Title

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Does Propofol Anesthesia Lead to Less Postoperative Pain Compared With Inhalational Anesthesia?: A Systematic Review and Meta-analysis

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BACKGROUND: Many studies have compared propofol-based anesthesia with inhalational anesthesia. Results from several studies have shown improved postoperative analgesia after propofol anesthesia, but other studies showed contradictory results. There are no large prospective studies that compare postoperative pain after propofol versus inhalational anesthesia. This meta-analysis was designed to focus on this question.
METHODS: A systematic literature search for randomized controlled trials that compared propofol-based anesthesia with volatile agents-based anesthesia in adults undergoing surgery was conducted. Published data were pooled for the meta-analysis with Review Manager (ie, RevMan). The main outcomes included postoperative pain intensity, opioid consumption, need for rescue analgesics, and time to first analgesia.
RESULTS: Thirty-nine clinical trials with a combined subject population of 4520 patients came within the purview of this meta-analysis. The investigated volatile agents included isoflurane, sevoflurane, and desflurane. Compared with inhalational anesthetics, the propofol use was associated with a reduced postoperative pain intensity at rest at 30 minutes, 1 hour, and 12 hours (mean difference in pain scores, 30 minutes, −0.48 [visual analog scale, 0–10]; 99% confidence interval [CI], −1.07 to 0.12, $P = 0.04$) and reduced morphine-equivalent consumption 0 to 24 hours postoperatively (mean difference in morphine-equivalent consumption, −2.68 mg; 99% CI, −6.17 to 0.82; $P = 0.05$). Fewer patients required postoperative rescue analgesics during 0 to 24 hours after surgery under propofol anesthesia (risk ratio, 0.87; 99% CI, 0.74–1.03; $P = 0.04$). In addition, patients anesthetized with propofol required administration of postoperative analgesia later than those anesthetized with volatiles (mean difference in time to first analgesic administration, 6.12 minutes; 99% CI, 0.02–12.21; $P = 0.01$). Considering that Z statistic in RevMan 5.3 does not perform optimally in highly heterogeneous samples among groups or many combinations of groups with small sample sizes, a P value of <.01 was considered statistically significant. On the basis of this threshold, none of the aforementioned results are statistically significant.
CONCLUSIONS: The current results are affected by substantial heterogeneity, which makes it difficult to predict significant differences in postoperative pain control between propofol anesthesia and inhalational anesthesia. Further large, randomized controlled trials are needed to corroborate these results and to detect differences (if any) between propofol and inhalational anesthesia on postoperative pain. (Anesth Analg 2016;123:846–58)

Inadequate management of acute postoperative pain is associated with a longer hospital stay and increased health care costs.[1] Despite the increasing use of minimally invasive surgery and advances in pain therapy, postoperative pain management often is challenging.[1] Any approach that reduces opioid requirements and also produces earlier ambulation could be of benefit to patients and society.

In some studies, propofol-based anesthesia has been shown to be associated with reduced postoperative pain compared with that associated with volatile agent–based anesthesia,[2–4] whereas other studies found no evidence of the superiority of propofol.[5,6] Most previous studies were not designed to detect differences in postoperative opioid consumption or did not include pain intensity as a primary outcome.

To date, no quantitative literature analysis has been published focusing on their postoperative analgesic effects. In this systematic review, we compared postoperative pain outcomes associated with the use of propofol-based and volatile agent–based anesthesia.

METHODS

This systematic review adheres with the current recommendations of the Cochrane Collaboration and is reported

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in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[7]

Systematic Literature Search

Three authors (K.P., H.-Y.L., and S.-R.W.) independently searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases using the following search terms: (1) (balanced OR volatile OR inhalation* OR halothane OR desflurane OR isoflurane OR sevoflurane) AND propofol AND (analgesi* OR opioid OR pain) AND postoperative for the MEDLINE and Cochrane Central Register of Controlled Trials searches; and (2) (balanced OR volatile OR inhalation* OR "halothane"/exp OR halothane OR "desflurane"/exp OR desflurane OR "isoflurane"/exp OR isoflurane OR "sevoflurane"/exp OR sevoflurane) AND ("propofol"/exp OR propofol) AND (analgesi* OR opioid OR "pain"/exp OR pain) AND postoperative AND [humans]/lim for the EMBASE search.

The last search was performed in March 2015. No language or publication date restriction was used. Additional studies were retrieved by review of the reference lists from relevant articles. The search results were collated and deduplicated in Endnote X7 (Thomson Reuters, NY).

Selection of Included Studies

Three authors (K.P., H.-Y.L., and S.-R.W.) independently screened the abstracts of articles shortlisted by the initial search. The same authors reviewed the full texts to identify studies that met the inclusion criteria. Any disagreement over study selection was resolved with a consensus with the other authors (H.L., Z.-C.Z., and F.-H.J).

The inclusion and exclusion criteria were determined before the systematic search. Inclusion criteria were (1) design: randomized controlled trials (RCTs); (2) population: adult patients undergoing surgery under general anesthesia; (3) intervention: comparison of propofol-based intravenous anesthesia with inhalational anesthesia; and (4) outcomes: postoperative pain intensity, opioid consumption, need for rescue analgesics, and time to first analgesia. Exclusion criteria were (1) procedures performed under sedation only; (2) use of different analgesic regimens (ie, remifentanil in one group and fentanyl in the other, or nitrous oxide in one group but not in the other group); (3) the use of neuraxial or nerve block; (4) pediatric patients; (5) trials that did not report on specific outcomes; and (6) lack of access to full text.

Data Extraction

Three authors (K.P., H.-Y.L., and S.-R.W.) independently extracted the following data from eligible studies: author details, publication year, number of patients, surgical procedure, premedication, anesthesia induction and maintenance, and intraoperative and postoperative analgesic regimens. Corresponding authors were contacted for missing data when necessary. Any disagreement over data extraction was resolved by discussion and consensus with the other authors (H.L., Z.-C.Z., and F.-H.J.).

Primary and Secondary Outcome Parameters

We designated postoperative pain score as the primary outcome, because it is the most direct data point representing pain intensity. Other data points representing supporting evidence associated with pain were designated as secondary outcomes.

The primary outcome was postoperative pain intensity rated on a numeric rating scale (0–10) at rest; and on movement at 8 time points (postoperative 30 minutes, 1, 2, 4, 6, 8, 12, and 24 hours). Pain intensity scores reported on a visual analog scale (0–10) or numerical analog scale (0–10) were rated as equivalent to a 0 to 10 numeric rating scale.

Secondary outcomes were (1) morphine-equivalent consumption during 0 to 2 hours (or in the postanesthesia care unit [PACU]), 0 to 4 hours, and 0 to 24 hours after surgery; (2) number of patients requiring analgesics during 0 to 2 hours (or in the PACU), 0 to 8 hours, and 0 to 24 hours after surgery; and (3) time to first postoperative analgesic administration.

Postoperative opioid consumption was transformed to morphine-equivalent consumption with the use of previously published equianalgesic conversion factors (morphine 10 mg = piritramide 10 mg = tramadol 100 mg = meperidine 100 mg = fentanyl 0.1 mg, intravenously).[8–10]

Risk of Bias Assessment

Three authors (K.P., H.-Y.L., and S.-R.W.) independently assessed the risk of bias in each identified study using the Cochrane Collaboration's tool.[11] This tool considered 6 different domains: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete data on outcomes (attrition bias); and (6) selective reporting (reporting bias). The estimated overall risk of bias for each trial was categorized as "low," "unclear," or "high." Any disagreement over assessment of bias was resolved by discussion and consensus with the other authors (H.L., Z.-C.Z., and F.-H.J.).

Statistical Analysis

Statistical analyses were performed with Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). Standard deviation not stated or graphically represented was estimated as range/4 or interquartile range/1.35 (range = maximum value – minimum value and interquartile range = Q3 – Q1, with Q1 and Q3 representing the first and third quartiles, respectively).[12] When standard error or confidence interval (CI) was reported, standard deviation was calculated with the calculator tool in the Review Manager. To increase the robustness of results, data were pooled only if at least 3 trials were included for an outcome.

Considering that the Z statistic in RevMan 5.3 does not perform optimally in highly heterogeneous samples among groups and procedures, or many combinations of groups and procedures with small sample sizes,[13] we set the threshold for statistical significance at a conservative level of P value <.01. Continuous outcomes were reported as weighted mean differences (MDs) and 99% CI, whereas categorical outcomes were reported as risk ratios with 99% CI. To assess whether the studies in this meta-analysis were affected by publication bias, a funnel plot using one of the main outcomes as an end point, was constructed.

Heterogeneity was assessed with the I^2 test. For outcome data with low heterogeneity ($I^2 \leq 30\%$), a fixed-effect model was used; for outcome data with evidence of significant heterogeneity ($I^2 > 30\%$), a random-effects model was selected.[11,14] Subgroup analyses were performed according to the use of remifentanil for intraoperative analgesia, and the use of patient-controlled analgesia (PCA) or opioids combined with nonsteroidal anti-inflammatory drugs (NSAIDs) for postoperative analgesia, when there were >8 trials included for an outcome.

RESULTS

As mentioned previously, 3 authors (K.P., H.-Y.L., and S.-R.W.) independently screened the abstracts, reviewed the full texts, and extracted the relevant data. As a result, they reached agreement for all the steps, without the need for additional discussion with the other authors (H.L., Z.-C.Z., and F.-H.J).

Characteristics of Included Trials

A total of 4375 potentially eligible publications were retrieved on online literature search, of which 322 studies were screened out after review of abstracts. Of these, only 39 articles, with a combined subject population of 4520 adult patients undergoing both minor and major surgery in different specialties (gynecology, ear-nose-throat surgery, urology, orthopedics, neurosurgery, and gastrointestinal surgery),[2–6,15–48] were included eventually in this meta-analysis (Figure 1). The characteristics of the included studies are shown in Table 1. All studies were RCTs that compared propofol with inhalational anesthesia for at least one of the pain outcomes mentioned in the inclusion criteria. In 19 RCTs, remifentanil was used as intraoperative analgesic,[3,6,17,18,21–24,29,30,32,34,37,41,43,44,46–48] whereas fentanyl, alfentanil, or morphine was used in 20 RCTs.[2,4,5,15,16,19,20,25–28,31,33,35,36,38–40,42,45] Isoflurane was used in 11 trials,[2,16,20,26,28,30,35,36,39,40,45] sevoflurane in 21 trials,[3–6,18,19,24,25,27,29,31,32,34,37,38,40–44,46] and desflurane in 12 trials.[5,15,17,20–23,33,36,40,47,48] PCA with opioids for postoperative analgesia was used in 7 trials[2,5,6,23,43,46,47] and opioids combined with NSAIDs for postoperative analgesia in 19 trials.[3–6,15,16,18,25,26,29,32,34,36–41,48]

Postoperative Pain Intensity

Twenty-five trials investigated postoperative pain scores (N = 2609).[2–6,15,16,20,21,23–25,29,31,34–38,40–43,46,47] The main outcomes of pain intensity at rest at the 8 time points and on movement at 3 time points after surgery are shown in Table 2. Lower pain scores at rest were reported by patients anesthetized with propofol, compared with those receiving volatile agents, at postoperative 30 minutes (Figure 2), 1 hour (Figure 3), and 12 hours (Figure 4). The MD in pain scores decreased from −0.48 (99% CI, −1.07 to 0.12; $P = 0.04$, $I^2 = 89\%$) at postoperative 30 minutes to −0.08 (99% CI, −0.30 to 0.14; $P = 0.33$, $I^2 = 43\%$) at postoperative 24 hours. Most of the pooled analyses, however, were affected by heterogeneity, and all the differences failed to show statistical significance given the P value cutoff <0.01.

In Figure 2, subgroup analysis was performed. Intraoperative administration of remifentanil was associated with a greater MD in pain scores and significantly reduced postoperative pain intensity at rest at 30 minutes (MD = −0.89; 99% CI, −1.63 to −0.16; $P = 0.002$), compared with fentanyl- or alfentanil-based intraoperative analgesia (MD, −0.17; 99% CI, −1.00 to 0.66; $P = 0.60$). Postoperative

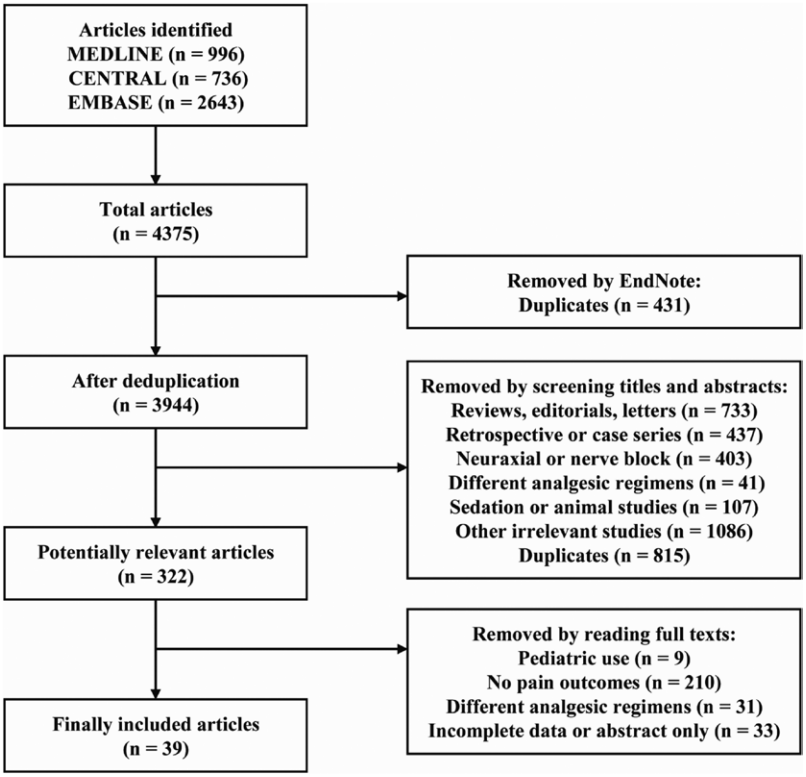

Figure 1. Schematic illustration of the methodology and criteria for study selection for the meta-analysis.

Table 1. Summary of Clinical Trials Included in the Meta-Analysis

Studies	Study Groups (N)	Surgery	Premedication	Anesthesia Induction/ Maintenance	Intraoperative/ Postoperative Analgesia
Akkurt et al[15]	1. Propofol (30) 2. Desflurane (30)	Laparoscopic cholecystectomy	Midazolam 2 mg	Propofol 2–2.5 mg/kg + lidocaine 0.5 mg/kg/ propofol or desflurane titrated to BIS 40–60	Alfentanil/diclofenac + meperidine, IM, if VAS > 5
Boccara et al[16]	1. Propofol (20) 2. Isoflurane (20)	Cosmetic abdominoplasty	Alprazolam 0.5 mg + hydroxyzine 50 mg	Propofol 3 mg/kg/ propofol or isoflurane titrated to clinical effects	Fentanyl + N_2O/ paracetamol + nalbuphine, IV, if VAS > 5
Braun et al[17]	1. Propofol (20) 2. Desflurane (20)	Laparoscopic prostatectomy	Dormicum salt 0.1 mg/kg	Propofol 1.5 mg/kg/ propofol or desflurane titrated to BIS 40–60	Remifentanil/ piritramide, IV
Cheng et al[2]	1. Propofol (20) 2. Isoflurane (20)	Open uterine surgery	Midazolam 0–2 mg	Propofol 2 mg/kg/ propofol or isoflurane titrated to BIS 50	Fentanyl/PCA with morphine
Citerio et al[18]	1. Propofol (138) 2. Sevoflurane (136)	Supratentorial craniotomy	Midazolam 5 mg	Propofol 2–3 mg/kg/ propofol or sevoflurane titrated to clinical effects	Remifentanil/ paracetamol + fentanyl or morphine, IV
Falsini et al[19]	1. Propofol (40) 2. Sevoflurane (40)	Extracavity surgery	Meperidine 1 mg/kg + atropine 0.007 mg/kg	Propofol or thiopental 3–5 mg/kg/propofol or sevoflurane titrated to clinical effects	Fentanyl + N_2O/ fentanyl, IV
Fassoulaki et al[5]	1. Propofol (35) 2. Sevoflurane (35) 3. Desflurane (35)	Abdominal hysterectomy or myomectomy	Droperidol 0.75 mg	Propofol 2.5 mg/kg/ propofol, sevoflurane, or desflurane titrated to BIS 40–60	Morphine + N_2O/ paracetamol + PCA with morphine
Fredman et al[20]	1. Propofol (25) 2. Sevoflurane (25) 3. Isoflurane (25)	TURT or TURP	No premedication	Propofol 1–2 mg/kg/ propofol, sevoflurane, or isoflurane titrated to clinical effects	Fentanyl + N_2O/ diclofenac, IM, if VAS > 5
Gokce et al[21]	1. Propofol (20) 2. Desflurane (20)	Septorhinoplasty	No premedication	Propofol 2 mg/kg/ propofol or desflurane titrated to clinical effects	Remifentanil/ meperidine, IM, if VAS > 3
Gozdemir et al[22]	1. Propofol (30) 2. Desflurane (30)	Lumbar disk surgery	No premedication	Propofol 2 mg/kg/ propofol or desflurane titrated to clinical effects	Remifentanil + N_2O/ meperidine, IV, if VAS > 3
Grundmann et al[23]	1. Propofol (25) 2. Desflurane (25)	Laparoscopic cholecystectomy	Diazepam 10 mg	Propofol 2 mg/kg/ propofol or desflurane titrated to clinical effects	Remifentanil/PCA with piritramide
Höcker et al[24]	1. Propofol (51) 2. Sevoflurane (52)	Abdominal or urological surgery	Midazolam 7.5 mg	Etomidate 0.3 mg/kg/ propofol or sevoflurane titrated to BIS 40–50	Remifentanil/ piritramide, IV
Hofer et al[25]	1. Propofol (155) 2. Sevoflurane (146)	Minor gynecological or orthopedic surgery	Midazolam 7.5 mg	Propofol 1.4 mg/kg + lidocaine 10 mg/ propofol or sevoflurane titrated to clinical effects	Fentanyl/paracetamol + opioids, IV
Jellish et al[26]	1. Propofol (34) 2. Isoflurane (34)	Middle ear surgery	Diazepam 10 mg	Propofol 2 mg/kg or thiopental 5 mg/kg/ propofol or isoflurane titrated to clinical effects	Fentanyl/paracetamol + fentanyl, IV
Jellish et al[27]	1. Propofol (93) 2. Sevoflurane (93)	Surgery expected to last for 3 h	Midazolam 1–2 mg	Propofol 1.5–2 mg/kg or sevoflurane from 0.5% to 4%/propofol or sevoflurane titrated to clinical effects	Fentanyl + N_2O/ morphine, IV
Jensen et al[28]	1. Propofol (30) 2. Isoflurane (30)	Major gastrointestinal surgery	Flunitrazepam 0.5–1 mg	Propofol 2 mg/kg or thiopental 4 mg/kg/ propofol or isoflurane titrated to clinical effects	Fentanyl + N_2O/ ketobemidone + meperidine, IM

(*Continued*)

Table 1. Continued

Studies	Study Groups (N)	Surgery	Premedication	Anesthesia Induction/ Maintenance	Intraoperative/ Postoperative Analgesia
Kim et al[29]	1. Propofol (48) 2. Sevoflurane (39)	Endoscopic thyroidectomy	No premedication	Propofol TCI 5 μg/mL or thiopental 4–5 mg/kg/ propofol or sevoflurane titrated to clinical effects	Remifentanil/ketorolac + meperidine, IV, if VAS > 5
Kochs et al[30]	1. Propofol (274) 2. Isoflurane (279)	Major abdominal surgery	Midazolam	Propofol 0.5 mg/kg + 10 mg/10 s to loss of consciousness/ propofol or isoflurane titrated to clinical effects	Remifentanil/morphine or fentanyl, IV
Konstantopoulos et al[31]	1. Propofol (35) 2. Sevoflurane (35)	Lumbar spondylodesis	Promethazine 0.1 g	Propofol 2.5 mg/kg or 8% sevoflurane/propofol or sevoflurane titrated to BIS 40–50	Fentanyl + N_2O/ infusion of morphine
Lauta et al[32]	1. Propofol (153) 2. Sevoflurane (149)	Supratentorial craniotomy	Ranitidine 0.1 g	Thiopental 4–6 mg/kg + lidocaine 1.5 mg/kg/ propofol or sevoflurane titrated to clinical effects	Remifentanil/ketorolac + infusion of tramadol
Lebenbom-Mansour[33]	1. Propofol (14) 2. Desflurane (30)	Outpatient peripheral orthopedic surgery	No premedication	Propofol 2.5 mg/kg or desflurane/propofol or desflurane titrated to clinical effects	Fentanyl + N_2O/ fentanyl, IV
Lee et al[34]	1. Propofol (31) 2. Sevoflurane (31)	Mastoidectomy and tympanoplasty	No premedication	Propofol TCI 3.5 μg/mL or propofol 2 mg/kg/ propofol or sevoflurane titrated to BIS 40–60	Remifentanil/ketorolac + meperidine, IV
Li et al[3]	1. Propofol (30) 2. Sevoflurane (30)	Gynecological laparoscopy	Phenobarbital 0.1 g + atropine 0.5 mg	Midazolam 0.03 mg/kg + propofol 1.5–2 mg/kg/ propofol or sevoflurane titrated to BIS 45–55	Fentanyl + remifentanil/ parecoxib + tramadol, IV
Liu et al[35]	1. Propofol (20) 2. Isoflurane (20)	Closed reduction of distal radius fracture	No premedication	Propofol 2 mg/kg or thiopental 5 mg/kg/ propofol or isoflurane titrated to clinical effects	Fentanyl + N_2O/ fentanyl, IV, if VAS > 3
Martikainen et al[36]	1. Propofol (32) 2. Isoflurane (38) 3. Desflurane (48)	Knee arthroscopy	No premedication	Propofol 2 mg/kg/ propofol, isoflurane, or desflurane titrated to clinical effects	Alfentanil/ketoprofen + fentanyl, IV
Mei et al[37]	1. Propofol (147) 2. Sevoflurane (148)	Gynecological laparoscopy	Phenobarbital 0.1 g + atropine 0.5 mg	Midazolam 0.03 mg/kg + propofol 1.5–2 mg/kg/ propofol or sevoflurane titrated to BIS 45–55	Remifentanil/parecoxib + tramadol, IV
Ogurlu et al[38]	1. Propofol (40) 2. Sevoflurane (40)	Abdominal hysterectomy	Midazolam 0.07 mg/kg + atropine 0.01 mg/kg	Propofol 2–2.5 mg/kg/ propofol or sevoflurane titrated to BIS 40–60	Fentanyl/diclofenac + meperidine, IV, if VAS > 4
Oikkonen[39]	1. Propofol (15) 2. Isoflurane (15)	Gynecological laparoscopy	Diazepam 2.5 mg + glycopyrrolate 0.2 mg	Propofol 3 mg/kg/ propofol or isoflurane titrated to clinical effects	Alfentanil/diclofenac + oxycodone, IV
Ortiz et al[40]	1. Propofol (18) 2. Isoflurane (18) 3. Desflurane (20) 4. Sevoflurane (18)	Laparoscopic cholecystectomy	Midazolam 1–2 mg	Propofol 2.5 mg/kg + lidocaine 1 mg/kg/ propofol, isoflurane, desflurane, or sevoflurane titrated to BIS 30–50	Fentanyl + wound infiltration/ acetaminophen + hydrocodone, PO, if VAS > 2 + morphine, IV, if VAS > 5
Park et al[41]	1. Propofol (32) 2. Sevoflurane (32)	Total thyroidectomy	No premedication	Propofol TCI 3.5 μg/mL or propofol 2 mg/kg/ propofol or sevoflurane titrated to BIS values	Remifentanil/ketorolac + meperidine, IV

(*Continued*)

Table 1. Continued

Studies	Study Groups (N)	Surgery	Premedication	Anesthesia Induction/ Maintenance	Intraoperative/ Postoperative Analgesia
Pokkinen et al[6]	1. Propofol (74) 2. Sevoflurane (74)	Laparoscopic hysterectomy	Midazolam 7.5 mg + cetirizine 10 mg	Propofol TCI or propofol 2–3 mg/kg/propofol TCI or sevoflurane titrated to state entropy <60	Remifentanil/ acetaminophen + PCA with oxycodone
Raeder et al[42]	1. Propofol (85) 2. Sevoflurane (84)	Knee arthroscopy	No premedication	Propofol 2–2.5 mg/kg/ propofol or sevoflurane titrated to clinical effects	Fentanyl + N_2O/ morphine, IV, if VAS > 3
Shin et al[43]	1. Propofol (96) 2. Sevoflurane (90)	Breast cancer surgery	Midazolam 3 mg + glycopyrrolate 0.2 mg	Propofol TCI 4 μg/mL or thiopental 5 mg/kg/ propofol or sevoflurane titrated to BIS 40–50	Remifentanil/PCA with morphine
Sneyd et al[44]	1. Propofol (24) 2. Sevoflurane (26)	Craniotomy	No detail provided	Propofol TCI or propofol infusion to loss of consciousness/ propofol or sevoflurane titrated to clinical effects	Remifentanil/morphine, IV
Talke et al[45]	1. Propofol (15) 2. Isoflurane (15)	Supratentorial craniotomy	Midazolam 1–2 mg	Propofol 3 mg/kg or thiopental 5 mg/kg/ propofol or isoflurane titrated to clinical effects	Fentanyl + N_2O/no detail provided
Tan et al[4]	1. Propofol (40) 2. Sevoflurane (40)	Gynecological laparoscopy	No detail provided	Propofol 2.5 mg/kg or 8% sevoflurane/propofol or sevoflurane titrated to BIS 40	Alfentanil/paracetamol + morphine, IV
Tang et al[46]	1. Propofol (101) 2. Sevoflurane (99)	Radical rectal resection	No premedication	Midazolam + propofol 1.5–2 mg/kg or 8% sevoflurane/propofol or sevoflurane titrated to BIS 30–60	Remifentanil/PCA with fentanyl
Yoo et al[47]	1. Propofol (31) 2. Desflurane (31)	RLRP	Midazolam 0.05 mg/ kg + glycopyrrolate 0.2 mg	Propofol TCI or propofol 1.5 mg/kg/propofol or desflurane titrated to BIS 40–60	Remifentanil/PCA with fentanyl
Zoremba et al[48]	1. Propofol (67) 2. Desflurane (67)	Minor peripheral surgery	Clorazepate 20 mg	Propofol 2 mg/kg/ propofol or desflurane titrated to BIS 40–60	Remifentanil/ acetaminophen + metamizole + piritramide, IV, if VAS > 4

Abbreviations: BIS, Bispectral index; IM, intramuscularly; IV, intravenously; N_2O, nitrous oxide; PCA, patient-controlled analgesia; PO, orally; RLRP, robot-assisted laparoscopic radical prostatectomy; TCI, target-controlled infusion; TURP, transurethral prostatectomy; TURT, transurethral bladder tumor resection; VAS, visual analog scale for pain.

pain intensity was lower when PCA with opioids was used for postoperative analgesia (MD in pain scores, −0.72; 99% CI, −1.52 to 0.07; $P = 0.02$) than that achieved with opioids on demand. Compared with postoperative analgesia regimen of opioids only, opioids combined with NSAIDs resulted in a reduced postoperative pain intensity (MD in pain scores, −0.59; 99% CI, −1.34 to 0.15; $P = 0.04$). Subgroup analysis was also performed (Figure 3). To summarize in brief, all the subgroups reached the same point as those shown in Figure 2, except for opioids alone versus opioids combined with NSAIDs for postoperative analgesia.

Secondary Outcomes

Fourteen trials reported on postoperative opioid consumption (N = 1174; Table 3).[2,4–6,22–24,28,33,35,40,43,44,48] Compared with patients anesthetized with volatile agents, morphine-equivalent consumption during 0 to 24 hours after surgery was lower in patients receiving propofol (MD in morphine-equivalent consumption, −2.68 mg; 99% CI, −6.17 to 0.82; $P = 0.05$, $I^2 = 62\%$; Figure 5). Morphine-equivalent consumption during 0 to 2 hours (or in PACU) and 0 to 4 hours after surgery was lower in patients treated with propofol, but the difference was also not statistically significant.

Twenty-six trials reported on the number of patients requiring rescue analgesics after surgery (N = 3236).[3,4,15–21,23,25–30,32,34,36,37,39,41,42,44,45,47] Fewer patients required rescue analgesics during 0 to 24 hours postoperatively when receiving propofol (risk ratio = 0.87; 99% CI, 0.74 to 1.03; $P = 0.04$, $I^2 = 0\%$; Figure 6).

Three studies reported on the time to first analgesic administration postoperatively (N = 787).[23,27,30] Patients

Table 2. Postoperative Pain Intensity at Rest at 8 Time Points and on Movement at 3 Time Points

Time Points	References	Patients (N)	Estimated Benefit (99% CI)	*P* Value	I^2 Test (%)
At rest					
30 min after operation	2–6, 15, 16, 20, 21, 23, 24, 35–38, 40, 42, 43	1833	MD = −0.48 (−1.07 to 0.12)	.04	89
1 h after operation	2–4, 6, 15, 16, 20, 23, 24, 34, 36, 38, 40–43, 47	1471	MD = −0.45 (−0.93 to 0.02)	.01	75
2 h after operation	2, 4–6, 16, 20, 23, 25, 29, 36, 37, 42	1582	MD = −0.14 (−0.57 to 0.30)	.42	67
4 h after operation	4–6, 16, 37, 38, 40	822	MD = −0.13 (−0.78 to 0.52)	.61	71
6 h after operation	6, 16, 29, 31, 37, 41, 43, 47	952	MD = 0.04 (−0.40 to 0.49)	.80	62
8 h after operation	5, 16, 37, 38, 40	594	MD = −0.12 (−0.43 to 0.20)	.34	6
12 h after operation	37, 38, 40, 43	635	MD = −0.23 (−0.48 to 0.03)	.02	25
24 h after operation	2, 3, 5, 6, 25, 29, 31, 34, 37, 38, 40, 41, 43, 47	1634	MD = −0.08 (−0.30 to 0.14)	.33	43
On movement					
30 min after operation	5, 6, 31, 38	403	MD = −0.09 (−1.07 to 0.90)	.82	73
2 h after operation	5, 6, 38	333	MD = −0.21 (−1.88 to 1.45)	.74	89
24 h after operation	5, 6, 31, 38	403	MD = 0.07 (−0.35 to 0.49)	.68	28

Pain intensity was scored on a visual analog scale, numerical analogue scale, or numeric rating scale, where 0 indicates no pain and 10 indicates the most severe pain imaginable.

Abbreviations: CI, confidence interval; MD, weighted mean difference.

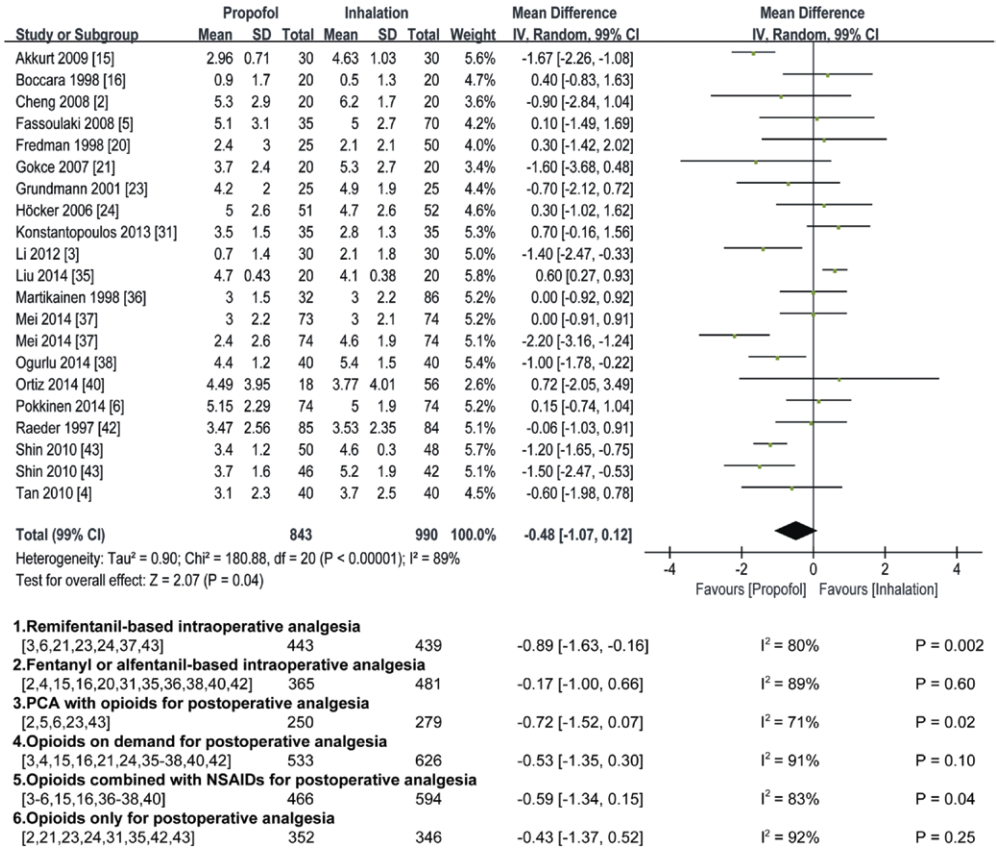

Figure 2. Propofol versus inhalational anesthesia: pain intensity at rest (numeric rating scale) at 30 minutes after surgery. CI indicates confidence interval; IV, intravenous; SD, standard deviation.

anesthetized with propofol required postoperative analgesia later than those who were anesthetized with volatile agents (MD in time to first analgesic administration, 6.12 minutes; 99% CI, 0.02 to 12.21; $P = 0.01$; Figure 7).

Risk of Bias in Included Studies

Risk assessment is summarized in Table 4. All included trials were randomized; 30 trials clearly documented the randomization method, and 35 detailed the methods of blinding. A funnel plot showed a fairly symmetrical shape when pain intensity at rest and at 30 minutes as an end point were used, indicating that there was no substantial publication bias (Figure 8).

DISCUSSION

This meta-analysis included 39 RCTs that compared postoperative pain outcomes after propofol-based anesthesia with that after inhalational anesthesia. Use of propofol was associated with lower postoperative pain scores at rest and opioid consumption. In addition, fewer patients required rescue analgesics in the propofol group, as evidenced by the longer time to first analgesic administration. None of the

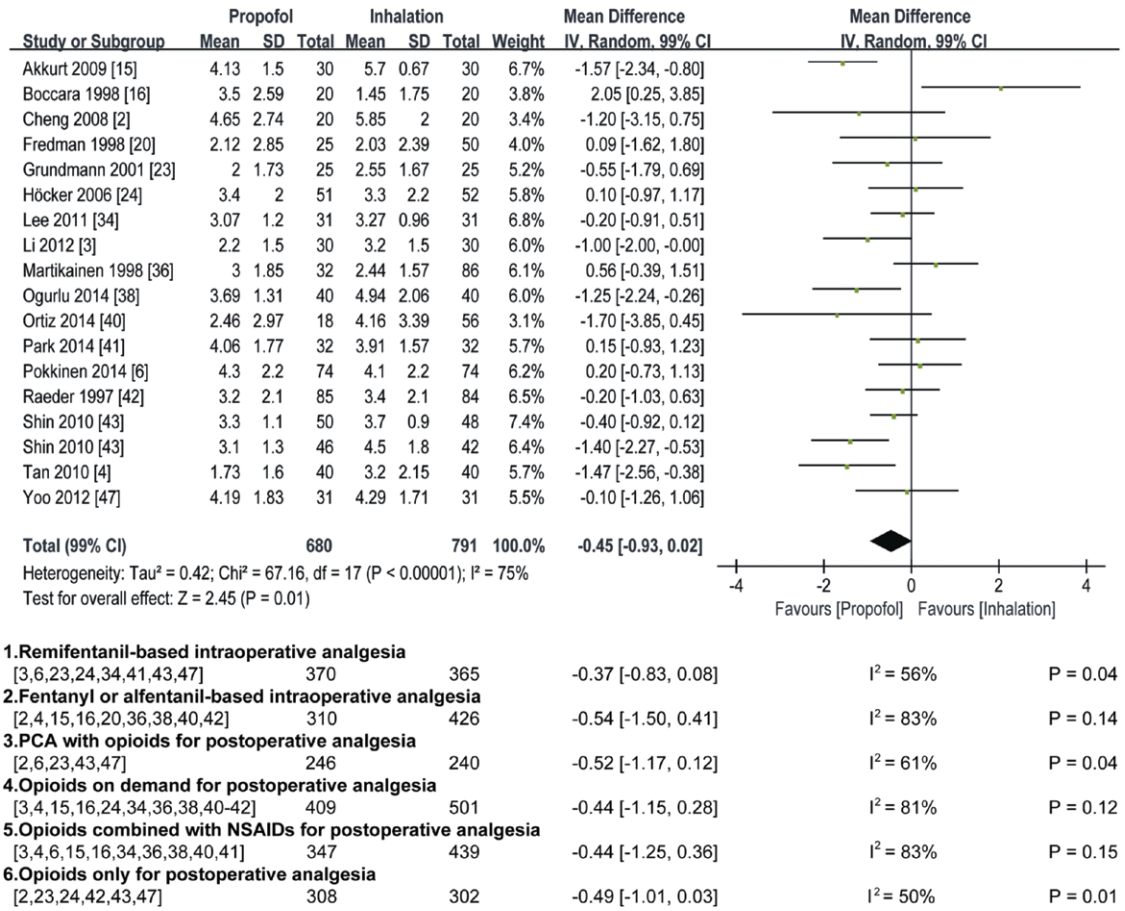

Figure 3. Propofol versus inhalational anesthesia: pain intensity at rest (numeric rating scale) at 1 hour after surgery. CI indicates confidence interval; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PCA, patient-controlled analgesia; SD, standard deviation.

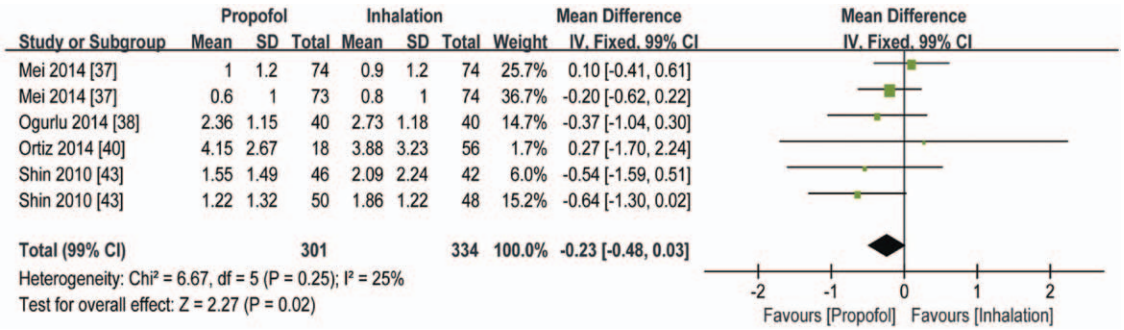

Figure 4. Propofol versus inhalational anesthesia: pain intensity at rest (numeric rating scale) at 12 hours after surgery. CI indicates confidence interval; IV, intravenous; SD, standard deviation.

differences remain significant, however, when a conservative *P* value of <.01 was applied.

Effects of Propofol or Volatile Agents on Acute Postoperative Pain

In this meta-analysis, we found lower pain scores and reduced pain intensity at rest (from 0.48 U at 30 minutes to 0.08 U at 24 hours postoperatively) associated with propofol anesthesia compared with inhalational anesthesia. Further, the use of propofol was associated with a lower morphine-equivalent consumption in the first 24 hours after surgery (MD, 2.68 mg), which indicates an opioid-sparing effect. Slightly superior postoperative pain relief with propofol anesthesia is indicated by reduced pain intensity and opioid consumption, a reduction in the use of rescue analgesia, and a longer time to first analgesia after surgery. This meta-analysis demonstrates for the first time the possible superiority of propofol anesthesia over inhalational anesthesia with respect to the analgesic effect, particularly in the early postoperative period. Although most of our results do indicate a benefit of propofol in this regard, it is noteworthy that all the differences are small and statistically nonsignificant if a *P* value cutoff of <.01 is used. Therefore, these differences may arguably not be clinically significant either.

Table 3. Postoperative Morphine-Equivalent Consumption, Rescue Analgesia, and Time to First Analgesia

Time Points	References	Patients (N)	Estimated Benefit (99% CI)	*P* Value	I^2 Test (%)
Morphine-equivalent consumption					
2 h after operation (or in PACU)	2, 4–6, 22–24, 33, 35, 43, 44	906	MD = −0.38 mg (−1.30 to 0.55)	.29	81
4 h after operation	4–6	333	MD = −0.90 mg (−2.69 to 0.89)	.20	0
24 h after operation	2, 5, 6, 28, 40, 43, 48	727	MD = −2.68 mg (−6.17 to 0.82)	.05	62
Rescue analgesia					
2 h after operation (or in PACU)	3, 17, 18, 20, 21, 23, 26, 27, 29, 30, 34, 36, 39, 41, 42, 44, 45, 47	2026	RR = 0.94 (0.83 to 1.06)	.18	56
8 h after operation	3, 15, 16	160	RR = 0.95 (0.03 to 27.36)	.97	87
24 h after operation	3, 4, 18, 19, 25, 28, 34, 37	1192	RR = 0.87 (0.74 to 1.03)	.04	0
Time to first analgesia	23, 27, 30	787	MD = 6.12 min (0.02 to 12.21)	.01	94

Abbreviations: CI, confidence interval; MD, weighted mean difference; PACU, postanesthesia care unit; RR, risk ratio.

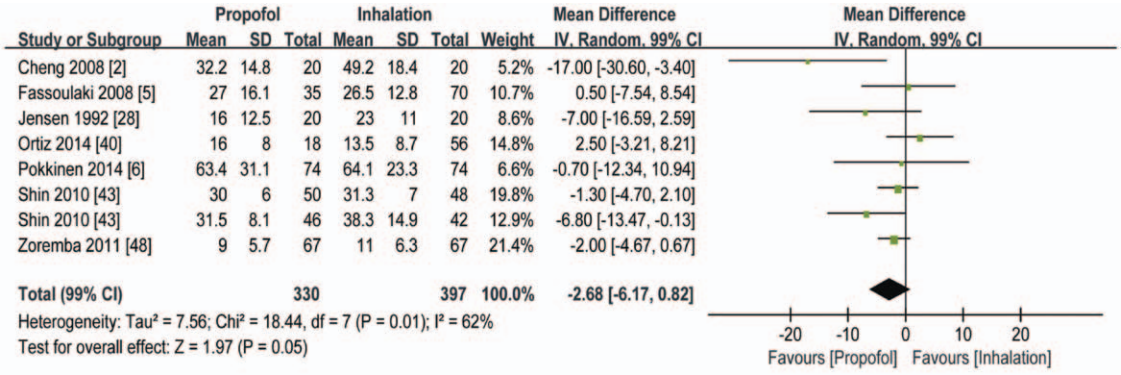

Figure 5. Propofol versus inhalational anesthesia: morphine-equivalent consumption during 0 to 24 hours after surgery. CI indicates confidence interval; IV, intravenous; SD, standard deviation.

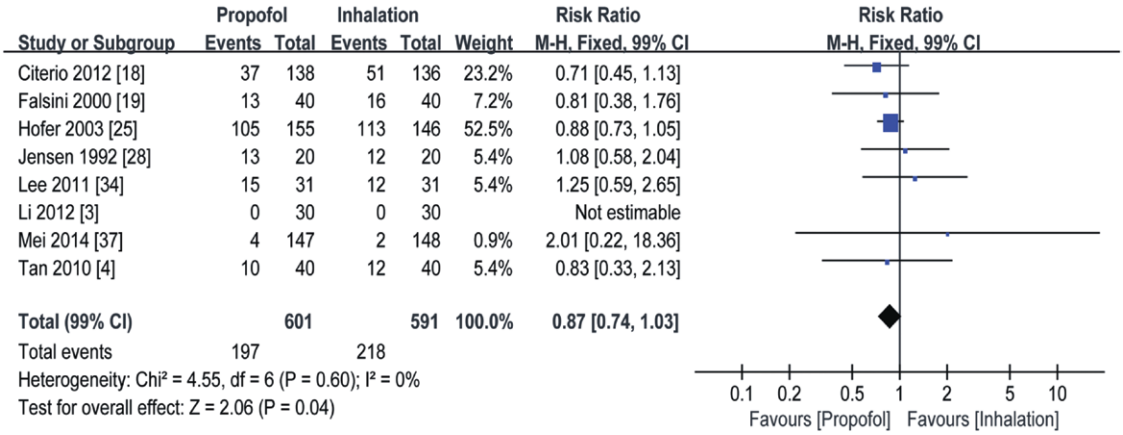

Figure 6. Propofol versus inhalational anesthesia: number of patients requiring rescue analgesia during 0 to 24 hours after surgery. CI indicates confidence interval.

Several possible mechanisms may help explain the effects of propofol and volatile agents on acute postoperative pain. Volatile agents are known to suppress the propagation of sensory afferent stimuli to the nervous system at anesthetic concentrations.[49,50] It is worth noting that inhaled anesthetics tend to cause hyperalgesia at 0.1 minimum alveolar concentrations, which may be responsible for increased pain perception during recovery from anesthesia.[51] The increased sensitivity to pain is mediated by modulation of central adrenergic and cholinergic transmission, as well as by 5-HT_3 receptor–mediated currents.[52,53] In contrast, propofol exhibits short-lasting analgesic properties with a trend toward reduced hyperalgesia and allodynia in healthy volunteers.[54] In animal models, propofol suppresses nociception induced by spinal sensitization and decreases the lumbar dorsal horn neuronal responses to noxious stimuli.[55,56] In addition, antioxidant and neuroprotective effects of propofol also have been documented.[57,58]

Opioid-induced Hyperalgesia

Use of opioids is the cornerstone of analgesic therapy for moderate-to-severe pain. Acute and chronic exposure to opioids, however, is associated with the development of hyperalgesia because of involvement of

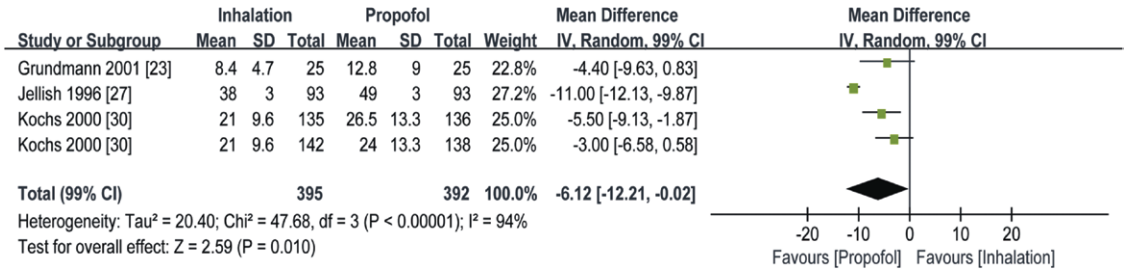

Figure 7. Propofol versus inhalational anesthesia: time to first analgesic administration after surgery. CI indicates confidence interval; IV, intravenous; SD, standard deviation.

Table 4. Risk Assessment for Bias in the Clinical Trials Included in the Meta-analysis

Studies	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)
Akkurt et al[15]	Low	Low	Low	Low	Low	Low
Boccara et al[16]	Low	Unclear	Low	Low	Unclear	Unclear
Braun et al[17]	Low	Unclear	Low	Low	Unclear	Unclear
Cheng et al[2]	Low	Low	Low	Low	Low	Low
Citerio et al[18]	Low	Low	Low	Low	Low	Low
Falsini et al[19]	Low	Unclear	Low	Low	Unclear	Unclear
Fassoulaki et al[5]	Low	Low	Low	Low	Unclear	Unclear
Fredman et al[20]	Low	Low	Low	Low	Unclear	Unclear
Gokce et al[21]	Low	Low	Low	Low	Unclear	Unclear
Gozdemir et al[22]	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Grundmann et al[23]	Low	Unclear	Low	Low	Unclear	Unclear
Höcker et al[24]	Low	Low	Low	Low	Unclear	Unclear
Hofer et al[25]	Low	Low	Low	Low	Low	Low
Jellish et al[26]	Low	Unclear	High	Low	Unclear	Unclear
Jellish et al[27]	Low	Low	Low	Low	Unclear	Unclear
Jensen et al[28]	Low	Low	Low	Low	Low	Low
Kim et al[29]	Low	Low	Low	Low	Low	Low
Kochs et al[30]	Low	Low	Low	Low	Low	Low
Konstantopoulos et al[31]	Low	Low	Low	Low	Unclear	Unclear
Lauta et al[32]	Low	Low	Low	Low	Low	Low
Lebenbom et al[33]	Low	Unclear	Low	Low	Unclear	Unclear
Lee et al[34]	Low	Low	Low	Low	Unclear	Unclear
Li et al[3]	Low	Low	Low	Low	Low	Low
Liu et al[35]	Low	Low	Low	Low	Unclear	Unclear
Martikainen et al[36]	Low	Unclear	Low	Low	Low	Low
Mei et al[37]	Low	Low	Low	Low	Low	Low
Ogurlu et al[38]	Low	Low	Low	Low	Low	Low
Oikkonen[39]	Low	Unclear	Unclear	Low	Unclear	Unclear
Ortiz et al[40]	Low	Low	Low	Low	Low	Low
Park et al[41]	Low	Low	Low	Low	Unclear	Unclear
Pokkinen et al[6]	Low	Low	Low	Low	Low	Low
Raeder et al[42]	Low	Unclear	Low	Low	Low	Low
Shin et al[43]	Low	Low	Low	Low	Low	Low
Sneyd et al[44]	Low	Low	Low	Low	Low	Low
Talke et al[45]	Low	Low	Low	Low	Unclear	Unclear
Tan et al[4]	Low	Low	Low	Low	Low	Low
Tang et al[46]	Low	Low	Low	Low	Low	Low
Yoo et al[47]	Low	Low	Low	Low	Low	Low
Zoremba et al[48]	Low	Low	Low	Low	Low	Low

N-methyl-D-aspartate (NMDA) receptor in pain facilitating systems.[59] Remifentanil, an ultra short–acting opioid, causes opioid-induced hyperalgesia through a cellular mechanism that involves rapid and prolonged up-regulation of NMDA receptor function.[60,61] Moreover, propofol directly activates γ-aminobutyric acid type A receptors, inhibits NMDA receptors, and modulates calcium influx through the slow calcium–ion channels.[62] Finally, maintenance of general anesthesia with propofol has been shown to prevent remifentanil-induced hyperalgesia.[43,63]

The subgroup analyses revealed better postoperative analgesia with propofol in patients who received concomitant intraoperative remifentanil. These findings suggest a synergistic effect between propofol and remifentanil leading

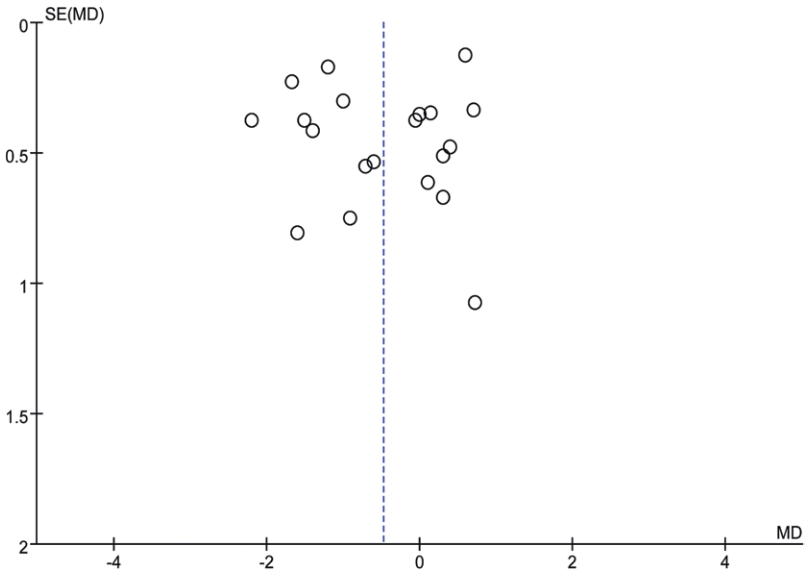

Figure 8. Funnel plot analysis with pain intensity at rest at 30 minutes as an end point. MD indicates mean difference; SE, standard error.

to a more potent NMDA antagonistic effect on opioid-associated hyperalgesia than that observed with volatile agents.

Limitations

There are several limitations of our study. First, when applying a conservative *P* value of <.01, the main differences between propofol and inhalational anesthesia are small and not statistically significant. The clinical relevance of these results needs to be further investigated. Second, there is difficulty in attributing the analgesic properties of propofol or hyperalgesic effects of sevoflurane, although there is evidence to support both. Complex interaction exists between general anesthetics and opioids in the pain facilitating systems. Third, the opioids used for postoperative pain relief varied between the studies, and the calculation of morphine-equivalents may have introduced a bias. Fourth, a multimodal analgesic approach with local anesthetics, NSAIDS, and opioids could mask any marginal difference that might exist between propofol and volatile agents. Fifth, despite subgroup analyses according to different techniques or analgesia regimens, this meta-analysis was affected by heterogeneity because of varied surgical procedures, different volatile anesthetics studied, various perioperative analgesic regimens used, and different indices used for titration of anesthesia depth; therefore, the results should be interpreted with caution. Finally, our study did not evaluate the effects of propofol or volatile agents on the long-term outcomes such as chronic pain. Further studies with adequate power to investigate long-term and short-term pain outcomes after propofol or inhalational anesthesia are required.

CONCLUSIONS

This meta-analysis did not demonstrate significant differences in postoperative pain control between propofol anesthesia and inhalational anesthesia because of substantial heterogeneity among studies. Large RCTs may be needed to verify whether the choice of anesthetics may contribute to a multimodal pain management and improved patient outcomes.

DISCLOSURES

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Name: Fu-Hai Ji, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
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