Systematic Review / Meta-analysis

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Efficacy and safety of ketamine wound infiltration for postoperative pain management: a systematic review, meta-analysis, and trial sequential analysis

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Background: Postoperative pain has a huge impact on the patients, families, healthcare practitioners, and healthcare delivery. Pain management with opioid-based analgesics and blind techniques have certain limitations, and ultrasound-based regional analgesia necessitates resources and experience, but ketamine wound infiltration is innovative with few side effects. However, its effectiveness is still uncertain.

Methods: A thorough search was carried out across various databases including PubMed/Medline, Cochrane, ScienceDirect, CINAHL, and LILACS, with no limitations on date or language. Only randomized trials comparing the effectiveness of ketamine wound infiltration for managing postoperative pain were considered for inclusion. Two authors independently conducted data extraction, and the quality of evidence was assessed using GRADEpro software. Trial sequential analysis (TSA) was utilized to ascertain the conclusiveness of the findings.

Results: The review showed that the first analgesic request was higher in the control group as compared to ketamine standard mean difference (SMD) = 1.68 (95% CI: 0.95–2.41). The TSA revealed that the cumulative *Z*-curve crosses both alpha-spending boundaries and reaches the required information size threshold, revealing strong power for current evidence. However, the quality of evidence was moderate.

Conclusion: Despite available evidence, the provision of a firm conclusion is less optimal with current evidence as the included studies were unpowered with low to very low quality of evidence.

Keywords: cesarean section, postoperative pain, wound infiltration

Introduction

Description of the condition

Surgery is increasingly recognized as a result of its initiative in reducing global surgical morbidity and mortality despite huge disparities in surgical and anesthesia access across regions globally[1]. Around 313 million individuals undergo surgery annually, with more operations performed in high-income countries[2].

The tremendous increase in the volume of surgery presents a substantial problem for healthcare personnel in terms of post-operative pain management[3]. Over the years, a variety of post-operative pain management strategies have been used, but they are associated with postoperative complications[4]. The most commonly used postoperative pain management treatments include but are not limited to, systemic opioid and non-opioid medications, regional blocks, and local wound infiltration of various local anesthetics and other adjuvants[4–8].

Evidence demonstrated that individual pain variability is highly impacted by pain sensitivity, gender, age, heredity, pre-operative anxiety, preoperative pain, history of depressive symptoms, and history of drug use[9–11].

HIGHLIGHTS

- The provision of a firm conclusion is less optimal with current evidence on the efficacy of ketamine wound infiltration, as the included studies were unpowered with low to very low quality evidence.
- The trial sequential analysis revealed that the cumulative *Z*-curve crosses both alpha-spending boundaries and reaches the required information size threshold, revealing strong power for current evidence.
- The odds of hallucination were approximately nine times more likely in the ketamine group compared to the comparators.

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Despite advances in our understanding of postoperative pain and the introduction of various postoperative analgesic drugs and modalities, the incidence of postoperative pain after surgery remains high, ranging from 4.4 to 50%[6,9–12].

Studies showed that inadequately managed postoperative pain is linked to a variety of undesirable consequences, including prolonged hospitalization, increased mortality, and the development of a chronic pain state as a result of brain plasticity[9,13,14]. However, systemic and intrathecal opioid usage can cause side effects such as nausea, vomiting, itching, and drowsiness[9,15].

Recent studies have shown a variety of postoperative pain management strategies, including but not limited to epidural analgesia, transverse abdominis plane (TAP) block, quadratus lumborum block, and wound infiltrations[6,12,16,17]. Wound infiltration procedures with ketamine, on the other hand, are gaining popularity because of its novelty, simplicity, and minimal complication profiles[18–21].

Description of the intervention

Postoperative wound infiltration techniques have recently gained popularity due to their ease of use and affordability in terms of administration strategies and side effects[6,12,16,17]. Recent studies comparing ketamine wound infiltration[6,21,22] with local anesthetics, glucocorticoids, opioids[22–24], nonsteroidal anti-inflammatory agents[25], and alpha-2 agonists[26,27] are released. The effectiveness and safety of low-dose preemptive and perioperative intravenous ketamine for postoperative pain is well established[20,21,28]. However, the efficacy and safety of subcutaneous infiltration of ketamine compared to local anesthetics and other adjuvants is still uncertain and a topic of debate.

How the intervention might work

The exact mechanism of ketamine infiltration wound is uncertain, but it prevents postoperative pain by inhibiting *N*-methyl-D-aspartate (NMDA) receptors, which modulate central sensory pain processing[21,29]. However, local anesthetics work by blocking sodium channels, preventing the propagation of action potentials and pain sensations[30–32]. While the exact mechanism of steroids is uncertain, it is thought to work via inhibition of the phospholipase α2 enzyme, which is responsible for the production of prostaglandin and other inflammatory mediators[33–35]. Opioids such as tramadol act by inhibiting inflammatory mediators, and research suggests that tramadol also has a local anesthetic-like effect of blocking sodium channels[17,36].

Why is it important to do this review?

Globally, the number and variety of surgeries have gradually increased in the last couple of decades. Deep venous thrombosis, paralytic ileus, depression, pulmonary infection, delayed wound healing, increased in-hospital length of stay, persistent pain, and increased healthcare expenses are all consequences of inadequate postoperative care.

Many postoperative pain treatment strategies are used. Opioid-based analgesics and landmark approaches are associated with undesirable effects. While regional analgesia with ultrasonography necessitates resources and experience, whereas an alternative wound infiltration technique with ketamine is an innovative option with low side effects and ease of administration. However, the effectiveness and safety of postoperative ketamine wound infiltration is unknown. Therefore, the objective of the systematic review and meta-analysis was to investigate the efficacy and safety of ketamine wound infiltration for postoperative pain management after surgery.

Research question

Currently, postoperative wound infiltration after surgery has been advocated because of its benefits, including but not limited to reduced opioid consumption, inexpensive, less adverse effects, minimal resource incentive, and better postoperative patient clinical outcomes. In this regard, a number of drugs have been tried over the years, but none of them have shown superiority, and further investigation is in demand. Therefore, this meta-analysis tried to assess the efficacy and safety of ketamine wound infiltration aimed to address the following research questions:

- Is ketamine wound infiltration effective for controlling postoperative pain as compared to local anesthetic, placebo, magnesium sulfate, tramadol, and dexmedetomidine wound infiltration?
- Do we have high-quality evidence to refute or conclude on the efficacy of ketamine wound infiltration for postoperative pain management?
- Can ketamine wound infiltration decrease opioid consumption compared to the comparators?
- What are the adverse effects of ketamine wound infiltration after surgery?
- Could we provide a firm conclusion and recommendation for stakeholders on the efficacy and safety of ketamine wound infiltration after surgery for postoperative pain management based on the current evidence?

Methods

Protocol and registration

The systematic review and meta-analysis were conducted based on the Preferred Reporting Items for Systematic and Meta-analysis[37]. This Systematic Review and Meta-Analysis protocol was registered in PROSPERO (CRD42021270710) on 5 September 2021.

Eligibility criteria

Types of studies

All randomized controlled trials comparing the efficacy and safety of ketamine wound infiltration for postoperative pain management were included. However, observational studies comparing wound infiltration to placebo and other drugs were excluded because they were conducted among heterogeneous groups of participants with different confounders, potentially masking the effect size of this systematic review and meta-analysis. Furthermore, comparisons of local anesthesia with regional block were excluded.

Types of participants

All American Society of Anesthesiologists physical status classifications (ASA) I and II, age greater than 18 years scheduled for surgery were included, and the rest were excluded. These inclusion and exclusion criteria were as per the definition of each primary included study.

Types of intervention

The treatment group was parturient allocated to one of the wound infiltration modalities, which were as per the included studies. The parturients allocated into comparator groups, as defined by each included study, were considered the control groups.

Outcome measures

The primary outcomes of this systematic review with meta-analysis and trial sequential analysis (TSA) will be postoperative pain severity, first analgesic request, total analgesic request, and patient satisfaction, while postoperative nausea and vomiting, sedation, and mortality were secondary outcomes.

Search strategy

The search method was designed to explore all available published and unpublished randomized controlled studies comparing the effectiveness of ketamine wound infiltration for postoperative pain management in surgical patients under spinal or general anesthesia, with no language or date limitation. A thorough first search in PubMed/Medline, Cochrane Library, CINAHL, Hinari, ScienceDirect, and Latin American and Caribbean Health Sciences Literature (LILACS) was conducted, followed by an examination of the text words contained in the Title/Abstract and indexed keywords. A second search was conducted by using Boolean operators to combine free text words with indexed phrases. The third search was undertaken using the reference lists of all recognized papers and journals. Finally, a grey literature search using Google Scholar was undertaken. EndNote reference manager was used to remove the duplicates. Then, the rest were evaluated for inclusion in the systematic review based on the PICO strategy as surgery OR operation OR surgical procedure AND local anesthetics OR bupivacaine OR Levobupivacaine OR Marcaine OR Lidocaine OR Opioids OR tramadol OR pethidine OR ketamine OR dexamethasone OR steroid OR Glucocorticoid OR Dexmedetomidine OR clonidine OR α2 agonist AND Normal saline OR placebo AND OR postoperative pain OR analgesia OR toxicity OR adverse effects AND RCT for PubMed/Medline database. The keywords were identified using Mesh browser and Medline medical subject heading words to be combined for advanced PubMed/Medline search. The results of the search strategy were summarized with a PRISMA flowchart[38].

Data extraction

The data from each study was retrieved by two separate reviewers using a modified Microsoft Excel 2013 format. The other two writers settled the differences between the two separate authors. Author names, country, date of publication, sample size, treatment and control groups, degree of pain, initial analgesic request, total analgesic intake, patient satisfaction, nausea and vomiting incidence, and sedation incidence were among the data collected. Finally, the data was transferred to the Review Manager for analysis and a summary of the risk of bias. The collected data was also imported into STATA 16 for meta-regression and publication bias analysis. Furthermore, the data was loaded into TSA program to determine the conclusiveness of the evidence.

Assessment of methodological quality

The methodological quality of the included studies was evaluated based on the Cochrane Handbook for Systematic Reviews of Intervention[39] by two independent reviewers, and the disagreement will be resolved by the other reviewers. The random sequence generation, allocation concealment, blinding of participants and treatment providers, blinding of result assessment, incomplete outcome data, selective outcome reporting, and other bias risks were assessed (Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/MS9/A518). A critical evaluation tool for systematic reviews that contain randomized or non-randomized trials of healthcare treatments, or both, was also used to assess the methodological quality of this systematic review (AMSTAR 2, Supplemental Digital Content 2, http://links.lww.com/MS9/A519)[40].

Random sequence generation

Studies done on random sequence generation using a computer random number generator or a random number table will be rated as low risk of bias. Besides, if random sequence generation is done with the lottery method, tossing a coin, shuffling cards, and throwing dice will also be considered adequate if performed by an independent adjudicator. If the method of randomization was not specified, but the trial was still presented as being randomized, it is considered an uncertain risk of bias. A high risk of bias is considered if the allocation sequence was not randomized or only quasi-randomized.

Allocation concealment

Allocation concealment is said to be low risk if the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, or containers prepared by an independent investigator. It is the uncertain risk of bias if the trial was classified as randomized, but the allocation concealment process was not described, and it is a high-risk bias if the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

If the participants and the treatment providers were blinded to intervention allocation, as described in the article, it is considered to be low risk of bias, and it is uncertain if the procedure of blinding was insufficiently described. If blinding of participants and the treatment providers was not performed at all, it was taken as a high risk of bias.

Blinding of outcome assessment

It is said to be a low risk of bias if the outcome assessors were blinded and this was sufficiently described, but it is uncertain if the outcome assessors in the trial were blinded or the extent of blinding was insufficiently described and high risk if no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

It is a low risk of bias if there were no drop-outs or withdrawals for all outcomes, if the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar to both groups or if drop-outs are less

than 5% and uncertain risk of bias is assumed if there was insufficient information to assess whether missing data were likely to induce bias on the results. If the results were likely to be biased due to missing data, either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data, it is taken as high risk of bias.

Selective outcome reporting

A low risk of bias is considered if a protocol was published before or at the time the trial began and the outcomes specified in the protocol were reported, and an uncertain risk of bias is rated if no protocol was published. If the outcomes in the protocol were not reported at all, a high-risk of bias is introduced.

Other risks of bias

If the trial appears to be free of other components (for example, academic bias or for-profit bias) that could put it at risk of bias, it is at low risk of bias. It is called uncertain risk of bias if the trial may or may not be free of other components that could put it at risk of bias, but it is not described. If there are other factors in the trial that could put it at risk of bias, such as authors conducting trials on the same topic or for-profit, it could introduce a high risk of bias.

Overall risk of bias

Overall, the study is said to have a low risk of bias only if all of the bias domains described are classified as low risk of bias and high risk of bias if any of the bias risk domains described above are classified as 'unclear' or high risk of bias.

Grading the quality of evidence

The overall quality of evidence for the studied outcome was evaluated using the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation)[26,41]. The system incorporates study quality (risk of bias), inconsistency (comparison

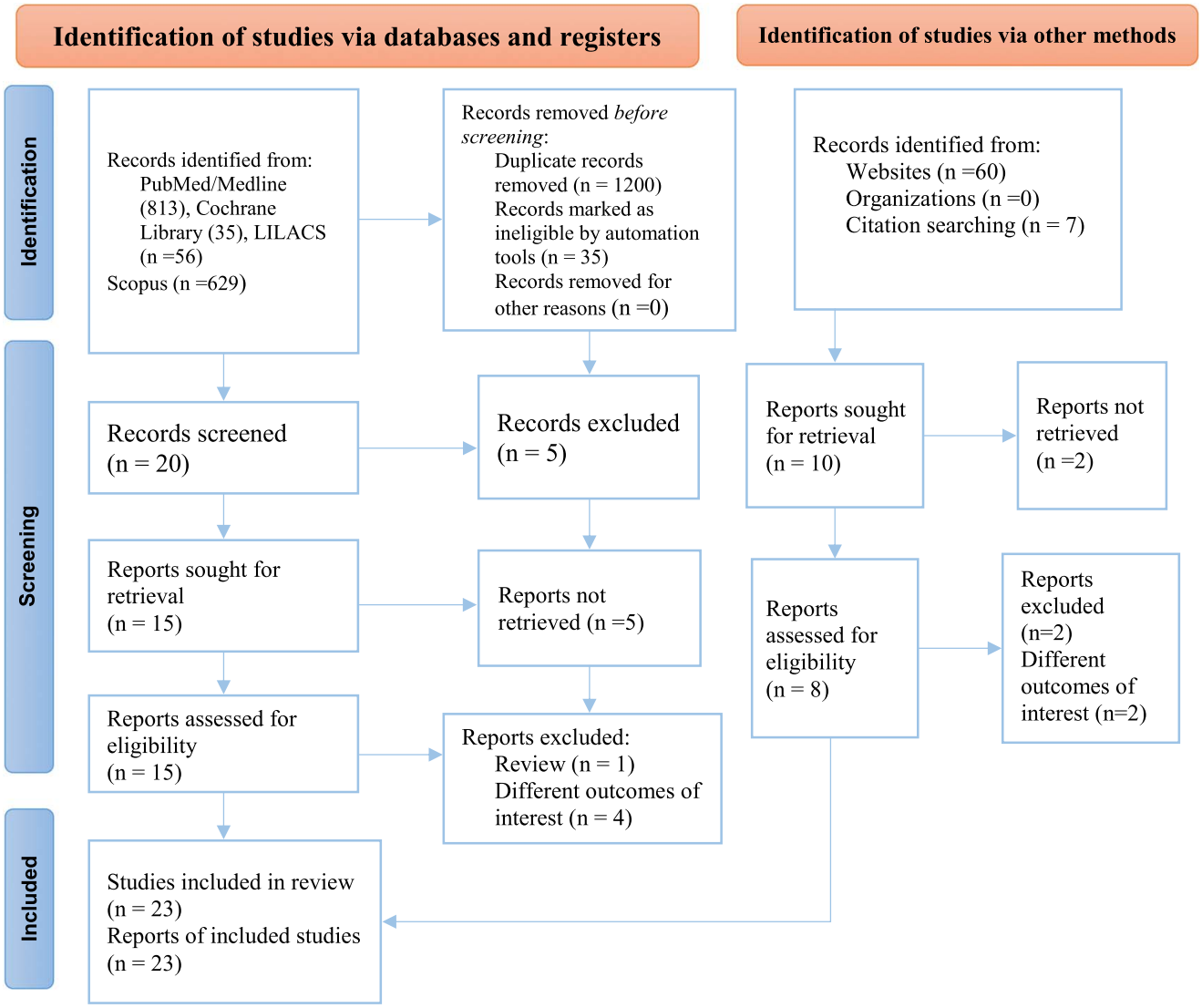

Figure 1. PRISMA flow diagram.

Table 1

Description of included studies.

Authors	Year	Country	N	Intervention	comparator	Procedure	ROB
Abdallah et al[65]	2017	Egypt	48	ketamine	Levobupivacaine	Hysterectomy	7
Behaeen et al[66]	2014	Iran	40	ketamine	placebo	Cesarean section	7
Bhola et al[67]	2019	India	60	ketamine	Bupivacaine	Cholecystectomy	6
Biomy et al[68]	2021	Egypt	60	ketamine	Dexmeditomidine	Cesarean section	7
Choudhary et al[69]	2020	India	120	ketamine	Bupivacaine	Cesarean section	7
Honarmand et al[70]	2011	Iran	60	ketamine	IV ketamine	Appendectomy	7
Jha et al[71]	2013	India	50	ketamine	Bupivacaine	palate repair	7
Kaler et al[72]	2019	India	60	ketamine	Levobupivacaine	Cesarean section	7
Kamali et al[73]	2019	Iran	84	ketamine	Dexmeditomidine	Hysterectomy	5
Khajavi et al[74]	2016	Iran	32	ketamine	Tramadol	Renal surgery	6
Maktabi et al[75]	2019	Iran	66	ketamine	Bupivacaine	Hysterectomy	7
Manouchehrian et al[76]	2014	Iran	60	ketamine	placebo	Laparotomy	7
Mohamed et al[77]	2017	Egypt	60	ketamine	Dexmeditomidine	Cesarean section	7
Mohamed et al[78]	2019	Egypt	100	ketamine	Magnesium	Cesarean section	7
Mostafa et al[79]	2016	Egypt	50	ketamine	Lidocaine	Laparoscopies	7
Mwase et al[80]	2017	Uganda	88	ketamine	placebo	Cesarean section	7
Othman et al[81]	2016	Egypt	60	ketamine	Bupivacaine	Mastectomy	5
Rahman et al[82]	2021	Bangladesh	60	ketamine	Bupivacaine	Laparotomy	7
Sacevich et al[83]	2018	Rwanda	59	ketamine	placebo	All surgery	5
Safavi et al[84]	2011	Iran	60	ketamine	placebo	Cholecystectomy	7
SANLI et al[85]	2016	Turkey	60	ketamine	Lidocaine	Rhinoplasties	7
Simin et al[86]	2011	Iran	70	ketamine	placebo	Cesarean section	7
Tan et al[87]	2007	Taiwan	40	ketamine	placebo	Circumcision	7

ROB, risk of bias.

of effect estimates across studies), indirectness (applicability of the population, intervention, comparator, and outcomes to the clinical decision), imprecision (certainty of confidence interval), and high probability of publication bias. The overall quality of evidence was categorized as high, moderate, low, and very low by combining the aforementioned five parameters.

Data analysis

Review Manager version 3.3.1, STATA 16, and TSA program were used to analyze the data. The pooled incidence of postoperative pain, the weighted mean difference of pain scores, the first analgesic request, total analgesic consumption adverse effects such as nausea and vomiting, sedation, hallucination, and dizziness with fixed and random effect models with the Restricted maximum likelihood (REML) method where appropriate, but the meta-analysis results were reported with random effect model as there was substantial heterogeneity between the included studies. Forest plot, I^2 test, and P values were used to examine for heterogeneity among the included studies, where I^2 was <25: no heterogeneity, 25–50: small heterogeneity, 50–75: moderate heterogeneity, and >75% was considered substantial heterogeneity. The subgroup analysis was conducted using different types of comparators. Publication bias was checked with a funnel plot, and the objective diagnostic test was conducted with Egger's correlation, Begg's regression tests, and the Trim and Fill method.

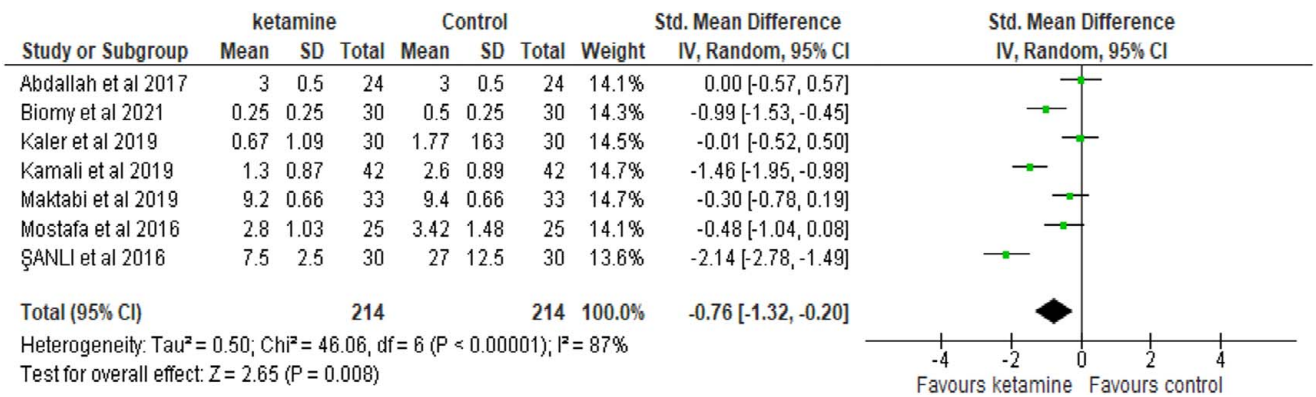

Figure 2. Forest plot for postoperative pain score at 1 h after wound infiltration with ketamine and different comparators: individual trials and meta-analysis total: the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR, inverse variance; VAS, visual analog scale.

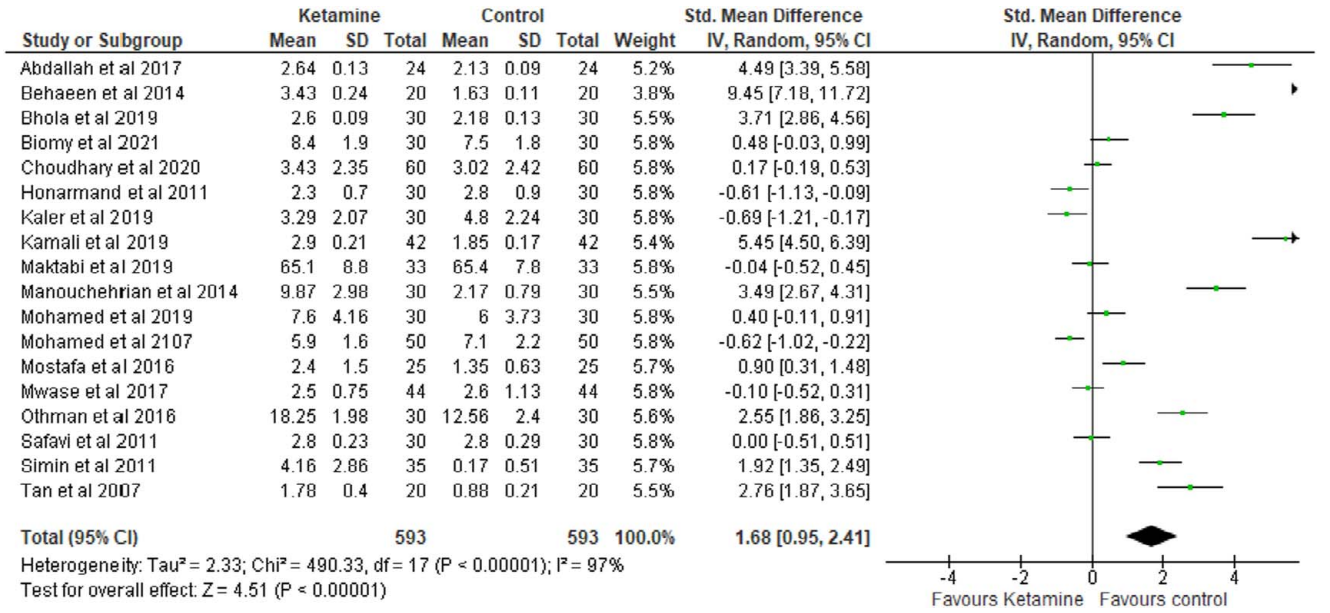

Figure 3. Forest plot for first analgesic request after wound infiltration with ketamine and different comparators: individual trials and meta-analysis total: the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR, inverse variance.

Data synthesis

Narration

The authors planned to describe the characteristics of each included study with respect to sample size, country, intervention and comparator, baseline clinical variables, primary and secondary outcomes, conclusion, and recommendation. Besides, descriptions of the included studies were summarized using a table.

Meta-analysis

This systematic review was conducted in compliance with the updated Cochrane Handbook for Systematic Reviews of Interventions[42]. The meta-analysis was conducted with Review Manager 5[43] to estimate the pooled effect sizes and risk of bias summary while STATA 16 software[44] and R software version 4.2[45] were used for meta-regression, sensitivity analysis, and publication bias analysis where appropriate. We conducted the meta-analysis with a Restricted maximum likelihood (REML) estimator with both random and fixed effects models as recommended by different authors[46,47]. Substantial heterogeneity among the included studies was investigated with subgroup analysis and meta-regression, and the final decision to report the finding either narratively or doing the meta-analysis with a random effect model depends on the clinical importance of the outcome[48–51]. Publication bias was checked with a funnel plot, and the objective diagnostic test was conducted with Egger's correlation, Begg's regression tests, and the Trim and Fill method.

Trial sequential analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We planned to control the risks of type I and II errors. We, therefore, perform TSA on the outcomes in order to calculate the required information size, which is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect and the cumulative *Z*-curve's breach of relevant trial sequential monitoring boundaries[52–57]. The required information size for dichotomous outcomes will be estimated based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20%, an $\alpha$of 1.4% for all our outcomes, a β of 20%, and the observed diversity as suggested by the trials in the meta-analysis while the observed SD, a mean difference of the observed SD/2, an α of 1.4% for all outcomes, a β of 20%, and the observed diversity was used as continuous outcomes[56–59].

Results

Selection of studies

A total of 1533 articles were identified from different databases with an initial search. Seventy articles were selected for evaluation after successive screening. Twenty-three articles with 13 179 participants were included in the systematic review and meta-analysis, while 17 studies were excluded with reasons[19,60–64] (Fig. 1).

Characteristics of included studies

This systematic review and meta-analysis included 23 studies that compared the efficacy and safety of ketamine wound infiltration for postoperative pain management in 13 179 surgical patients (Table 1). For a variety of reasons, 17 studies were excluded (Fig. 1). According to the Cochrane risk of bias assessment for randomized controlled trials (ROB), the methodological quality

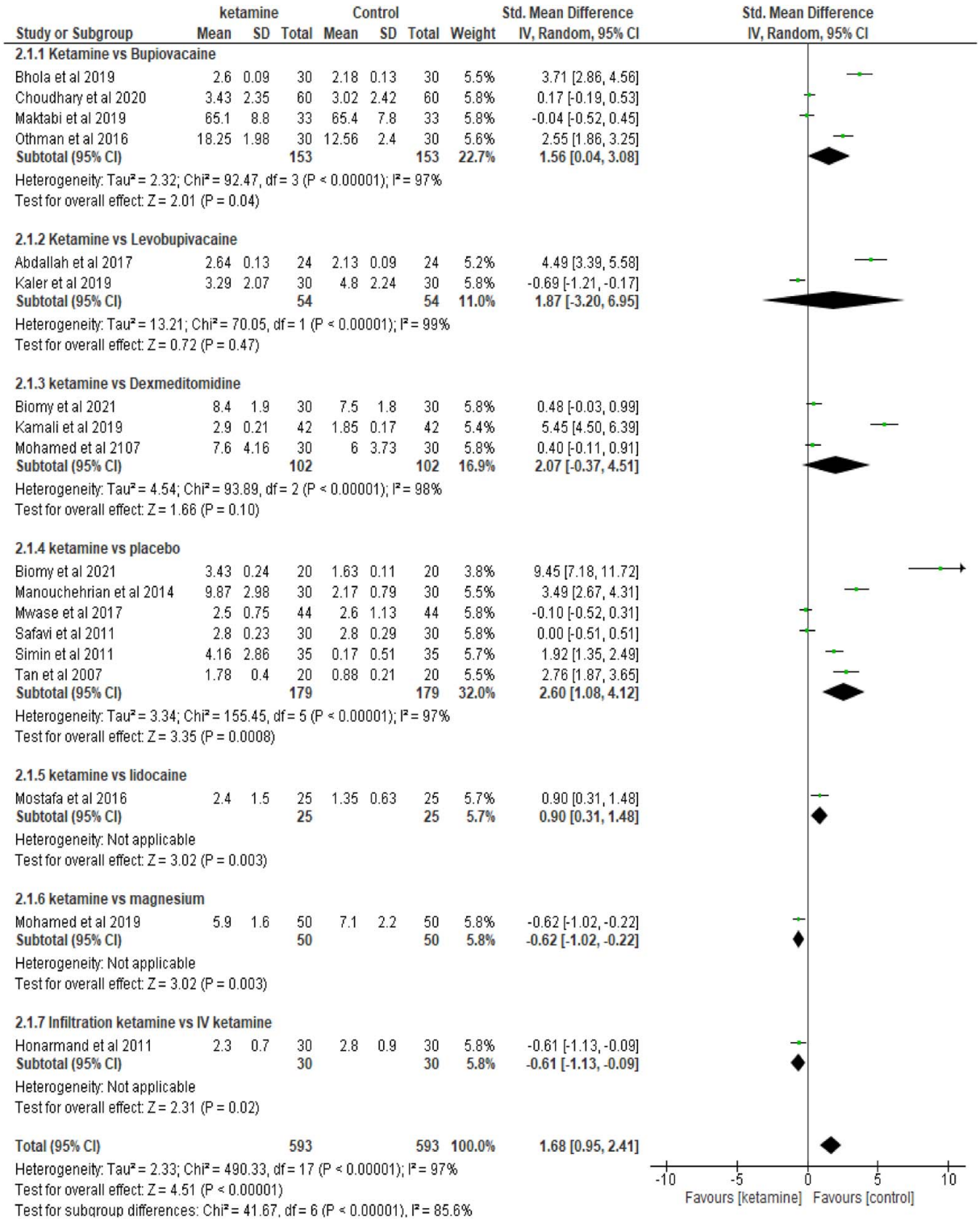

Figure 4. Forest plot for subgroup analysis of first analgesic request after wound infiltration with ketamine and different comparators: individual trials and meta-analysis total: the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR, inverse variance.

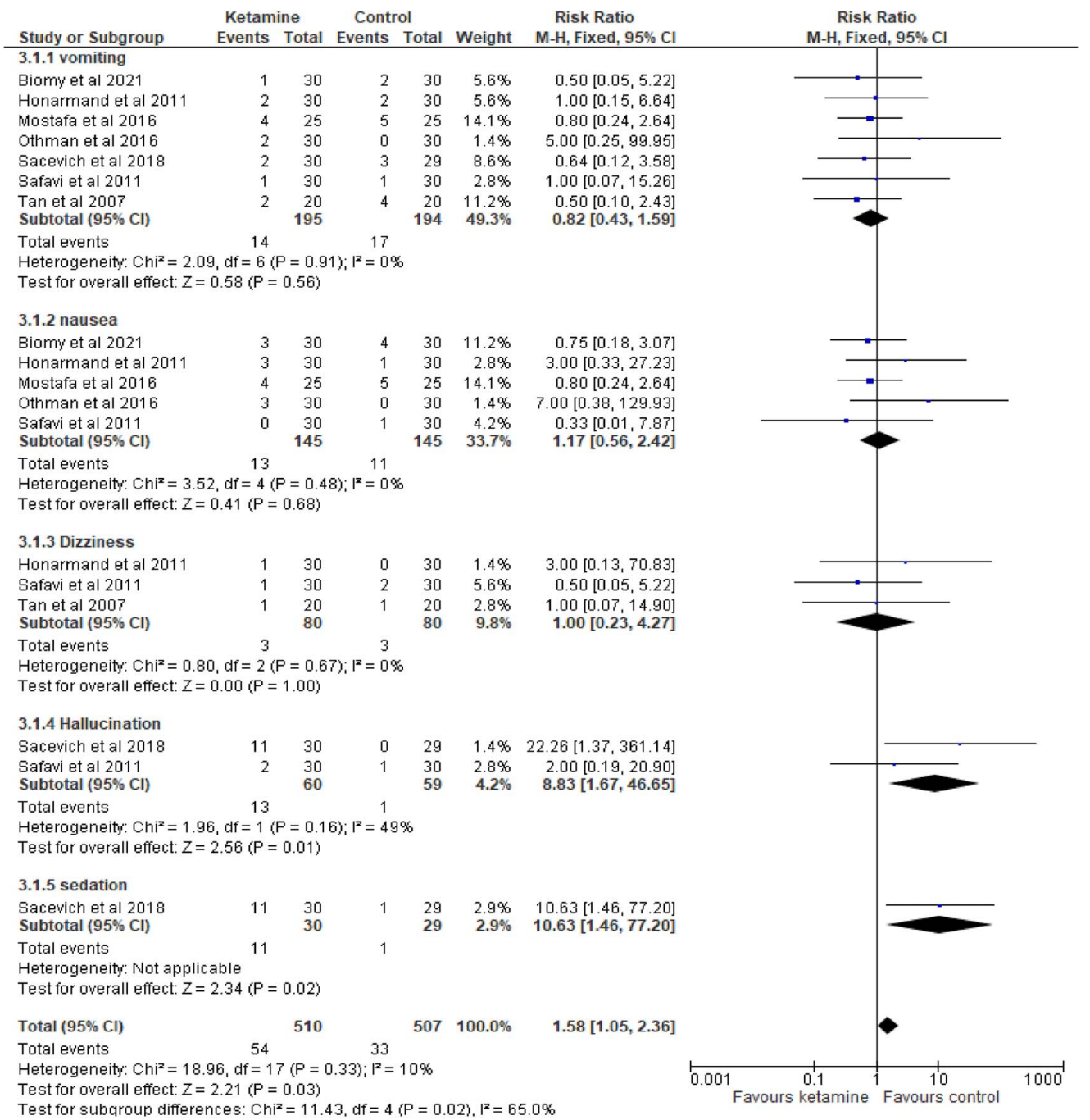

Figure 5. Forest plot for subgroup analysis of complications after wound infiltration with ketamine and different comparators: individual trials and meta-analysis total: the total number of participants in intervention and control. Weight: sample size contribution of the study relative to the pooled sample size of the meta-analysis. IR, inverse variance.

of included studies was moderate to high (Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/MS9/A518).

The studies included in this meta-analysis were conducted between 2007 and 2022, with sample sizes ranging from 32 to 120 participants. The mean age of the participants ranged from 227.5 to 38.78.53 years in the ketamine and control groups, respectively. The majority of the included studies took place in Iran, Egypt, and India, with the remaining studies taking place in Bangladesh, Taiwan, Turkey, Rwanda, and Uganda, with one study in each country.

The majority of surgical procedures performed in the included studies were cesarean section and abdominal hysterectomy, with a few others being mastectomy, cholecystectomy, appendectomy, laparotomy, laparoscopy, cleft palate repair, and circumcision.

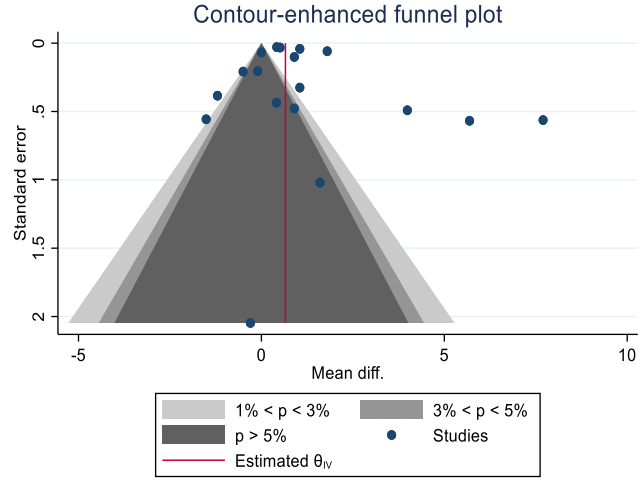

Figure 6. Funnel plot to assess publication bias. The vertical line indicates the effect size, whereas the diagonal line indicates the precision of individual studies with a 95% confidence interval.

For postoperative pain scoring, the majority of the studies utilized a visual analogue score, while a few used a numeric rating scale. Sedation, hallucination, nausea, vomiting, hypertension, hypotension, and dizziness were reported as postoperative adverse effects in some of the included studies.

Meta-analysis

This meta-analysis was intended to provide evidence on the efficacy and safety of ketamine wound infiltration for postoperative pain management among surgical patients. The first analgesic request, total analgesic consumption, and the average pain scores at 1, 2, 4, 6, 12, and 2 h were pooled with a random effect model in meta-analysis with substantial heterogeneity. Besides, postoperative complications were pooled from among studies reporting these complications. The meta-analysis showed that the postoperative pain score at 1 h was lower in the intervention group as compared to comparators, standard mean difference (SMD) = – 0.76 (95% CI: – 1.32 to – 0.20) (Fig. 2). However, postoperative pain score at 2, 6, 12, and 24 h did not show any statistical significant difference, SMD = – 0.34 (95% CI: – 0.76 to – 0.09) (Supplementary Figs S1, Supplemental Digital Content 3, http://links.lww.com/MS9/A520, S2, Supplemental Digital Content 4, http://links.lww.com/MS9/A521, S3, Supplemental Digital Content 5, http://links.lww.com/MS9/A522, and S4, Supplemental Digital Content 6, http://links.lww.com/MS9/A523). The meta-analysis revealed that the first analgesic request was higher by 1.68 h in the control group as compared to the Ketamine group SMD = 1.68 (95% CI: 0.95–2.41, 18 studies, 1186 participants) (Fig. 3). The subgroup analysis with different comparators such as Dexmedetomidine and Levobupivacaine did not show a significant difference ($P > 0.05$). However, analgesic request reduced in magnesium sulfate and intravenous Ketamine groups as compared to ketamine; SMD = – 062 (95% CI: – 1.02 to – 0.22) and SMD = – 0.61 (95% CI: – 1.13 to – 0.090 respectively ($P < 0.05$) (Fig. 4).

The postoperative adverse events such as vomiting, nausea, hallucination, dizziness, sedation, and patient satisfaction were reported in a few of the included studies. The meta-analysis revealed that the risk of hallucination was approximately nine times more likely in the ketamine group compared to the comparator group (OR = 8.83 (95% CI: 1.67–46.65), while the risk of sedation increased by 37% (OR = 1.63 (95% CI: 1.46–77.20) (Fig. 5).

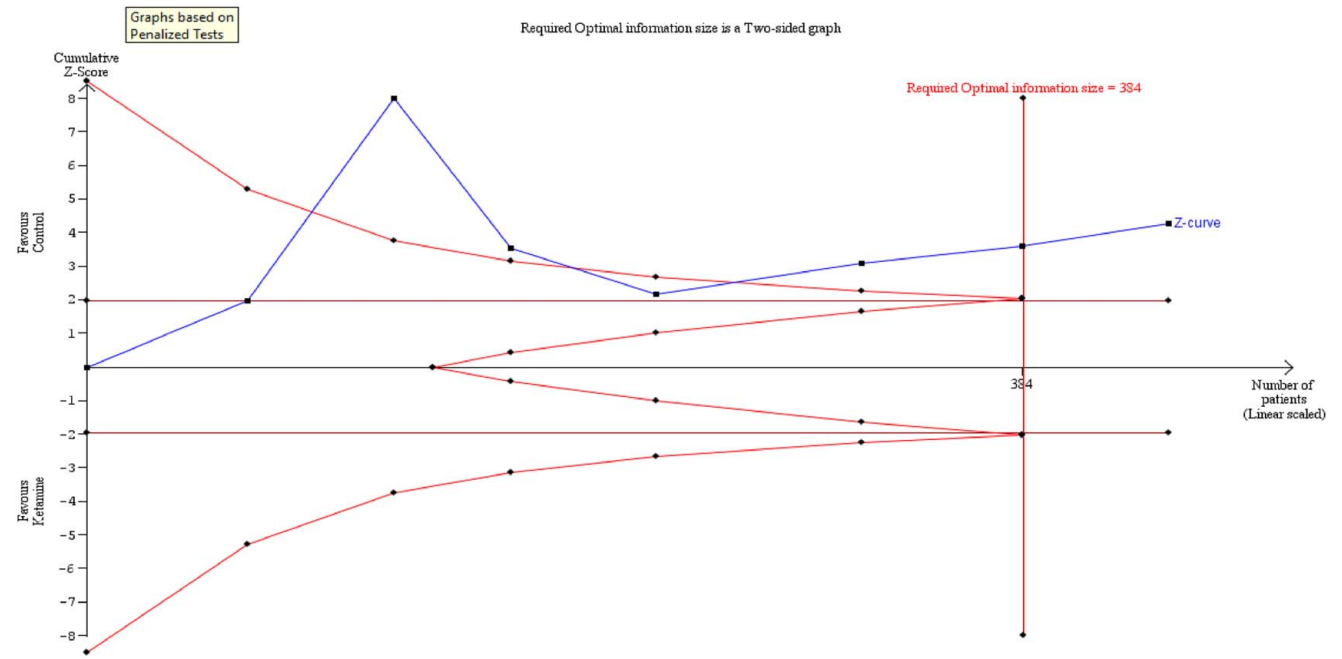

Figure 7. Trial sequential analysis for the outcome 'first analgesic request'. The cumulative *Z*-curve crosses both alpha-spending boundaries and reaches the required information size threshold, revealing strong power for current evidence.

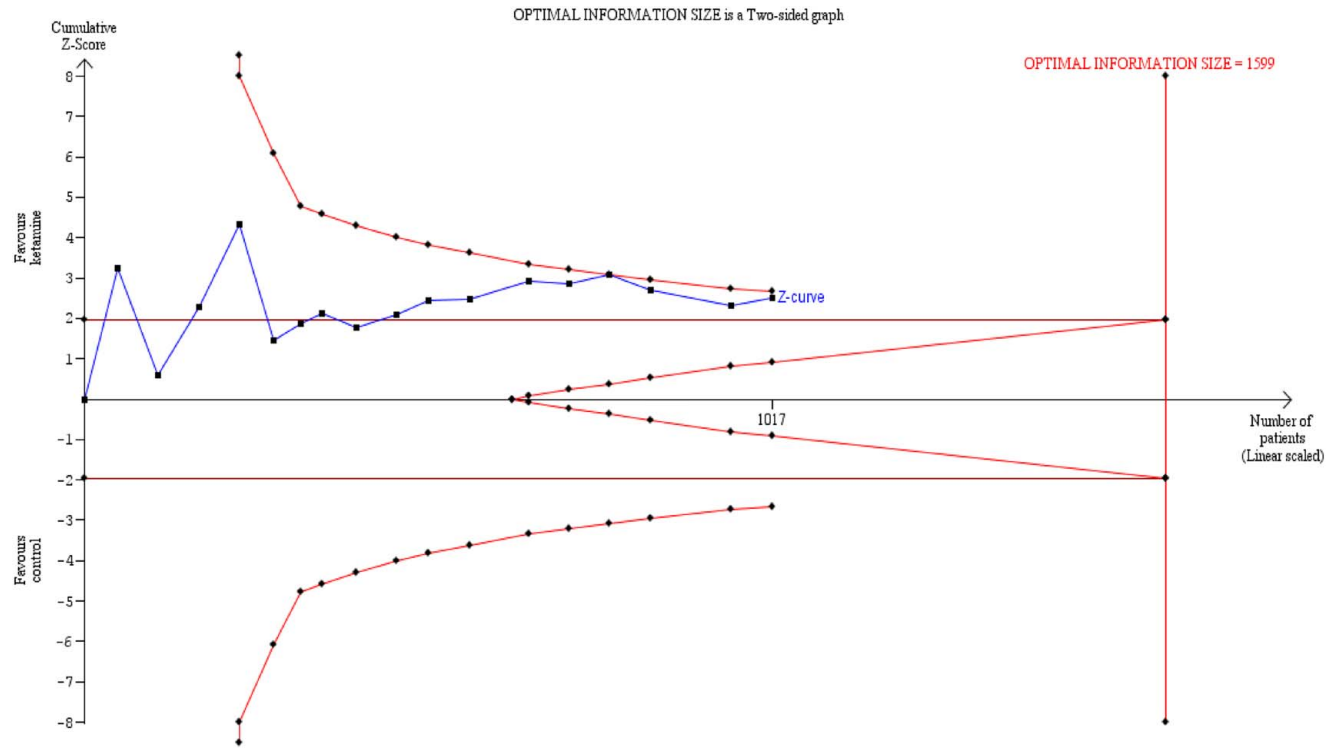

Figure 8. Trial sequential analysis for the outcome 'postoperative analgesic consumption'. The cumulative *Z*-curve crossed both alpha-spending boundaries but did not reach the required information size threshold, revealing a moderate power for current evidence.

Sensitivity analysis and publication bias

We used sensitivity analysis to identify the most influential study on the pooled summary effect by removing each study one at a time; however, there was no significant influencing summary effect. There was no evidence of publication bias in the funnel plot. Furthermore, both Egger's regression and Begg's correlation rank correlation failed to indicate a significant difference ($P = 0.62$ and $P = 0.19$), respectively (Fig. 6).

Trial sequential analysis

TSA was used to control for random errors by calculating the diversity-adjusted required information size (DARIS), which is the number of participants necessary in a meta-analysis to detect or reject a predetermined intervention effect. As a result, we performed TSA for both primary and secondary outcomes, which had a significant effect on conventional meta-analysis. Besides, primary and secondary outcomes with no statistical significance with meta-analysis was not presented in here, but it was discussed somewhere in this review along with GRADEpro summary of the table (Supplementary Figs S5–S11, Supplemental Digital Content 7, http://links.lww.com/MS9/A524; Supplemental Digital Content 8, http://links.lww.com/MS9/A525; Supplemental Digital Content 9, http://links.lww.com/MS9/A526; Supplemental Digital Content 10, http://links.lww.com/MS9/A527; Supplemental Digital Content 11, http://links.lww.com/MS9/A528; Supplemental Digital Content 12, http://links.lww.com/MS9/A529; Supplemental Digital Content 13, http://links.lww.com/MS9/A530).

First analgesic request

The TSA for the outcome 'first analgesic request' revealed that the cumulative *Z*-curve crosses both alpha-spending boundaries and reaches the required information size threshold, revealing strong power for current evidence. The estimated required information size of 384 patients was calculated using $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (power 80%), an anticipated estimated mean difference reduction of – 1.48, and a heterogeneity correction of 98% in the control group (Fig. 7).

Analgesic consumption

The TSA for the outcome 'cumulative postoperative analgesic consumption showed that the cumulative *Z*-curve crosses both alpha-spending boundaries but does not reach the required information size threshold, revealing a moderate power for current evidence and further randomized trials with 582 participants are required to provide a firm conclusion. The estimated required information size of 1599 patients was calculated using $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (power 80%), an anticipated estimated mean difference reduction of – 1.12, and a heterogeneity correction of 96% in the control group. The TSA-adjusted pooled effect and confidence interval were – 2.8 (– 5.79 to – 0.18) (Fig. 8).

Dizziness

The TSA for the outcome 'postoperative dizziness' showed that postoperative dizziness did not cross either the conventional boundaries for benefit or trial sequential monitoring boundaries for benefit, revealing insufficient evidence to accept or

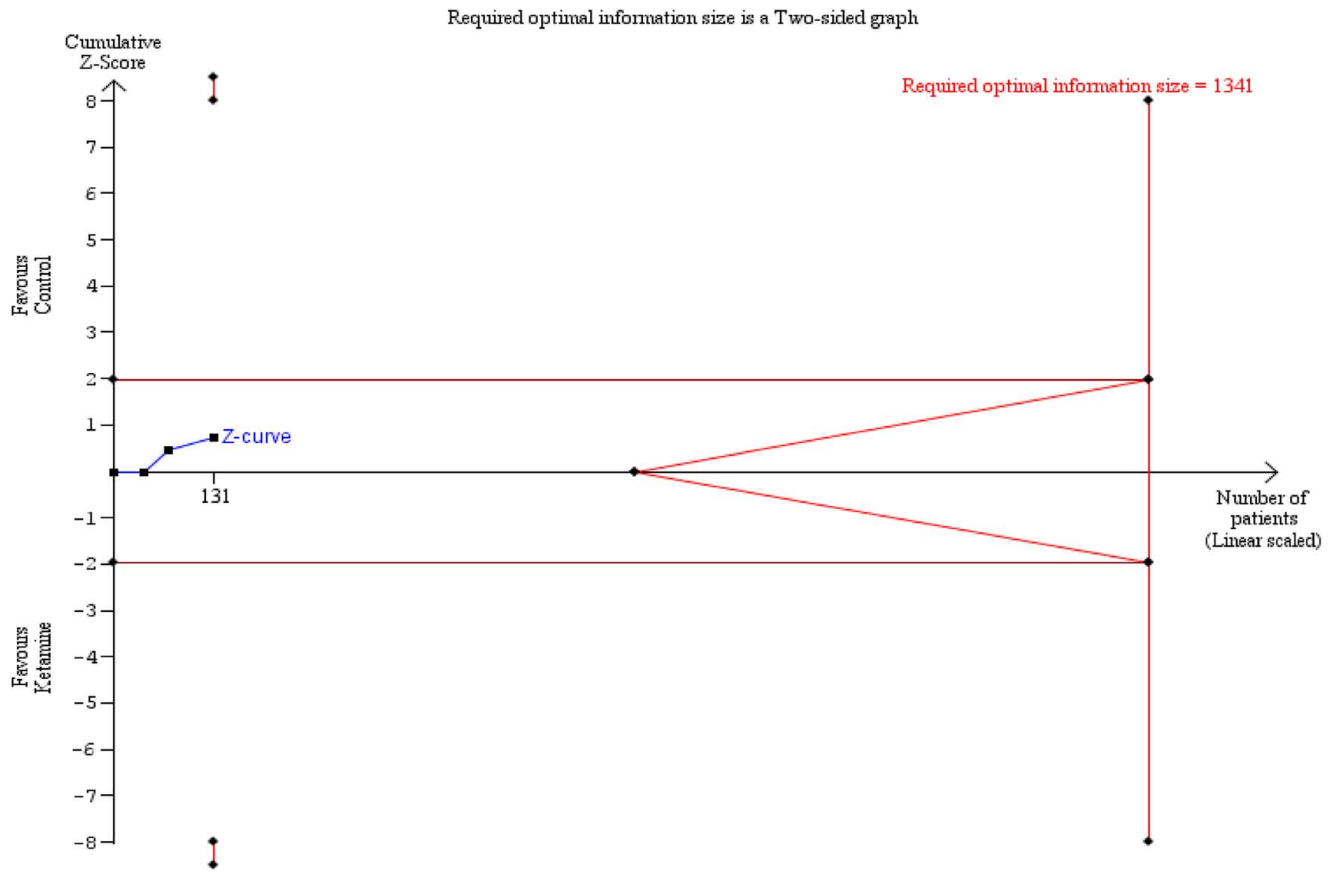

Figure 9. Trial sequential analysis for the outcome 'dizziness'. The cumulative *Z*-curve does not cross both alpha-spending boundaries and does not reach the required information size threshold, revealing a low power for current evidence.

reject a 33% anticipated relative risk reduction of postoperative dizziness. The estimated required information size of 1404 patients was calculated using $\alpha = 0.05$ (two-sided) and $\beta = 0.20$ (power 80%), an anticipated relative risk reduction of 33%, 15% of the incidence of dizziness in the control arm. The TSA-adjusted pooled effect and confidence interval were 0.55 (0.01–268) (Fig. 9).

Certainty of evidence

The GRADE system was used to assess the certainty of evidence for the study outcome against five criteria: quality (risk of bias), consistency (comparison of effect estimates across studies), indirectness (applicability of the population, intervention, comparator, and outcomes to the clinical decision), imprecision (certainty of confidence interval), and high risk of publication bias. By combining the aforementioned five parameters, the overall quality of evidence was classified as high, moderate, low, and very low. According to GRADEpro, the overall quality of the meta-analysis was moderate to very low (Tables 2 and 3).

In addition, TSA was used to control random errors caused by repeated significance testing for each primary and secondary outcome. We attempted to integrate the certainty of evidence with the outcomes of the TSA (Supplementary Figs S5–S12, Supplemental Digital Content 7, http://links.lww.com/MS9/A524; Supplemental Digital Content 8, http://links.lww.com/MS9/A525; Supplemental Digital Content 9, http://links.lww.com/MS9/A526; Supplemental Digital Content 10, http://links.lww.com/MS9/A527; Supplemental Digital Content 11, http://links.lww.com/MS9/A528; Supplemental Digital Content 12, http://links.lww.com/MS9/A529; Supplemental Digital Content 13, http://links.lww.com/MS9/A530; Supplemental Digital Content 14, http://links.lww.com/MS9/A531).

Discussion

The most challenging consequence of surgery is postoperative pain, and poorly managed postoperative pain has a huge impact on patients, families, healthcare practitioners, and healthcare delivery. It is a basic human right to give every patient with postoperative pain treatment that is realistic in terms of resources, technique, cost, and adverse event profile.

Systemic analgesics, epidural analgesia, TAP (transversus abdominis plane) block, quadratus lumborum block, and wound infiltrations have all been used over the years[7,8,12,15,22,24,88–95]. However, wound infiltration with local anesthetics, moderate opioids, glucocorticoids, ketamine, magnesium, NSAIDs, and alpha-2 agonists; on the other hand, is gaining popularity due to its novelty, ease of use, and low risk of complications. Intravenous ketamine has been used as induction and pain management for over a century, and in recent years, there are few studies showing ketamine wound infiltration for postoperative

Table 2

GRADEpro summary of findings table for continuous outcomes.

Outcomes	Number of participants	Overall certainty of the evidence	Anticipated absolute effect: Risk difference with ketamine	Comments
Postoperative pain score at 1 h	428 (7 RCTs)	⨁⨁◯◯: Low quality of evidence due to inconsistency and imprecision	SMD 0.76 SD lower (1.32 lower to 0.2 lower)	Trial sequential analysis showed that the cumulative *Z*-curve crossed both the conventional and TSA monitoring boundaries for harm and reached the required information size threshold, revealing a strong quality of evidence. However, the quality of evidence was low because of inconsistency and imprecision
Postoperative pain score at 2 h	488 (8 RCTs)	⨁⨁⨁◯: Moderate quality of evidence due imprecision	SMD 0.56 SD higher (0.36 lower to 1.49 higher)	Trial sequential analysis showed that the cumulative *Z*-curve didn't cross both the conventional and TSA monitoring boundaries for harm or benefit, revealing insufficient evidence to accept or reject the intervention effect. However, the quality of evidence was moderate due to downgrading for imprecision
Postoperative pain score at 6 h	648 (10 RCTs)	⨁⨁◯◯: Low quality of evidence due to inconsistency and imprecision	SMD 0.08 SD lower (0.45 lower to 0.29 higher)	Trial sequential analysis showed that the cumulative *Z*-curve didn't cross both the conventional and TSA monitoring boundaries for harm or benefit revealing insufficient evidence to accept or reject the intervention effect. However, the quality of evidence was low due to downgrading for imprecision and inconsistency
Postoperative pain score at 12 h	814 (12 RCTs)	⨁⨁◯◯: Low quality of evidence due to inconsistency and imprecision	The mean postoperative pain at 12 h was 0	Trial sequential analysis showed that the cumulative *Z*-curve crossed the futility boundary, which reveals sufficient evidence to reject a − 1.23 estimated mean difference reduction. However, the quality of evidence was low due to downgrading for imprecision and inconsistency
Postoperative pain score at 24 h	814 (12 RCTs)	⨁⨁◯◯: Low quality of evidence due to inconsistency and imprecision	SMD 0.07 SD lower (0.51 lower to 0.37 higher)	Trial sequential analysis showed that the cumulative *Z*-curve crossed the futility boundary, which reveals sufficient evidence to reject a − 1.23 estimated mean difference reduction. However, the quality of evidence was low due to downgrading for imprecision and inconsistency
First analgesic request	1146 (18 RCTs)	⨁⨁⨁◯: Moderate quality of evidence due to inconsistency	SMD 1.61 SD higher (0.87 higher to 2.35 higher)	Trial sequential analysis showed that the cumulative *Z*-curve crosses both alpha-spending boundaries and reaches the required information size threshold, revealing strong power for current evidence. However, the quality of evidence was moderate due to downgrading for inconsistency
Morphine equivalent cumulative analgesic consumption	1017 (17 RCTs)	⨁◯◯◯: very low quality of evidence due to risk of bias, inconsistency, and imprecision	3.54 lower (6.27 lower to 0.81 lower)	Trial sequential analysis showed that the cumulative *Z*-curve crossed both alpha-spending boundaries but did not reach the required information size threshold, revealing a moderate power for current evidence. However, the quality of evidence was very low due to downgrading for risk of bias, imprecision, and inconsistency

RCTs, randomized controlled trials; SD, standard deviation; SMD, standard mean difference; TSA, trial sequential analysis.

pain management despite disparities in its effectiveness and complications[18–21].

The meta-analysis showed that the Ketamine group had a lower postoperative pain score at 1 h than the control group, SMD = − 0.76 (95% CI: − 1.32 to − 0.20). However, there was no statistically significant difference in postoperative pain scores at 2 h and thereafter. Besides, the TSA revealed that the cumulative *Z*-curve crossed both the conventional and TSA monitoring boundaries for harm and reached the required information size threshold, revealing a strong quality of evidence. However, the quality of evidence was low due to inconsistency and imprecision. The conclusiveness of this evidence may be influenced by a number of factors, including underpowered studies, various types of procedures ranging from minor to painful invasive surgeries, and patients' inherited pain threshold characteristics[65–68,70,71,73,74,79,81,83,85,87].

A meta-analysis by Tong *et al*. including ten studies with 522 participants to investigate the analgesic efficacy of ketamine paratonsillar infiltration for tonsillectomy showed that ketamine infiltration prevents postoperative pain for the first hour, which is consistent with our meta-analysis[96]. However, a prior meta-analysis conducted back in 2011 by Dahmani *et al*. demonstrated that ketamine wound infiltration provides good postoperative pain for 6–24 h despite no change in total analgesic consumption[97]. This discrepancy might be attributable to differences in sample size, types of surgical incision, and sociodemographic characteristics of participants, which calls for cautious interpretation of effect estimate and clinical application with less optimal evidence.

According to the meta-analysis, the first analgesic request was higher in the control group than in the Ketamine group. Subgroup analysis with different comparators such Dexmedetomidine and Levobupivacaine revealed no significant differences ($P > 0.05$), which is consistent with the included studies[65,68,72,73,77], but first analgesic requests were lower in magnesium sulfate[78], and intravenous Ketamine groups[70], unlike bupivacaine[67] and lidocaine[79] where the first analgesic request was higher than

Table 3

GRADEpro summary of finding table for dichotomous outcomes.

Outcomes	Number of participants	Overall certainty of the evidence	Studies event rates (%)		Relative effect (95% CI)	Relative effect (TSA CI)	Comments
			Control	Ketamine			
Postoperative vomiting	389 (7 RCTs)	⨁⨁◯◯: Low quality of evidence due to imprecision	72/1000	88/1000	RR 0.82 (0.43–1.59)	RR 0.82 (0.82–0.82)	Trial sequential analysis showed that the cumulative *Z*-curve crossed the futility boundary for benefit, revealing sufficient evidence to reject a 33% estimated relative risk reduction. However, the quality of evidence was low because it was downgraded by 2 levels for imprecision
Postoperative nausea	290 (5 RCTs)	⨁⨁◯◯: low quality of evidence due to imprecision	90/1000	76/1000	RR 1.17 (0.56–2.42)	RR 0.26 (0.03–40.27)	Trial sequential analysis showed that the cumulative *Z*-curve didn't cross both the conventional and TSA monitoring boundaries for harm or benefit, revealing insufficient evidence to accept or reject the intervention effect. However, the quality of evidence was moderate due to downgrading for imprecision
Postoperative dizziness	160 (3 RCTs)	⨁⨁◯◯: Low quality of evidence due to imprecision	38/1000	38/1000	RR 1.00 (0.23–4.27)		Trial sequential analysis showed that the cumulative *Z*-curve does not cross both alpha-spending boundaries and does not reach the required information size threshold, revealing a low power for current evidence. However, the quality of evidence was low due to downgrading for imprecision by 2 levels
Postoperative hallucination	119 (2 RCTs)	⨁⨁◯◯: Low quality of evidence due to inconsistency and imprecision	217/1000	17/1000	RR 8.83 (1.67–46.65)	RR 8.48 (0.02–3700.7)	Trial sequential analysis showed that the cumulative *Z*-curve does not cross both alpha-spending boundaries and does not reach the required information size threshold, revealing a low power for current evidence. Besides, the quality of evidence was low due to downgrading for imprecision and inconsistency
Postoperative sedation	59 (1 RCT)	⨁⨁◯◯: Low quality of evidence due to imprecision	367/1000	17/1000	RR 10.63 (1.46–77.20)	RR 1.28 (0.05–33.94)	Trial sequential analysis showed that the cumulative *Z*-curve didn't cross both the conventional and TSA monitoring boundaries for harm or benefit, revealing insufficient evidence to accept or reject the intervention effect

RCTs, randomized controlled trials; RR, relative risk; TSA, trial sequential analysis.

ketamine group. The TSA revealed that the cumulative *Z*-curve crosses both alpha-spending boundaries and reaches the required information size threshold, indicating strong power for current evidence. However, the evidence's quality was moderate due to downgrading for inconsistency.

The current meta-analysis showed that ketamine for postoperative analgesia, particularly after 1 h of surgery, was less optimal as compared to the comparators; however, there was a heterogeneous control group, population, surgical procedure, and ketamine dosage, where the provision of the firm conclusion might be less likely. A meta-analysis by Tong *et al*. showed a similar result, but the author conducted the meta-analysis with a homogenous population and similar surgical procedure,[96] which might not be comparable with our meta-analysis. However, a meta-analysis by Dahmani *et al*. showed better postoperative analgesia up to 24 h as compared to placebo[97].

Postoperative adverse events such as postoperative vomiting, nausea, and dizziness did not show a statistically significant difference, whereas sedation and hallucination showed a 42% risk increase and were approximately eleven times more likely in the ketamine group, respectively, which is consistent with the included studies. However, the included studies were few in number, underpowered, and of low to very low evidence quality. Furthermore, the cumulative *Z*-curve did not cross both the conventional and TSA monitoring boundaries for harm or benefit, indicating that there was insufficient evidence to accept or reject a 33% risk reduction in the intervention.

Strength and limitation

This meta-analysis has a number of strengths. Firstly, the protocol was registered in the International Prospective Register of Systematic Reviews. Secondly, the meta-analysis was conducted as per the PRISMA (Supplemental Digital Content 15, http://links.lww.com/MS9/A532) guidelines and the recommendations of the Cochrane Collaboration. Thirdly, we applied TSA to assess the impact of random error and repetitive testing to improve the robustness of our meta-analysis. Finally, we evaluated the quality of evidence for the outcomes using GRADE to help healthcare professionals make better clinical decisions. This meta-analysis also has some limitations. The included trials in our meta-analysis were conducted on varying numbers and types of patients, had different control drugs, and used different dosages to determine the effectiveness of ketamine wound infiltration. As a result, the risk of introducing potentially significant heterogeneity is

inevitable. Besides, the included studies were low-powered, had different comparators, and had low to very low quality evidence.

Clinical implications for health managers and policymakers

The meta-analysis revealed that postoperative wound infiltration after surgery provides brief postoperative pain relief. However, wound infiltration with local anesthetics, dexmedetomidine, and magnesium sulfate showed superiority with respect to the first analgesic request, analgesic consumption, and postoperative adverse effects. Furthermore, there was significant postoperative sedation among patients with ketamine. However, the TSA failed to provide a firm conclusion on the safety and efficacy of ketamine wound infiltration, in which case, ketamine wound infiltration should be individualized when other options are not available.

Recommendations for future research

This is the meta-analysis and the TSA is investigating the efficacy and safety of ketamine wound infiltration after surgery. However, the included studies were low-powered with a high risk of bias. Besides, the quality of evidence was low to very low, in which case, further multicenter randomized controlled trials with large sample sizes and homogenous participants are still in demand.

Conclusion

Though ketamine has been used as anesthetic for years, and little evidence comes on its effectiveness as wound infiltration for postoperative pain management, the provision of a firm conclusion is less optimal with current evidence as the included studies were unpowered with low to very low quality of evidence. Besides, the included studies in the meta-analysis were heterogeneous, which entails further multicenter randomized controlled trials with large sample sizes, and homogenous participants and surgical procedures.

Ethical approval

Ethical approval was not required for this systematic review and meta-analysis.

Consent

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Author contribution

S.M.A. and G.M.: conceived the design idea for the project; S.M. A., G.M., B.B., M.G., and A.A.: searching strategy, data extraction, quality assessment, analysis, and manuscript preparation. All authors read and approved the manuscript.

Conflicts of interest disclosure

The authors declare that there are no conflicts of interest.

Research registration unique identifying number (UIN)

PROSPERO (CRD42021270710).

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Data availability statement

Data can be available on a reasonable request.

Provenance and peer review

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