Systematic Review

Application of Dexmedetomidine as an Opioid Substitute in Opioid-Free Anesthesia: A Systematic Review and Meta-analysis

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Background: Opioid-based general anesthesia was previously used to alleviate perioperative pain; however, several complications associated with using anesthesia have raised several concerns. Various studies have investigated the application prospect of using opioid-free general anesthesia, such as dexmedetomidine, as an opioid substitute.

Objectives: We performed a systematic review and meta-analysis to explore and highlight the safety and effectiveness of dexmedetomidine as an opioid substitute for opioid-free anesthesia.

Study Design: A systematic review and meta-analysis.

Setting: We screened for suitable clinical trials from electronic databases, including "PubMed," "Cochrane Library," "EMBASE," and "Web of Science." Eligible trials were included in this meta-analysis.

Methods: The quality of the screened randomized controlled trials (RCTs) was determined using the risk of bias assessment criteria by the Cochrane Collaboration tool. We used the "Review Manager 5.3" and "Stata 10.0" software to perform the meta-analysis. We evaluated the quality of evidence using the "Grading of Recommendations Assessment, Development, and Evaluation" approach.

Results: For the analysis, we included 32 RCTs encompassing 2,509 patients. In the opioid-free group, the 2-hour postoperative pain score of patients (mean difference = -0.53, 95% CI: -1.00, -0.07; $P = 0.02$, I^2=78%) was significantly lower compared to those in the opioid-based group. In addition, several patients required rescue analgesia (risk ratio = 0.70, 95% CI: 0.58, 0.84, $P < 0.05$, $I^2 = 71\%$) and opioids postsurgery. However, the duration of extubation and postanesthesia care unit, as well as the incidences of bradycardia, were high in patients receiving dexmedetomidine as opioid-free general anesthesia.

Limitations: Subgroup analysis for different anesthesia-maintaining drugs had not been conducted. The heterogeneity did not reduce after subgroup analysis. Different doses of dexmedetomidine had not been evaluated.

Conclusions: These findings indicate that opioid-free general anesthesia based on dexmedetomidine could be effective; however, prolonged extubation time and cardiovascular complications are a few risks associated with dexmedetomidine.

Key words: Opioid-free anesthesia, dexmedetomidine, meta-analysis

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Opium derivatives have been used for centuries; however, opioids were not used until the 1970s in clinical settings to induce and maintain anesthesia (1). Currently, opioids have been widely used as analgesics to maintain auxiliary sedation in patients under general anesthesia, as well

as provide stable intraoperative hemodynamics. Hence, opioids play a significant role during the perioperative period. However, several adverse reactions, including respiratory depression (2), constipation (3), urine retention (4), immunosuppression (5), and hyperalgesia (6) are associated with opioid use. Furthermore, studies (7,8) have shown a high mortality rate in individuals who misuse, abuse, and overuse opioids.

Recently, several studies (9-11) have explored various opioid-free anesthesia techniques. Opioid-free anesthesia is used to eliminate the intraoperative use of opioids upon implementing multimodal nonopioid analgesic techniques (12). However, due to the availability of several alternate drugs and nerve-blocking agents, strong evidence supporting the widespread use of opioid-free anesthesia is still lacking. Several clinical studies (13-15) have used dexmedetomidine as opioid-free anesthesia. A study (16) showed that the pain scores of patients receiving dexmedetomidine postsurgery were lower, along with fewer side effects compared to those receiving remifentanil. However, some studies included in that review used alternative approaches as opioid-free treatments during the anesthesia induction period, which complicated their conclusions. Moreover, a high-quality multicenter randomized controlled trial (RCT) (10) revealed that dexmedetomidine as opioid-free anesthesia was associated with severe adverse events compared to remifentanil.

Therefore, in this study, we only included studies comparing opioid-free approaches for inducing anesthesia and maintained anesthesia using opioids to explore the safety and effectiveness of dexmedetomidine as an opioid substitute for inducing opioid-free anesthesia.

Methods

This systematic review and meta-analysis were performed and reported based on the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. The International Prospective Register of Systematic Reviews registration number is CRD42022356554.

Systematic Literature Search

We systematically searched electronic databases, including "PubMed," EMBASE," "Cochrane Library," and "Web of Science." The literature was screened without any language restrictions from the establishment of these databases till September 30, 2022. The strategy for screening literature from PubMed is described in the supplemental data. Furthermore, references for these studies were systematically screened and investigated.

Criteria for Selection

The inclusion criteria were as follows: (1) Patients (P): patients who underwent surgery under general anesthesia; (2) Intervention (I): trials reporting the use of dexmedetomidine as an opioid substitute for inducing anesthesia; (3) Comparison (C): opioid-based anesthesia; (4) Outcomes (O): trials reporting the effectiveness of the dexmedetomidine as an opioid substitute; and (5) Study design (S): RCTs.

The exclusion criteria were as follows: (1) using other anesthesia techniques; (2) dexmedetomidine was not administrated intravenously; (3) incomplete studies, such as conference abstracts; and (4) opioids were administered for inducing or maintaining anesthesia, or before emergence in the opioid-free group.

Extraction of Data and Outcomes

First, 2 authors independently used EndNote to exclude duplicate studies. Second, the authors assessed if these RCTs met the inclusion and exclusion criteria based on the title and abstract of the articles. Finally, we carefully examined the full text of these articles to determine if these studies met the inclusion criteria. These articles were retrieved and cross-checked by 2 authors independently for the following information: the name of authors, publication year, type of surgery performed, sample size, patient's age, details of general anesthesia, and postoperative pain management. We emailed the corresponding authors of these articles to obtain important information that was unavailable. If these authors did not respond after more than a week, another reminder email was sent for consultation.

The primary outcomes were 2-hour postoperative pain scores and the number of times rescue analgesia was required during the postoperative period. The secondary outcomes were 4-hour postoperative pain scores, postoperative opioid consumption, emergence parameters (postanesthesia care unit (PACU) stay/discharge and extubation time), and the incidence of complications, including hypotension, bradycardia, postoperative nausea, and vomiting (PONV), and hypoxia.

Evaluation of the Quality and Risk

We used the Cochrane Collaboration tool to evaluate the risk of bias in these studies. The risk of bias included the following: selection bias (whether the random sequence was generated and the allocation

methods were blinded), performance bias (whether the study patients, as well as personnel, were blinded), detection bias (whether the methods used to detect the study outcomes were blinded), attrition bias (reporting of incomplete outcome data of the study), reporting bias (whether selected outcomes were reported), and other biases. The trials were evaluated as high risk, with some concerns, or low risk. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used for assessing the degree of confidence. The studies were divided into the level of certainty as very low, low, moderate, or high.

Statistical Analysis

We performed meta-analysis using the following statistical software: "Review Manager 5.3" (version 5.3, Copenhagen) and "Stata version 12.0" (Stata Corp LP, USA). We calculated the combined risk ratio (RR) and 95% CIs for dichotomous outcomes. For continuous data with the same units, we calculated the mean differences (MD) and 95% CIs; however, only standardized MD (SMD) was reported. If continuous data was defined as median (IQRs) or median (min-max), we transformed the values to the corresponding mean and SD to adhere to the previous methods. $P < 0.05$ was considered statistically significant. The concentration of opioids used postsurgery was converted into equianalgesic doses of intravenous morphine for further analysis. The pain scores were reported as visual, verbal, or Numeric Rating Scale and transformed into a standardized 0-10 analog scale for quantitative assessment. Heterogeneity in the trials was evaluated using the I^2 statistic, wherein $I^2 > 50\%$ was considered "highly heterogeneous." Moreover, the primary causes of high heterogeneity are clinical and methodological concerns. Hence, we used the random effects model for the studies with low I^2 values.

We performed subgroup analyses based on different opioid substitutes used (dexmedetomidine alone vs dexmedetomidine combined with other drugs or nerve-blocking agents) and different types of surgeries performed (abdominal surgery vs nonabdominal surgery). We used the "Funnel plot" and "Bgger's test" to assess the publication bias. Finally, we performed a sensitivity analysis to evaluate the stability of the primary outcomes.

Results

Search Results

We screened 1,202 studies from electronic databases. Based on the exclusion criteria, we excluded 294 duplicate articles and 860 studies after reading their titles and abstracts. Next, we analyzed the full texts of the remaining 48 articles to determine if they could be included for subsequent analysis. Of which, we excluded 16 articles for the following reasons: Patients in the opioid-free group were administered opioids (n = 6) (17-22), dexmedetomidine was not administered intravenously (n = 1) (23), using other types of anesthesia (n = 1) (24), outcomes unavailable (n = 1) (25), and dexmedetomidine was not used as an opioid substitute (n = 7) (26-32). Finally, we included 32 articles based on the inclusion criteria (10,13-15,33-60). The process for screening the literature is shown in Fig. 1.

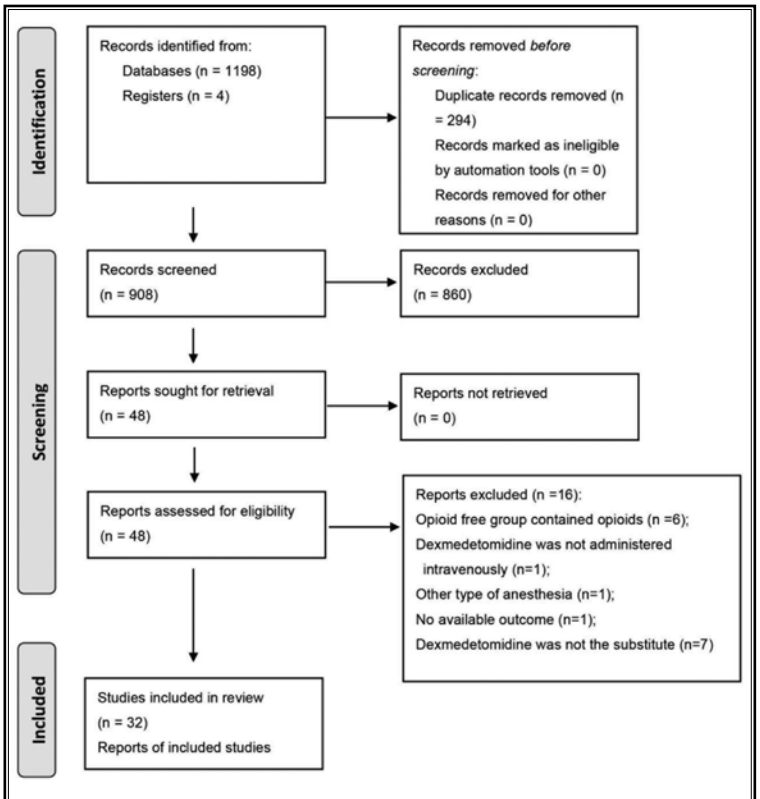

Fig. 1. *The inclusion process of the literature search.*

Study Characteristics

The publication year of these articles screened ranged from 2009 to 2020, and the sample size of these studies was 30-314. The types of surgeries included were thoracic, breast, gynecological, urological, abdominal, etc. In the opioid-free group, 14 studies used dexmedetomidine alone as the opioid substitute. Moreover, 18 studies used a combined formula (> 2 anesthetic agents or combined with nerve-blocking agents). Four studies (15,34,37,43) used dexmedetomidine for inducing anesthesia, 3 studies (42,49,58) used dexmedetomidine for maintaining anesthesia, and the remaining studies used dexmedetomidine for both inducing and maintaining anesthesia. In the opioid-based group, 13 studies (13-15,33,34,38,44,46,47,53,57,58,60) used fentanyl as an opioid agent, 13 studies (10,40,41,43,45,48-52,55,56,59) used remifentanil, 3 studies (35,36,39) used the combination of sufentanil and remifentanil, 2 studies (37,42) used the combination of fentanyl and remifentanil , and one study (54) used sufentanil. Detailed information on these studies is shown in Table 1.

Risk of Bias

Figure 2 summarizes the risk of bias. Two trials (52,60) did not report the randomization method. Three trials (14,40,60) failed to specify if allocation methods were blinded. Eight trials (14,40,49,51-54,60) did not adopt double blinding. Seven trials (13,14,44,50,52,53,59) reported that the outcome assessors were not blinded. A trial (58) reported an "unclear risk" for "selective reporting." Five trials (38,49,51,58,59) failed to calculate the sample size, and the "Other bias" included "unclear risk."

Outcomes

Primary Outcomes

Two-hour Postoperative Pain Score

Eight trials reported a 2-hour postoperative pain score. The forest plot showed that in the opioid-free group, the pain scores of patients were significantly lower compared to those in the opioid-based group (MD = -0.53, 95% CI: -1.00, -0.07; $P < 0.05$, $I^2 = 78\%$, Fig. 3), and the heterogeneity was high. Therefore, we performed subgroup analyses based on the different types of opioids used and surgeries performed to identify the source of heterogeneity. However, this did not reduce heterogeneity (Suppl. Figs. 1-2).

Number of Patients who Required Rescue Analgesics

A total of 15 trials reported the number of patients who required rescue analgesics during the postoperative period. The forest plot showed that the opioid-free strategy significantly reduced the requirement of postoperative analgesics (RR = 0.70, 95% CI: 0.58, 0.84, $P < 0.05$, $I^2 = 71\%$, Fig. 4), and the heterogeneity was high. Furthermore, subgroup analyses did not reduce heterogeneity (Suppl. Figs. 3-4).

Secondary Outcomes

Four-hour Postoperative Pain Score

A total of 4 trials examined 4-hour postoperative pain scores. The forest plot results revealed that the pain scores of patients in the opioid-free group were significantly lower (MD = -0.84, 95% CI: -1.45, -0.23; $P < 0.05$, $I^2 = 43\%$, Fig. 5).

Opioid Consumption Postsurgery

Eight trials reported opioid consumption postsurgery. The forest plot showed that the opioid-free strategy significantly reduced opioid consumption postsurgery (SMD = -1.45, 95% CI: -2.11, -0.79; $P < 0.05$, $I^2 = 94\%$, Fig. 6).

Emergence Parameters

A total of 18 RCTs reported the extubation time. The forest plot showed that the opioid-free strategy significantly prolonged the extubation time (MD = 2.40 minutes, 95 % CI: 0.09, 4.70; $P < 0.05$, $I^2 = 98\%$, Fig. 7).

Furthermore, 17 RCTs reported PACU stay time. The result demonstrates that in the opioid-free group, the duration of PACU stay of patients was significantly longer (SMD = 0.65, 95% CI: 0.20, 1.09; $P < 0.05$, $I^2 = 98\%$, Fig. 8).

Adverse Effects

A total of 7 trials reported the incidence of hypotension. The forest plots showed no significant differences in the incidences of hypotension between both groups (RR = 1.41, 95% CI: 0.75, 2.66; $P = 0.28$, $I^2 = 40\%$, Suppl. Fig. 5). Three trials reported the incidence of hypertension; however, no significant difference was observed between both groups (RR = 1.07, 95% CI: 0.45, 2.50; $P = 0.88$, $I^2 = 54\%$, Suppl. Fig. 6). Nine trials reported bradycardia incidences in patients. The forest plot showed significantly high bradycardia incidences in patients in the opioid-free group (RR = 2.13, 95% CI: 1.41, 3.22, $P < 0.05$, $I^2 = 0\%$, Suppl. Fig. 7). A total

Table 1. *Detailed informational of included studies.*

Study	Type of Surgery	Sample Size		Age	Anesthetic Induction		Anesthetic Maintenance		Postoperative pain management
		OF	OB		OF	OB	OF	OB	
Abdelrahman 2021	Oesophagectomy	15	15	18-64	Loading: Dex 1 μg/kg, Induction: propofol 2.0 mg/kg; rocuronium 0.5 mg/kg.	Loading: Fentanyl 1 μg/kg; Induction: propofol 2.0 mg/kg, rocuronium 0.5 mg/kg.	Ketamine 0.5 mg/kg, lidocaine 1 mg/kg, 0.1 μg/kg/h dex, 0.1 mg/kg/h ketamine and 1 mg/kg/h lidocaine, 2% sevoflurane.	Fentanyl 1 μg/kg, fentanyl 0.4 μg/kg/h, 2% sevoflurane.	Acetaminophen, ketorolac trometha-min, nalbuphine.
Ahmed 2022	Laparoscopic bariatric surgeries	40	40	> 21	Loading: A mixture of 100 μg dex, 25 mg ketamine, 200 mgf lidocaine, 2 g magnesium; Induction: propofol 2 mg/kg, rocuronium 1 mg/kg.	Loading: Saline; Induction: fentanyl 0.1 mL/kg, propofol 2 mg/kg, rocuronium 1 mg/kg.	Sevoflurane 2%, the previous mixture fluid.	Sevoflurane 2%, fentanyl of 0.5 μg/kg.	Acetaminophen.
An 2022	Laparoscopic radical colectomy	51	50	18-65	Loading: Dex 0.6 μg/kg; Induction: dex 0.5 μg/kg/h, ketorolac 30 mg, propofol 2 mg/kg, cisatracurium 0.2 mg/kg.	Loading: None; Induction: sufentanil 0.5 μg/kg, propofol 2 mg/kg, cisatracurium 0.2 mg/kg.	Dex 0.5 μg/kg/h, cisatracurium, sevoflurane 1-3%.	Remifentanil 200-500 μg/h, atracurium, sevoflurane 1-3%.	PCA: OF: dex 6 μg/kg, ketorolac 180 mg; OB: dezocine 0.5 mg/kg, ketorolac 180 mg.
An 2021	Video-assisted thoracoscopic surgery	49	48	18-65	Loading: Dex 1 μg/kg; Induction: etomidate 0.2-0.3 mg/kg, ketorolac 30 mg, cisatracurium 0.2 mg/kg.	Loading: None; Induction: sufentanil 0.5 μg/kg, etomidate 0.2-0.3 mg/kg, cisatracurium 0.2 mg/kg.	Dex 0.5 μg/kg/h, sevoflurane 1-3%, cisatracurium.	Remifentanil 200-500 μg/h, sevoflurane 1-3%, cisatracurium.	None.
Bakan 2015	Laparoscopic chole-cystectomy	40	40	20-60	Loading: Dex 0.6 μg/kg; Induction: dex 0.3 μg/kg/h, lidocaine 1.5 mg/kg, propofol 1.5 mg/ kg, vecuronium 0.1 mg/kg.	Loading: Fentanyl 2 μg/kg; Induction: remifentanil 0.25 μg /kg/min, propofol 1.5 mg/kg, vecuronium 0.1 mg/kg.	Lidocaine 2 mg /kg/h, propofol 3-12 mg/kg/h, vecuronium.	Propofol 3-12 mg/kg/h, vecuronium.	Dexketoprofen, paracetamol, fentanyl PCA.
Beloeil 2021	Major or intermediate scheduled surgery	157	157	> 18	Propofol 1.5-2 mg/kg, lidocaine 1.5 mg/kg, ketamine 0.5 mg/kg, cisatracurium 0.15 mg/kg, dex 0.4-1.4 μg/kg.	Propofol 1.5-2 mg/kg, lidocaine 1.5 mg/kg, ketamine 0.5 mg/kg, cisatracurium 0.15 mg/kg, TCI of remifentanil 3-5 ng/mL.	Desflurane, lidocaine: 1.5 mg/kg/h, ket-amine 0.25 mg/kg/h, cisatracurium, dex-medetomidine 0.4-1.4 μg/kg/h.	Desflurane, lidocaine: 1.5 mg/kg/h, ket-amine 0.25 mg/kg/h, cisatracurium, TCI of remifentanil 2-5 ng/mL.	OB: morphine 0.05 mg/kg; Al: lidocaine, paracetamol, nefopam, morphine PCA.
Bhardwaj 2019	Laparoscopic urological surgery	40	40	20-60	Loading: Dex 0.5 μg/kg; Induction: propofol 2.5-3.5 mg/kg, atracurium 0.5 mg/kg, lidocaine 1.5 mg/kg, ketamine 0.5 mg/kg.	Loading: None; Induction: fentanyl 2 μg/kg, propofol 2.5-3.5 mg/kg, atracurium 0.5 mg/kg.	Propofol 50-200 μg/kg/min, dexmedetomidine 0.1-0.3 μg/kg/h	Propofol 50-200 μg/kg/min, fentanyl 0.5 μg/kg	Diclofenac, paracetamol; tramadol for rescue analgesia.
Chen 2022	Laparoscopic gynecologic surgery	39	39	18-70	Loading: Dex 0.6 μg/kg, lidocaine 1.5 mg/kg; Induction: TCI of propofol 6 μg/mL, rocuronium 0.6 mg/kg.	Loading: Sufentanil 0.5 μg/kg; Induction: TCI of propofol 6 μg/mL, rocuronium 0.6 mg/kg.	TCI of propofol 2-4 μg/mL, dex 0.5–1.5 μg/kg/h, lidocaine 1.5mg/kg/h, rocuronium.	TCI of propofol 2-4 μg/mL, remifentanil 0.05-0.25 μg/kg/min, rocuronium.	Ketorolac, sufentanil PCA; oxycodone for rescue analgesia.

Table 1 continued. *Detailed informational of included studies.*

Study	Type of Surgery	Sample Size		Age	Anesthetic Induction		Anesthetic Maintenance		Postoperative pain management
		OF	OB		OF	OB	OF	OB	
Choi 2017	Thyroidectomy	40	40	18-60	Loading: Dex 1 μg/kg; Induction: propofol 1.5-2.5 mg/kg, rocuronium 0.6-1 mg/kg.	Loading: None; Induction: propofol 1.5-2.5 mg/kg, rocuronium 0.6-1 mg/kg, TCI of remifentanil 4 ng/mL.	Dex 0.3-0.5 μg/kg/h, sevoflurane 1-2.5%.	TCI of remifentanil 2-3 ng/mL, sevoflurane 1-2.5%.	Ketorolac for rescue analgesia.
Choi 2022	Gynecological laparoscopy	37	38	20-65	Loading: Dex 0.7 μg/kg; Induction: propofol 1.5-2 mg/kg, rocuronium 0.8 mg/kg, dex 0.5 μg/kg/h, lidocaine 1.5 mg/kg bolus, lidocaine 1.5 mg/kg/h.	Loading: None; Induction: propofol 1.5-2 mg/kg, rocuronium 0.8 mg/kg, TCI of remifentanil 3.5 ng/mL.	Dex 0.1 μg/kg/h, desflurane 4-6%, rocuronium.	TCI of remifentanil 0.5 ng/mL, desflurane 4-6%, rocuronium.	Acetaminophen, ketorolac, fentanyl PCA.
Choi 2016	Laparoscopic total hysterectomy	32	30+30	18-60	Lidocaine 40 mg, propofol 2 mg/kg, rocuronium 0.6 mg/kg.	Lidocaine 40 mg, propofol 2 mg/kg, rocuronium 0.6 mg/kg.	Dexmedetomidine loading 1 μg/kg, dex 0.5 μg/kg/h, desflurane, N_2O.	Fentanyl loading 1 μg/kg, fentanyl 0.4 μg/kg/h OR remifentanil loading 1 μg/kg, remifentanil 0.08 μg/kg/min, desflurane, N_2O.	Ketorolac.
Ciftci 2015	Mandibular fracture surgery	35	35	18-60	Loading: Dex 1 μg/kg; Induction: propofol 2 mg/kg, rocuronium 0.6 mg/kg.	Loading: Remifentanil 1 μg/kg; Induction: propofol 2 mg/kg, rocuronium 0.6 mg/kg.	Sevoflurane 2%, N_2O.	Sevoflurane 2%, N_2O.	NR
Elshafie 2022	Hepatic resection	20	20	18-65	Propofol 1.5-2 mg/kg, rocuronium 0.9 mg/kg, lidocaine 60 mg, magnesium sulfate 1g dex 0.7 μg/kg/h.	Propofol 1.5-2 mg/kg, fentanyl 2μg/kg, rocuronium 0.9 mg/kg.	Dex 0.2-0.7 μg/kg/h, bilateral erector spinae plane block, rocuronium, sevoflurane.	Opioids, rocuronium, sevoflurane.	OF: acetaminophen; fentanyl for rescue analgesia. OB: fentanyl for rescue analgesia.
Gazi 2018	Hysteroscopy	15	15	18-65	Loading: Dex 1 μg/kg; Induction: propofol 2 mg/kg, rocuronium 0.5 mg/ kg.	Loading: Remifentanil 1 μg/kg; Induction: propofol 2 mg/kg, rocuronium 0.5 mg/ kg.	Sevoflurane 2%, dex 0.2-0.7 μg/kg/h.	Sevoflurane 2%, remifentanil 0.05-0.5 μg/kg/min.	Paracetamol.
Greiss 2022	Laparoscopic surgery	41	41	18-65	Loading: Dex 1 μg/kg; Induction: lidocaine 1 mg/kg, propofol 2 mg/kg, atracurium 0.5 mg/kg.	Loading: Fentanyl 1 μg/kg; Induction: lidocaine 1 mg/kg, propofol 2 mg/kg, atracurium 0.5 mg/kg.	Isoflurane 1%, dex 0.2-0.7 μg/kg/h.	Isoflurane 1%, fentanyl 0.2-0.7 μg/kg/h.	Paracetamol; morphine for rescue analgesia.
Hakim 2019	Gynecological laparoscopic surgery	40	40	21-50	Loading: Dex 0.6 μg/kg; Induction: propofol 2 μg/kg, cisatracurium 0.1 mg/kg.	Loading: Fentanyl 1 μg/kg; Induction: propofol 2 μg/kg, cisatracurium 0.1 mg/kg.	Propofol 5-10 mg/kg/h, dex 0.2 μg/kg/h.	Propofol 5-10 mg/kg/h, fentanyl 0.5 μg/kg/h.	Ketorolac, acetaminophen; tramadol for rescue analgesia.

Table 1 continued. *Detailed informational of included studies.*

Study	Type of Surgery	Sample Size		Age	Anesthetic Induction		Anesthetic Maintenance		Postoperative pain management
		OF	OB		OF	OB	OF	OB	
Hwang 2015	Posterior lumbar interbody fusion	19	18	18-70	Loading: Dex 0.01 μg/kg/min for 10 mins; Induction: propofol 1-2 mg/kg, rocuronium 1 mg/kg.	Loading: Remifentanil 0.01 μg/ kg/min for 10 mins; Induction: propofol 1-2 mg/ kg, rocuronium 1 mg/kg.	Propofol 3-12 mg/ kg/h, dex 0.01-0.02 μg/ kg/min.	Propofol 3-12 mg/ kg/h, remifentanil 0.01-0.02 μg/ kg/min.	Hydromorphone PCA; Fentanyl and tramadol for rescue analgesia.
Ibrahim 2022	Sleeve gastrectomy	51	52	18-65	Loading: Dex 0.1 μg/kg for 10 mins; Induction: propofol 2 mg/kg, ketamine 0.5 mg/kg, cisatracurium 0.15 mg/kg, dex 0.5 μg/kg/h, ketamine 0.5 mg/ kg/h, lidocaine 1 mg/kg/h.	Loading: None; Induction: propofol 2 mg/kg, fentanyl 1 μg/kg, cisatracurium 0.15 mg/kg,	Sevoflurane to 1.5-2.0 MAC. Ultrasound-guided bilateral oblique subcostal transverse abdominis plane.	Sevoflurane to 1.5-2.0 MAC. Ultrasound-guided bilateral oblique subcostal transverse abdominis plane.	Paracetamol; Pethidine for rescue analgesia. (In PACU) Paracetamol, parecoxib; pethidine for rescue analgesia. (In ward)
Jung 2011	Total laparoscopic hysterectomy	25	25	18-65	Propofol 2 mg/kg, lidocaine 40 mg, rocuronium 0.6 mg/kg.	Propofol 2 mg/kg, lidocaine 40 mg, rocuronium 0.6 mg/ kg.	Loading: Dex 1μg/kg over 10 mins; Maintenance: dex 0.2-0.7 μg/kg/h, N_2O 3 L/min, desflurane 6-7%.	Loading: Remifentanil 0.8-1.2 μg/kg over 1 min; Maintenance: remifentanil 0.05-0.1 μg/kg/min, N_2O 3 L/ min, desflurane 6-7%.	Ketorolac.
Karabayirli 2017	Endoscopic sinus surgery	23	24	NR	Loading: Dex 1μg/kg over 10 mins; Induction: propofol 2.5 mg/kg, dex 0.7 μg/kg/h, rocuronium 0.6 mg/kg.	Loading: None; Induction: remifentanil 1 μg/kg propofol 2.5 mg/kg, 0.7 μg/kg/h, rocuronium 0.6 mg/kg.	Sevoflurane 2%, N2O, dex 0.7 μg/kg/h.	Sevoflurane 2%, N2O, remifentanil 0.25-0.50 μg/kg/min.	Tramadol; Paracetamol for rescue analgesia.
Lee 2013	Endoscopic sinus surgery	32	34	20-60	Loading: Dex 1μg/kg; Induction: propofol 2-2.5 mg/ kg, rocuronium 0.6 mg/kg.	Loading: Remifentanil 1μg/ kg; Induction: propofol 2-2.5 mg/kg, rocuronium 0.6 mg/kg.	Dex 0, 4-0, 8 μg/kg/h, desflurane 5-7 % + N20.	Remifentanil 0.2-0.4 μg/kg/min, desflurane 5-7 % + N_20.	Ketarolac for rescue analgesia.
Li 2015	Cesarean delivery	22	22	NR	Loading: Dex 0.4 μg/kg over 10 min; Induction: propofol 2 mg/kg, cisatracurium 0.2 mg/kg.	Loading: Remifentanil 2 μg/ kg over 10 min; Induction: propofol 2 mg/kg, cisatracurium 0.2 mg/kg.	Propofol, cisatracurium, dex 0.4 μg/kg/h.	Propofol, cisatracurium, Remifentanil 2 μg/ kg/h.	Sufentanil PCA.
Lotfy 2022	Open abdominal hysterectomy	30	30	NR	Dex 0.4 μg/kg, lidocaine 1.5 mg/ kg.	Propofol 2 mg/kg, rocuronium 0.5 mg/kg.	Sevoflurane at 1.7 MAC, dex 0.2-0.7 μg/ kg/h, lidocaine 1-2 mg/kg/ h.	Sevoflurane at 1.7 MAC, fentanyl 1 μg/kg.	Morphine for rescue analgesia.
Massoth 2021	Gynecological laparoscopy	76	76	NR	Loading: Dex 0.6 μg/kg over 7 min; Induction: propofol 1-2 mg/ kg, rocuronium 0.6 mg/kg, esketamine 0.15 mg/kg.	Loading: None. Induction: sufentanil 0.3 μg/kg, propofol 1-2 mg/kg, rocuronium 0.6 mg/kg.	Dex 0.3 μg/kg/h, esketamine 0.15 mg/ kg/h, sevoflurane at MAC 1.0-1.4.	Sufentanil 0.15 μg/ kg repetitive bolus, sevoflurane at MAC 0.8-1.0.	Ibuprofen, morphine PCA.

Table 1 continued. *Detailed informational of included studies.*

Study	Type of Surgery	Sample Size		Age	Anesthetic Induction		Anesthetic Maintenance		Postoperative pain management
		OF	OB		OF	OB	OF	OB	
Mona 2017	Laparoscopic cholecystectomy	40	40	40-50	Loading: Dex 0.7 μg/kg; Induction: dex 0.4 μg/kg/h, propofol 2.5 mg/kg, rocuronium 0.6 mg/kg.	Loading: Remifentanil 0.7 μg/kg; Induction: remifentanil 0.2 μg/kg/h, propofol 2,5 mg/kg, rocuronium 0.6 mg/kg.	Dex 0.4 μg/kg/h, sevoflurane, rocuronium 0.3 mg/kg.	Remifentanil 0.2 μg/kg/h, sevoflurane, rocuronium 0.3 mg/kg.	Fentanyl as rescue medication.
Salman 2009	Ambulatory gynecologic laparoscopic surgery	30	30	20-40	Loading: Dex 1 μg/kg; Induction: propofol 2 mg/kg, vecuronium 0.1 mg/kg.	Loading: Remifentanil 1 μg/kg; Induction: propofol 2 mg/kg, vecuronium 0.1 mg/kg.	Dex 0.4 μg/kg/h, desflurane 6%.	Remifentanil 0.2 μg/kg/min, desflurane 6%.	Paracetamol oral; morphine for rescue analgesia.
Saravanaperumal 2022	Oocyte retrieval	31	31	20-38	Loading: Dex 0.5μg /kg; Induction: propofol 1.5 mg/kg.	Loading: Fentanyl 1 μg/kg; Induction: Propofol 1.5 mg/kg.	Dex 0.5 μg/kg.	Fentanyl 1 μg/kg.	Paracetamol for rescue analgesia.
Shah 2020	Modified radical mastectomy	35	35	18-75	Loading: Dex 0.5μg /kg; Induction: propofol, esmolol 0.5 mg/kg, atracurium 0.6 mg/kg.	Loading: None. Induction: fentanyl 2 μg/kg, propofol, atracurium 0.6 mg/kg.	Pectoralis block, ketamin 0.5 mg/kg, dex infusion to maintain BIS in 40-60 range.	Paracetamol 1,000 mg, morphine 0.1 mg/kg, sevoflurane to maintain BIS in 40-60 range	OB: Morphine and fentanyl for rescue analgesia. OF: Paracetamol, ketorolac; fentanyl for rescue analgesia.
Soudi 2022	Major breast cancer surgery	30	30	18-65	Loading: Dex 1 μg /kg, ketamine: 0.5 mg/kg; Induction: propofol 1.5-2 mg/kg, rocuronium 0.5 mg/kg.	Loading: Fentanyl 2 μg/kg; Induction: propofol 1.5-2 mg/kg, rocuronium 0.5 mg/kg.	Isoflurane, dex0.5 μg/kg/h, ketamine 0.25 mg/kg/h.	Isoflurane, fentanyl 1 μg/kg/h.	Paracetamol, diclofenac; nalbuphine for rescue analgesia.
Techanivate 2012	Ambulatory gynecologic diagnostic laparoscopy	20	20	NR	Propofol 2 mg/kg, atracurium 0.5 mg/kg.	Propofol 2 mg/kg, atracurium 0.5 mg/kg.	Dex 0.5 μg/kg, desflurane, N2O.	Fentanyl 0.5 μg/kg, desflurane, N2O.	Fentanyl for rescue analgesia.
Turgut 2009	Supratentorial craniotomy	25	25	18-80	Loading: Dex 1 μg /kg; Induction: propofol, cisatracurium 0.2 mg/kg.	Loading: Remifentanil 1 μg/kg; Induction: propofol, cisatracurium 0.2 mg/kg.	Propofol, dex 0.2-1 μg/kg/h.	Propofol, remifentanil 0.05-1μg/kg/min.	Not report.
Ziemann-Gimmel 2014	Bariatric surgery	60	59	> 18	Loading: Dex 0.5 μg /kg; Induction: propofol 1-2.5 mg/kg, succinylcholine 1-1.5 mg/kg OR rocuronium 0.5-1.0 mg kg.	Loading: Fentanyl 0.5 μg/kg; Induction: propofol 1-2.5 mg/kg, succinylcholine 1-1.5 mg/kg OR rocuronium 0.5-1.0 mg kg.	Dex 0.1-0.3 μg/kg/h, propofol 75-150 μg/kg/min, ketamine 0.5 mg/kg.	Sevoflurane or desflurane at 0.7-1.3 MAC, fentanyl, morphine or hydromorphone.	Acetaminophen, ketorolac; oxycodone or hydromorphone for rescue analgesia.

Abbreviations: OF, opioid free; OB, opioid based; dex, dexmedetomidine; PCA, patient-controlled analgesia; TCI, target-controlled infusion; MAC, minimum alveolar concentration.

of 21 trials reported PONV incidences. The forest plot results revealed lowered PONV incidence in patients in the opioid-free group (RR = 0.40, 95% CI: 0.30, 0.53; $P < 0.05$, $I^2 = 47\%$, Suppl. Fig. 8). The incidence of hypoxemia was similar between both groups (RR = 0.95, 95% CI: 0.30, 3.02; $P = 0.93$, $I^2 = 53\%$, Suppl. Fig. 9).

Publication Bias and Sensitivity Analysis

The funnel plot showed the symmetrical distribution of 2-hour postoperative pain scores (Suppl. Fig. 10), with $P = 0.6$ for the Bgger's test (Suppl. Fig. 11) and no publication bias. In addition, sensitivity analysis revealed stable results (Suppl. Fig. 12).

The plots for patients who required rescue analgesics were asymmetric (Suppl. Fig. 13), with $P = 0.607$ for Bgger's test (Suppl. Fig. 14), which indicates no obvious publication bias. Furthermore, the sensitivity analysis indicated that the results were stable (Suppl. Fig. 15).

Quality of Evidence

The quality of evidence was reported from low to high. Table 2 shows the summary of GRADE.

Discussion

To the best of our knowledge, our meta-analysis is the first to investigate the safety and effectiveness of dexmedetomidine as an opioid substitute for inducing anesthesia. The results indicated that dexmedetomidine as an opioid-free anesthesia strategy could significantly reduce the pain scores of patients after surgery, the consumption of opioids, and PONV incidence. However, the duration of extubation and PACU stay were longer, and the incidences of bradycardia were higher in patients in the opioid-free group. Moreover, the evidence quality was low to moderate.

In this meta-analysis, patients receiving dexmedetomidine-based opioid-free general anesthesia experienced less postoperative pain, consistent with previous meta-analyses. Grape et al (16) showed an increase in postoperative pain in patients treated with opioid-based anesthesia, thereby supporting the use of opioid-based analgesics. Frauenknecht et al (61) showed that opioid-based anesthesia could not decrease postoperative pain and was associated with a high risk of PONV. The primary cause could be opioid-induced hyperalgesia (OIH), wherein patients treated with opioids experience enhanced sensitivity to pain stimuli. The mechanism of OIH is relatively complex. A recent study (62) showed that HCN-channel-dependent hyperexcitability of IL-mPFC output neurons leads to the development and maintenance of OIH in male rats.

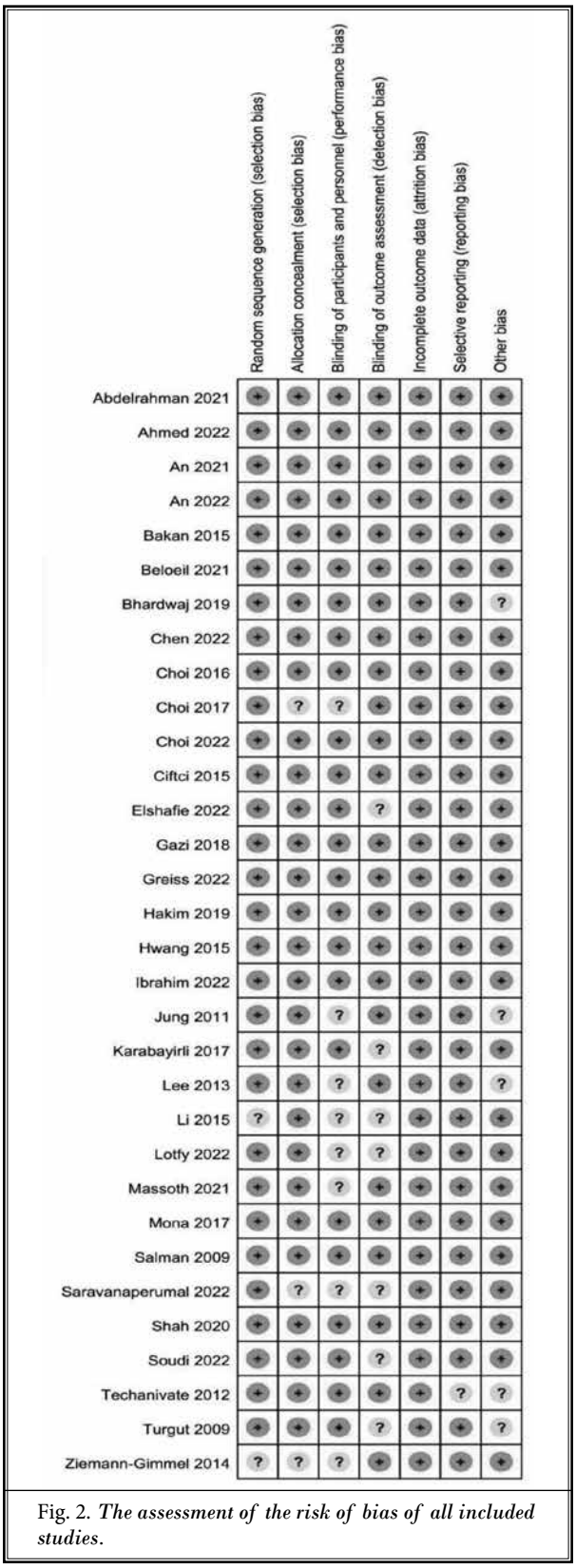

Fig. 2. *The assessment of the risk of bias of all included studies.*

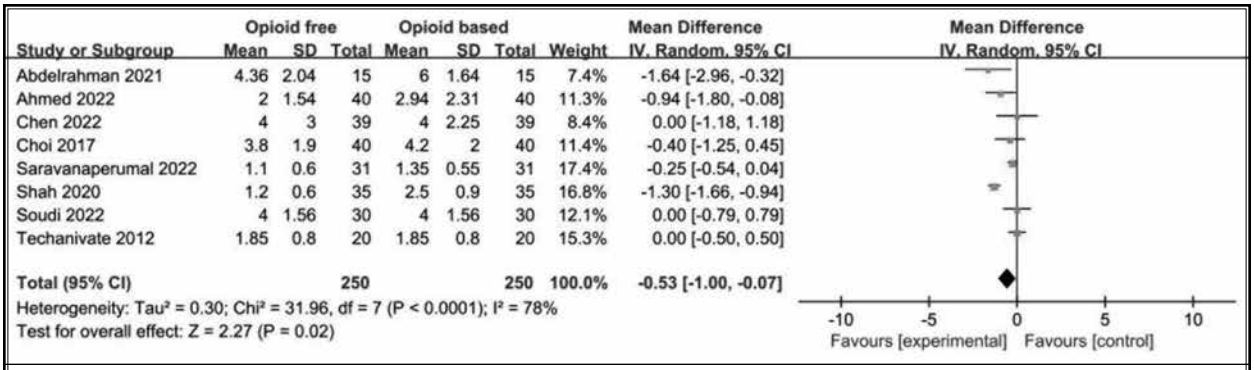

Fig. 3. *Forest plot showing a 2-hour postoperative pain score.*

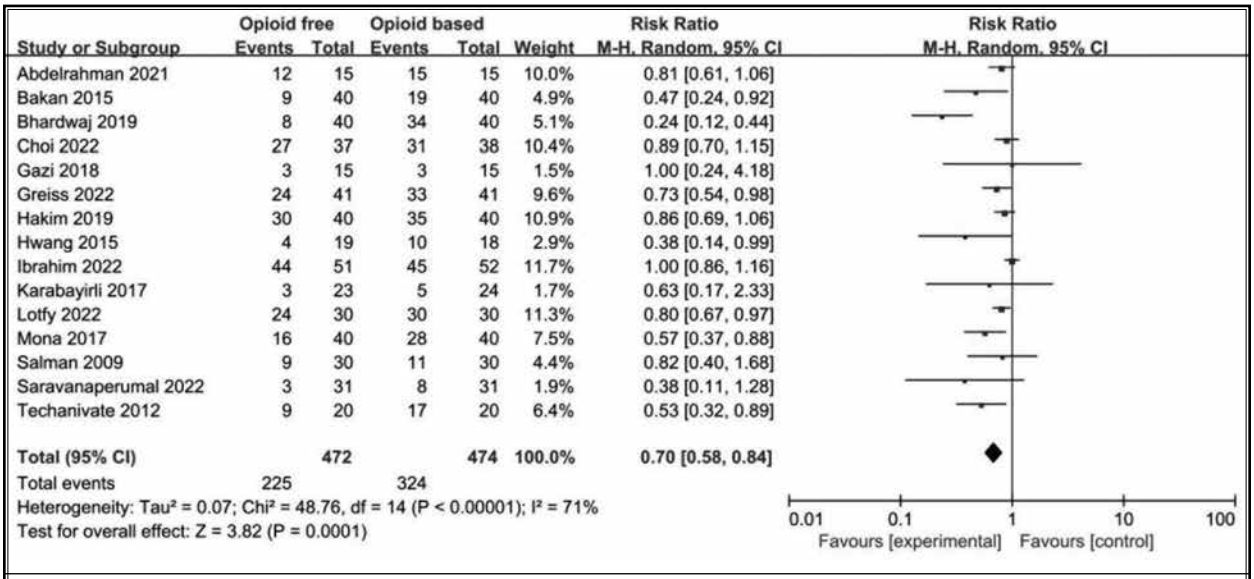

Fig. 4. *Forest plot showing the number of patients who needed rescue analgesia during the postoperative period.*

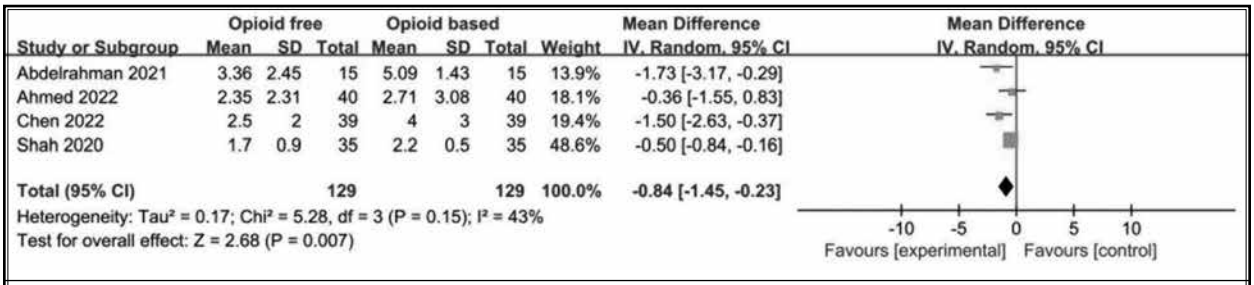

Fig. 5. *Forest plot showing a 4-hour postoperative pain score.*

Therefore, maintaining hemodynamic stability using opioid drugs to relieve pain during the perioperative period will be challenged. A study (61) stated a similar viewpoint. Multimode analgesics, such as regional block technology, ketamine, magnesium, and esmolol, could reduce opioid consumption (63,64).

Additionally, our results revealed a significantly low PONV incidence in patients in the opioid-free group, indicating the benefit of not using opioids. PONV is one of the common adverse reactions of opioid drugs and a serious complication during the postoperative rehabilitation of patients, thereby prolonging the duration

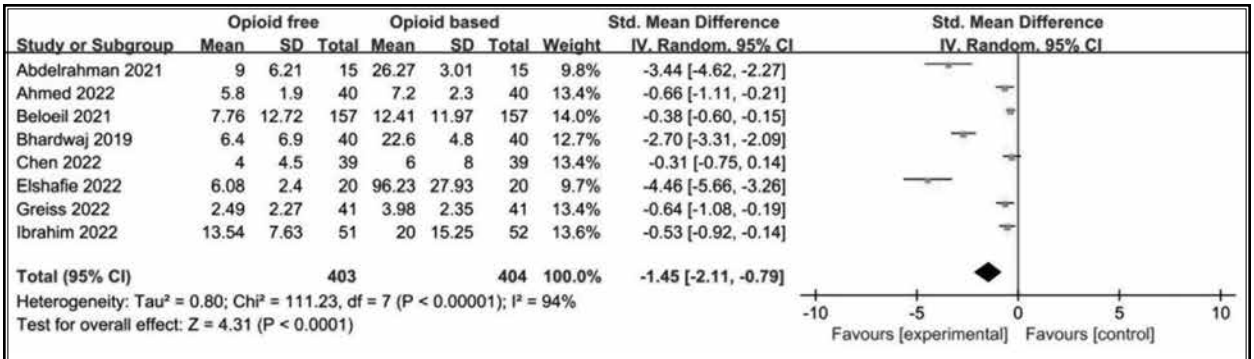

Fig. 6. *Forest plot showing opioid consumption postsurgery.*

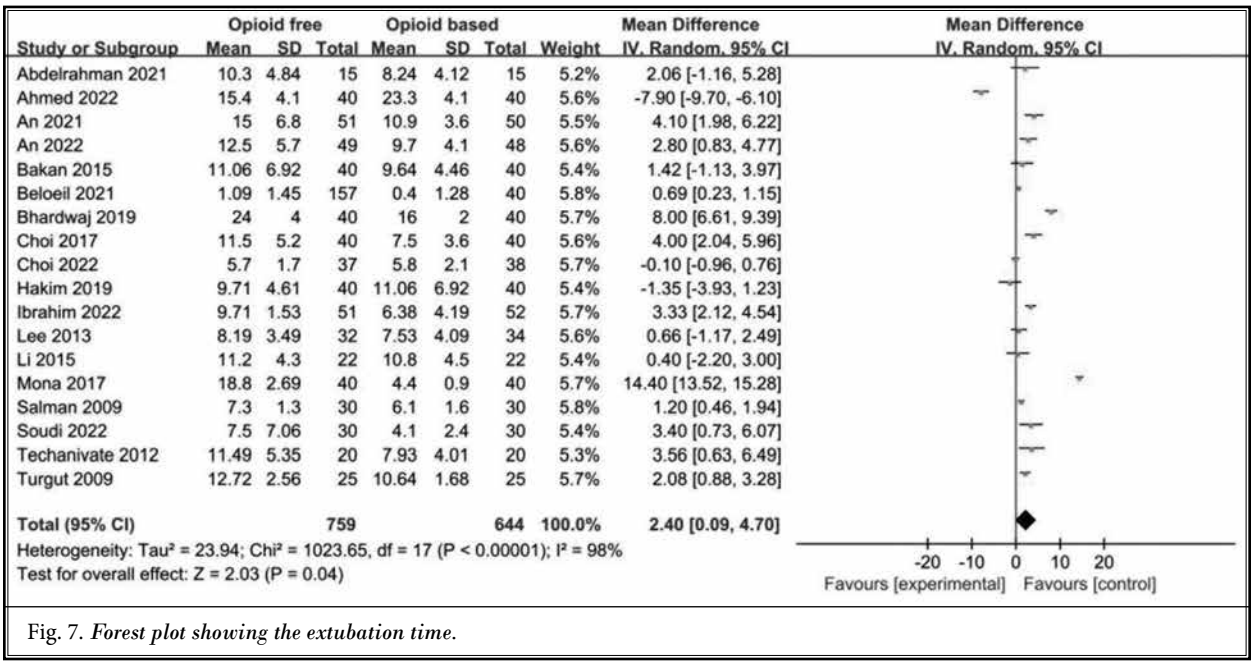

Fig. 7. *Forest plot showing the extubation time.*

of hospital stay and increasing the medical burden (65). Recent studies (54,60) have supported the use of opioid-free anesthesia as an alternative to reduce PONV risk.

Our results revealed a longer duration of extubation and PACU stays and a higher incidence of bradycardia in patients in the opioid-free group, which could be related to the efficacy of dexmedetomidine, consistent with a previous study (10). However, due to insufficient data, we could not conduct a subgroup analysis for different doses of dexmedetomidine. Furthermore, we observed no differences in the incidence of hypotension, hypertension, and hypoxemia in patients.

Although we set strict inclusion criteria, such as no opioid consumption in the perioperative period, clinical heterogeneity is still inevitable. Factors like using different types of general anesthesia, surgeries, ethical differences, and multimodal analgesic methods could lead to clinical differences. Therefore, in this meta-analysis, we used the random-effects model with low I^2 values.

However, our study has a few limitations. First, due to insufficient data availability, we could not conduct a subgroup analysis using different anesthesia-maintaining drugs, such as inhaled anesthetics and propofol. Second, we conducted subgroup analysis for the different types of surgeries and opioid substitutes; however, heterogeneity did not reduce significantly. Finally, we did not analyze the effect of different doses of dexmedetomidine.

Conclusions

Current evidence indicates that dexmedetomidine-based opioid-free general anesthetic is effective in induc-

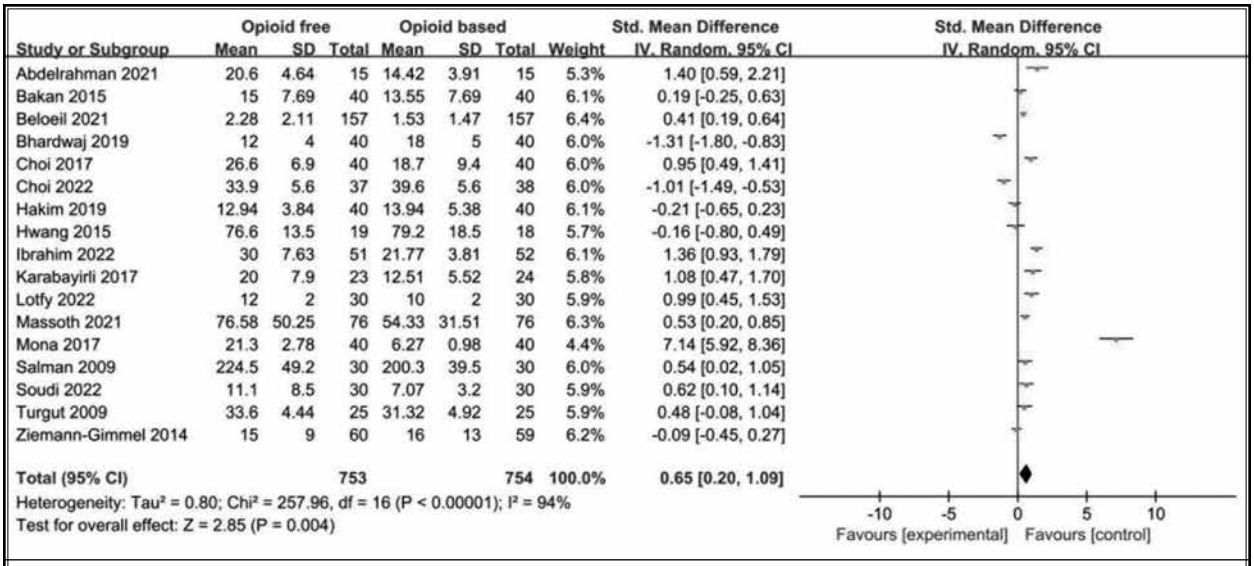

Fig. 8. *Forest plot showing the duration of PACU stay.*

Table 2. *Summary for GRADE.*

Outcome	Included Studies (n)	Patients (n)	Quality of Evidence	Reasons
Pain score at postoperative 2 hour	8	500	⊕⊕⊕◯ MODERATE	"Inconsistency" was downgraded to "serious."
Number of patients need rescue analgesia	15	946	⊕⊕⊕◯ MODERATE	"Inconsistency" was downgraded to "serious."
Pain scores at postoperative 4 hour	4	258	⊕⊕⊕⊕ HIGH	NONE.
Postoperative opioid consumption	8	807	⊕⊕⊕◯ MODERATE	"Inconsistency" was downgraded to "serious."
Extubation time	18	1,403	⊕⊕⊕◯ MODERATE	"Inconsistency" was downgraded to "serious."
PACU stay time	17	157	⊕⊕⊕◯ MODERATE	"Inconsistency" was downgraded to "serious."
Incidence of hypotension	7	704	⊕⊕⊕⊕ HIGH	NONE.
Incidence of hypertension	3	444	⊕⊕⊕◯ MODERATE	"Inconsistency" was downgraded to "serious."
Incidence of bradycardia	9	834	⊕⊕⊕⊕ HIGH	NONE.
Incidence of PONV	21	1,711	⊕⊕⊕⊕ HIGH	NONE.
Incidence of hypoxemia	3	444	⊕⊕⊕◯ MODERATE	"Inconsistency" was downgraded to "serious."

Abbreviations: PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting.

ing analgesia. However, prolonged extubation time and cardiovascular complications are some of the complications associated with dexmedetomidine. Therefore, additional studies are required to determine the safety and efficacy of dexmedetomidine as an opioid substitute.

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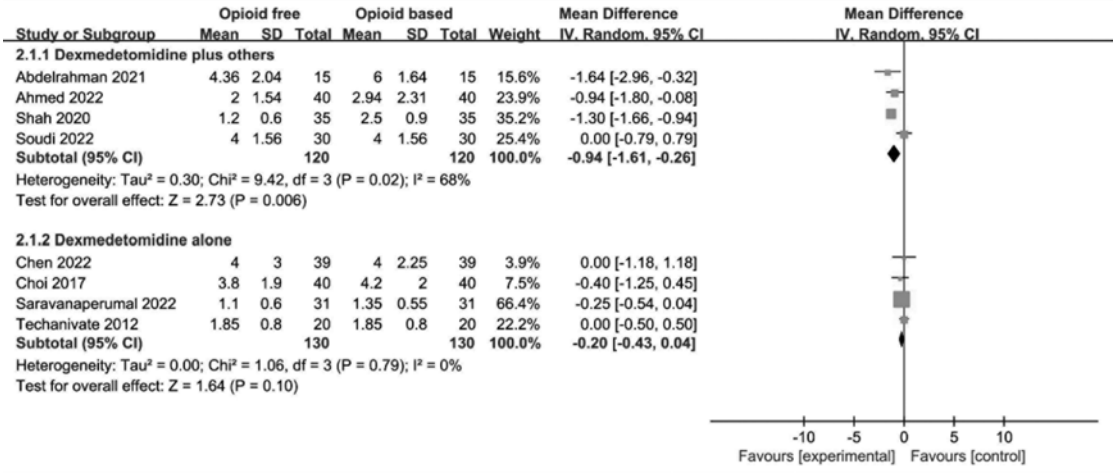
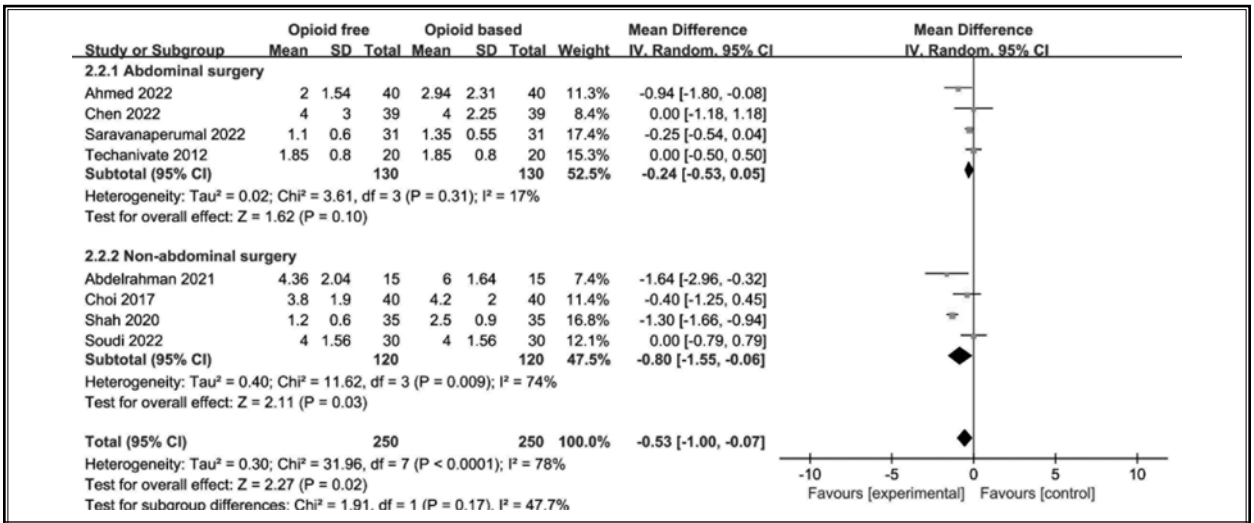
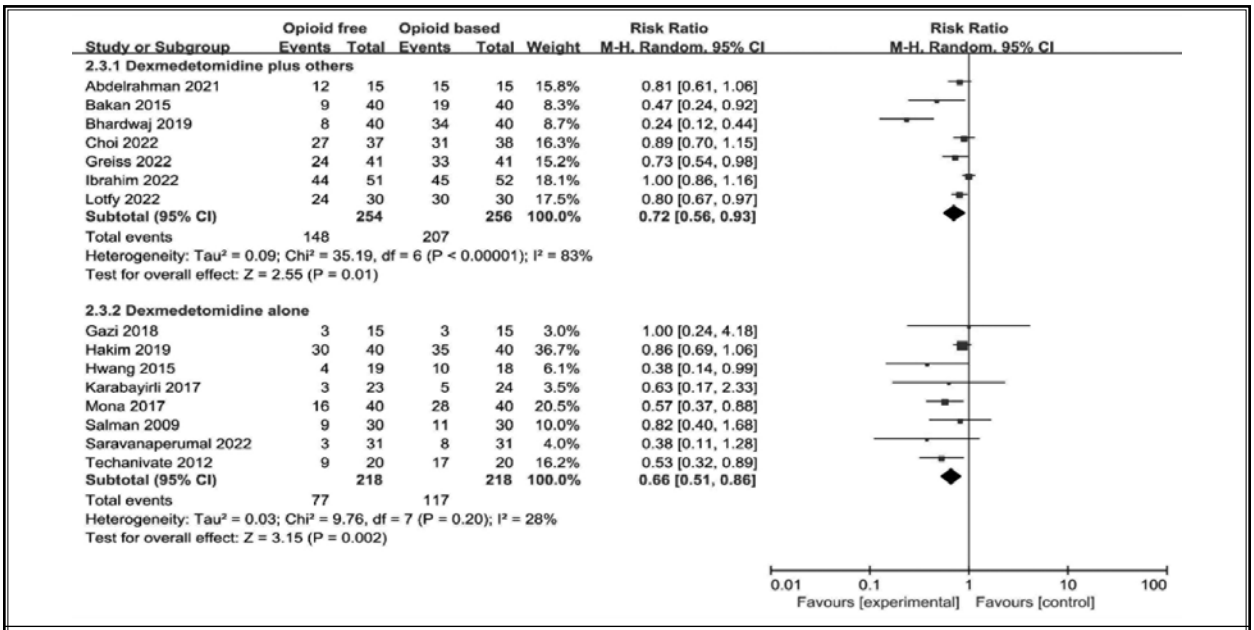
("analgesics non narcotic"[Pharmacological Action] OR "analgesics, non narcotic"[MeSH Terms] OR ("analgesics"[All Fields] AND "Non-narcotic"[All Fields]) OR "non-narcotic analgesics"[All Fields] OR "nonopioid"[All Fields] OR "nonopioids"[All Fields] OR "Opioid-free"[All Fields] OR (("analgesics opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields] OR "opioids"[All Fields] OR "opioid s"[All Fields]) AND "free"[All Fields] AND ("anaesthesia"[All Fields] OR "anesthesia"[MeSH Terms] OR "anesthesia"[All Fields] OR "anaesthesias"[All Fields] OR "anesthesias"[All Fields])) OR "OFA"[All Fields] OR "Non-narcotic"[All Fields] OR ("nonnarcotic"[All Fields] OR "nonnarcotics"[All Fields])) AND ("dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[All Fields] OR "mpv1440"[All Fields] OR ("dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[All Fields] OR "precedex"[All Fields] OR "dexmedetomidine s"[All Fields]) OR ("dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[All Fields] OR ("dexmedetomidine"[All Fields] AND "hydrochloride"[All Fields]) OR "dexmedetomidine hydrochloride"[All Fields]) OR ("dexmedetomidine"[MeSH Terms] OR "dexmedetomidine"[All Fields] OR ("hydrochloride"[All Fields] AND "dexmedetomidine"[All Fields]) OR "hydrochloride dexmedetomidine"[All Fields]) OR "DEX"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields] OR ("controlled clinical trial"[Publication Type] OR "controlled clinical trials as topic"[MeSH Terms] OR "controlled clinical trial"[All Fields]) OR "RCT"[All Fields] OR ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "random"[All Fields] OR "randomization"[All Fields] OR "randomized"[All Fields] OR "randomisation"[All Fields] OR "randomisations"[All Fields] OR "randomise"[All Fields] OR "randomised"[All Fields] OR "randomising"[All Fields] OR "randomizations"[All Fields] OR "randomize"[All Fields] OR "randomizes"[All Fields] OR "randomizing"[All Fields] OR "randomness"[All Fields] OR "randoms"[All Fields])) AND ("general anaesthesia"[All Fields] OR "anesthesia, general"[MeSH Terms] OR ("anesthesia"[All Fields] AND "general"[All Fields]) OR "general anesthesia"[All Fields] OR ("general"[All Fields] AND "anesthesia"[All Fields]) OR ("general anaesthesia"[All Fields] OR "anesthesia, general"[MeSH Terms] OR ("anesthesia"[All Fields] AND "general"[All Fields]) OR "general anesthesia"[All Fields] OR ("general"[All Fields] AND "anesthesia"[All Fields])))



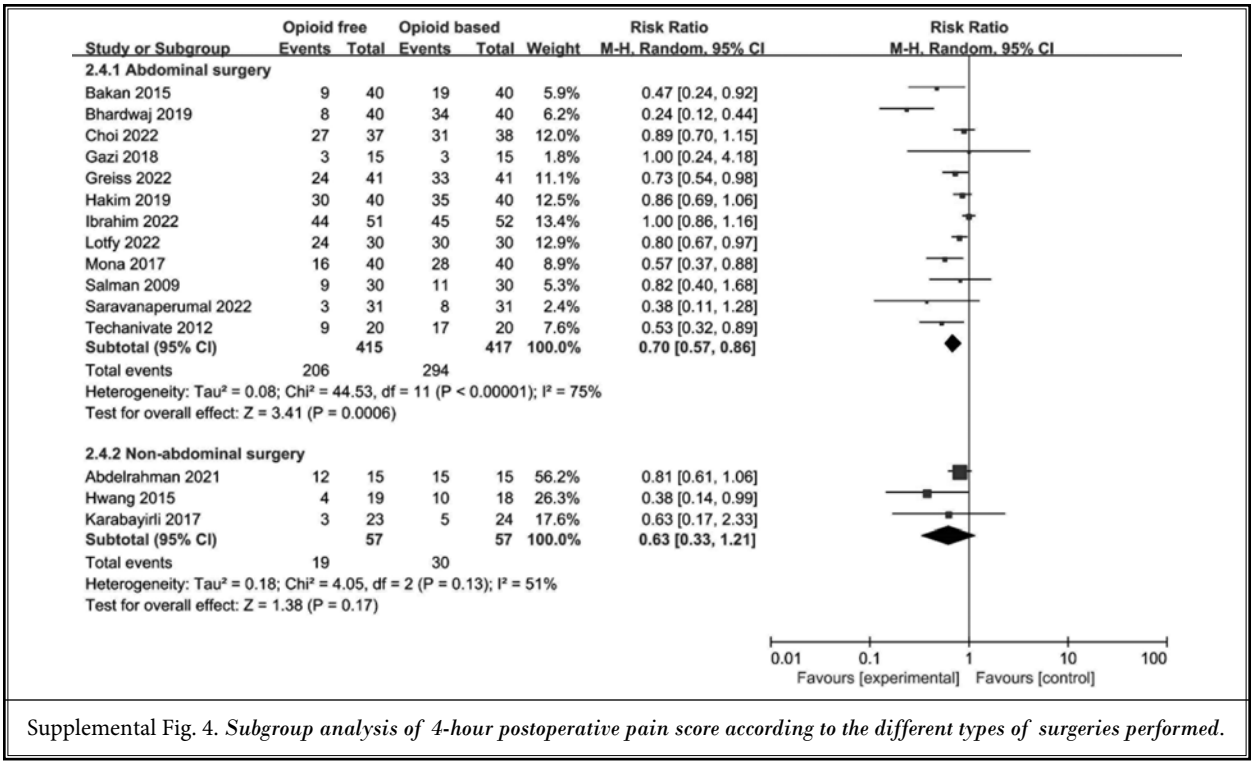
Supplemental Fig. 1. *Subgroup analysis of 2-hour postoperative pain score according to the different types of opioids.*



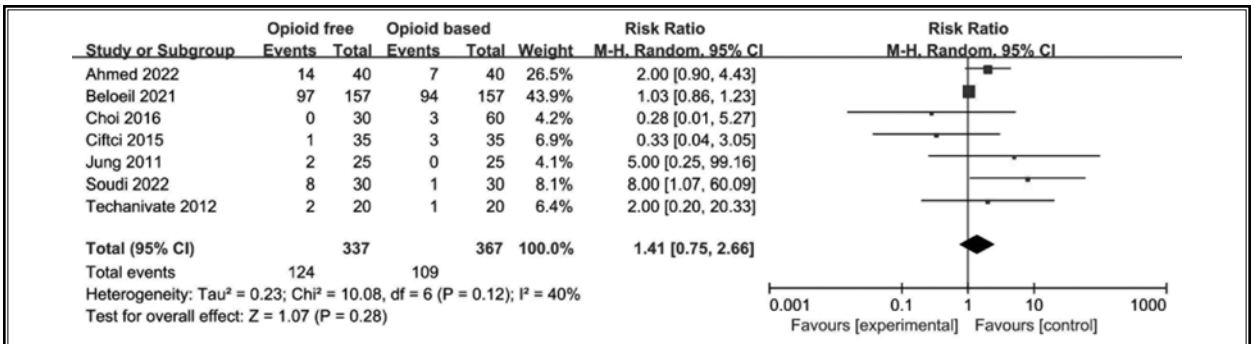
Supplemental Fig. 2. *Subgroup analysis of 2-hour postoperative pain score according to the different types of surgeries.*



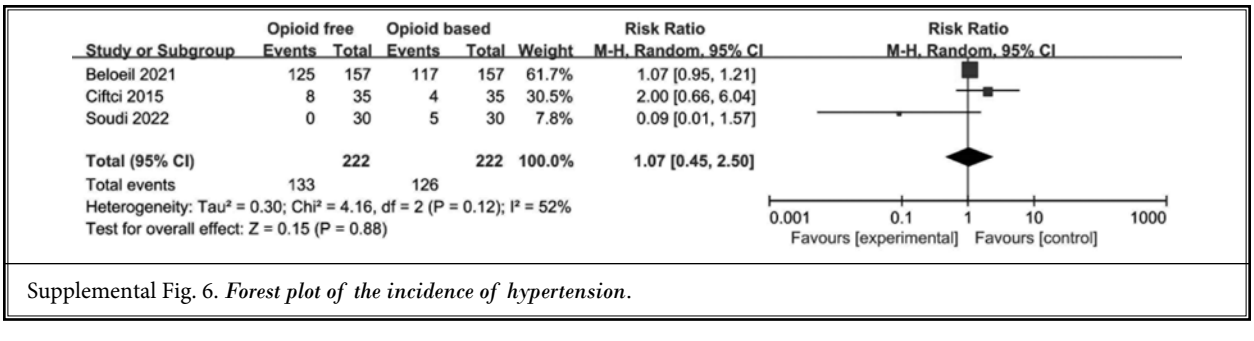
Supplemental Fig. 3. *Subgroup analysis of 4-hour postoperative pain score according to the application of different types of opioids for pain score.*



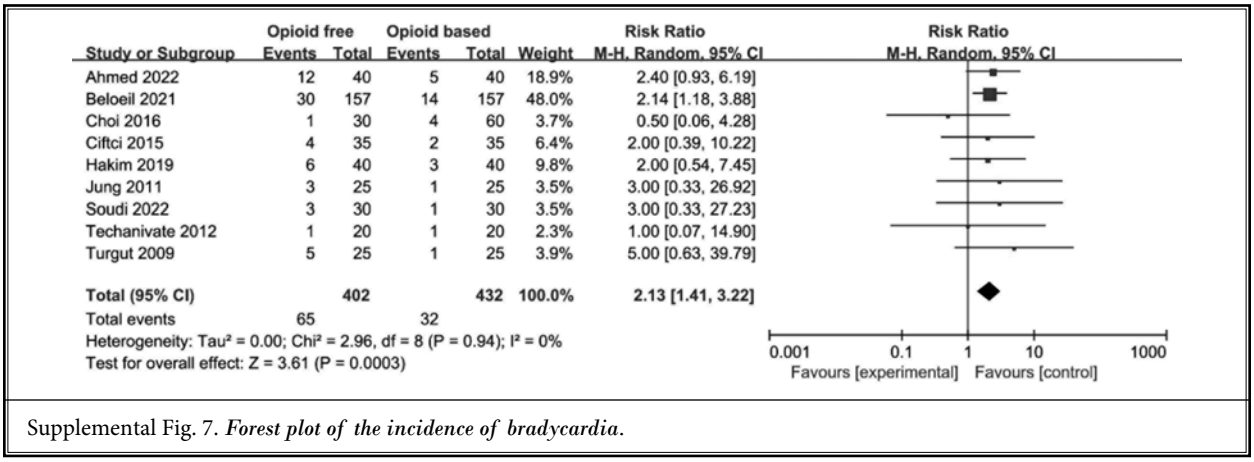
Supplemental Fig. 4. *Subgroup analysis of 4-hour postoperative pain score according to the different types of surgeries performed.*



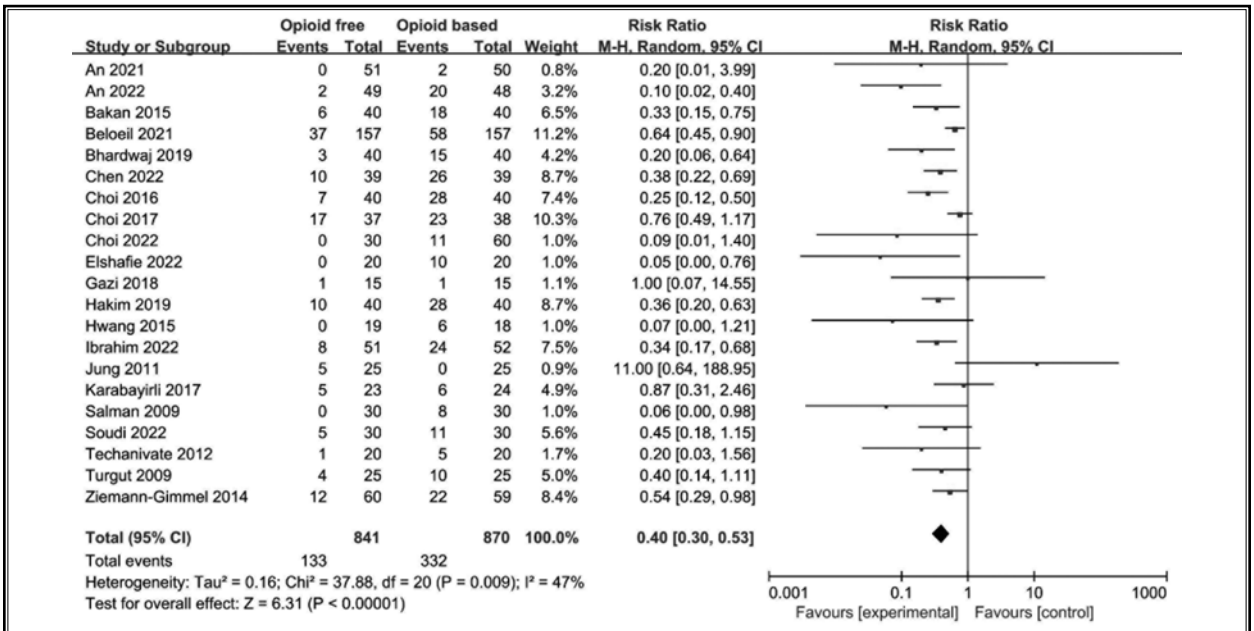
Supplemental Fig. 5. *Forest plot of the incidence of hypotension.*



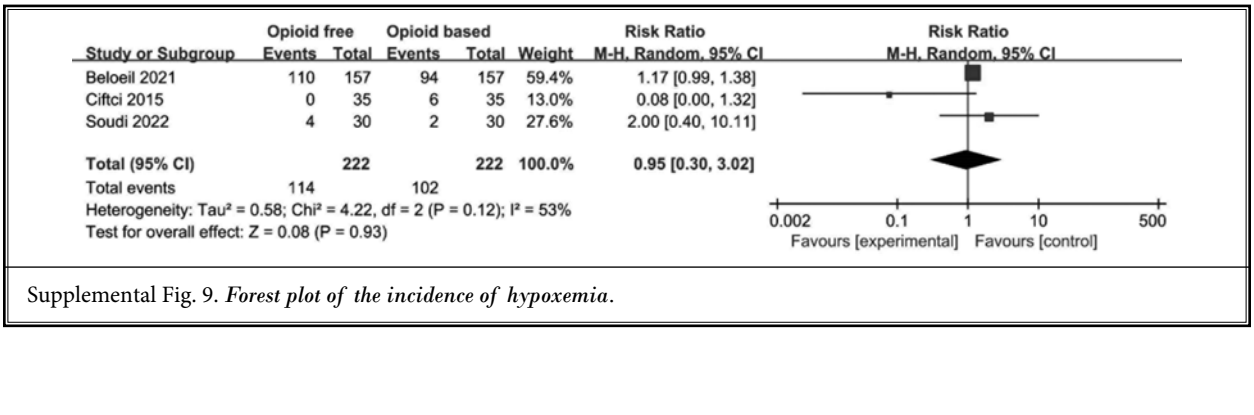
Supplemental Fig. 6. *Forest plot of the incidence of hypertension.*



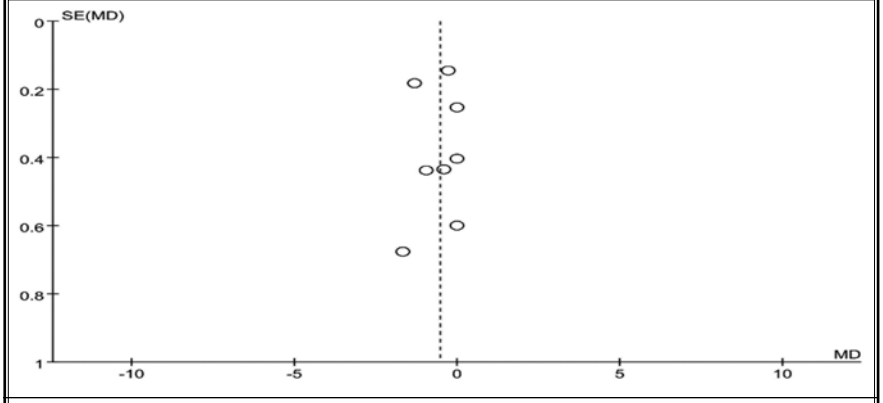
Supplemental Fig. 7. *Forest plot of the incidence of bradycardia.*



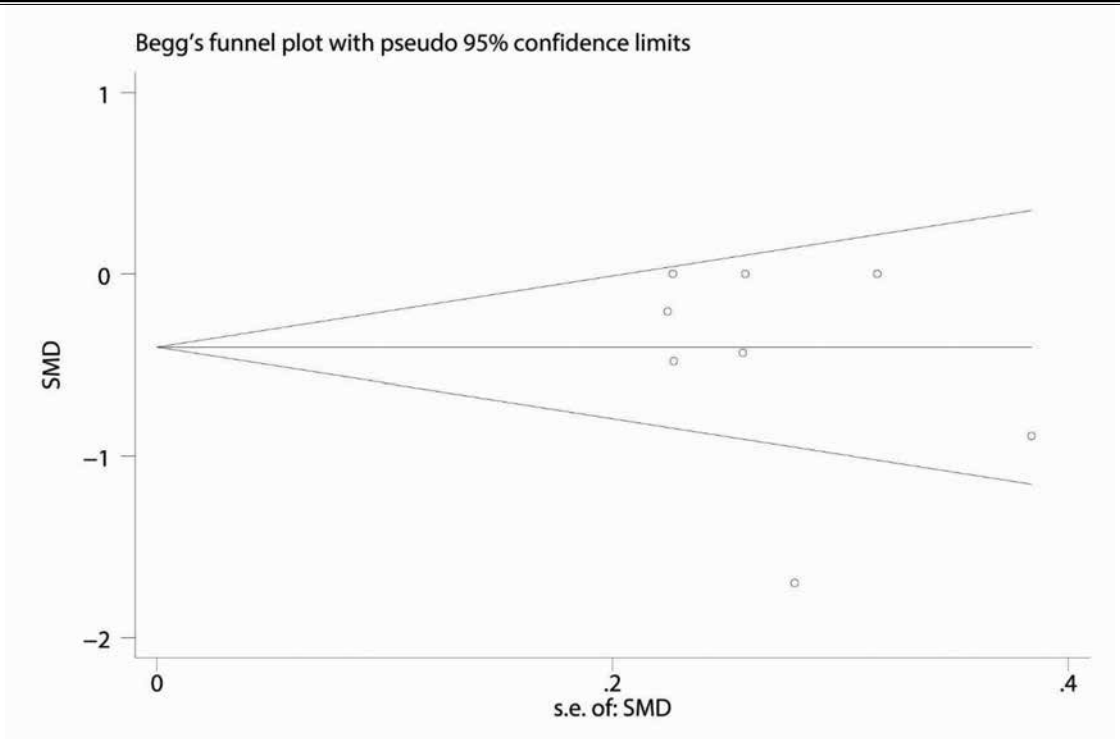
Supplemental Fig. 8. *Forest plot of the incidence of PONV.*



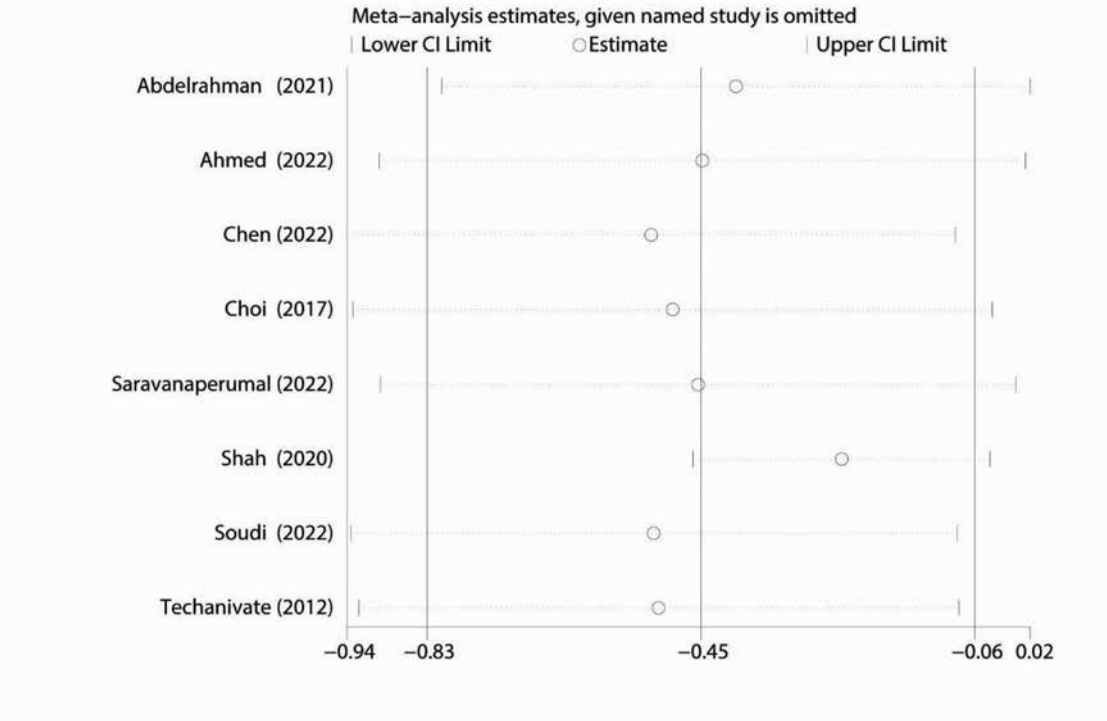
Supplemental Fig. 9. *Forest plot of the incidence of hypoxemia.*



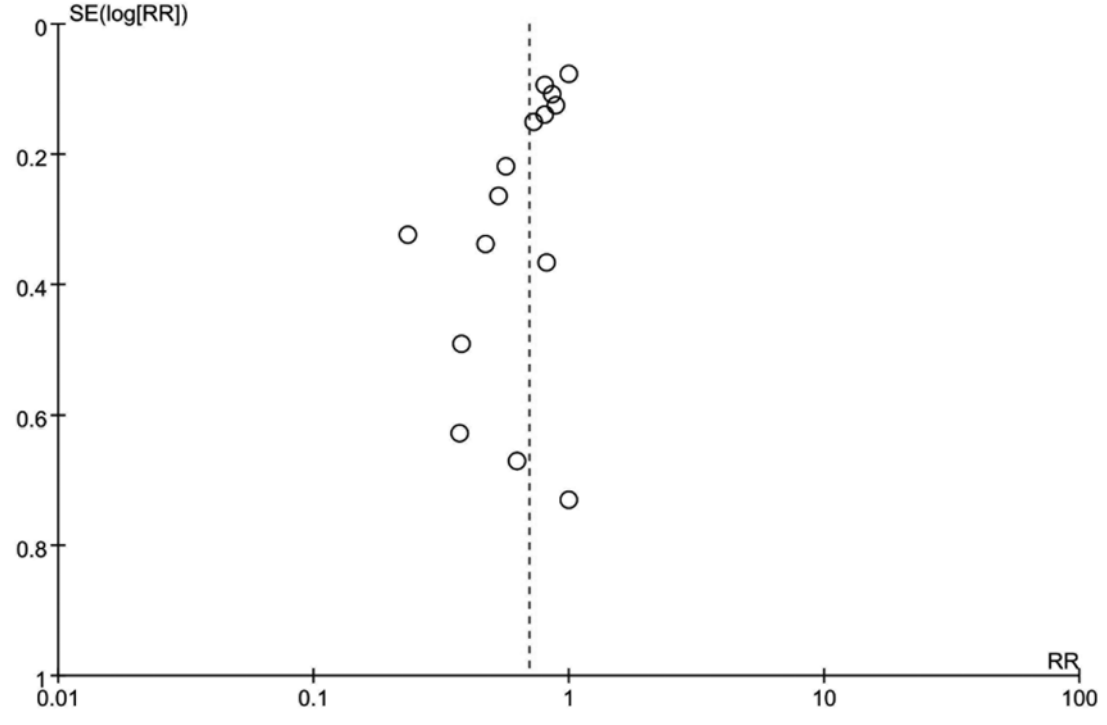
Supplemental Fig. 10. *Funnel plot of 2-hour postoperative pain score.*



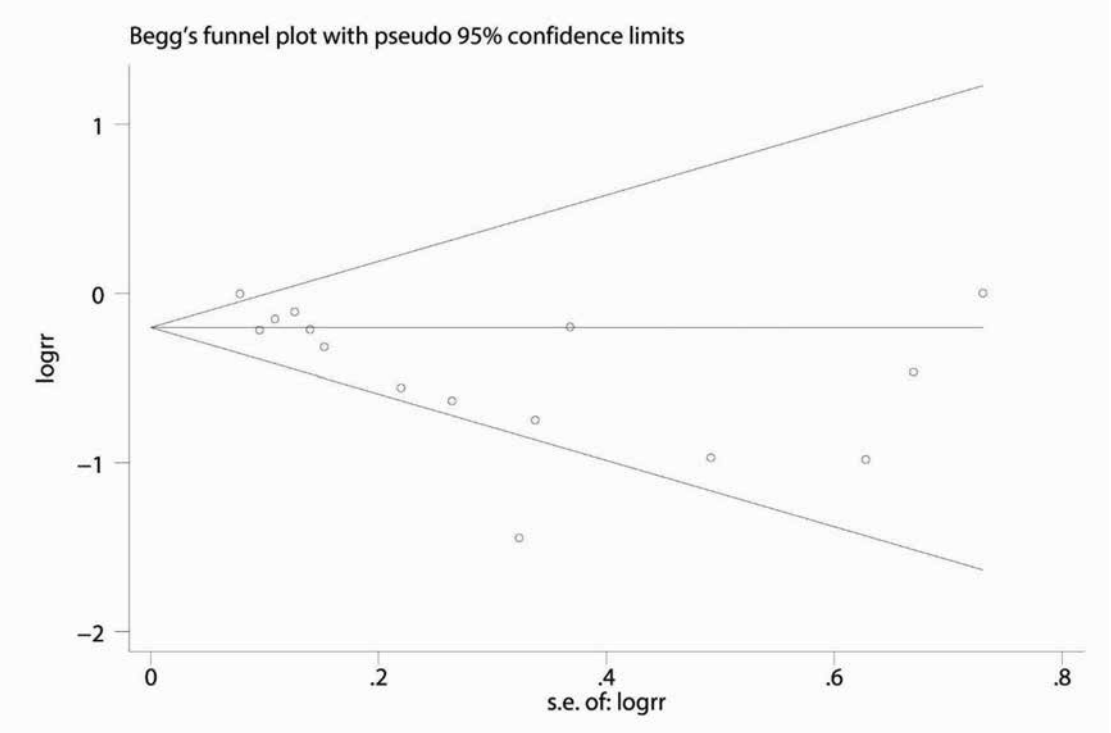
Supplemental Fig. 11. *Begger's test of 2-hour postoperative pain score.*



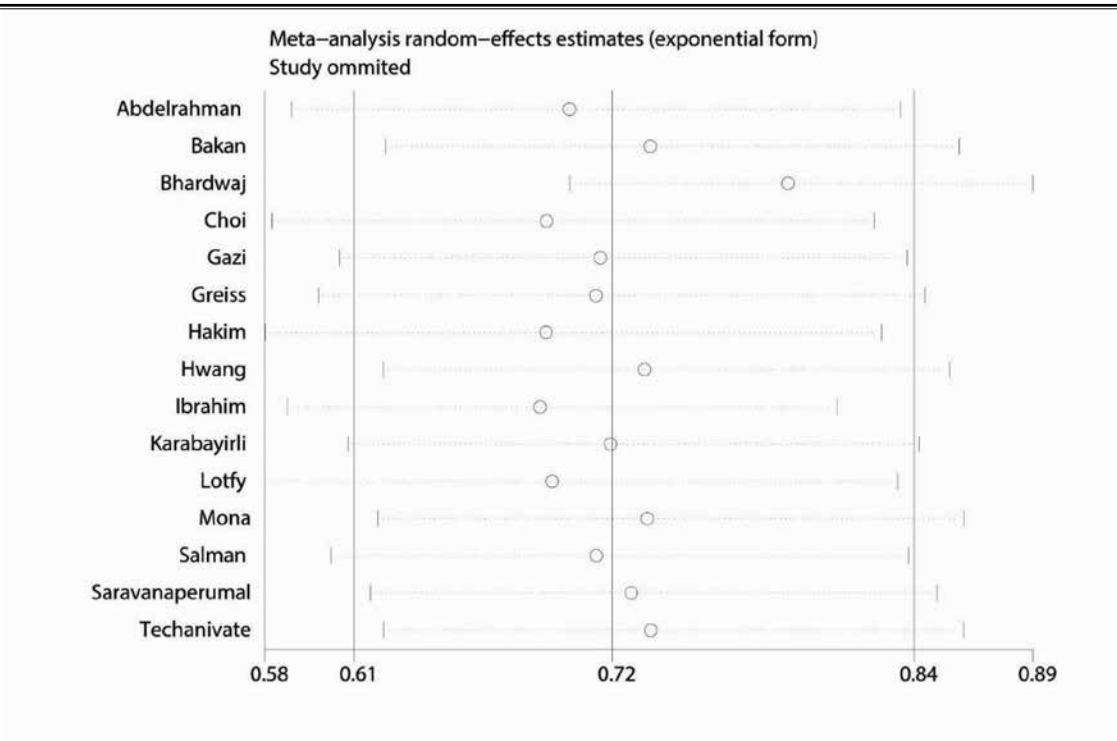
Supplemental Fig. 12. *Sensitivity analysis test outcomes 2 hours postoperatively.*



Supplemental Fig. 13. *Funnel plot of the number of patients who required rescue analgesia during the postoperative period.*



Supplemental Fig. 14. *Begger's test of the number of patients who required rescue analgesia during the postoperative period.*



Supplemental Fig. 15. *Sensitivity analysis test outcomes for the number of patients who required rescue analgesia during the postoperative period.*