


# The role of perioperative intravenous low-dose dexamethasone in rapid recovery after total knee arthroplasty: a meta-analysis

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## Abstract

**Purpose:** The purpose of this meta-analysis was to evaluate the overall safety and effectiveness of perioperative intravenous dexamethasone to facilitate postoperative rehabilitation in patients after total knee arthroplasty (TKA).

**Methods:** A comprehensive literature search was performed using the Embase, PubMed, Cochrane Library, and China National Knowledge Infrastructure (CNKI) databases for relevant randomized controlled trials (RCTs) from inception to 2020. Methodological quality of the trials was assessed using the Cochrane Risk of Bias Tool, and the relevant data were extracted using a predefined data extraction form.

**Results:** Ten RCTs with 1100 knees were included. Our study showed a significant reduction in pain using a postoperative pain visual analog scale (VAS) at 24 hours and 48 hours, total opioid consumption at 24 hours and 48 hours, postoperative nausea and vomiting (PONV), active range of motion (ROM) limitation, and passive ROM limitation at 72 hours in dexamethasone-treated groups compared with controls.

**Conclusion:** Intravenous low-dose dexamethasone is potentially useful in the perioperative setting for reducing postsurgical immediate ROM limitations, pain, opioid consumption, and PONV. There are no data that directly attribute an increase in postoperative complications to intravenous dexamethasone. More high-quality studies are necessary to draw these conclusions.

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## Keywords

Intravenous dexamethasone, rapid recovery, low-dose, total knee arthroplasty, meta-analysis, pain, range of motion, opioid consumption, postoperative nausea and vomiting

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## Introduction

Over the past decades, the number of total knee arthroplasty (TKA) surgeries that have been performed has greatly increased, and future demands for this surgery are predicted to continue to rise rapidly.<sup>1-3</sup> However, moderate to severe pain and poor postoperative range of motion (ROM) in the early postoperative period occur frequently as a result of soft tissue injury, extensive bone resection, and surgical trauma.<sup>4,5</sup> Moreover, postoperative nausea and vomiting (PONV) is also an ongoing problem. Postoperative pain, poor postoperative immediate ROM, and PONV can cause delayed discharge and patient dissatisfaction.<sup>6,7</sup> Therefore, the perioperative period should focus on pain management, improving postoperative immediate ROM, and preventing PONV.

Dexamethasone is a highly efficient, long-acting glucocorticoid steroid with an anti-inflammatory effect, and it has been used extensively during the TKA perioperative period. Dexamethasone can inhibit the lipoxygenase and cyclooxygenase pathways in the inflammatory chain reaction, which decreases the level of inflammatory mediators including leukotrienes and prostaglandins.<sup>8</sup> However, it can also block the release of neuropeptides from nerve endings and decrease the level of bradykinin in tissues,<sup>9,10</sup> both of which increase the sense of injury in surgical wounds and inflammatory tissues. Heterogeneity among studies regarding the dose and

administration protocol of dexamethasone, and the perioperative management of TKA makes it difficult to determine the practical value of dexamethasone. To date, no large-scale dose-finding studies have been performed to examine the analgesic effects. To the best of our knowledge, all current high-quality prospective studies use low-dose (no more than 20mg) of dexamethasone. Additionally, through its central antiemetic effect, this steroid reduces PONV by systemic application rather than topical application.<sup>11</sup> Thus, assessing the role of intravenous low-dose dexamethasone in rapid recovery after TKA using a meta-analysis should be a top priority.

Statistical heterogeneity, which was high in previous meta-analyses,<sup>12,13</sup> likely originated from different doses and routes of administration. Additionally, the sample size in previous meta-analyses was also small, and they did not report postoperative knee ROM, which was an important parameter for early postoperative recovery. Furthermore, new high-quality randomized controlled trials (RCTs)<sup>14,15,17</sup> have been published with seemingly mixed results. Two RCTs<sup>16,18</sup> that were written in Chinese were not part of the previous reviews, which caused publication bias and statistical bias.

Thus, a new meta-analysis is needed to evaluate the overall safety and effectiveness of perioperative intravenous dexamethasone for a rapid recovery in patients undergoing TKA.

## Methods

### Search strategy

The Embase, PubMed, Cochrane Library, and China National Knowledge Infrastructure (CNKI) databases were searched from their inception to 2020 by two of the authors. Prospective randomized trials were searched using combinations of the following terms: dexamethasone, total knee arthroplasty, TKA, and total knee replacement (TKR). Language restrictions were not applied, and the reference lists of searched articles were carefully reviewed to identify additional studies for inclusion.

### Inclusion and exclusion criteria

RCTs comparing the clinical efficacy between intravenous low-dose (no more than 20 mg) dexamethasone with placebo or nothing in patients who underwent primary TKA were included in our study. The relevant outcomes included postoperative immediate ROM, visual analog scale (VAS), opioid consumption, length of stay (LOS), adverse effects, and complications during follow-up. Exclusion criteria included the following: studies that were not RCTs; non-intravenous dexamethasone administration; or studies involving revision knee arthroplasty, bilateral TKA, and other surgical approaches such as total hip arthroplasty. Ethics approval and informed consent are not applicable because the data are from articles that have been previously published.

### Data extraction

We carefully extracted related data from all eligible studies using a standard extraction worksheet, and disagreements were resolved through discussion. We extracted only the data of interest when the articles had multiple comparisons. If there were no data available in the original article, the

authors were contacted by e-mail for further information, or the data were calculated from the available coefficients. Milligrams dispensed for all the named narcotics were converted into morphine milligram equivalent using the following multiplication factors to convert one dispensed milligram of the named narcotic to its morphine milligram equivalent: tramadol  $\times 0.10$ ; oxycodone  $\times 1.50$ ; morphine  $\times 1.00$ ; and fentanyl  $\times 0.01$ . These potency ratios have been validated in clinical studies.<sup>19–21</sup>

### Quality assessment and risk of bias

The included RCTs were assessed by two authors in accordance with the Cochrane Handbook for Systematic Reviews of Interventions version.<sup>22</sup> The following specific items were included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, incomplete outcome data, and other bias. Disagreements were resolved through discussions with a third author.

### Statistical analysis

Statistical analysis was performed using Stata 14.0 software (College Station, TX, USA), and a  $P$  value  $< 0.05$  was considered to be a significant difference. For continuous outcomes, such as ROM, LOS, VAS, and blood glucose, the standard mean difference (SMD) or the weighted mean difference (WMD) with 95% confidence interval (CI) was calculated. For dichotomous variables such as PONV and complications, a risk ratio (RR) with 95% CI was used to measure the risk evaluation. The primary assessment for statistical heterogeneity was performed using chi-squared and  $I^2$  tests. If  $P > 0.05$  or  $I^2 < 50\%$ , the heterogeneity was not considered. Our study used the random-effects model for all outcomes.

In addition, publication bias was evaluated using a Begg's funnel plot, and  $P > 0.1$  indicated that there was no significant publication bias.

## Results

### Search results

There were 378 related studies that were initially identified through database searching. Among these, 109 duplicates were excluded using Endnote X8 (Clarivate, Philadelphia, PA, USA), and 250 studies were removed on the basis of the title and abstract. Ten files<sup>14-18,23-27</sup> that met the inclusion criteria were ultimately identified after carefully and completely reading each

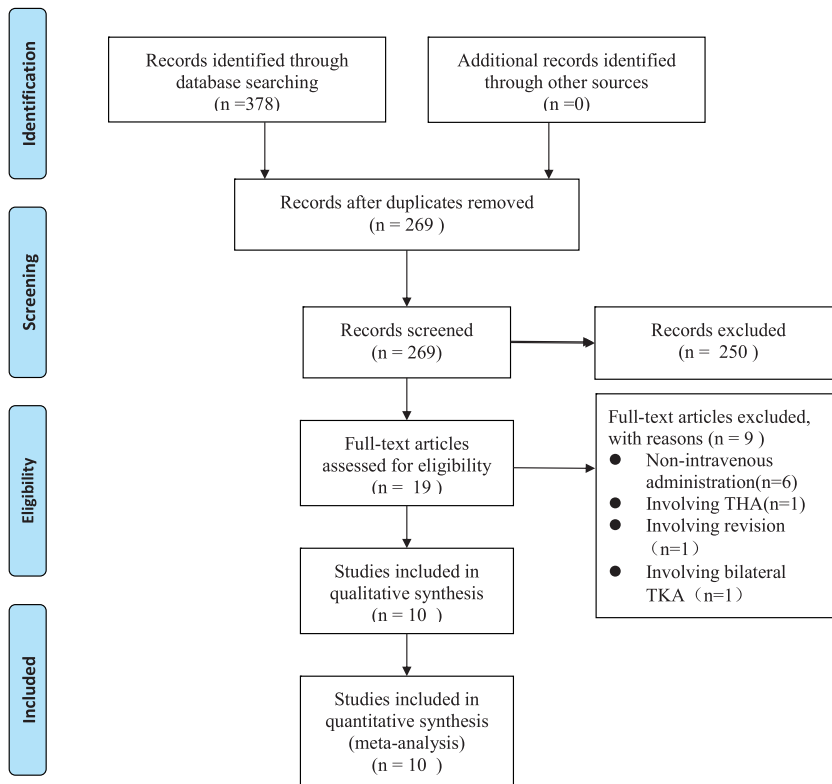
of the 19 remaining studies. The specific process of including studies is shown in Figure 1.

The sample size of the included studies ranged from 40 to 269 participants, and average age range in the different studies was 58.5 to 72 years. Basic characteristics of the included studies are described in Table 1.

The results of the risk of bias assessment are presented in Figure 2.

### Primary outcomes

**Pain visual analog scale.** A pain VAS following TKA was reported in nine studies.<sup>14-18,23-26</sup> All of these nine studies assessed VAS at 24 hours,<sup>14-18,23-26</sup> and the VAS at 48 hours was evaluated in six



**Figure 1.** Flow diagram of the literature search. THA, total hip arthroplasty.

**Table 1.** Basic characteristics of the included studies.

| Studies                               | Year | Country | BMI       | Gender (M:F)<br>(D/C)  | Surgical<br>approach   | Sample<br>size (D/C) | Mean age<br>(D/C) | Primary<br>diagnosis | Dexamethasone<br>group                   | Control<br>group | Postoperative<br>medication   | Relevant<br>outcome                                   | Follow-up |
|---------------------------------------|------|---------|-----------|------------------------|--|----------------------|-------------------|----------------------|--|------------------|---|---|-----------|
| Fujii and<br>Nakayama <sup>27</sup>   | 2005 | Japan   | 23.7/22.3 | 11:29/10:30<br>(D/C)   | TKA  | 40/40                | 59/58.5           | Unknown              | Postoperative IV<br>8 mg or 16 mg<br>DXM | vehicle          | A continuous epidural<br>infusion of combina-<br>tion bupivacaine<br>0.125% 100 mL plus<br>morphine 0.1 mg/kg.<br>Indomethacin 50 mg<br>was given as rescue<br>analgesia.   | adverse effects                                       | 24 hours  |
| Koh et al. <sup>24</sup>              | 2013 | Korea   | 26.3/26.1 | 18:117/15:119<br>(D/C) | TKA with a<br>standard<br>medial para-<br>patellar<br>arthrotomy | 135/134              | 72.0/72.0         | OA                   | Preoperative IV 10<br>mg DXM             | NS               | PCA (1 mL of a 100-mL<br>solution containing<br>1500 g or 2000 g fen-<br>tanyl), 200 mg cele-<br>coxib, 75 mg<br>pregabalin, and 650<br>mg acetaminophen<br>every 12 hours, and<br>IV ketoprofen (100<br>mg) or IV metoclo-<br>pramide (10 mg) as<br>required.              | VAS, adverse<br>effects, and<br>complications         | 12 months |
| Deng et al. <sup>18</sup>             | 2016 | China   | 25.7/24.9 | 13:7/9:11<br>(D/C)     | TKA  | 20/20                | 68.3/66.9         | OA                   | Preoperative IV 10<br>mg DXM             | NS               | PCA (sufentanil 250<br>µg + droperidol 10<br>mg + 250 mL NS), a<br>routine anti-infection<br>and anticoagulant<br>treatment.  | VAS, ROM,<br>adverse effects,<br>and<br>complications | 6 months  |
| Morales-Munoz<br>et al. <sup>25</sup> | 2017 | Spain   | 31.1/30.2 | 8:19/6:21<br>(D/C)     | TKA  | 27/27                | 68.8/68.8         | Unknown              | Preoperative IV<br>8 mg DXM              | NS               | Postoperative analgesia<br>for the first 48 hours<br>consisted of continu-<br>ous perfusion of<br>metamizol (5 mg/<br>minute) and ondanse-<br>tron (16 g/minute)<br>together with 3-mg<br>boluses of morphine<br>delivered intermit-<br>tently using a PCA<br>infusion pump | VAS, ROM,<br>adverse effects,<br>and<br>complications | 48 hours  |

(continued)

**Table 1.** Continued.

| Studies                          | Year | Country   | BMI       | Gender (M:F)<br>(D/C) | Surgical approach  | Sample size (D/C) | Mean age (D/C) | Primary diagnosis | Dexamethasone group   | Control group | Postoperative medication  | Relevant outcome                             | Follow-up |
|----------------------------------|------|-----------|-----------|-----------------------|--|-------------------|----------------|-------------------|---|---------------|---|--|-----------|
| Xu et al. <sup>26</sup>          | 2017 | China     | 24.2/24.3 | 8:46/9:45             | TKA with a midline skin incision, medialpara-patellar approach | 54/54             | 64.6/64.6      | OA                | Pre- and post-operative IV 10 mg DXM respectively   | NS            | MOAD (50 mg diclofenac every 12 hours, 75 mg pregabalin every 8 hours), oral oxycodone (10 mg every 8 hours) or an IV parecoxib (40 mg) with IV metoclopramide (10 mg) as required. A routine anticoagulant treatment with LMWH.  | VAS, ROM, adverse effects, and complications | 2 months  |
| Dissanayake et al. <sup>23</sup> | 2018 | Australia | Unknown   | 41:45/42:36           | TKA  | 86/78             | 68.7/66.7      | Unknown           | Preoperative IV 8 mg DXM, and another 8 mg DXM was injected when the BGL was less than 8 mmol/L postoperatively | NS            | Oxycodone/naloxone 10/5 mg twice daily for 4 to 5 days after surgery; paracetamol 1 g every 6 hours, gabapentin 300 mg daily for 2 to 3 days after surgery, ibuprofen 200–400 mg every 8 hours or celecoxib 100 mg twice daily, oxycodone 5–10 mg every 3 hours and tramadol slow release 100–200 mg twice daily as required. | VAS, adverse effects, and complications      | 6 weeks   |
| Wu et al. <sup>14</sup>          | 2018 | China     | 26.1/25.9 | 17:33/18:42           | TKA with a midlineskin incision, medial para-patellar approach | 50/50             | 66.9/67.4      | OA                | Preoperative IV 10 mg DXM   | NS            | MOAD (200 mg celecoxib every 12 hours, every 8 hours), oral oxycodone (10 mg every 8 hours) or IV pethidine hydrochloride (100 mg) with IV metoclopramide (10 mg) as required. Routine anticoagulant  | VAS, ROM, adverse effects, and complications | 72 hours  |

(continued)

**Table 1.** Continued.

| Studies                                | Year | Country  | BMI       | Gender (M:F)<br>(D/C) | Surgical<br>approach   | Sample<br>size (D/C) | Mean age<br>(D/C) | Primary<br>diagnosis | Dexamethasone<br>group  | Control<br>group | Postoperative<br>medication  | Relevant<br>outcome                          | Follow-up |
|--|------|----------|-----------|-----------------------|--|----------------------|-------------------|----------------------|---|------------------|--|--|-----------|
| Xu et al. <sup>15</sup>                | 2018 | China    | 25.7/28.8 | 11:49/853             | TKA with a midline skin incision, medial parapatellar approach | 60/61                | 64.5/65.8         | OA                   | Preoperative IV 20 mg DXM   | NS               | treatment with LMWH, Oral diclofenac (50 mg every 12 hours), oral mosapride (5 mg 3 times daily), oral oxycodone HCl (10 mg) or IV morphine (10 mg) with an IV metoprolol (10 mg) as required.   | VAS, ROM, adverse effects, and complications | 72 hours  |
| Wang et al. <sup>16</sup>              | 2019 | China    | 26.5/26.9 | 12:20/13:19           | TKA with a midline skin incision, medialparapatellar approach  | 32/32                | 65.3/65.9         | OA                   | Preoperative IV 8 mg DXM  | NS               | Anticoagulant with rivaroxaban 12 hours after surgery, analgesic treatment with oral and IV paroxib for the first 3 days after surgery, oral celecoxib after 3 days, and IV tramadol as required.  | VAS and adverse effects                      | 72 hours  |
| Tammachote and Kanitnate <sup>17</sup> | 2020 | Thailand | 27.0/27.0 | 8:42/6:44             | TKA with a standard medial parapatellar arthroscopy            | 50/50                | 67.0/69.0         | OA                   | Preoperative IV 0.15 mg/kg of DXM, the maximum dose of DEX was 12 mg. | NS               | An IV 15 or 30 mg of ketorolac every 6 hours and 3 mg of IV morphine every 3 hours as required for the first 2 days after surgery; 250 mg of oral naproxen twice daily, 1300 mg of extended-release acetaminophen every 8 hours, 25 mg of nortriptyline plus 75 mg of pregabalin and 50 mg of tramadol as required on postoperative day 3. | VAS, ROM, adverse effects                    | 12 weeks  |

BGL, blood glucose level; DXM, dexamethasone; IV, intravenous; LMWH, low-molecular-weight heparin; LOS, length of stay; MOAD, multimodal oral analgesic drugs; NS, normal saline; PCA, patient-controlled analgesia; TKA, total knee arthroplasty; VAS, visual analog scale; OA, osteoarthritis; ROM, range of motion; D, dexamethasone group; C, control group.

|                               | 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) | Other bias |
|-------------------------------|---|---|---|---|--|--------------------------------------|------------|
| Deng 2016                     | +   | ?                                       | ?   | ?   | +  | +                                    | +          |
| Dissanayake 2018              | +   | +                                       | +   | +   | +  | +                                    | +          |
| Fujii 2005                    | +   | +                                       | +   | +   | +  | +                                    | +          |
| Koh 2013                      | +   | ?                                       | +   | +   | +  | +                                    | +          |
| Morales-Muñoz 2017            | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Tammachote and Kanitnate 2020 | +   | +                                       | +   | +   | +  | +                                    | +          |
| Wang 2019                     | +   | ?                                       | +   | ?   | +  | +                                    | +          |
| Wu 2018                       | +   | ?                                       | +   | +   | +  | +                                    | +          |
| Xu 2017                       | +   | +                                       | +   | +   | +  | +                                    | +          |
| Xu 2018                       | +   | +                                       | +   | +   | +  | +                                    | +          |

**Figure 2.** Risk of bias summary for the included studies. (+ represents yes; – represents no; ? represents unclear).

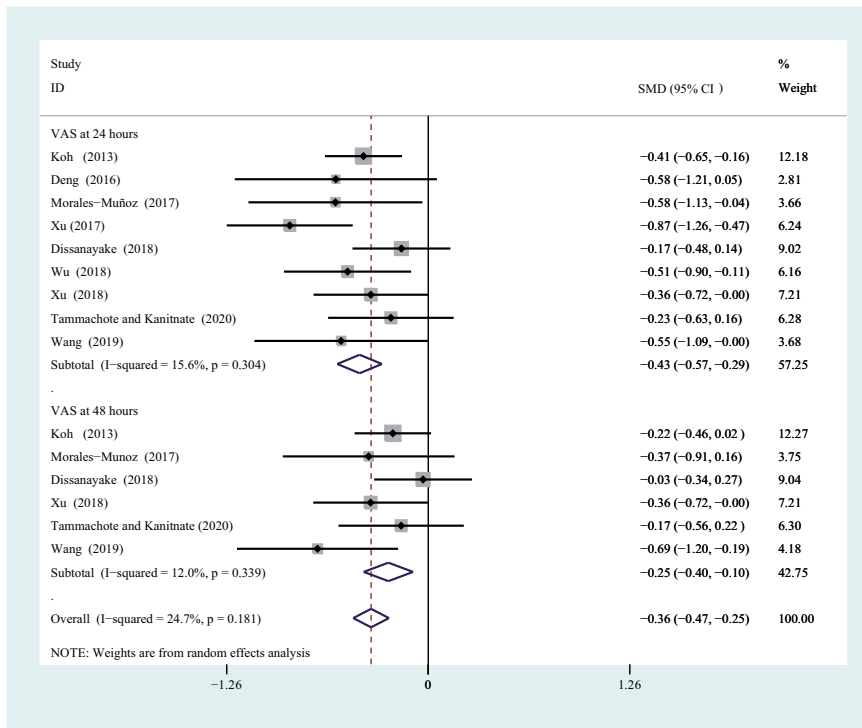
studies.<sup>15–17,23–25</sup> The pooled results demonstrated that perioperative intravenous low-dose dexamethasone decreased the postoperative pain score at 24 hours (SMD =  $-0.430$ ; 95%CI:  $-0.570$  to  $-0.291$ ;  $P < 0.001$ ) and 48 hours (SMD =  $-0.250$ ; 95%CI:  $-0.405$  to  $-0.096$ ;  $P = 0.002$ ). The statistical heterogeneity among trials was low in the VAS at 24 hours ( $I^2 = 15.6\%$ ) and 48 hours ( $I^2 = 12.0\%$ ) (Figure 3).

**Immediate range of motion.** Four studies<sup>14,15,18,26</sup> provided ROM data at 72 hours after TKA. Among these four studies,

three<sup>14,15,26</sup> assessed passive ROM at 72 hours, and one study<sup>18</sup> assessed active ROM at 72 hours. The overall results showed that intravenous low-dose dexamethasone improved the active ROM (SMD =  $1.254$ ; 95%CI:  $0.573$  to  $1.935$ ;  $P < 0.001$ ) and passive ROM (SMD =  $0.371$ ; 95%CI:  $0.152$  to  $0.589$ ;  $P = 0.001$ ). Heterogeneity was not identified for ROM between articles ( $I^2 = 0$ ) (Figure 4).

**Postoperative nausea and vomiting.** Data from six studies<sup>15,17,18,24,26,27</sup> investigated the PONV. The overall results clarified that perioperative intravenous dexamethasone





**Figure 3.** Forest plot for the comparison of VAS at 24 hours and 48 hours after surgery. VAS, visual analog scale.

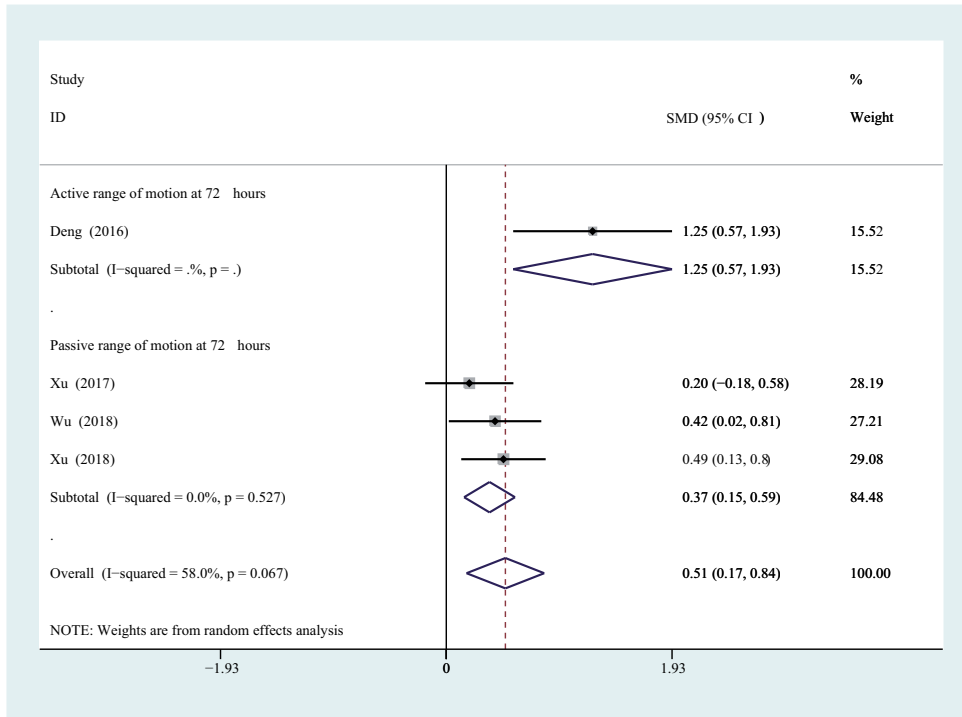
(10 to 20 mg) decreased the incidence of PONV (RR = 0.623; 95%CI: 0.508 to 0.765;  $P < 0.001$ ). Statistical heterogeneity in PONV was not identified between articles ( $I^2 = 0$ ) (Figure 5).

**Complications.** Seven studies<sup>14,15,18,23–26</sup> reported the postoperative complications including deep vein thrombosis (DVT), infection, inadequate wound healing, and pulmonary embolism (PE). The pooled outcomes showed that perioperative intravenous dexamethasone at doses of 8 to 20 mg did not increase the risk of postoperative early complications compared with the control groups (RR = 0.964; 95%CI: 0.527 to 1.762). There was no statistical heterogeneity found between trials ( $I^2 = 0$ ) (Figure 6).

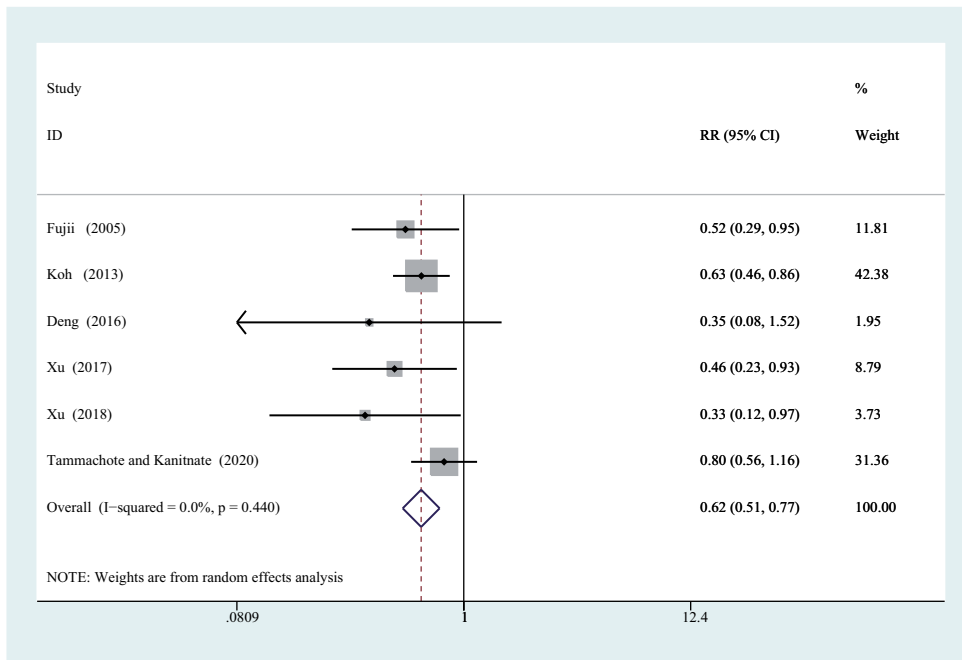
### Secondary outcomes

**Total opioid consumption at 24 and 48 hours.** Four studies<sup>17,23–25</sup> reported the total opioid consumption at 24 hours and 48 hours after surgery. The pooled results demonstrated that perioperative intravenous low-dose dexamethasone decreased the total opioid consumption at 24 hours (SMD = -0.474; 95%CI: -0.850 to -0.098;  $P = 0.013$ ) and 48 hours (SMD = -0.323; 95%CI: -0.533 to -0.114;  $P = 0.003$ ). The statistical heterogeneity among trials was high for the total opioid consumption at 24 hours ( $I^2 = 77.8%$ ,  $P = 0.004$ ) and low at 48 hours ( $I^2 = 32.7%$ ) (Figure 7).

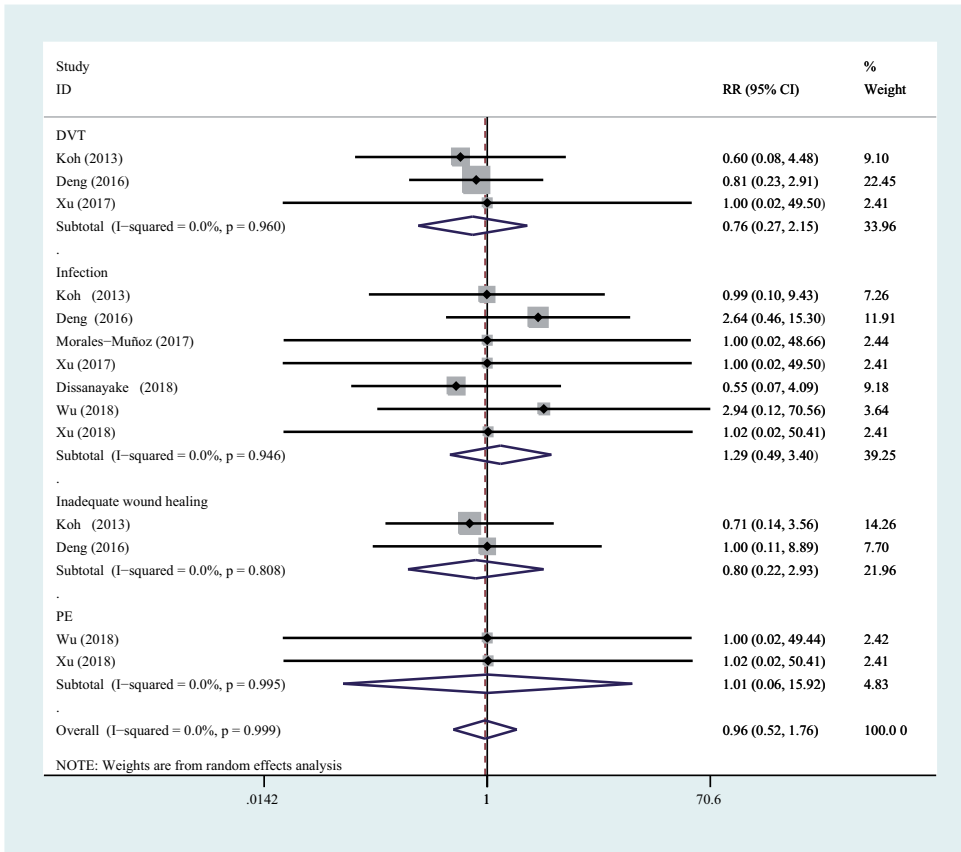
**Length of stay.** Five studies<sup>14,15,17,23,26</sup> reported the outcome of LOS after TKA.



**Figure 4.** Forest plot for the comparison of ROM at 72 hours after surgery among the two subgroups. ROM, range of motion.



**Figure 5.** Forest plot for the comparison of PONV. PONV, postoperative nausea and vomiting.



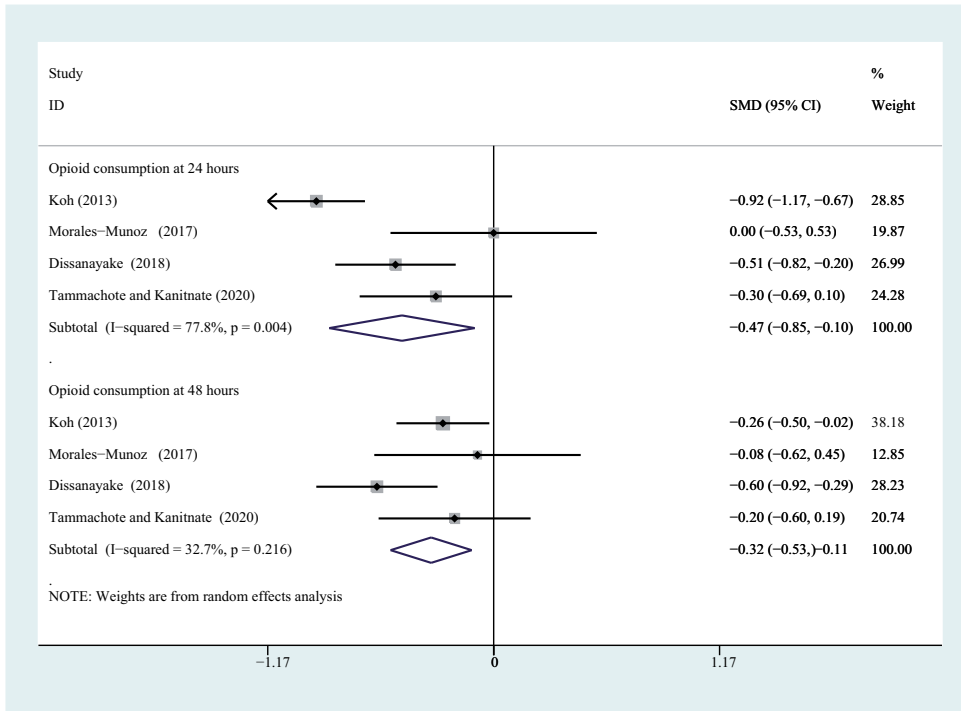
**Figure 6.** Forest plot for the comparison of complications.

The overall pooled outcomes illustrated that there was no significant difference in LOS between the dexamethasone group and the control group (WMD = -0.110; 95%CI: -0.245 to 0.025). No statistical heterogeneity was detected for LOS between the analyzed articles ( $I^2 = 0$ ) (Figure 8).

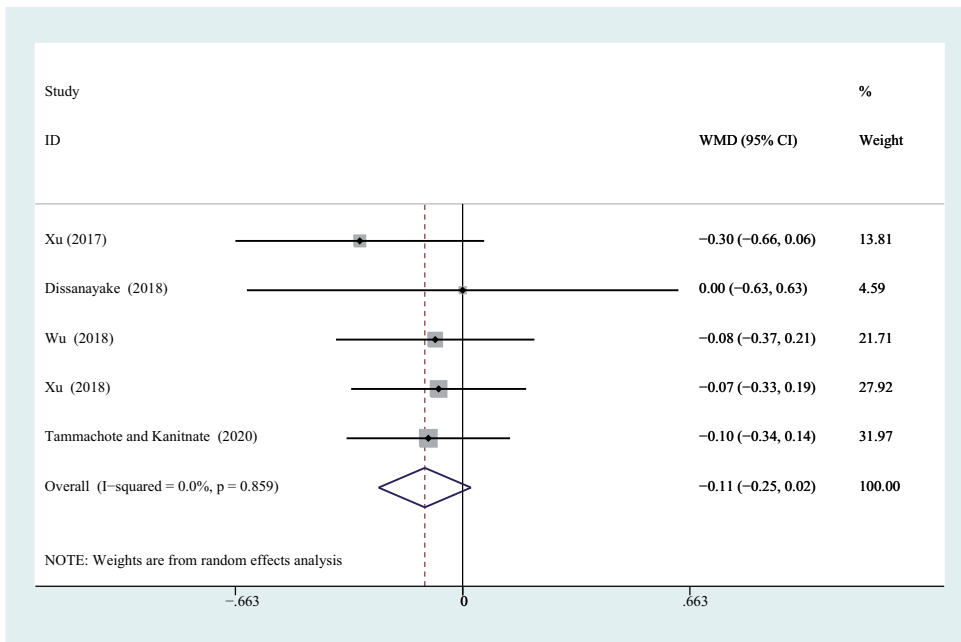
**Blood glucose.** Postoperative blood glucose at 24 hours was reported in four studies,<sup>15-17,23</sup> and two studies<sup>15,16</sup> recorded blood glucose at 72 hours. Compared with the control group, perioperative intravenous administration of low-dose dexamethasone remarkably increased the postoperative blood glucose levels at 24 hours (WMD = 0.750; 95%CI: 0.408 to

1.092;  $P < 0.001$ ), but there was not much difference in the postoperative blood glucose at 72 hours (WMD = -0.188; 95% CI: -0.595 to 0.359). The degree of statistical heterogeneity among trials was low for blood glucose at 24 hours ( $I^2 = 0$ ) and 72 hours ( $I^2 = 33.9%$ ) (Figure 9).

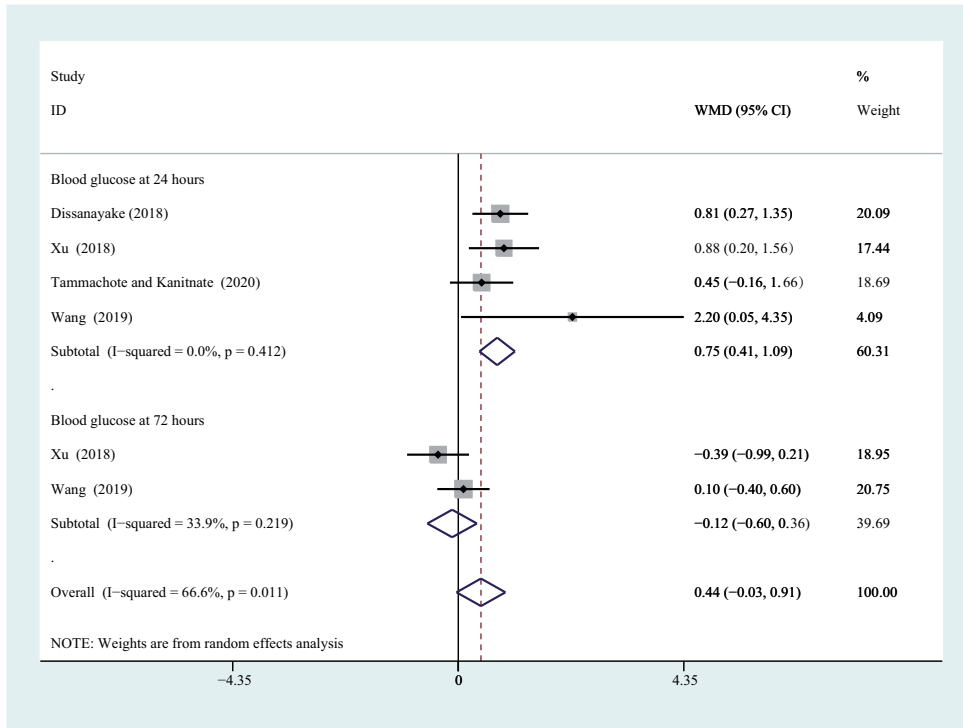
**Publication bias.** Publication bias was evaluated using a Begg’s funnel plot for VAS at 24 hours, which showed a low risk of publication bias. However, the publication bias cannot be eliminated because of the limited number (less than 10) of studies that were included in each analysis (Figure 10).



**Figure 7.** Forest plot for the comparison of total opioid consumption at 24 hours and 48 hours after surgery.



**Figure 8.** Forest plot for the comparison of LOS. LOS, length of stay.



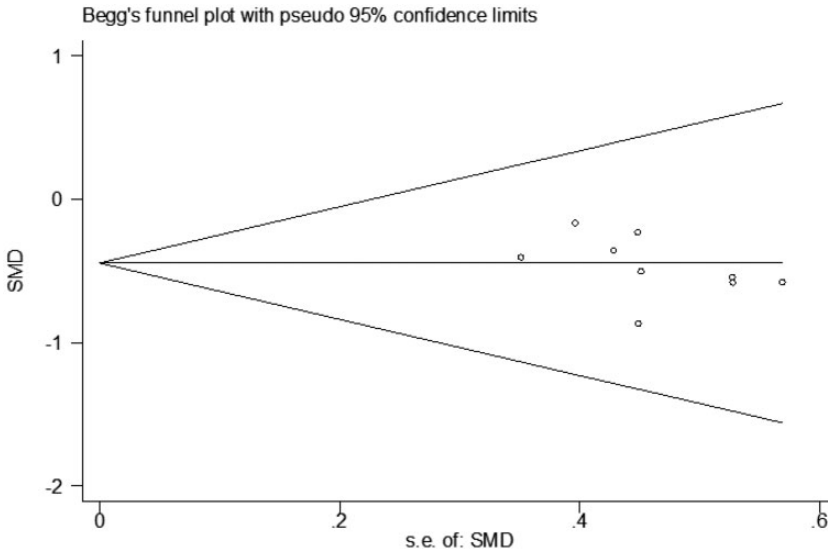
**Figure 9.** Forest plot for the comparison of blood glucose at 24 hours and 72 hours after surgery.

## Discussion

The main findings of this meta-analysis were that perioperative intravenous low-dose dexamethasone may be useful for improving the immediate ROM, lowering pain, and decreasing opioid consumption and the incidence of PONV in the early postoperative period without increasing related adverse events during the follow-up period.

Pain management is the key to quick postoperative rehabilitation and satisfactory recovery of patients.<sup>28</sup> Moreover, postoperative pain can contribute to postponement of discharge, prolonged stiffness, immobility-related complications, inability to perform rehabilitation exercise, poor outcome, delayed recovery, and greater consumption of care resources.<sup>29,30</sup> In this study, we observed that, compared

with placebo, perioperative use of dexamethasone was an effective approach to decrease the VAS score at 24 hours and 48 hours, which was consistent with two previous meta-analyses.<sup>12,13</sup> Inflammation markers including C-reactive protein (CRP) and interleukin (IL)-6 achieved effective control during the corresponding period. Thus, we believe that surgical trauma after undergoing TKA often leads to severe postoperative inflammatory reactions, which are concurrent with postoperative pain.<sup>31</sup> Opioid consumption is another important component of postoperative pain assessment. Our meta-analysis stated that perioperative intravenous low-dose dexamethasone could decrease the consumption of opioids at 24 hours and 48 hours after TKA, which were also consistent with studies by Li et al.<sup>12</sup> and Fan et al.<sup>13</sup> However, Zhou et al.<sup>32</sup> found that there was no



**Figure 10.** Begg's funnel plot of the current meta-analysis of VAS at 24 hours after surgery. VAS, visual analog scale.

significant difference in terms of opioid requirements at 24 hours and 48 hours, but the p-value was very close to 0.05. For these distinctions, we believe that one of the most likely reasons is the different routes of administration. Zhou et al.'s study included two articles<sup>33,34</sup> that were not listed in this study or in Li et al.'s<sup>12</sup> or Fan et al.'s<sup>13</sup> study. The intervention in these two studies<sup>33,34</sup> was periarticular injection of dexamethasone, which has been shown to have no effect on opioid consumption at 24 hours and 48 hours postoperatively compared with intravenous administration.<sup>35</sup> Therefore, the difference is greatly reduced in the pooled results when these two articles<sup>33,34</sup> are included.

ROM is a significant parameter for postoperative functional recovery of patients who are undergoing TKA. An angle of 67° of knee flexion is required for the swing phase of gait, 80° is required to walk up stairs, 90° is required to walk down stairs, 93° is required to stand up from a chair after TKA,<sup>36</sup> and 106° is

necessary for related activities such as tying shoelaces.<sup>37</sup> Lei et al.<sup>38</sup> found that two intravenous doses of 10 mg dexamethasone improved the functional outcomes of total hip arthroplasty. However, it is still uncertain whether dexamethasone is effective for improving knee function after primary TKA. A few studies reported an improvement in intravenous dexamethasone groups,<sup>14,15,18</sup> while another study did not show a difference.<sup>26</sup> This is the first systematic review and meta-analysis to provide important evidence that intravenous low-dose dexamethasone may improve early postoperative ROM. The most likely reason for this improvement is the increased willingness of the patient to perform early functional exercises due to the relief of immediate postoperative pain. However, many other variables may influence immediate postoperative ROM including the surgical technique, presurgical training and education, and implant design, as well as postoperative care within the hospital, which was not reported

in the included papers. Because of these limitations and because only four trials reported the immediate postoperative ROM, further investigation is required.

Through a central antiemetic effect, steroids reduce PONV via systemic application. However, the links between PONV control and the dose of systemic dexamethasone have not been investigated thoroughly. Several reviews have confirmed and documented the efficacy of perioperative dexamethasone at doses of 4 to 10 mg as PONV prophylaxis, and there was no risk of side effects.<sup>39–41</sup> However, our study found that 10 to 20 mg of intravenous dexamethasone is also effective in preventing PONV. Bustos et al.<sup>42</sup> found that two scheduled doses of 8 mg of dexamethasone seemed to be a safe adjunct to the perioperative protocol that reduced PONV. This seems to be in agreement with perioperative intravenous low-dose dexamethasone for prophylactic PONV.

Because of the low incidence rate of complications such as DVT, infection, inadequate wound healing, and symptomatic PE after TKA, it is difficult to obtain sufficient power in RCTs to show any potential superiority of intravenous dexamethasone for these results. Vuorinen et al.<sup>43</sup> revealed that use of a low dose of dexamethasone did not increase the incidence of postoperative prosthetic joint infections. To date, there are no data that reliably and directly attribute the result of an increase in postoperative complications to intravenous dexamethasone. In addition, our study illustrated that perioperative intravenous dexamethasone might contribute to postoperative hyperglycemia. Thus, we suggest that blood glucose monitoring and management should be strengthened after surgery, especially in diabetics.

Current rapid recovery protocols have changed total joint replacement by reducing the hospital stay, and there was no increase in the readmission rate.<sup>44</sup> As mentioned

above, perioperative intravenous low-dose dexamethasone was associated with an immediate improvement in the ROM and a lower pain score and PONV. However, these benefits did not seem to translate into a shorter LOS in this study. One possible explanation for this was that five related studies<sup>14,15,17,23,26</sup> had different discharge criteria, which might greatly reduce the clinical significance of this parameter.

Our meta-analysis has several advantages compared with meta-analyses that were previously published.<sup>12,13,32</sup> First, our study included three additional high-quality RCTs<sup>14,15,17</sup> and two RCTs<sup>16,18</sup> that were written in Chinese and had been excluded from previous meta-analyses, and this would reduce statistical bias and publication bias. Second, we reported the postoperative knee ROM, which is an important parameter for early postoperative recovery and discharge criteria, and it was not included in the previous study. Third, we excluded studies with different routes of administration such as periarticular and perineural dexamethasone, which significantly reduced the heterogeneity in the pooled results. Our study also has several limitations. Only ten RCTs with 1100 knees were included. The follow-up varied from 24 hours to 12 months, and the absence of mid-term and long-term follow-up did not allow robust assessment of the incidence of complications. Statistical heterogeneity was inevitable because of the different dexamethasone doses. There was no standardization for concomitant painkillers, which also introduces statistical bias when evaluating the efficacy of dexamethasone. The results of this study cannot be applied to other types of steroids because there were significant differences in pharmacological properties such as half-life and anti-inflammatory effects in different steroids.

## Conclusion

Perioperative intravenous low-dose dexamethasone may play a critical role in rapid recovery after TKA by reducing the immediate ROM limitation, pain, opioid consumption, and PONV. There are no data that reliably and directly attribute intravenous dexamethasone to an increase in postoperative complications, and high-quality studies with a large sample size are required to explore the relationship between complications and the dose and response before dexamethasone is extensively used.

## Data availability

The data that support the findings of this study are available upon request from the corresponding author.

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## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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## Authors' contributions

YGZ and YYZ designed the study. YTH, RGY, CLW, and JY participated in the literature search and data extraction. YGZ, HYW, and RGY oversaw quality assessment and statistical analysis. YGZ was responsible for manuscript review.

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