P_{\text{chi}^2} = 0.192$; $\tau = 0.22$; 95% PI, -1.35 to 0.07		Cross	Not cross	Not cross	14.2% (231 of 1623 patients)
Time to spontaneous respiration	6	267	Not significant (SMD, -0.16; 95% CI -0.64 to 0.33)	$I^2 = 73.76$; $P_{\text{chi}^2} = 0.002$; $\tau = 0.52$; 95% PI, -1.50 to 1.18		Not cross	Not cross	Not cross	23.5% (267 of 1138 patients)
Time to orientation	3	176	Significant (SMD, -0.77; 95% CI -1.08 to -0.46)	$I^2 = 85.08$; $P_{\text{chi}^2} = 0.001$; $\tau = 0.72$; 95% PI, -4.00 to 2.20		Cross	Not cross	Not cross	4.3% (176 of 4115 patients)
Time to emergence	5	240	Significant (SMD, -0.44; 95% CI -0.70 to -0.19)	$I^2 = 0.00$; $P_{\text{chi}^2} = 0.985$; $\tau = 0.00$		Cross	Cross	Not cross	84.8% (240 of 283 patients)

No Number, RR Relative risk, MD Mean difference, SMD Standardized mean difference, CI Confidence interval, PI Predictive interval, RIS Required information size, NNT Number needed to treat, NNTB Number needed to treat to benefit, SBP Systolic blood pressure, Pre Preoperative, Intra Intraoperative, Post Postoperative, MAP Mean arterial pressure, DBP Diastolic blood pressure, HR Heart rate, PON Postoperative nausea, POV Postoperative vomiting, NNTB Number needed to treat to harm, POW Postoperative nausea and vomiting, RA Rescue anti-emetics, SpO₂ Saturation of percutaneous oxygen

sufentanil is a highly selective agonist for the μ -opioid receptor [8]. This selectivity is underscored by its 100-fold greater affinity for the μ -opioid receptor compared to fentanyl and morphine, indicating that sufentanil possesses ≈ 10 times the potency of fentanyl [6, 10]. Pharmacokinetically, remifentanil is rapidly eliminated by non-specific plasma and tissue esterases, resulting in a systemic half-life of 9–11 min [2]. The context-sensitive half-time of remifentanil, which is defined as the time taken for the effective site concentration to decrease by 50% after discontinuation of continuous infusion [80], is ≈ 4 min, irrespective of the infusion duration [2]. Contrastingly, sufentanil has a longer terminal half-life of 2.5 h [9], with a context-sensitive half-time of ≈ 1 h after an intravenous infusion lasting for 6 h [81]. The variance in duration of action led to divergent administration protocols across the included studies. Remifentanil infusion was sustained until the end of surgical procedure, whereas administration of sufentanil, whether by bolus or continuous infusion, typically ceased 30–60 min before the end of surgery. The lower requirement for additional analgesics in the sufentanil group suggests superior analgesic efficacy and may contribute to improved patient comfort and satisfaction in the postoperative period. The higher need for analgesics and shorter time until first analgesic administration in the remifentanil group may be attributed to acute opioid tolerance [82] or remifentanil-induced hyperalgesia [83, 84].

Furthermore, our findings indicated between-group differences in intraoperative hemodynamic variables. Compared with remifentanil, sufentanil was associated with higher intraoperative SBP and MAP, indicating better hemodynamic stability with sufentanil administration. Although there were significant among-study differences, incomplete accrual of data regarding intraoperative SBP according to TSA suggests the need for large-scale studies to validate these findings [85]. Additionally, our findings demonstrated a lower intraoperative HR in the remifentanil group than in the sufentanil group. Meta-regression also showed significant correlation between ratio of sufentanil and remifentanil dose and both intraoperative MAP and HR. In 2007, Komatsu et al. reported that remifentanil administration was associated with more frequent episodes of bradycardia (RR 1.46, 95% CI 1.04–2.05) and hypotension (RR 1.68, 95% CI 1.36–2.07) [86]. Elliot et al. recommended continuous remifentanil infusion, especially in patients with coronary artery disease, since bolus administration can cause severe cardiovascular suppression [87]. Remifentanil can induce bradycardia through parasympathetic activation or other negative chronotropic effects, with stronger adverse effects being observed in adults, including bradycardia and asystole [88–90].

Regarding side effects, the incidence of PON was higher in the remifentanil group than in the sufentanil group, with an RR of 1.39 (95% CI 1.13–1.71). However, TSA indicated the need for more studies to confirm these findings. Opioid administration is a risk factor for PONV [91]. Presumably, remifentanil, with its comparatively brief elimination time [2], would not contribute to PONV. Nevertheless, studies have demonstrated that remifentanil has a comparable incidence of PONV as other opioids [92–94]. In contrast to previous findings, we observed a higher PON occurrence in the remifentanil group than in the sufentanil group, which could be attributed to the higher postoperative analgesic consumption in the remifentanil group. There were no significant between-group differences in other side effects, including POV, PONV, respiratory depression, or oxygen saturation. These findings suggest comparable safety profiles for sufentanil and remifentanil with respect to respiratory function and oxygenation.

Regarding recovery profiles, remifentanil showed significantly shorter times to extubation, eye opening, orientation, and emergence than sufentanil. These results suggest a more rapid recovery from anesthesia with remifentanil, which may be attributed to its shorter duration of action and rapid offset of effect [2]. Moreover, the time to extubation was validated by TSA results, which further supported the findings. Time to spontaneous respiration showed no between-group difference. Although multiple factors may influence discharge, faster extubation in the remifentanil group may facilitate earlier recovery and readiness for discharge, and thus alleviate the workload of the postoperative care unit staff [95].

In the meta-regression analysis, we used duration of operation or anesthesia, age, and the ratio of sufentanil to remifentanil dose (sufentanil dose/remifentanil dose used) as independent variables, with each outcome serving as the dependent variable. This analysis was conducted to evaluate the impact of these covariates on the observed outcomes. The results provided further insights into how these factors may influence postoperative pain scores, hemodynamic stability, and recovery profiles among patients receiving sufentanil or remifentanil during general anesthesia [96].

This study has several limitations. First, even after a comprehensive search, small numbers of studies were included for some outcomes, which may have led to underpowered and inconclusive findings. Second, there was clinical and methodological heterogeneity across the studies, including differences in timing, dose, and method of analgesic administration, and different surgical procedures. Meta-regression was not performed for outcomes with fewer than 10 studies, as it may yield

unreliable results, underscoring the importance of cautious interpretation.

In conclusion, our findings support the use of sufentanil for perioperative pain management in elective surgeries under general anesthesia. Specifically, sufentanil demonstrated superior analgesic efficacy and better hemodynamic stability, while maintaining comparable safety profiles, compared with remifentanil. Notably, remifentanil exhibits a faster recovery profile than sufentanil. Nonetheless, opioid selection should be tailored to individual patient characteristics, surgical considerations, and institutional protocols to optimize perioperative pain control and patient outcomes. Further studies, including large-scale RCTs and comparative effectiveness studies, are warranted to validate these findings and inform evidence-based practice in perioperative care.

Abbreviations

RCTs	Randomized controlled trials
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
VAS	Visual analogue scale
NRS	Numerical rating scale
PRS	Pain relief score
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HR	Heart rate
PON	Postoperative nausea
POV	Postoperative vomiting
PONV	Postoperative nausea and vomiting
RR	Risk ratio
MD	Mean difference
SMD	Standardized mean difference
PI	Prediction interval
NNT	Number needed to treat
TSA	Trial sequential analysis
RIS	Required information size
SD	Standard deviation
RoB 2.0	Revised Cochrane risk of bias tool for randomized trials
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Authors' contributions

KHJ and CGJ designed the search template and did the search and data collection in detail. The data analysis was done by HJK and HK, the bias assessment by GJC and KHJ, and quality of evidence was assessed by GJC and HK. All authors contributed to manuscript development, and participated in the critical scrutiny and revision of the manuscript. All authors read and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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