Is intraoperative corticosteroid a good choice for postoperative pain relief in total joint arthroplasty? A meta-analysis of 11 randomized controlled trials

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1. Introduction

Total joint arthroplasty (TJA) is one of the most effective methods for end-stage osteoarthritis.\textsuperscript{[1,2]} It was reported that the demand for primary total knee arthroplasty (TKA) is expected to grow by 673% to 3.48 million in America when it comes to 2030.\textsuperscript{[3]} While postoperative pain following TJA is the most common problem which concerns surgeons.\textsuperscript{[4–7]} Postoperative pain following TJA is an inevitable question which may delay functional exercise and hospitalization days.\textsuperscript{[8,9]} Adequate pain relief following total knee and hip arthroplasty can promote early rehabilitation.

Corticosteroids have strong anti-inflammatory properties and relieve pain following surgeries.\textsuperscript{[10–14]} Recently several published studies demonstrate the superiority of corticosteroids in analgesic effect compared to the non-corticosteroids group.\textsuperscript{[15–17]} There is a growing consensus that the corticosteroids should be recommended as the analgesic choice for patients undergoing TJA. However, the safety and effectiveness of corticosteroids remain controversial. Thus, we made the meta-analysis.

The hypothesis of this meta-analysis was that the corticosteroids have effects on pain relief following TJA?

2. Materials and methods

The study was approved by the Ethics Committee of the Xiaoshan Traditional Chinese Medical Hospital.

2.1. Search strategy

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and Cochrane Handbook were used to evaluate the quality of the included studies to insure our results were reliable and verifiable. We systematically searched PubMed (1996–December 2020), Embase (1996–December 2020), and the Cochrane Library (CENTRAL, December 2020)
We also searched related references and Google Scholar meanwhile. Only randomized controlled trials (RCTs) were included in our study. ‘Total knee arthroplasty’, ‘Total hip arthroplasty’, ‘Total joint arthroplasty’, ‘corticosteroids’ were used as key words using Boolean operators ‘AND’ or ‘OR’. The search results are shown in Figure 1.

2.2. Inclusion and exclusion criteria

Trials were included in our meta-analysis on condition they met the PICOS criteria (patients, intervention, comparator, outcome, study design). Patients: patients had underwent TKA or total hip arthroplasty for the first time. Intervention: corticosteroids for TKA or total hip arthroplasty. Comparator: non-corticosteroids. Outcomes: visual analogue scale (VAS) at rest, VAS at movement, total morphine consumption, periprosthetic joint infection (PJI), and length of stay (LOS). Study design: RCT.

2.3. Data extraction and bias risk assessment

Two researchers collected available data from included studies independently, and any disagreement between the 2 researches was judged by a third reviewer. Basic characteristics included patients, age, gender, body mass index, surgery type, and reference type. The VAS was the primary outcome in our meta-analysis. In order to compare the opioids consumption, all opioids were converted to equivalent morphine consumption dosage according the standard formula (Table 1). In order to compare the total amount of corticosteroid used by patients, all corticosteroid was converted to dexamethasone dosage according to standard formula (Table 2). The VAS score consists of 11 pain level with 0 being no pain and 10 representing the worst pain. Secondary outcomes consisted of VA, PJI, and LOS. We chose the Cochrane Handbook for systematic review of interventions (Review Manager Version 5.3 (Cochrane Collaboration’s software) to evaluate the risk bias of included studies.

2.4. Statistical analysis

We used Review Manager software 5.3 for our meta-analysis. For continuous data, the mean differences (MDs) with 95% confidence intervals (CIs) were applied to weigh the effect interval. Conversely, the risk ratio with 95% CIs was used to figure the effect interval. We used the values of $P$ and $I^2$ to assess statistical heterogeneity among the included studies. When $I^2 < 50\%$ and $P > .05$ we applied a fixed-effect model, otherwise a random-effect model was applied.
3. Results

3.1. Search results

A total of 301 articles were identified, and their records were included in Endnote X7 (Clarivate Analytics, Philadelphia, PA). After removing 55 duplicates, remaining 301 articles were screened according to the titles and abstracts. A full-text assessment was conducted on the rest of the 63 articles. Finally, 11 RCTs\(^\text{16–26}\) were included in this meta-analysis. The basic characteristics and interventions are summarized in Tables 3 and 4.

3.2. Risk of bias and quality assessment

According to the Cochrane Handbook for Systematic Reviews of Interventions, the risk of bias of the included RCTs were evaluated as follows: randomization; allocation concealment; blind method; selective reporting; incomplete outcome data; and other bias. The bias of assessment of RCTs are presented in Figures 2 and 3. We used funnel plot to evaluated reporting bias, which are presented in Figure 4. The symmetrical funnel plot diagram indicated that there were no significant risks of publications bias of VAS at rest and movement, total morphine equivalent consumption, PJI, and LOS.

### Table 1

| Analgesics                              | Dosage of morphine equivalents (mg) |
|-----------------------------------------|-------------------------------------|
| Morphine (subcutaneous or intramuscular) | 10                                  |
| Hydromorphone (subcutaneous or intramuscular/oral) | 1.5/7.5                             |
| Codeine (subcutaneous or intramuscular/oral) | 120/200                             |
| Oxycodone (oral)                        | 20                                  |
| Demerol (subcutaneous or intramuscular/oral) | 80/300                              |

### Table 2

| Corticosteroids             | Dosage (mg) |
|----------------------------|-------------|
| Dexamethasone              | 0.75        |
| Triamcinolone acetonide    | 4           |
| Methylprednisolone         | 5           |
| Hydrocortisone             | 20          |

### Table 3

| Corticosteroid group/control group | Patients (n) | Ages (yrs) | Female gender (%) | BMI | Surgery | Reference type |
|-----------------------------------|--------------|------------|-------------------|-----|---------|----------------|
| Tammachote et al (2018)           | 54/54        | 69/68      | 79.6/81.5         | 27/27 | TKA     | RCT            |
| Li et al (2018)                   | 36/32        | 63.9/64.7  | 80.6/84.3         | 25.3/24.7 | TKA     | RCT            |
| Samona et al (2017)               | 55/47        | 64.8/62.6  | 54.5/59.6         | N/A  | TKA     | RCT            |
| Luna et al (2017)                 | 21/19        | 68/67      | 71.4/42.1         | 28.8/28.2 | TKA     | RCT            |
| Tsukada et al (2016)              | 40/37        | 75/72      | 87.5/86.5         | 26.7/27.3 | TKA     | RCT            |
| Rytt et al (2015)                 | 35/37        | 65/66      | 51.4/45.9         | 28.3/30.4 | TKA     | RCT            |
| Koh et al (2013)                  | 135/134      | 72/72      | 87/89             | 26.3/26.1 | TKA     | RCT            |
| Chia et al (2013)                 | 42/43        | 66.8/65    | N/A               | 31/31.4 | TKA     | RCT            |
| Lunn et al (2012)                 | 24/24        | 66/66      | 50/62             | 27/27 | THA     | Use            |
| Lunn et al (2010)                 | 24/24        | 66/67      | 45.8/66.7         | 28/30 | TKA     | RCT            |
| Kardash et al (2008)              | 25/25        | 69/68.8    | 52/44             | N/A  | THA     | RCT            |

BMI = body mass index, N/A = not applicable, RCT = randomized controlled trial, THA = total hip arthroplasty, TKA = total knee arthroplasty.

### Table 4

| Corticosteroid   | Type                        | Dosage (mg) | Surgical approach          | Anesthesia                                      | Pneumatic tourniquet |
|------------------|-----------------------------|-------------|----------------------------|-------------------------------------------------|----------------------|
| Tammachote et al (2018) | Triamcinolone acetonide     | 100         | Medial parapatellar approach | Spinal epidural + epidural anesthesia             | N/A                  |
| Li et al (2018)  | Hydrocortisone              | 8           | Medial parapatellar approach | Local infiltration analgesia                     | Use                  |
| Samona et al (2017)| Dexamethasone               | 40          | N/A                        | Spinal or general anesthesia                     | N/A                  |
| Luna et al (2017)| Methylprednisolone          | 125         | N/A                        | Spinal or general anesthesia                     | N/A                  |
| Tsukada et al (2016)| Methylprednisolone         | 125         | N/A                        | Spinal or general anesthesia                     | N/A                  |
| Rytt et al (2015)| Methylprednisolone          | 125         | N/A                        | Spinal or general anesthesia                     | N/A                  |
| Koh et al (2013) | Dexamethasone               | 10          | N/A                        | Spinal or general anesthesia                     | N/A                  |
| Chia et al (2013)| Dexamethasone               | 100         | Medial parapatellar approach | Spinal or general anesthesia                     | N/A                  |
| Lunn et al (2012)| Methylprednisolone          | 125         | N/A                        | Spinal or general anesthesia                     | N/A                  |
| Lunn et al (2010)| Methylprednisolone          | 125         | N/A                        | Spinal or general anesthesia                     | N/A                  |
| Kardash et al (2008)| Dexamethasone             | 125         | N/A                        | Spinal or general anesthesia                     | N/A                  |

N/A = not applicable.
3.3. Results of meta-analysis

3.3.1. VAS at rest. Data from 8 studies with 1941 patients reported the VAS at rest. Subgroup analysis showed that the corticosteroids group had lower VAS at 12 hours (MD = -0.66, 95% CI: [-0.99, -0.34], P < .05; Fig. 5), 24 hours (MD = -1.24, 95% CI: [-2.18, -0.30], P < .05; Fig. 5), 48 hours (MD = -0.23, 95% CI: [-0.43, -0.03], P < .05; Fig. 5), and 72 hours (MD = -0.30, 95% CI: [-0.34, -0.26], P < .05; Fig. 5) when compared to the control group. A random effect model was used due to moderate heterogeneity in union time (x² = 1641; df = 19; P < .05; I² = 99%; Fig. 5).

3.3.2. VAS at movement. Four articles with 718 patients showed the outcome of VAS at movement. Subgroup analysis indicated compared with the control group, the corticosteroid group showed lower VAS at 12 hours (MD = -0.80, 95% CI: [-0.99, -0.61], P < .05; Fig. 6), 24 hours (MD = -2.33, 95% CI: [-4.63, -0.04], P < .05; Fig. 6), and 72 hours (MD = -0.71, 95% CI: [-1.38, -0.04], P < .05; Fig. 6). No significant differences were found at 48 hours between 2 groups (MD = -0.94, 95% CI: [-2.26, 0.38], P = .16; Fig. 6). We used random effect model due to the statistical heterogeneity (x² = 399; df = 9; P < .05; I² = 98%; Fig. 6).

3.3.3. Total equivalent morphine consumption. Data from 5 studies with 510 patients reported the total equivalent morphine consumption. Pooled data indicated that the corticosteroid group consumed less morphine compared to the control group (MD = -10.56, 95% CI: [-13.10, -8.01], P < .05; Fig. 7). A fixed effect model was used because of the low heterogeneity (x² = 4.68; df = 4; P = .32; I² = 15%; Fig. 7).

3.3.4. Periprosthetic joint infection. Five studies with 328 patients recorded the PJI. No significant differences were found between the corticosteroid group and the control group (risk ratio = 1.23, 95% CI: [0.36, 4.21], P = .74; Fig. 8). We used fixed effects model due to the low heterogeneity (x² = 0.23; df = 1; P = .63; I² = 0%; Fig. 8).

3.3.5. Length of stay. We extracted the data of LOS from 3 studies. No significant differences were found between the corticosteroid group and the control group (MD = -0.24, 95% CI: [-0.7, 0.23], P = .32; Fig. 9). We used a random effect model.
due to the statistical heterogeneity ($x^2 = 8.17; \text{df} = 2; P < .05; I^2 = 76\%$; Fig. 9).

4. Discussion

As far as we know, several meta-analyses compared the efficacy of corticosteroid on pain relief in TJA. Considering the inconsistencies results and limitations of these meta-analysis, we were inspired to make the meta-analysis.\cite{27-30} Our meta-analysis has several advances and strengths compared with previous studies. First, compared with previous studies, we included the largest number of RCTs. Hence, the pooled data are more feasible, convincing, and instructive. Second, we firstly evaluated the postoperative VAS in terms of 2 parts: at rest and movement, which made our results more objective and specific. Third, we also analyzed the safety of corticosteroids by evaluating the postoperative prosthesis infection rate between the 2 groups, which contribute a more comprehensive evaluation.
Finally, we analyzed the source of heterogeneity between the RCTs, which made the pooled data more reliable.

VAS was the primary outcome assessed in our meta-analysis. VAS is used to assess the pain of patients after knee and hip surgeries. Our pooled data showed that corticosteroids are better for postoperative pain relief in patients with total knee or hip arthroplasty. Meanwhile, an RCT conducted by Li et al. demonstrated that corticosteroids showed better analgesic effects in VAS at rest at 12 hours, 24 hours, and 48 hours postoperatively. This was consistent with our findings. In our meta-analysis, we demonstrated that corticosteroids group got better VAS at rest and movement. Similar findings were reported by Koh et al. and Tsukada et al. Therefore, we conducted a comparison between the control group, the corticosteroid group provided better VAS at rest and movement. Similar findings were reported by Koh et al. and Tsukada et al. Therefore, we conducted a comparison between the control group and corticosteroid group. The length of hospital stay between the 2 groups also showed no significant differences.

Also, there are some limitations in our meta-analysis. Firstly, only 11 studies in our meta-analysis. The test power for statistical would be more credible if more RCT are included. Secondly, unavoidable heterogeneity (racial differences, surgery procedures, anesthesia methods, age, and so on) between the included studies may affect the results of pooled data. Thirdly, with regard

| Study or Subgroup | Corticosteroid | Control | Mean Difference (IV, Random, 95% CI) |
|-------------------|---------------|---------|-------------------------------------|
| 1.1.1 at 12 hours |               |         |                                     |
| Kardon et al. 2008 | 2.4           | 1.7     | -0.70 [-1.69, 0.39]                 |
| Li et al. 2016    | 2.7           | 0.3     | -1.10 [-1.27, -0.93]                |
| Ryttar et al. 2015| 2.2           | 2.5     | -2.80 [-5.35, -0.20]                |
| Tsukada et al. 2016| 0.8           | 2.1     | -0.20 [-1.18, 0.78]                 |
| Subtotal (95% CI) | 133           | 131     | 18.00 [-2.18, -0.30]                |

Heterogeneity: tau^2 = 0.76; chi^2 = 23.17, df = 3 (P < 0.0001); I^2 = 87%

Test for overall effect: Z = 2.56 (P = 0.010)

1.1.2 at 24 hours

| Study or Subgroup | Corticosteroid | Control | Mean Difference (IV, Random, 95% CI) |
|-------------------|---------------|---------|-------------------------------------|
| Kardon et al. 2008 | 2.5           | 0.0     | 0.40 [-1.23, 0.04]                  |
| Koh et al. 2013    | 2.3           | 0.3     | 3.73 [-0.94, 0.66]                  |
| Li et al. 2018     | 2.1           | 2.5     | 3.62 [-0.81, 1.59]                  |
| Lunn et al. 2010   | 0.6           | 1.3     | 0.40 [-1.06, 0.26]                  |
| Lunn et al. 2012   | 2.6           | 0.9     | 0.50 [-0.96, -0.04]                 |
| Tsukada et al. 2016| 1.7           | 2.3     | 0.90 [-1.81, 0.01]                  |
| Subtotal (95% CI)  | 316           | 313     | 34.14 [-1.15, 0.47]                 |

Heterogeneity: tau^2 = 0.43; chi^2 = 127.51, df = 6 (P < 0.00001); I^2 = 97%

Test for overall effect: Z = 3.54 (P = 0.0003)

1.1.3 at 48 hours

| Study or Subgroup | Corticosteroid | Control | Mean Difference (IV, Random, 95% CI) |
|-------------------|---------------|---------|-------------------------------------|
| Kardon et al. 2008 | 5.0           | 0.5     | 0.20 [-0.11, 0.51]                  |
| Koh et al. 2013    | 3.5           | 0.2     | -0.40 [-0.46, -0.34]                |
| Li et al. 2018     | 1.7           | 0.3     | -0.30 [-0.46, -0.14]                |
| Lunn et al. 2010   | 0.5           | 0.8     | -0.50 [-0.74, 0.26]                 |
| Tamamchote et al. 2018 | 1.3         | 1.8     | -0.30 [-1.10, 0.50]                 |
| Tsukada et al. 2016| 3.4           | 1.5     | 0.50 [-0.21, 0.21]                  |
| Subtotal (95% CI)  | 305           | 301     | 23.52 [-0.43, -0.03]                |

Heterogeneity: tau^2 = 0.04; chi^2 = 21.62, df = 5 (P = 0.0006); I^2 = 77%

Test for overall effect: Z = 2.27 (P = 0.02)

1.1.4 at 72 hours

| Study or Subgroup | Corticosteroid | Control | Mean Difference (IV, Random, 95% CI) |
|-------------------|---------------|---------|-------------------------------------|
| Koh et al. 2013    | 3.4           | 0.1     | -0.30 [-0.34, -0.26]                |
| Tamamchote et al. 2018 | 0.9       | 1.3     | -0.40 [-1.02, 0.22]                 |
| Tsukada et al. 2016| 2.9           | 1.8     | -0.10 [-0.91, 0.71]                 |
| Subtotal (95% CI)  | 222           | 220     | 15.32 [-0.34, -0.26]                |

Heterogeneity: tau^2 = 0.00; chi^2 = 0.33, df = 2 (P = 0.85); I^2 = 0%

Test for overall effect: Z = 14.95 (P = 0.00001)

Total (95% CI)

| Mean Difference (IV, Random, 95% CI) |
|-------------------------------------|
| 976                                 |
| 985                                 |
| 100.00%                             |

Heterogeneity: tau^2 = 0.46; chi^2 = 1641.19, df = 19 (P < 0.0001); I^2 = 99%

Test for overall effect: Z = 3.99 (P < 0.0001)

Test for subgroup differences: chi^2 = 15.82, df = 3 (P = 0.01); I^2 = 72.3%

Figure 5. A forest plot diagram showing the VAS at rest. VAS = visual analogue scale.
to the significant heterogeneity of VAS at postoperatively 24 hours ($I^2 = 97\%$) at rest, we tried to find the source of heterogeneity. When we did not include the RCT of Koh et al.[21] the heterogeneity of VAS at postoperatively 24 hours ($I^2 = 67\%$) reduced significantly. Thus we thought the study of Koh et al.[21] was the sources of the heterogeneity. In the study of Koh et al.[21] they used the dosage of 10mg in the corticosteroids group. While other studies applied at least a dosage of 40mg of corticosteroids. Hence, we thought the dosage of corticosteroids may be a cause of heterogeneity. Although some limitations exist in our study, high quality of included studies and accurate statistical method ensured the reliability of our meta-analysis.

5. Conclusions
In conclusion, we found the corticosteroid group in our meta-analysis is superior in terms of VAS at rest and movement, and total morphine equivalent consumption, without increasing the risk of PJI and LOS, when compared to the control group. Thus, we conclude that the corticosteroid is a feasible analgesic choice for patients undergoing TJK. However, further high-quality research is necessary to confirm these findings.
studies are needed to explore the optimal dosage of corticosteroid.

**Author contributions**

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