Systematic Review

Effect of Intravenous Dexamethasone on Postoperative Pain in Patients Undergoing Total Knee Arthroplasty: A Systematic Review and Meta-Analysis

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Background: Postoperative pain after total knee arthroplasty (TKA) is intense and remains an unsolved problem. Some studies show that perioperative, multimodal analgesia, including intravenous dexamethasone, can provide a better analgesic effect; however, the validity of studies has raised concerns and questions remain around the efficacy, dosing, and safety of dexamethasone in patients undergoing total knee arthroplasty.

Objectives: The purpose of this systematic review and meta-analysis was to evaluate the impact of intravenous dexamethasone on postoperative pain among patients undergoing TKA.

Study Design: Systematic review and meta-analysis.

Setting: Web of Science, Embase, PubMed, and the Cochrane Central Register of Controlled Trials were searched to identify relevant randomized controlled trials. The last search was in August 2021.

Methods: The risk of bias of the included trials was assessed by the Cochrane Risk of Bias Tool. The primary outcome was postoperative visual analog scale (VAS) pain scores and secondary outcomes included cumulative equivalent intravenous morphine consumption, number of patients requiring rescue analgesic, length of hospital stay, and adverse events. We assessed the certainty of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: Eleven studies with 1,671 patients were included. The pooled results indicated that patients receiving dexamethasone had lower VAS pain scores at rest (24 h, MD = -0.68, [95% CI: -0.87 to -0.49]; 48 h, MD = -0.33, [95% CI: -0.46 to -0.21]) and at movement (24 h, MD = -0.74, [95% CI: -1.10 to -0.37]; 48 h, MD = -0.46, [95% CI: -0.66 to -0.26]), required less morphine (24 h, MD = -2.84 mg, [95% CI: -5.13 to -0.54]; 48 h, MD= -4.16 mg, [95% CI: -5.55 to -2.78]) and rescue analgesics, and had shorter hospitalization. There was no increase in infection, gastrointestinal hemorrhage, wound healing problems, or blood glucose levels with dexamethasone. Subgroup analysis did not observe difference between single dose and repeat dose groups.

Limitations: The perioperative multimodal analgesia measures were varied throughout the studies. The sample size was small for some outcomes and high heterogeneity was observed.

Conclusions: Our results supported the addition of perioperative intravenous dexamethasone to multimodal analgesia in total knee arthroplasty to reduce postoperative pain, opioids consumption, and length of hospital stay. Current evidence did not support the superiority of repeated-dose dexamethasone over single-dose dexamethasone; thus, we recommended perioperative 8-10 mg intravenous dexamethasone to be used based on adequate basic analgesia; however, the results may have been affected by small sample sizes and heterogeneity.

Key words: Dexamethasone, intravenous, total knee arthroplasty, total knee replacement, postoperative pain, systematic review, meta-analysis, randomized controlled trial

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Total knee arthroplasty (TKA) is an effective treatment for advanced osteoarthritis and other knee diseases. The number of patients demanding TKA has substantially increased over the past decades and researchers have also predicted that this number will continue to grow (1); however, pain management remains a major challenge for TKA, and patients suffer severe postoperative pain due to extensive bone resection and soft tissue injury involved in the surgical process (2). As the era of outpatient TKA emerges, a more comprehensive pain management protocol is required (3,4).

There is a growing interest in adding steroids into a multimodal analgesia protocol, since steroids seem to reduce the inflammatory response to surgery, therefore reducing pain and fatigue and enhancing postoperative recovery (5,6). Dexamethasone is a high potency, long-acting corticosteroid drug with fewer mineralocorticoid effects than other steroids. The antiemetic effect of dexamethasone is well known and dexamethasone has been widely used to prevent postoperative nausea and vomiting (7).

Evidence from 2 meta-analyses suggested that a single dose of intravenous dexamethasone can reduce postoperative pain as well as opioid consumption after surgery, but those meta-analyses did not include TKA surgery (8,9). Five previous meta-analyses addressing similar research questions have been published (10-14); however, the inclusion of case-control studies, multiple routes of dexamethasone administration, and combined TKA with total hip arthroplasty compromised the reliability of the results (15). Recently, a published guideline recommended intraoperative 8-10 mg intravenous dexamethasone to be used in total hip arthroplasty for its analgesic and antiemetic effects (16). Whether intravenous dexamethasone can provide analgesic effects in patients undergoing TKA needs more evidence.

Thus, we performed a systematic review and meta-analysis to evaluate the impact of perioperative intravenous dexamethasone on postoperative pain in patients undergoing TKA.

Methods

This systematic review and meta-analysis were conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (17) and the Cochrane Handbook (18). Our protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42020167541).

Data Sources and Search Strategy

We searched the Web of Science, Embase, PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases without language restrictions to find relevant articles. The last search was in August 2021. Keywords used in the search included "dexamethasone" and "total knee arthroplasty". The full search strategy is outlined in the supplementary material (Supplementary Table 1). We also searched the ClinicalTrials.gov registry and manually checked the references of the included studies and previous meta-analyses to identify additional relevant studies.

Study Selection and Eligibility Criteria

We included randomized controlled trials (RCTs) with humans that met all of the following criteria: 1) Trials that enrolled adult patients undergoing primary unilateral TKA; 2) Trials that compared perioperative intravenous dexamethasone alone or in combination with another drug versus placebo or normal saline. When dexamethasone was combined with another drug, the comparator had to be this drug alone given in the same dose and by the same route of administration as in the combination; 3) Trials that reported at least one of the following outcomes: 1) pain outcomes, such as pain scores, opioid consumption, and the number of patients who needed rescue analgesic after surgery, 2) the length of hospital stay, 3) adverse events related to dexamethasone administration, such as infection, gastrointestinal hemorrhage, hyperglycemia, wound healing, and perineal pruritus.

Studies that did not meet the inclusion criteria were excluded. Additionally, we excluded study that was retracted from the journal due to fraud (8,19,20).

Two authors (SL and SSJ) independently carried out the initial search, deleted duplicate records, screened the titles and abstracts, and determined the final included publications. Any disagreement was resolved by discussion among researchers.

Data Extraction and Risk of Bias Assessment

Two authors (SL and SSJ) independently extracted data from the included trials into a spreadsheet. The following data were collected: first author, year of publication, number of patients, type of anesthesia, dose(s) of dexamethasone and comparators, timing of administration, follow-up period, primary outcome measure of the study, and outcome data. We contacted the corresponding author of the study when additional data were required, or to clarify the methodology in

their study. Data were extracted from figures if not displayed numerically and the authors did not respond to our request.

In papers evaluating different doses of dexamethasone or more than one comparator, the data from all doses and comparators were pooled for analysis. Pain scores measured at 24 h and 48 h after surgery were included for analysis. Pain scores reported using 11-point numeric rating scales (NRS) or 0-100-mm visual analog scales (VAS) were converted to 11-point VAS scales. We calculated the standard deviation from the interquartile range and assumed the median as the mean based on the formula provided in the Cochrane Handbook. If opioid drugs other than morphine were given, we converted different opioids to equivalent intravenous morphine based on the service provided on the website https://opioidcalculator.practicalpainmanagement.com/.

The Cochrane Collaboration Risk of Bias Tool was used to assess the risk of bias of each trial. We reviewed each included trial and scored it as "low", "high", and "unclear" risk based on the following 7 domains mentioned in the handbook: 1) random sequence generation, 2) allocation sequence concealment, 3) blinding of patients and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other biases. Trials with ≥ 1 items that had high risk of bias were considered to have a high risk of bias, whereas trials with low risk of bias for all items were considered at low risk of bias; otherwise, they were considered to be unclear risk of bias.

Outcome Definition

The primary outcomes of this current meta-analysis were postoperative pain scores at rest and movement at 24 h and 48 h after surgery. Secondary outcomes included cumulative equivalent intravenous morphine consumption within 24 h and 48 h after surgery, the number of patients requiring rescue analgesics, length of hospital stay (LOS), and adverse events, including the incidence of infection, gastrointestinal hemorrhage, wound healing problems, and blood glucose levels.

Grading Certainty of Evidence

We followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (21) to evaluate the certainty of evidence for the primary and secondary outcomes. The risk of bias, inconsistency, indirectness, imprecision, and other bias for each outcome and evidence was classified as very low, low, moderate, and high. The summary table was constructed based on the service provided on the website https://gdt.gradepro.org/app/#projects.

Statistical Analysis

We calculated weighted mean difference (WMDs) with 95% confidence intervals (CIs) for the continuous variables and risk ratios (RRs) with 95% CI for dichotomous variables. WMD or RR was considered statistically significant if the corresponding P values < 0.05 and 95% CI did not include 0 for WMD and 1 for RR. Heterogeneity among studies was quantified by using the I^2 statistic. $I^2 > 50\%$ was considered to indicate significant heterogeneity. A random effects model was set as a default, as we accounted for significant clinical heterogeneity among the included studies. A funnel plot was performed to analyze the publication bias if the number of included studies exceeded 10.

In addition to the main analysis, we performed subgroup analyses according to doses of dexamethasone administration (single dose versus repeat dose). According to the Cochrane handbook (18), only subgroup analyses showing a statistically significant test of interaction ($P < 0.05$) across subgroups were considered to provide an intervention effect and warrant further discussion. All statistical analyses were conducted by using RevMan 5.4.1 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2020)

Trial Selection (Literature Search)

The PRISMA flow chart shows the literature search process, study selection, and reasons for exclusion. Finally, 11 RCTs (22-32) were deemed eligible for inclusion (Fig.1).

Systematic Review and Study Characteristics

The main characteristics of the included trials are listed in Table 1. Eleven studies with a total of 1,671 patients were included. Among these studies, a single dose of dexamethasone ranged from 8 mg to 20 mg, with 10 mg being the most common dose used. Six trials (22, 27-31) included a repeat dose of dexamethasone. TKA surgeries were performed under general anesthesia (27-31), spinal anesthesia (22,23,26,32), spinal anesthesia combined with continuous femoral nerve block (24), or epidural anesthesia (25). There was a considerable difference in perioperative pain management between studies and the follow-up period ranged from 3 days to 1 year.

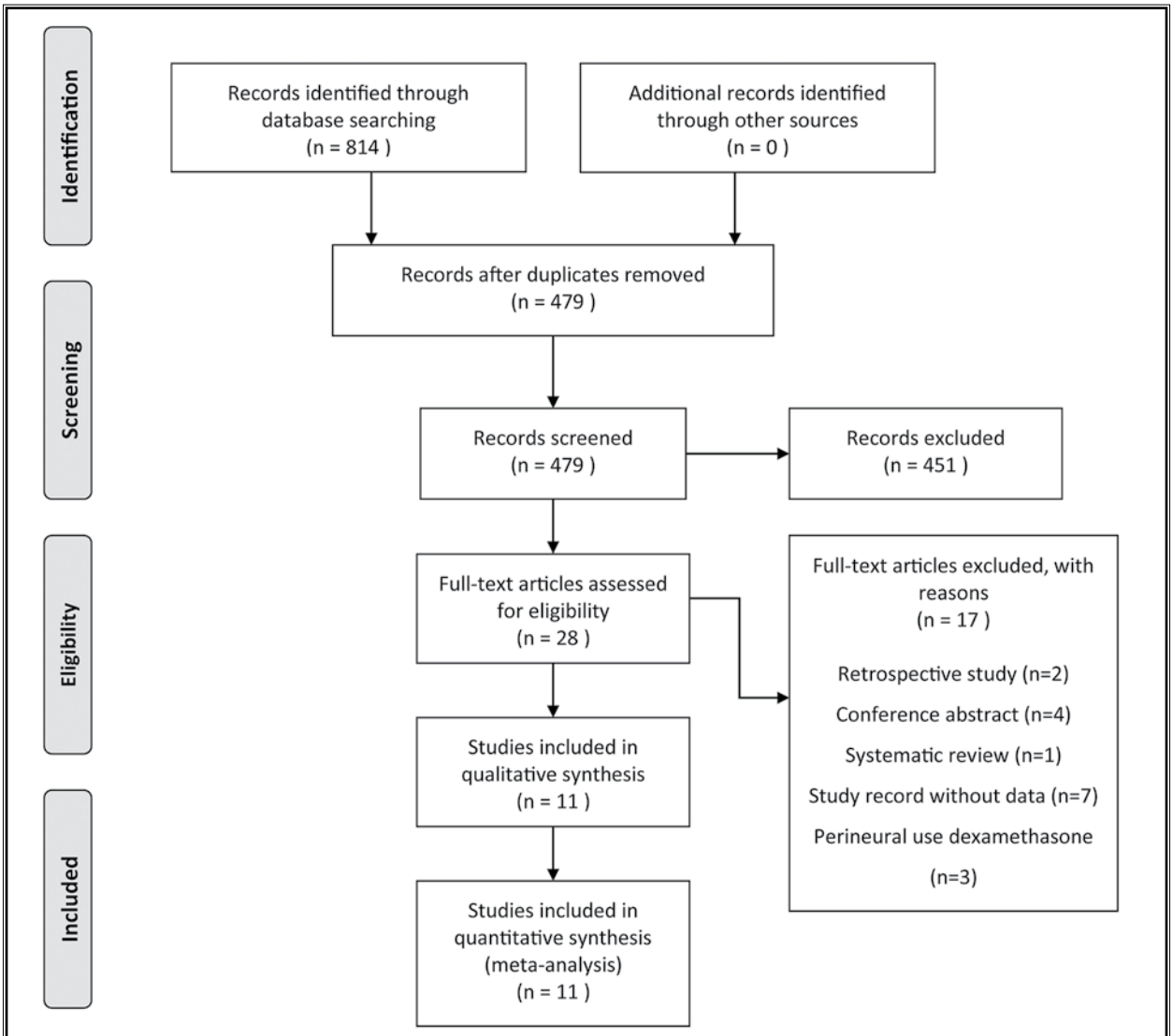

Fig. 1. *PRISMA flow diagram of the study selection process.*

Risk of Bias Assessment

Based on our assessment using the Cochrane Collaboration Risk of Bias Tool, 5 trials (23,26-28,32) were at low risk of bias, 5 trials (22,24,29-31) were at unclear risk of bias, and 1 trial (25) was at high risk of bias. (Fig. 2).

There were 3 studies (27,28,31) that included different doses of dexamethasone treatment arms. In order to avoid inappropriate count of patients in the control groups for meta-analysis, according to the Cochrane handbook (18), data from these studies were split using a previously reported method (33). The study by Dissanayake, et al (22) included TKA and THA patients, and we only extracted TKA-specific data.

Pain Scores

At 24 h after surgery, patients treated with dexamethasone had a lower pain scores at rest (MD = -0.68, 95% CI: -0.87 to -0.49, $P < 0.0001$, $I^2 = 73\%$) and movement (MD = -0.74, 95% CI: -1.10 to -0.37, $P < 0.0001$, $I^2 = 91\%$) (Fig. 3). Dexamethasone was also associated with pain score reduction at 48 h after surgery at rest (MD = -0.33, 95% CI: -0.46 to -0.21, $P < 0.00001$, $I^2 = 34\%$) and movement (MD = -0.46, 95% CI: -0.66 to -0.26, $P < 0.00001$, $I^2 = 85\%$) (Fig. 4). However, no difference was

Table 1. *Characteristics of the included studies.*

Study	Anesthesia Type	Dex intervention and comparator, (n)	Use of Tourniquet (Y/N)	Perioperative pain management				Follow-up period	Primary outcome(s)
				Periarticular injection	Drugs	PCA	Peripheral nerve block		
Dissanayake, (2018) (22)	SA	E:8 mg Dex at the induction of anesthesia+ 8 mg Dex 24 h after surgery (N = 86) C: Equal volume of NS at the same time points (N = 78)	Both	Yes	Opioid+ NSAID	No	No	6 Weeks	LOS
Jong-Keun Kim, (2019) (23)	SA	E1:10 mg Dex 1 h before surgery (N = 45) E2: 0.1 mg/kg Dex 24 h after surgery (N = 46) E3: 0.2 mg/kg Dex 24 h after surgery (N = 45) C: NS injection (N = 46)	Yes	Yes	Opioid+ NSAID	Yes	No	1 Week	Pain and nausea level
Koh, (2013) (24)	SA + cFNB	E:10 mg Dex 1 h before surgery+ ramosetron after surgery (N = 134) C: Ramosetron immediately after surgery (N = 135)	Yes	Yes	Opioid+ NSAID + Acetaminophen	Yes	Yes	1 Month	Pain level
Liu M, (2019) (25)	EA	E:10 mg Dex 1h before surgery (N = 50) C: Equal volume of normal saline (N = 50)	Yes	Yes	Opioid+ NSAID	No	No	1 Year	Unclear
Tammachote, (2020) (26)	SA	E:0.15 mg/kg Dex (maximum dose 12 mg) before surgery (N = 50) C: Isotonic saline before surgery (N = 50)	Yes	Yes	Opioid+ NSAID	No	No	3 Months	Pain level
Wu Y, (2018) (27)	GA	E1:10 mg Dex 1 h before surgery + NS 6 h after surgery (N = 50) E2:10 mg Dex 1 h before surgery +10 mg Dex 6 h after surgery (N = 50) C: Two doses of NS at the same time points (N = 50)	No	No	Opioid+ NSAID	No	No	3 Months	Pain level
Xu,H, (2018) (28)	GA	E1:20 mg Dex before induction+ two doses of NS (N = 60) E2:20 mg Dex before induction+10 mg Dex 24 h after first dose+10 mg Dex 48 h after first dose (N = 61) C: Equal volume of NS at the same time points (N = 61)	No	Yes	Opioid+ NSAID	No	No	3 Months	Pain level
Xu B, (2018) (29)	GA	E:10 mg Dex after anesthesia +10 mg Dex when patients return to ward (N = 54) C: Equal volume of isotonic saline (N = 54)	No	Yes	Opioid+ NSAID	No	No	3 Days	Pain level
Yu Y, (2019) (30)	GA	E:10 mg Dex after induction+10mg Dex 24 h after surgery+ TXA 15mg/kg 10 min before incision+ TXA 1g 3 h after surgery (N = 45) C: Equivalent doses of TXA at the same time point (N = 43)	No	No	Opioid	No	No	3 Months	Pain level

Table 1 (cont.). *Characteristics of the included studies.*

Study	Anesthesia Type	Dex intervention and comparator, (n)	Use of Tourniquet (Y/N)	Perioperative pain management				Follow-up period	Primary outcome(s)
				Periarticular injection	Drugs	PCA	Peripheral nerve block		
Lei Y (2021) (31)	GA	E1: 20 mg Dex before anesthesia induction + NS 24 h after surgery (N = 62) E2: 10 mg Dex before anesthesia induction + 10 mg Dex 24 h after surgery (N = 67) C: Equivalent doses of NS at the same time point (N = 63)	No	Yes	Opioid + NSAID	No	No	3 Months	Pain level
Chan T (2020) (32)	SA	E1: 8 mg Dex before anesthesia induction (N = 46) E2: 16 mg Dex before anesthesia induction (N = 45) C: Equivalent NS at the same time (N = 45)	Yes	Yes	Prebalin + NSAID + Acetaminophen	Yes	No	1 Year	Pain level

Abbreviations: GA, General anesthesia; SA, Spinal anesthesia; EA, Epidural anesthesia; cFNB, Continuous femoral nerve block; Dex, dexamethasone; E, Experiment group; C, Control group; TXA, tranexamic; NS, Normal saline; hs, hours; IV, intravenous; VAS, visual analog scale; LOS, Length of hospital stay

Fig. 2. *Risk of bias summary.*

observed between single dose and repeat dose (all, $P > 0.05$).

Cumulative Equivalent Intravenous Morphine Consumption

Three studies (22,25,32) reported postoperative opioid consumption at 24 h and 2 studies (23,26) reported postoperative opioid consumption at 48 h. Due to the limited number of studies were included, we did not conduct subgroup analysis. Patients receiving intravenous dexamethasone used less opioids (mg, equivalent intravenous morphine) within 24 hours af-

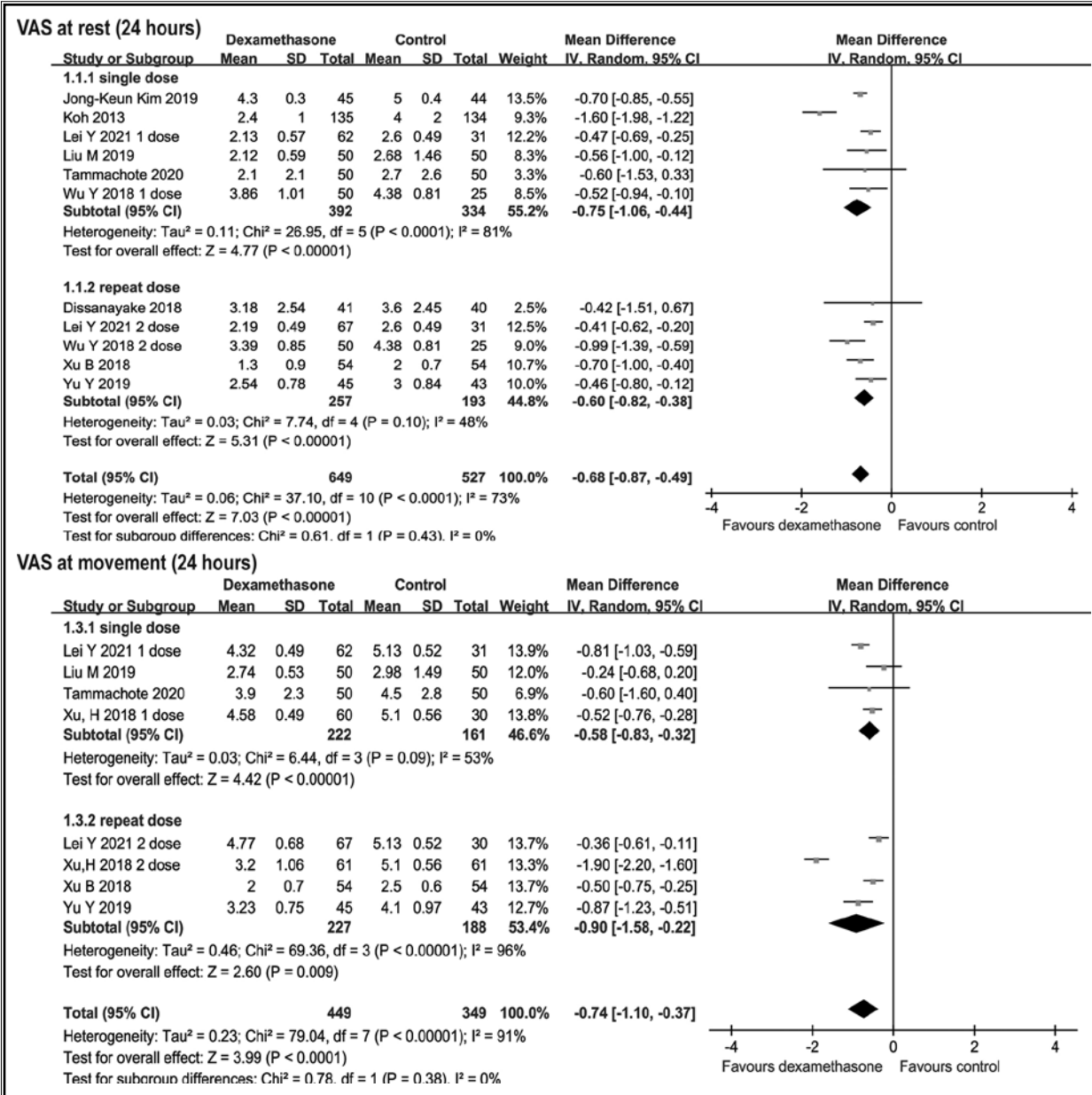

Fig. 3. *Forest plot of VAS pain scores at 24 hours after surgery.*

ter surgery (MD = -2.84, 95% CI: -5.13 to -0.54, $P = 0.02$, $I^2 = 52\%$) and 48 hours after surgery (MD = -4.16, 95% CI: -5.55 to -2.78, $P < 0.00001$, $I^2 = 93\%$) (Fig. 5).

The Number of Patients Requiring Rescue Analgesics

Four studies (28-31) with 6 treatment arms reported the number of patients who needed rescue analgesics for intolerant pain. The number of patients who needed rescue analgesics was lower in the dexamethasone group (RR = 0.23, 95% CI: 0.16 to 0.35, $P < 0.00001$, $I^2 = 28\%$), with no difference observed between single dose and repeat dose groups ($P = 0.14$) (Fig. 6).

LOS

Eight studies (22,25-30,32) with 10 treatment arms reported the length of hospital stay after TKA. Patients receiving dexamethasone had significantly shorter

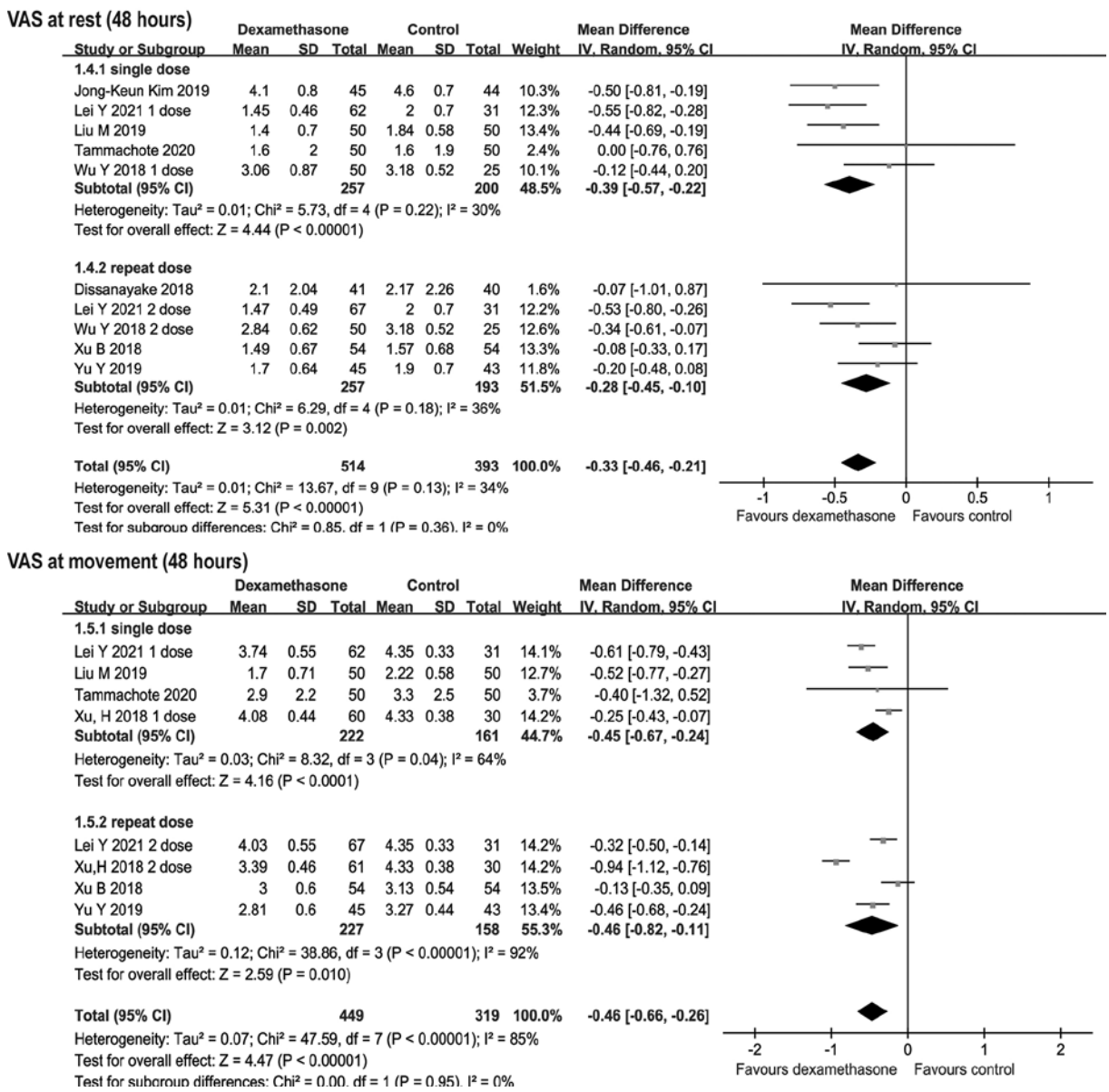

Fig. 4. *Forest plot of VAS pain scores at 48 hours after surgery.*

hospitalization (MD = -0.13, 95% CI: -0.24 to -0.01, *P* = 0.03, I^2 = 0%). A repeat dose of dexamethasone was associated with a greater reduction in LOS (*P* = 0.01); however, test of difference did not significant between single dose and repeat dose groups (*P* = 0.14) (Fig. 7).

Adverse Events

There was no increase in the incidence of infection (RD = 0, 95% CI: -0.01 to 0.01, *P* = 0.78, I^2 = 0%), gastrointestinal hemorrhage (RD = 0, 95% CI: -0.01 to 0.01, *P* = 1, I^2 = 0%), or wound healing problems (RD = -0.01, 95% CI: -0.03 to 0.02, *P* = 0.63, I^2 = 0%) in patients receiving intravenous dexamethasone. A repeat dose of dexamethasone did not increase the incidence of infection and gastrointestinal hemorrhage compare with single-dose dexamethasone (Fig. 8). Five studies (22,23,26,28,31) measured blood glucose levels in nondiabetic patients after surgery, 2 studies (28,31) measured fasting blood sugar, one study

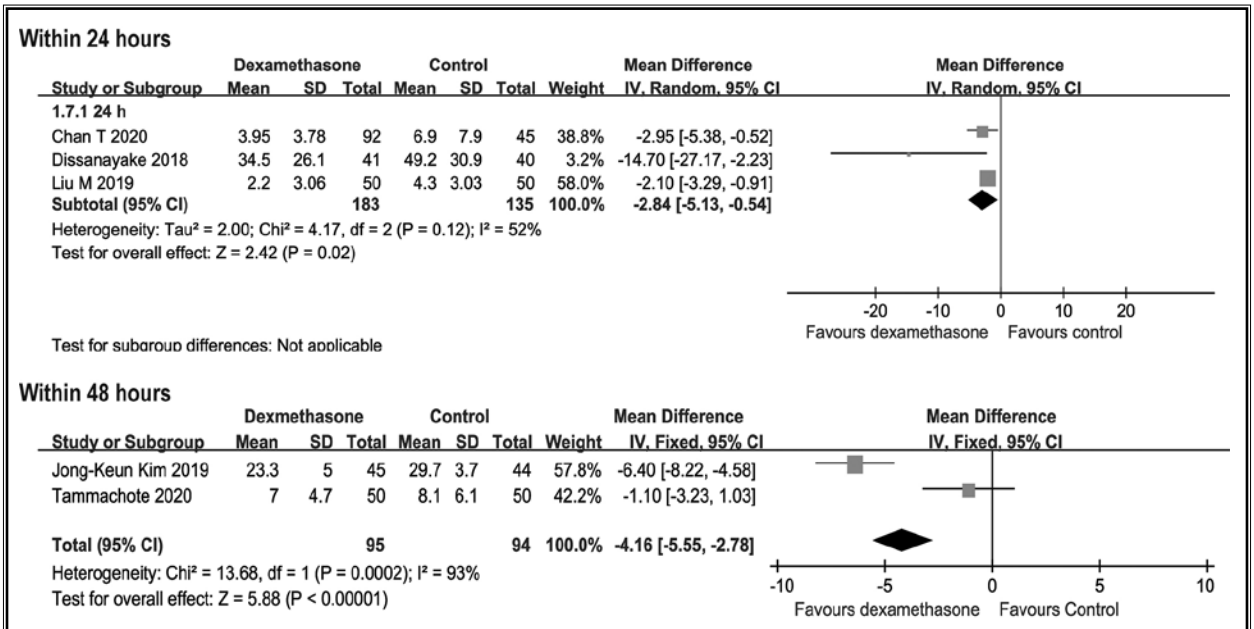

Fig. 5. *Forest plot of cumulative morphine consumption (mg of equivalent intravenous morphine) within 24 hours and 48 hours.*

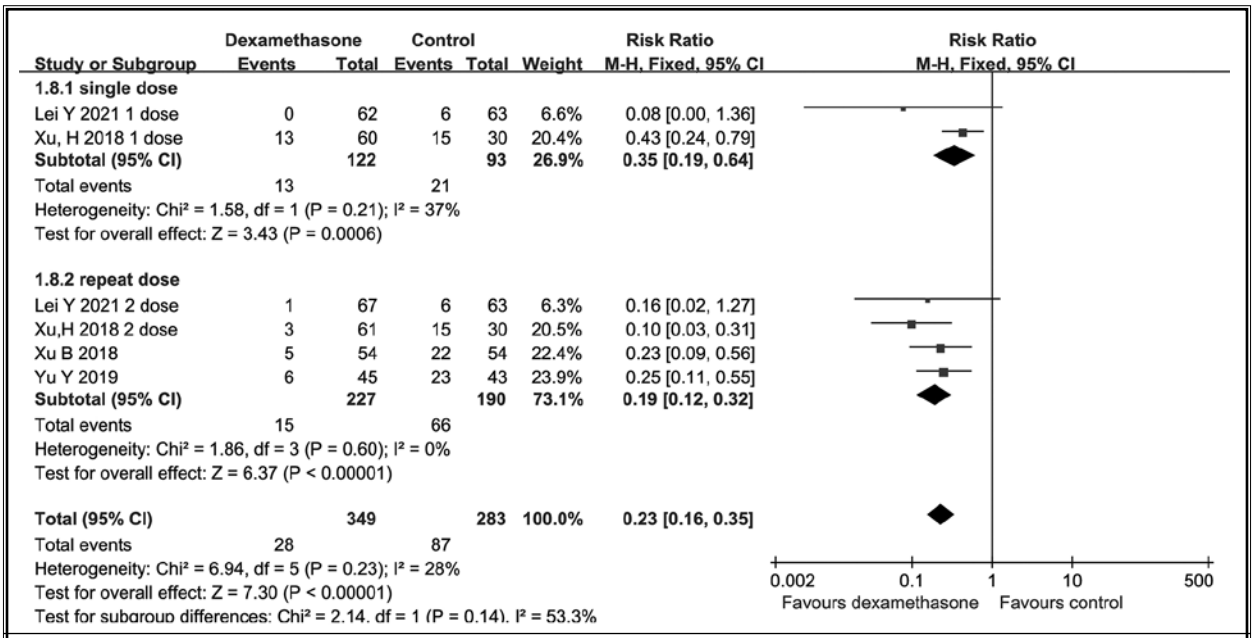

Fig. 6. *Forest plot of patients who needed rescue analgesics.*

(26) measured random blood sugar, and the remaining 2 studies (22,23) did not report when blood glucose levels were measured. A similar blood glucose level in the dexamethasone group and comparator group was reported in 4 studies, and the remaining study (22) found that the blood glucose level was slightly, but statistically, elevated in the dexamethasone group on POD1.

GRADE Certainty of Evidence

GRADE certainty of evidence for primary and sec-

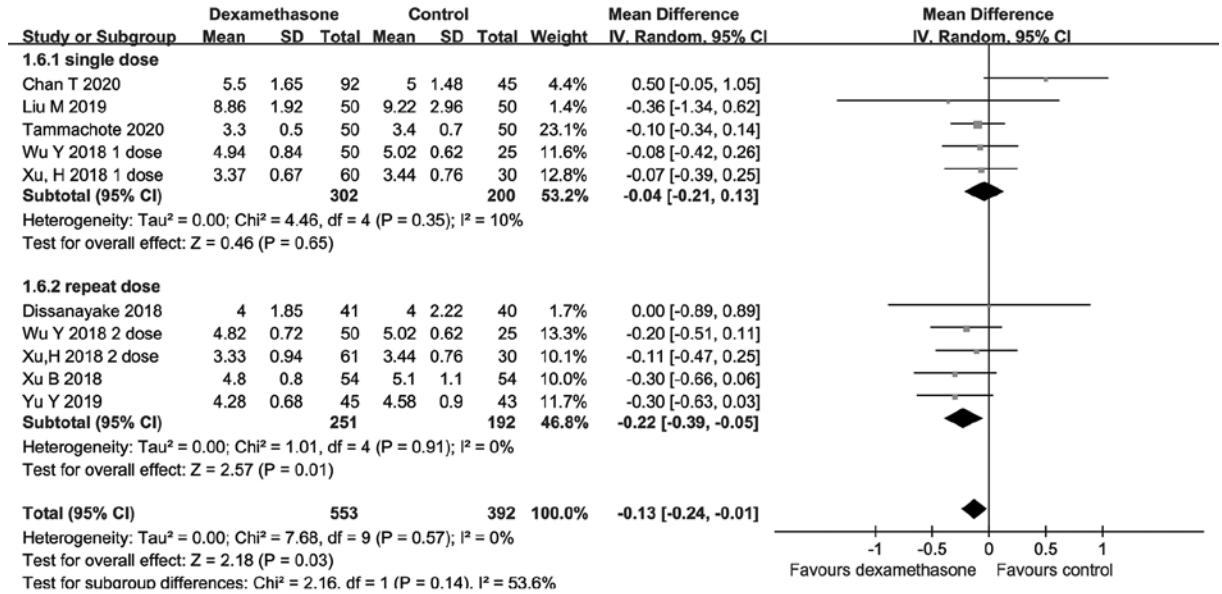

Fig. 7. *Forest plot of length of hospital stay.*

ondary outcomes is shown in Supplementary Table 2. The certainty of evidence was very low for cumulative equivalent intravenous morphine consumption within 24 hours and 48 hours; low for pain scores at movement at 24 hours and 48 hours after surgery, number of patients requiring rescue analgesia, and wound healing problem. Moderate for pain scores at rest at 24 hours and 48 hours after surgery, length of hospital stay, gastrointestinal hemorrhage, and blood glucose level, and high for the incidence of infection.

Discussion

In the present meta-analysis, we found that patients undergoing TKA surgery receiving perioperative intravenous dexamethasone experienced less postoperative pain, both at rest and at movement, at 24 hours and 48 hours after surgery, required less postoperative opioids, needed less rescue analgesia, and had shorter hospitalizations, without an associated increase in adverse events. There is a trend that a repeat dose of dexamethasone may further reduce the length of hospital stay; however, this effect did not associate with pain score reduction, or the need of rescue analgesic.

Pain after TKA is intense and poor management of severe acute pain may contribute to the development of chronic postoperative pain (34). Efforts toward minimizing postoperative pain not only improve patient satisfaction, but also accelerate early ambulation after TKA, resulting in reduced LOS and incidence of postoperative complications. Our findings were consistent with previous meta-analyses (10-14) showing that dexamethasone was associated with postoperative pain score reductions. What's more, we found a similar pain score reduction between single dexamethasone dose and repeat dexamethasone dose. This result conflicts with recent randomized controlled trials (27,28) with evidence supporting that repeated doses of dexamethasone further reduce pain scores after TKA, compared with single-dose dexamethasone. However, the efficacy of dexamethasone lasts about 36-54 hours (35), and a previous study has confirmed a plateau effect in analgesia when 6-8 mg dexamethasone is used (36), which implies that an additional dose of dexamethasone given within 24 hours later may not be effective in further analgesic effect. Whether repeated doses of dexamethasone provide more analgesic effect than a single dose of dexamethasone needs more research.

In addition, we would like to emphasize that small but statistically significant differences do not indicate relevant clinical significance. The minimal clinically important difference (MCID) has been defined as the smallest important change perceived by patients (37). The MCID is a useful tool to determine whether a treatment intervention has a clinically meaningful effect. Previous studies demonstrated that the MCID for VAS was not influenced by the patient's initial pain scores

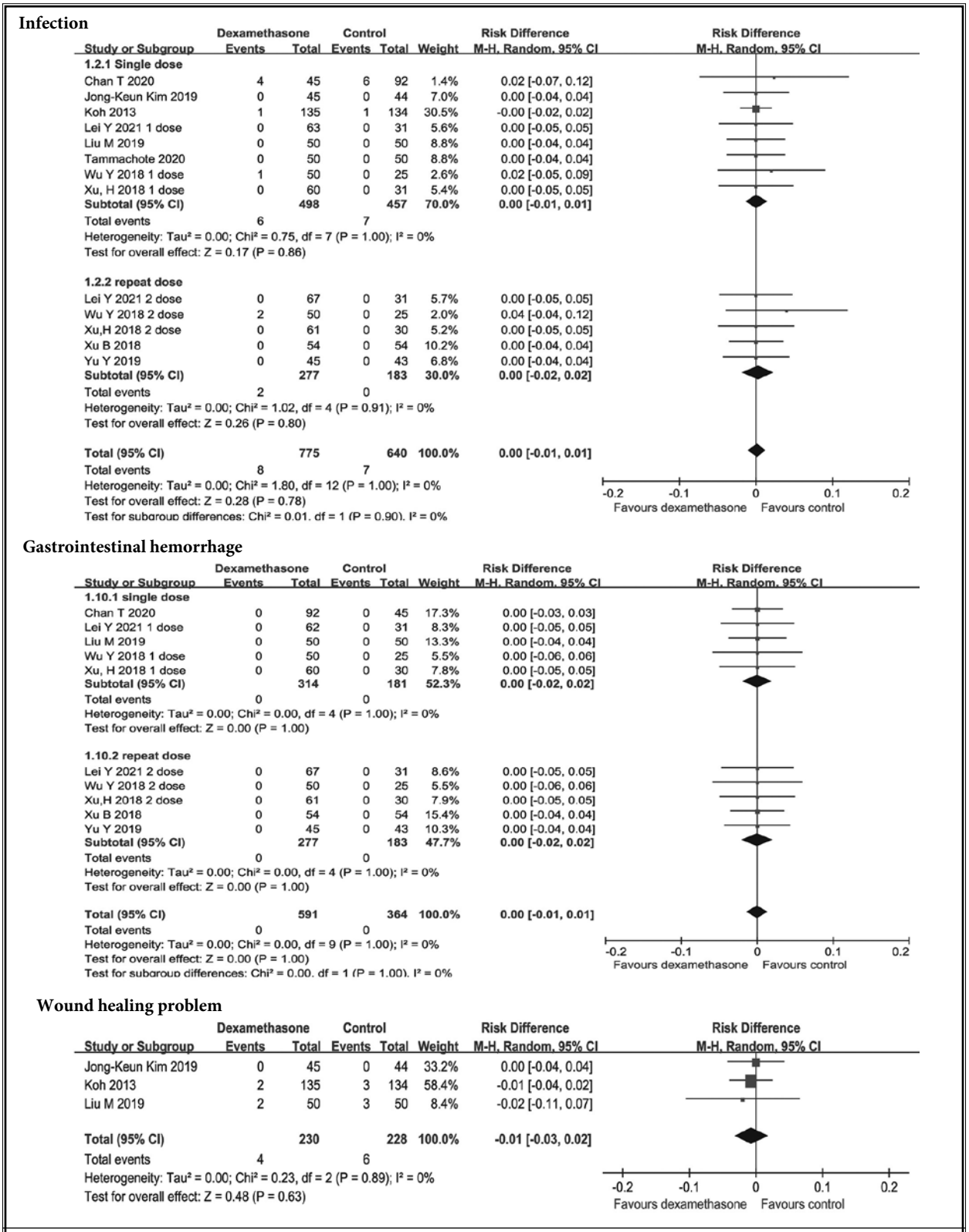

Fig. 8. *Forest plot of the incidence of adverse events.*

(37,38) and was controlled by disease diagnosis. Our meta-analysis found a pain score reduction of -0.68 points at rest and -0.74 points at movement at 24 h after surgery and -0.33 points at rest and -0.46 points at movement at 48 h after surgery. Given that the MCID for VAS pain score reduction for TKA was 22.6 mm (39), the observed differences in each group were below the MCID, which makes the changes less clinically significant; thus, we recommend intravenous dexamethasone be used based on adequate basic analgesia.

Opioid consumption and rescue analgesic requirement are important aspects of analgesic effect evaluation. Opioid sparing effect was found in patients treated with dexamethasone in our study, we assumed that this effect was due to a reduction in pain scores and a reduction in the number of patients requiring rescue analgesic; however, the limited number of included studies and high level of heterogeneity should be noted. To what extent, dexamethasone can save opioids after TKA surgery still needs more study. Meanwhile, most of the included studies did not report postoperative opioid consumption, or only reported the total amount of postoperative analgesic consumption, mean and standard deviation were not given, which hindered the combination of evidence in meta-analysis. Thus, we call for future research to clearly report the analgesic consumption after surgery.

Reducing pain levels and postoperative opioid consumption may result in early discharge from the hospital after surgery. Our study found that intravenous dexamethasone was associated with a shorter length of hospital stay of 0.13 d; however, a recent meta-analysis did not observe this benefit in the dexamethasone group [MD = -0.11, (-0.25,0.02)] (14). One possible explanation for this discrepancy was that the inclusion criteria were different between studies. Although the study illustrated to include studies examining ≤ 20 mg intravenous dexamethasone, 3 studies (23,25,30) that meet the inclusion criteria were not include for analysis, which may lead to a smaller sample size and lower statistical power; whereas, the effect size of our finding was small (-0.13), which seems less clinically significant.

Similar to other studies (8,40), we found no increase in the risk of adverse events with dexamethasone administration. A recent multi-center RCT with a total of 8,725 patients also found no increase in the risk of surgical-site infection with systemic dexamethasone administration 30 days after surgery (41). Meanwhile, evidence from a previous retrospective study suggested that intravenous dexamethasone is also safe for diabetic patients undergoing total knee and hip replacement (42). However, due to all the included trials except one in our study excluded patients with diabetes, we advise caution in using intravenous dexamethasone in diabetic patients undergoing TKA. Further prospective studies are needed to evaluate the safety of systemic dexamethasone in those patients at risk.

Neuraxial or general anesthesia and peripheral nerve block combined with general anesthesia are commonly used in TKA surgery; however, the effect of different anesthesia methods on postoperative outcomes is inconclusive. Recent guideline and retrospective studies favored spinal anesthesia over general anesthesia because of fewer postoperative complications (43,44). On the contrary, RCTs and a systematic review that only included prospective cohort studies and RCTs found little difference between these 2 anesthesia regimens (45-47). It is difficult to make an overall conclusion since the evidence is still conflicting. In our study, we assumed that different anesthesia methods may have a small effect on perioperative and long-term outcomes of TKA patients. Therefore, more studies are needed to test this hypothesis.

Several meta-analyses (10-14) on this topic have been previously published, as shown in Table 2. Although these studies also showed that dexamethasone improves pain outcomes without increasing the incidence of adverse events, differences between our study and previous studies should be noted. First, TKA and THA are two very different operations with respect to pain levels after surgery. These meta-analyses included a study by Backes and his colleague (48), which combined TKA and THA and lacked TKA-specific data, and one study (13) included a THA trial. In comparison, we excluded Backes's study in the study selection process and specifically focused on TKA. Second, our current meta-analysis did not mix different routes of dexamethasone administration, enhancing the ability to interpret the results. Third, previous meta-analyses did not indicate whether VAS pain scores were obtained at rest or at movement; in contrast, we clearly reported the different conditions under which pain scores were reported. Fourth, we considered the MCID of pain outcomes and evaluated the certainty of evidence for outcomes by the GRADE approach to help clinical decision-making.

Our meta-analysis still has several limitations. First, perioperative pain management plans were significantly different between studies (Supplementary Table 3), which may have introduced clinical heterogeneity and influenced our findings. Meanwhile, for some

Table 2. *Comparison with Previous Meta-analyses*

Author/year	Meng et al 2017	Zhou et al 2018	Fan et al 2018	Li et al 2018	Zhuo et al 2021	Current Meta-analysis
Prospective registration	No	No	Yes	No	No	Yes
No of included trials	4	6	8	4	10	11
Included study by Fujii (19)	No	No	Yes	No	Yes	No
Included THA study	Yes	No	No	No	No	No
Included Non-RCT trials	No	No	Yes	No	No	No
Route of dexamethasone administration	Periarticular, Intravenous	Periarticular, Intravenous	Periarticular, Intravenous	Periarticular, Intravenous	Intravenous	Intravenous
Given MCID for VAS reduction	Not applied	No applied	No applied	No applied	No applied	Applied
GRADE certainty of evidence	Applied	Applied	Not applied	Applied	Not applied	Applied

Abbreviations: THA, Total hip arthroplasty; MCID, Minimal clinically important difference; VAS, Visual analog scale.

outcomes, only a few studies were included; thus, no conclusions may be drawn from it. Second, the range of follow-up periods was relatively short in some of the included studies and the absence of mid-term or long-term follow-up did not provide a robust assessment of the incidence of adverse events. Third, although we found that repeated doses of dexamethasone were not superior to a single dose of dexamethasone, there is a limited number of studies with these comparisons with the same overall dose. Only one study compared the effect of a high single dose (20 mg) versus 2 doses (10 mg) of dexamethasone and found that the former was more effective than the latter (31). This result supported our findings in some way. Due to the limited number of included studies with the same overall dose, we could not perform further analysis. In addition, it is hard to rule out the existence of publication bias, as only 11 RCTs were included in the analysis.

Conclusions

Our results supported the addition of perioperative intravenous dexamethasone to multimodal analgesia in total knee arthroplasty to reduce postoperative pain, opioids consumption, and length of hospital stay. Current evidence did not support the superiority of repeated-dose dexamethasone over single-dose dexamethasone. Thus, we recommend perioperative 8-10 mg dexamethasone to be used based on adequate basic analgesia. However, the results may have been affected by small sample sizes and heterogeneity.

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Supplemental material available at www.painphysicianjournal.com.

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Supplementary Table 1. ***Database search strategy (PubMed)***.

#1	"Arthroplasty, Replacement, Knee"[Mesh]
#2	Knee Replacement Arthroplast*[Title/Abstract]
#3	Knee[Mesh]
#4	Knee*[Title/Abstract]
#5	Arthroplasty[Mesh]
#6	joint prosthesis[Mesh]
#7	((arthroplast*[Title/Abstract]) OR (prosthe*[Title/Abstract])) OR (replac*[Title/Abstract])
#8	(#3) OR (#4)
#9	#5 OR #6 OR #7
#10	(#8) AND (#9)
#11	TKA[Title/Abstract]
#12	TKR[Title/Abstract]
#13	((((#1) OR (#2)) OR (#10)) OR (#11)) OR (#12)
#14	Dexamethasone[Mesh]
#15	Dexamethason*[Title/Abstract]
#16	(#14) OR (#15)
#17	(#13) AND (#16)

Supplementary Table 2. *GRADE evidence profile.*

Certainty assessment						Summary of findings				
No.of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Number of patients		Effect		Certainty
						Dexamethasone	Control	Relative (95%CI)	Absolute (95%CI)	
Pain scores at rest at 24h after surgery (assessed with: VAS; Scale from 0 to 10)										
9	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected	553	392	-	MD = -0.68 (-0.87,0.49)	⊕⊕⊕◯ MODERATE
Pain scores at movement at 24h after surgery (assessed with: VAS; Scale from 0 to 10)										
6	Not serious	Serious [b]	Not serious	Not serious	Publication bias strongly suspected	449	349	-	MD = -0.74 (-1.1,-0.37)	⊕⊕◯◯ LOW
Pain scores at rest at 48h after surgery (assessed with: VAS; Scale from 0 to 10)										
8	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [c]	514	393	-	MD = -0.33 (-0.46,-0.21)	⊕⊕⊕◯ MODERATE
Pain scores at movement at 48h after surgery (assessed with: VAS; Scale from 0 to 10)										
6	Not serious	Serious [b]	Not serious	Not serious	Publication bias strongly suspected [c]	449	319	-	MD = -0.46 (0.66,0.26)	⊕⊕◯◯ LOW
Cumulative equivalent intravenous morphine consumption (within 24 h)										
3	Serious [a]	Serious [b]	Not serious	Not serious	Publication bias strongly suspected [c]	183	135	-	MD = -2.84 (5.13,0.54)	⊕◯◯◯ VERY LOW
Cumulative equivalent intravenous morphine consumption (within 48 h)										
2	Serious a	Serious [b]	Not serious	Not serious	Publication bias strongly suspected [c]	95	94	-	MD = -4.16 (5.55,2.78)	⊕◯◯◯ VERY LOW
Number of patients requiring rescue analgesic										
4	Serious [a]	Not serious	Not serious	Not serious	Publication bias strongly suspected [c]	28/349	87/283	RR = 0.23 (0.16 0.35)	237 fewer per 1,000 (from 258 fewer to 200 fewer)	⊕⊕◯◯ LOW
Length of hospital stay										
8	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [c]	553	392	-	MD = -0.13 (-0.24,-0.01)	⊕⊕⊕◯ MODERATE
Infection										
10	not serious	Not serious	Not serious	Not serious	Not serious	8/775	7/640	RD = 0.00 (-0.01, 0.01)	-	⊕⊕⊕⊕ HIGH
Gastrointestinal hemorrhage										
7	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [c]	0/591	0/364	RD = 0.00 (-0.01, 0.01)	-	⊕⊕⊕◯ MODERATE

Supplementary Table 2 (cont.). *GRADE evidence profile.*

Certainty assessment						Summary of findings				
No.of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Number of patients		Effect		Certainty
						Dexamethasone	Control	Relative (95%CI)	Absolute (95%CI)	
Wound healing problem										
3	Serious [a]	Not serious	Not serious	Not serious	Publication bias strongly suspected [c]	4/230	6/228	RD = -0.01 (-0.03, 0.02)	-	⊕⊕◯◯ LOW
Blood glucose level										
5	Not Serious	Not serious	Not serious	Not serious	Publication bias strongly suspected [c]	-	-	-	-	⊕⊕⊕◯ MODERATE

[a] Only few studies were included
[b] I^2 >50% indicates a significant heterogeneity
[c] It is hard to rule out the existence of publication bias since less than 10 trials were included.

Supplementary Table 3. *Perioperative pain management methods of the included studies*.

Study	Perioperative pain management methods							Analgesia mechanism
	PI	Paracetamol	NSAIDs	Opioids	Pregabalin	Nortriptyline	PNB	
Dissanayake (2018) (22)	√	√	√	√	-	-	-	The adding of intravenous dexamethasone to the multimodal analgesia plan may provide analgesic effects through its anti-inflammatory property, reduce tissue swelling, prolong the duration of local anesthetics, and reduce the synthesis of bradykinin and neuropeptides around the surgical sites. It may promote the effect of NSAIDs to some degree and decrease the incidence of opioid drug-related vomiting. The mechanism of other multimodal analgesic measures involved in the studies are as follows: 1. PI or PNB with local anesthetics inhibited the transductor of the pain nerve and reduced the pain signal. 2. Paracetamol and NSAIDs are similar which exerted analgesic effects by inhibiting the synthesis of prostaglandin in the cellular system and inhibiting cox-1 and cox-2 enzymes, respectively. 3. Opioids activated opioid receptors (μ,κ) and exerted analgesic effects. 4. Pregabalin regulation α 2- δ voltage-gated calcium channels and nortriptyline inhibits serotonin and norepinephrine reuptake.
Jong-Keun Kim (2019) (23)	√	√	√	√	-	-	-	
Koh (2013) (24)	√	√	√	√	√	-	√	
Liu M (2019) (25)	√	-	√	√	-	-	-	
Tammachote (2020) (26)	√	√	√	√	-	√	-	
Wu Y (2018) (27)	-	√	√	√	√	-	-	
Xu, H (2018) (28)	√	-	√	√	-	-	-	
Xu B (2018) (29)	√	-	√	√	-	-	-	
Yu Y (2019) (30)	√	-	√	√	-	-	-	
Lei Y (2021) (31)	√	-	√	√	-	-	-	
Chan T (2020) (32)	√	√	√	√	√	-	-	

Abbreviations: PI, Periarticular infiltration; NSAIDs, Nonsteroidal anti-inflammatory drugs; PNB, Peripheral nerve block