

A meta-analysis of dexamethasone for pain management in patients with total knee arthroplasty

Guanghong Zhou, MB^a, Liping Ma, MD^b, Junhai Jing, DR^c, Hao Jiang, MD^{a,*}

Abstract

Background: Pain management after a total-knee arthroplasty (TKA) has become an important issue in the field of medicine. This study conducted a meta-analysis from randomized controlled trials (RCTs) to assess the efficacy and safety of dexamethasone for pain management after TKA.

Methods: PubMed, Medline, Embase, ScienceDirect, and the Cochrane Library were searched up to December 2017 for comparative RCTs involving dexamethasone and placebo for pain control after TKA. Primary outcomes were postoperative pain scores and opioid consumption. Secondary outcomes were length of hospital stay, adverse effects, and postoperative complications. We assessed statistical heterogeneity for each RCT with the use of a standard Chi-squared test and the I^2 statistic. All data were carried out with Stata 14.0 software.

Results: A total of 6 RCTs were included. The present meta-analysis indicated that there were significant differences between dexamethasone-treated groups and placebo groups regarding postoperative pain scores at 12, 24, and 48 hours after TKA. Administering dexamethasone could significantly reduce opioid consumption at 12 hours after TKA. However, no significant difference was found in opioid consumption at 24 and 48 hours after TKA. There was a decreased risk of adverse effects in dexamethasone groups.

Conclusion: Use of dexamethasone could result in a significant reduction in postoperative pain while minimizing adverse effects after TKA. Based on the current evidence available, more RCTs are needed for further investigation.

Abbreviations: CI = confidence interval, PCA = patient-controlled analgesia, RCT = randomized controlled trials, RD = risk difference, TKA = total-knee arthroplasty, VAS = visual analog scale, WMD = weighted mean difference.

Keywords: dexamethasone, meta-analysis, pain, total-knee arthroplasty

1. Introduction

Total-knee arthroplasty (TKA) is a surgical procedure for the treatment of degenerative joint disease of the knee. Among aging populations, the number of TKAs has vastly and sharply increased in recent years. It was reported that more than 500,000 TKAs were performed in the United States in 2016, which predicted a rising trend for future demand of TKA.^[1] TKA has shown improved outcomes for relieving pain and knee function. However, it has been associated with pain during the early postoperative period, due to extensive bone resection and soft-tissue manipulation.^[2] Numerous methods for pain man-

agement, including periarticular infiltration analgesia, femoral nerve block, epidural anesthesia, and patient-controlled analgesia (PCA) have been tested, and the optimal method is currently still under debate.^[3–6] Multimodal analgesic regimen has become a standard protocol to minimize postoperative pain and improve functional recovery following TKA.^[7,8]

Glucocorticoid is a class of steroid hormones that has been shown to reduce systemic inflammatory response with well-documented anti-inflammation effects. A high-potency, long-acting glucocorticoid, dexamethasone is extensively used in surgical procedures for the management of acute pain in the postoperative setting. Dexamethasone has been reported to inhibit peripheral phospholipase, which reduces pain-aggravating products from the cyclooxygenase and lipoxygenase pathways.^[9] Previous studies have demonstrated that dexamethasone appeared to be effective and safe for postoperative pain control in arthroplasties.^[10,11] Additionally, preoperative administration of dexamethasone has been shown to reduce postoperative nausea and vomiting.^[12] Based on its high efficiency and wide application, we chose dexamethasone as the target drug in our study. Whether dexamethasone was associated with an increase in adverse effects in TKA remains controversial.

Therefore, it is necessary to carry out a meta-analysis study to evaluate the safety and efficiency of dexamethasone in TKA. The purpose of the meta-analysis is to determine whether dexamethasone has been associated with the following conditions: less postoperative pain, less opioid consumption, and fewer adverse effects compared to the control groups.

Editor: Eric Bush.

The authors have no funding and conflicts of interest to disclose.

^a Operating Room, China-Japan Union Hospital of Jilin University, ^b Nursing Department, Nanhui District of China-Japan Union Hospital of Jilin University,

^c Department of Oncology, Changling People's Hospital, Jilin, China.

* Correspondence: Hao Jiang, Operating Room, China-Japan Union Hospital of Jilin University, Jilin 130021, China (e-mail: happy132122@163.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2018) 97:35(e11753)

Received: 2 December 2017 / Accepted: 8 July 2018

<http://dx.doi.org/10.1097/MD.00000000000011753>

2. Materials and methods

Ethical approval for this study was deemed unnecessary because it was a review of existing literature and did not involve any handling of individual patient's data.

2.1. Search methodology

Two reviewers independently searched PubMed, OVID, Embase, ScienceDirect, and Web of Science for relevant studies. All databases were searched up to November 2017, without restrictions on publication date and language. The terms were used to search the databases were: “dexamethasone” OR “hexadecadrol” AND (“TKA” OR “TKR” OR “total knee arthroplasty” OR “total knee replacement” OR “Arthroplasty, Replacement, knee”). Search terms were combined using the Boolean operators “AND” or “OR.” Reference lists of relevant articles were manually searched to identify additional trials.

2.2. Inclusion and exclusion criteria

Studies searched were considered eligible when they met following criteria: clinical randomized controlled trials (RCTs) published between 1966 and 2017; patients aged older than 18 years diagnosed with end-staged knee osteoarthritis; in case of patients undergoing TKAs, intervention groups received intravenous or periarticular dexamethasone for pain management and control groups received placebo or nothing; studies with at least one of the following outcomes: visual analog scale (VAS) scores, opioid consumption, duration of hospitalization, adverse effects, and postoperative complications. Studies excluded from the present meta-analysis were comprised of incomplete data, case reports, conference abstracts, or review articles.

2.3. Study selection

Two investigators independently selected articles according to the aforementioned criteria. Based on the inclusion criteria, full studies were reviewed and were determined to be included or excluded in the meta-analysis study. If no consensus was reached, a third investigator was consulted on a study's eligibility.

2.4. Data extraction

Two investigators independently extracted data from eligible studies that met the inclusion criteria. A 2-check procedure was performed to test the accuracy of the extracted data. The information extracted from the studies were as follows: the family name of the first author, publication year, the number of patients in the study, the number of female patients in each study, the mean age of patients, intervention of each group, and follow-up duration after TKA. Primary outcomes included VAS and total narcotic use. Secondary outcomes were duration of hospitalization, adverse effects, and postoperative complications. We sent emails to authors to obtain incomplete outcome data.

2.5. Statistical analysis

All data were carried out with Stata 14.0 software. For continuous outcomes, the number of patients, mean values, and standard deviations were pooled to a weighted mean difference (WMD) and a 95% confidence interval (CI). For dichotomous outcomes, the risk difference (RD) and the 95% CI were assessed. The assessment for statistical heterogeneity was

calculated using Chi-squared and I^2 tests. A fixed-effects model was adopted when $I^2 < 50\%$ and $P > .05$; otherwise, the random-effects model was adopted. We did not perform a publication bias, if there were < 10 included articles.

2.6. Quality assessment

The methodologic qualities of included studies were assessed independently by the 2 reviewers described by the Cochrane Collaboration for Systematic Reviews. The 6 items of sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential risks were considered to be meaningfully evaluation index. Disagreements were by consensus after discussion, and if necessary, the third reviewer was consulted.

The evidence grade was assessed using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group including the following items: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The recommendation level of evidence was classified into the following categories: high, which indicates that further research is unlikely to alter confidence in the effect estimate; moderate, which indicates that further research is likely to significantly alter confidence in the effect estimate and may change the estimate; low, which indicates that further research is likely to significantly alter confidence in the effect estimate and to change the estimate; and very low, which indicates that any effect estimate is uncertain.

3. Results

3.1. Search result

A total of 450 potentially relevant studies related to dexamethasone and TKA were reviewed.

After the scan of all titles and abstracts, 444 articles were excluded. Six RCTs^[12–17] published between 2013 and 2017 satisfied the eligibility criteria for this study. There were 291 participants in the dexamethasone groups and 285 patients in the control groups. Figure 1 showed the process of included studies.

3.2. Description of included studies

The sample size of included trials ranged from 40 to 269, and the mean age of patients ranged from 64 to 72 years. In these RCTs, the intervention groups received intravenous or periarticular administration dexamethasone, and the control groups received placebo or nothing. Concomitant pain control included intravenous opioid or PCA. Duration of follow-up after TKA ranged from 3 to 12 months. Characteristics of the included studies are described in Table 1.

3.3. Risk of bias

Seven aspects of the RCTs related to the risk of bias were assessed, following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions (Figs. 2 and 3). All RCTs were randomized and 5 mentioned that the lists of random numbers were generated through computers.^[12–14,16,17] All articles^[12–17] used sealed envelopes for allocation concealment. Four articles^[14–17] reported double blinding to the surgeons and participants and 3 RCTs reported blinding to assessors.^[12,13,15] Low risk of bias due to incomplete outcome data and selective outcome reporting was detected. None of the RCTs reported whether an “intention-to treat” analysis was conducted.

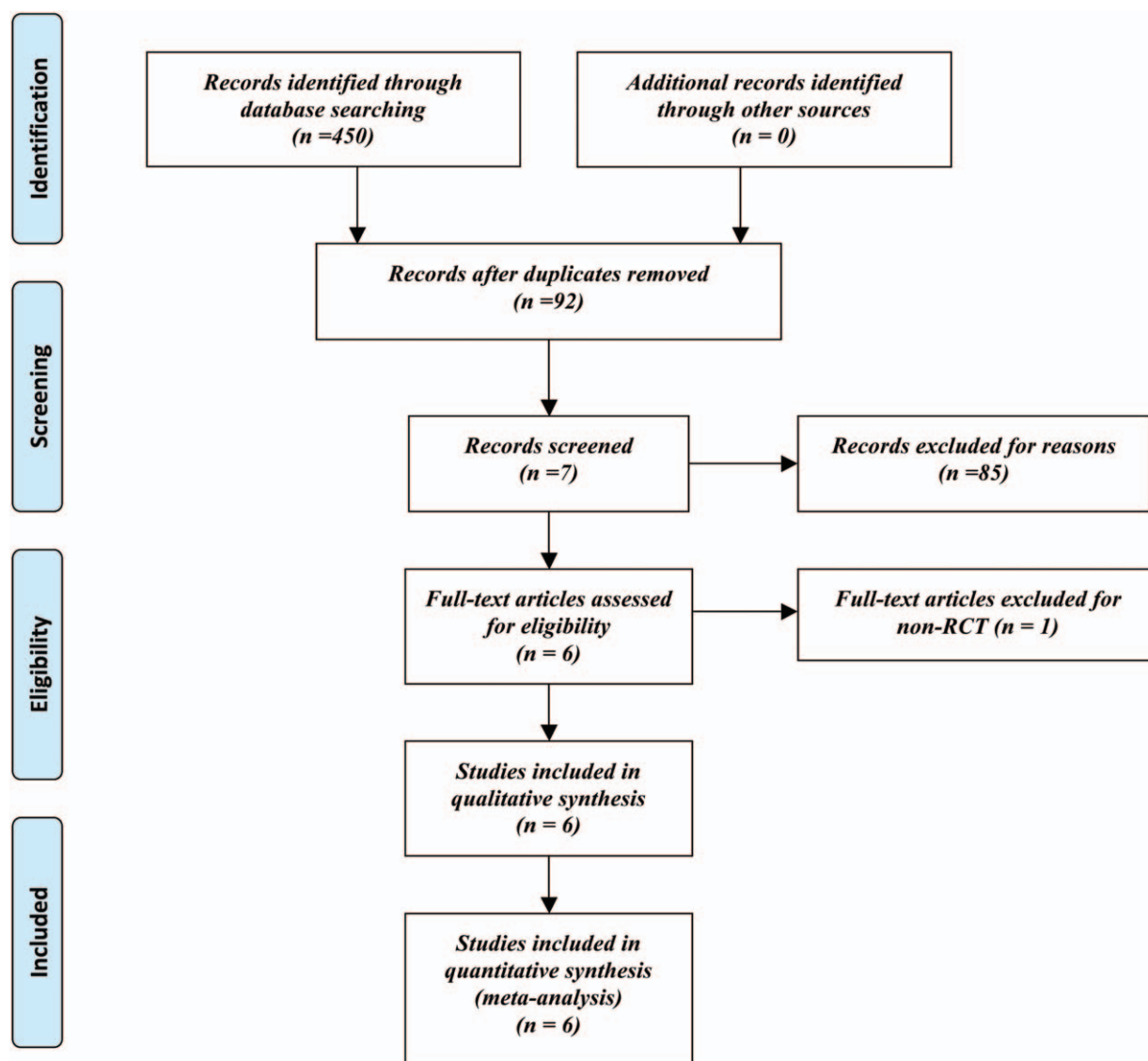


Figure 1. Flow diagram showing details of literature search.

3.4. Primary outcomes

3.4.1. Visual analog scale. All RCTs^[12–15] reported VAS at 12 hours after TKA. There was significant heterogeneity among the articles ($\chi^2=30.50$, $df=5$, $I^2=83.6\%$, $P=.000$) and a random-effects model was adopted for analysis. The pooled results showed that there was a significant difference between dexamethasone versus controls in VAS at 12 hours after TKA (WMD = -0.793 , 95% CI: -1.522 to -0.064 , $P=.033$; Fig. 4). All RCTs^[12–15] showed the outcome of postoperative VAS at 24 hours after TKA. The results showed that there was significant difference between the groups regarding to postoperative VAS at 24 hours after TKA (WMD = -1.215 , 95% CI: -2.109 to -0.321 , $P=.008$; Fig. 4). All studies^[12–15] tested the effect of dexamethasone in postoperative VAS at 48 hours after TKA. A random-effects model was performed. There was significant difference in terms of postoperative VAS at 48 hours after TKA between 2 groups (WMD = -0.705 , 95% CI: -1.283 to -0.126 , $P=.017$; Fig. 4).

3.4.2. Opioid requirements. All RCTs^[12–15] reported opioid requirements at 12 hours after TKA. There was no significant heterogeneity ($\chi^2=2.92$, $df=5$, $I^2=0.0\%$, $P=.712$); therefore, a fixed-effects model was used. The overall pooled results indicated that compared with placebo treatment, dexamethasone can significantly reduce postoperative opioid requirement at 12 hours (WMD = -2.131 , 95% CI: -3.816 to -0.447 , $P=.013$; Fig. 5). Opioid requirements at 24 hours after TKA were documented in all RCTs.^[12–15] A fixed-effects model was adopted because no statistical heterogeneity was detected between the articles analyzed ($\chi^2=1.54$, $df=5$, $I^2=0.0\%$, $P=.909$). This study's meta-analysis indicated that there was no significant difference in terms of opioid requirements at 24 hours after TKA (WMD = -2.192 , 95% CI: -4.484 to 0.099 , $P=.061$; Fig. 5). All RCTs^[12–15] provided opioid requirements at 48 hours postoperatively. A fixed-effects model was used ($\chi^2=2.31$, $df=5$, $I^2=0.0\%$, $P=.805$). There was no significant difference between the groups

Table 1
Trial characteristics.

Author	Country	Study design	Surgical type	Cases (D/P)	Mean age (D/P)	Male patient (D/P)	Dexamethasone group	Control group	Concomitant pain control	Follow-up
Koh (2013)	Korea	RCT	TKA	135/134	72/72	18/15	Intravenous 10 mg dexamethasone 1 h before surgery	Normal saline	PCA	12 mo
Backes (2014)	USA	RCT	TKA	42/37	66/66	9/8	Intravenous dexamethasone 10 mg immediately prior to induction of anesthesia	Normal saline	PCA	6 mo
Ikeuchi (2014)	Japan	RCT	TKA	20/20	77/76	2/4	Periarticular injection of 6.6 mg dexamethasone	None	PCA	3 mo
Xu (2017)	China	RCT	TKA	54/54	64/64	8/9	2 doses of 10 mg intravenous dexamethasone	Isotonic saline	Intravenous opioid	3 mo
Chu (2017)	China	RCT	TKA	20/20	65/65	10/10	Periarticular injection of 10 mg dexamethasone	Normal saline	PCA	4 mo
Liu (2016)	China	RCT	TKA	20/20	67/67	8/7	Periarticular injection of 5 mg dexamethasone	Normal saline	PCA	6 mo

D=dexamethasone, P=placebo, PCA = patient-controlled analgesia, RCT=randomized controlled trial.

with respect to opioid requirements at 48 hours after TKA (WMD = -2.221, 95% CI: -3.427 to -1.016, P = .064; Fig. 5).

3.5. Secondary outcomes

3.5.1. Length of hospitalization. Five RCTs^[12-16] showed the outcome of length of hospitalization after TKA. There was significant heterogeneity between articles ($\chi^2=19.48$, $df=4$, $I^2=79.5\%$, $P=.001$). Meta-analysis revealed that there was no significant difference between the groups regarding to length of a

hospital stay (WMD = -0.067, 95% CI: -0.274 to 0.139, P = .523; Fig. 6).

3.5.2. Adverse effects. Five RCTs^[12-16] reported postoperative adverse effects, including nausea, vomiting, and pruritus. No significant heterogeneity was found across articles, and a fixed-effects model was applied ($\chi^2=6.03$, $df=13$, $I^2=0.0\%$, $P=.945$). The pooled results showed that dexamethasone was associated with a significant reduction in the incidence rate of adverse effects (RD = -0.095, 95% CI: -0.132 to -0.059, P = .000; Fig. 7).

3.5.3. Postoperative complications. Five studies^[12-15,17] showed the postoperative complications, including deep venous thrombosis and pulmonary embolism. No significant heterogeneity was found between article, and a fixed-effects model was applied ($\chi^2=1.51$, $df=9$, $I^2=0.0\%$, $P=.997$). The present meta-analysis indicated that there was no significant difference between groups regarding the risk of postoperative complications (RD = -0.000, 95% CI: -0.117 to 0.016, P = .963; Fig. 8).

3.6. Evidence level and recommendation strengths

Quality evidence for each set of results was evaluated by the GRADE system. The overall evidence was low, which indicated that further research is likely to significantly change confidence in the effect estimate and to change the estimate overall (Table 2).

3.7. Subgroup analysis

Subgroup analysis was performed for the outcomes of VAS and opioid requirements. We excluded the study of Ikeuchi because the dexamethasone was periarticularly injected in post-TKA patients. However, a high degree of heterogeneity still remained across studies (Fig. 9). More RCTs were still required for further investigation.

4. Discussion

In our study, we compared the use of dexamethasone and placebo as TKA pain management methods to determine whether dexamethasone was associated with improved pain relief or increased adverse effects post TKA. Recently, a similar meta-analysis has been published.^[18] However, it also included a retrospective study of TKA. More importantly, our study indicates that dexamethasone is not associated with a reduction of opioid consumption at 24 to 48 hours postoperatively, which was contrary to the previous meta-analysis study mentioned.

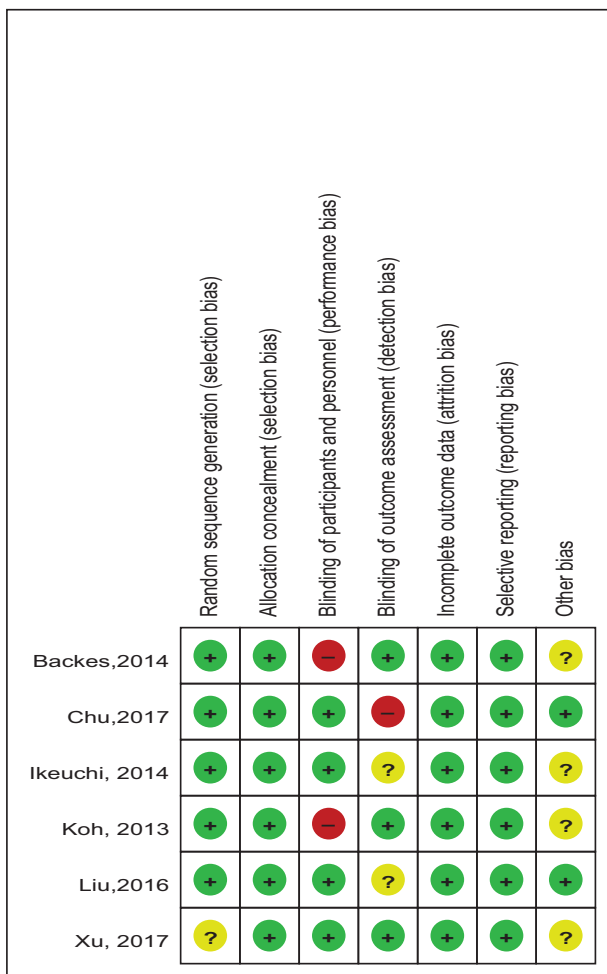


Figure 2. Methodologic quality of the randomized controlled trials.

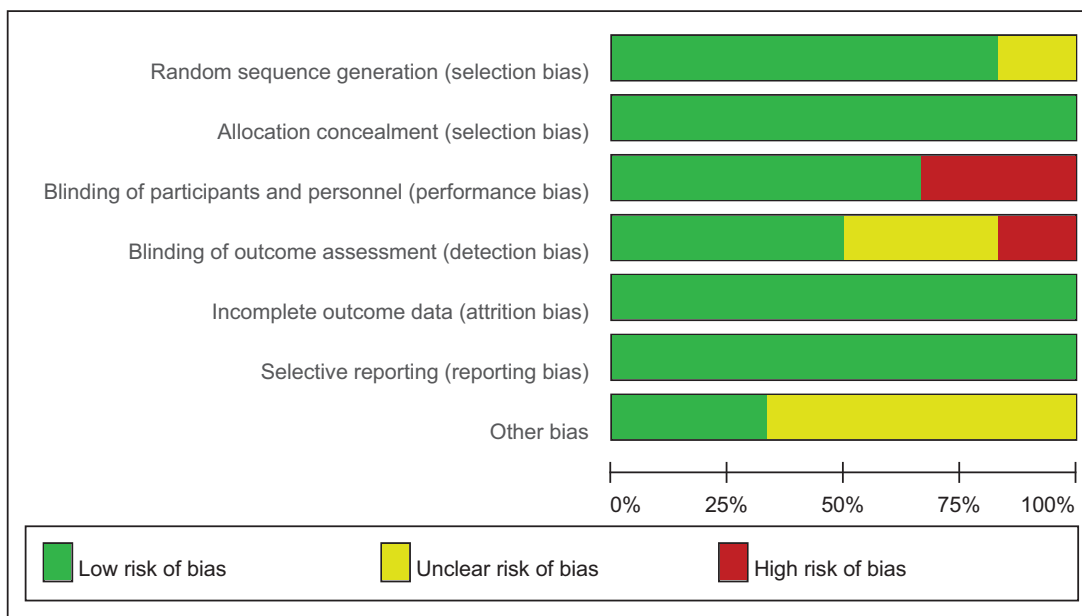


Figure 3. Risk of bias.

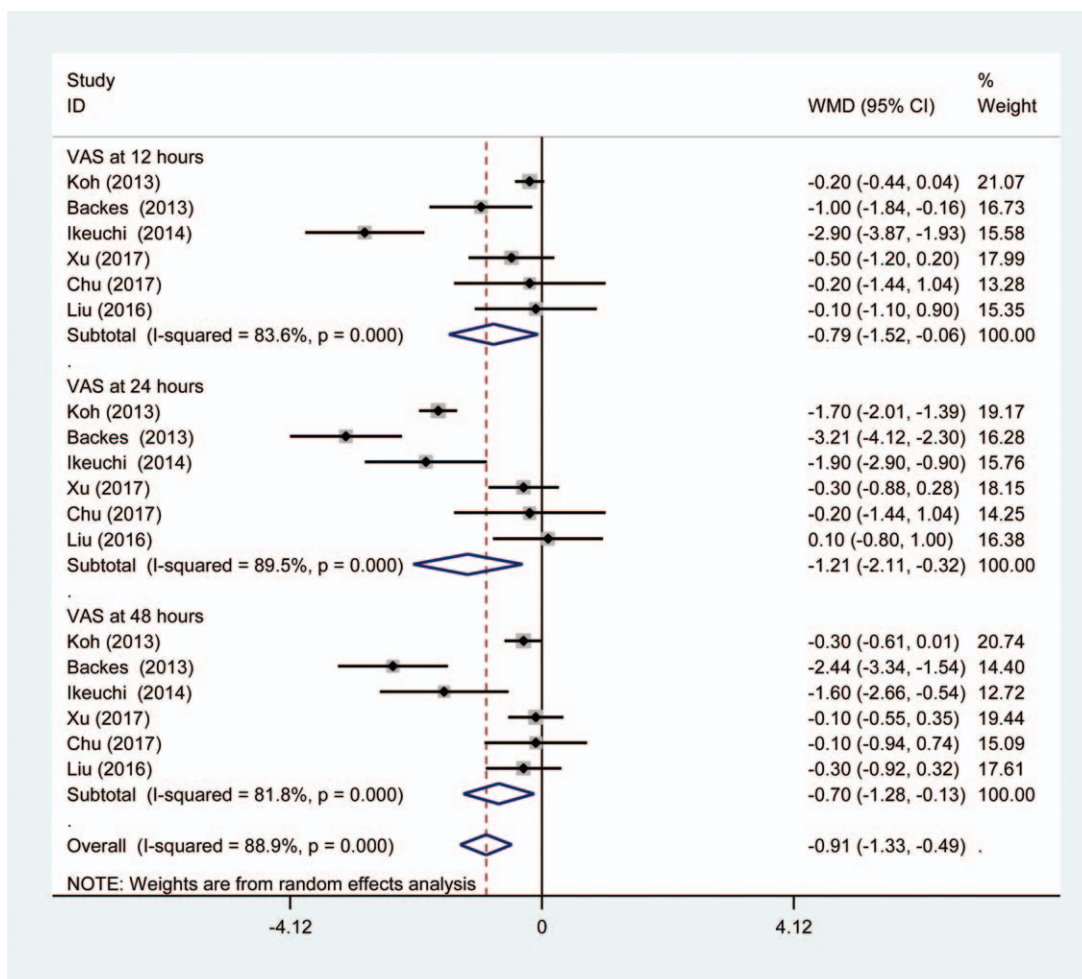


Figure 4. Forest plot diagram showing VAS scores after TKA.

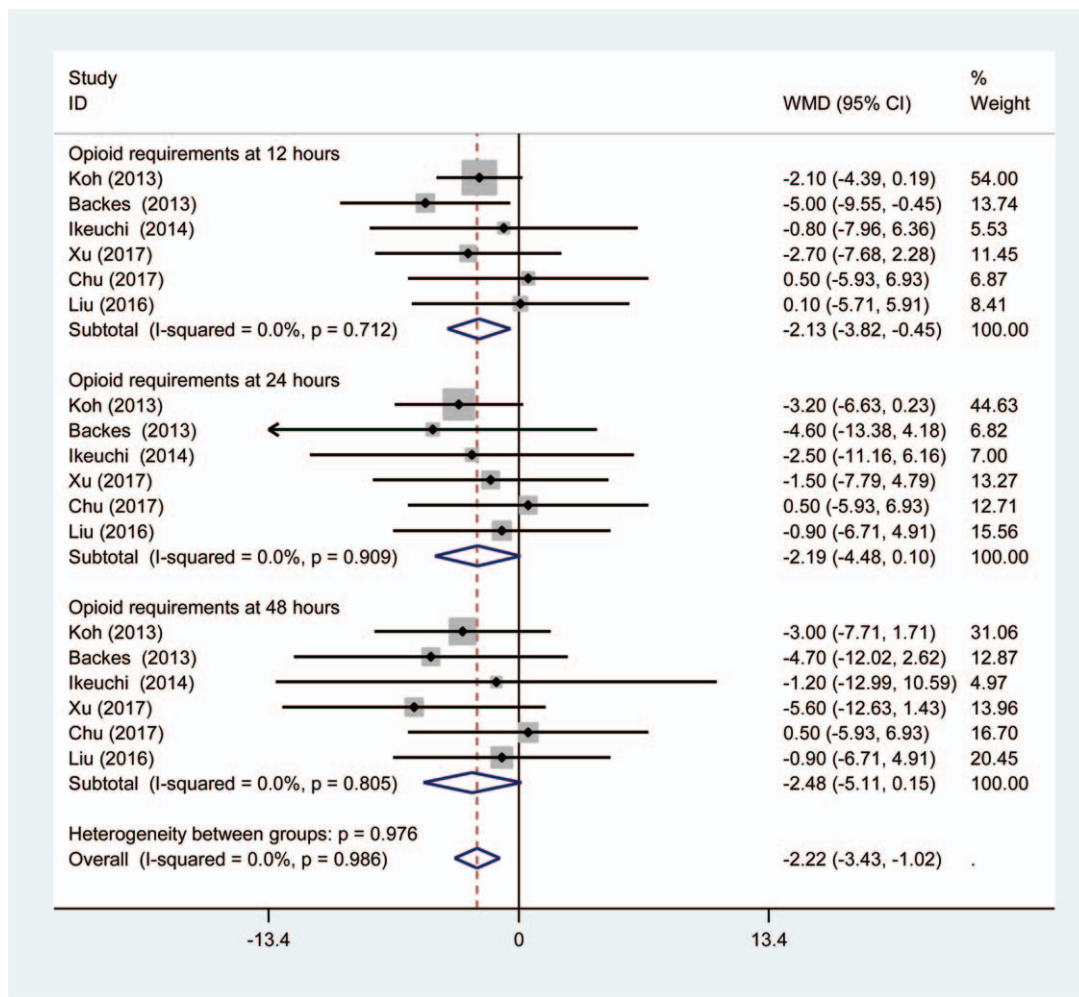


Figure 5. Forest plot diagram showing opioid requirement after TKA.

The most interesting finding of this meta-analysis was that the administration of dexamethasone was associated with significant reductions in postoperative VAS scores compared with controls, in addition to a lower risk of adverse effects. No increased risk of postoperative complications was identified in both groups. However, we found high degree of heterogeneity across studies for the outcome of VAS, while subgroup analysis was conducted. Since the dose of dexamethasone, anesthesia method, and general condition of patients may cause heterogeneity, more RCTs were necessary for further study. The overall evidence quality was low, which means that further research is likely to significantly change confidence in the effect estimate and to change the estimate.

Among aging populations, the occurrence of osteoarthritis has been increasing. It is reported that 52.5 million people suffer from knee osteoarthritis in the United States.^[19] The annual number of primary TKA procedures are expected to reach 3.48 million in the United States by 2030.^[20] Pain management after TKA has become a serious clinical problem. Including inflammatory components, surgical stress response may be of importance for postoperative pain and recovery. Although multimodal regimes were applied, postoperative pain, moderate to severe, still occurred in approximately 50% of TKA patients.^[21] Effective pain control may improve functional outcomes, decrease the length of hospitalization duration, and reduce postoperative

complications. Recently, perioperative use of glucocorticoids has been administered as adjunct to multimodal regimes for pain control and has shown improved outcomes for TKA patients. Mattila et al^[22] reported that administering oral glucocorticoid was associated with a reduction of pain, postoperative nausea, and vomiting following surgical correction of hallux valgus. Bjornsson et al^[23] demonstrated that glucocorticoids could significantly reduce inflammatory factors such as interleukin-6 and C-reactive protein in total hip arthroplasty. Dexamethasone is a long-acting glucocorticoid with potent anti-inflammatory properties. Few articles have evaluated the efficacy and safety of dexamethasone in orthopedic surgery. Therefore, due to the limited number of published studies concerning the clinical use of dexamethasone for pain management post-TKA remains a controversy. In our study, postoperative pain was assessed using a 10-point VAS scale. This meta-analysis revealed that administration of dexamethasone could significantly reduce postoperative pain at 12, 24, and 48 hours after TKA.

Opioid treatment was widely applied as pain management after major orthopedic surgery.^[24] PCA with opioids was a method of allowing a person in pain to administer one's own pain relief, which was highly popular, convenient, and safe. Also, the analgesic effect of additional opioid use provided a long postoperative period without any pain experienced by the

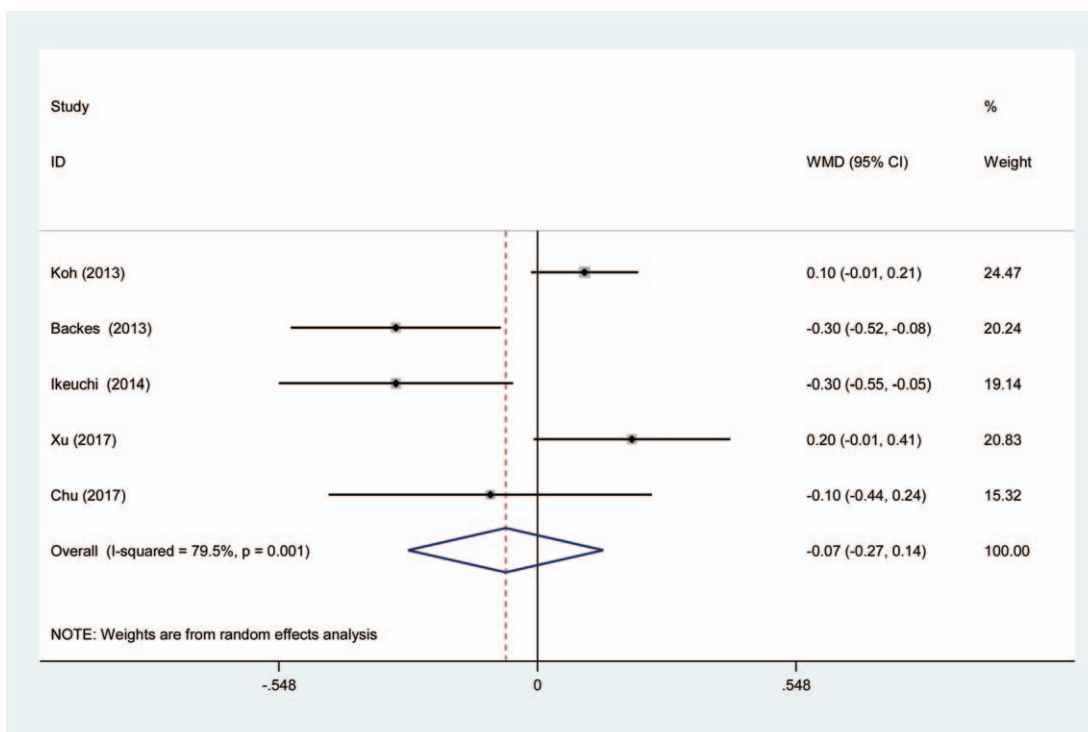


Figure 6. Forest plot diagram showing length of a hospital stay.

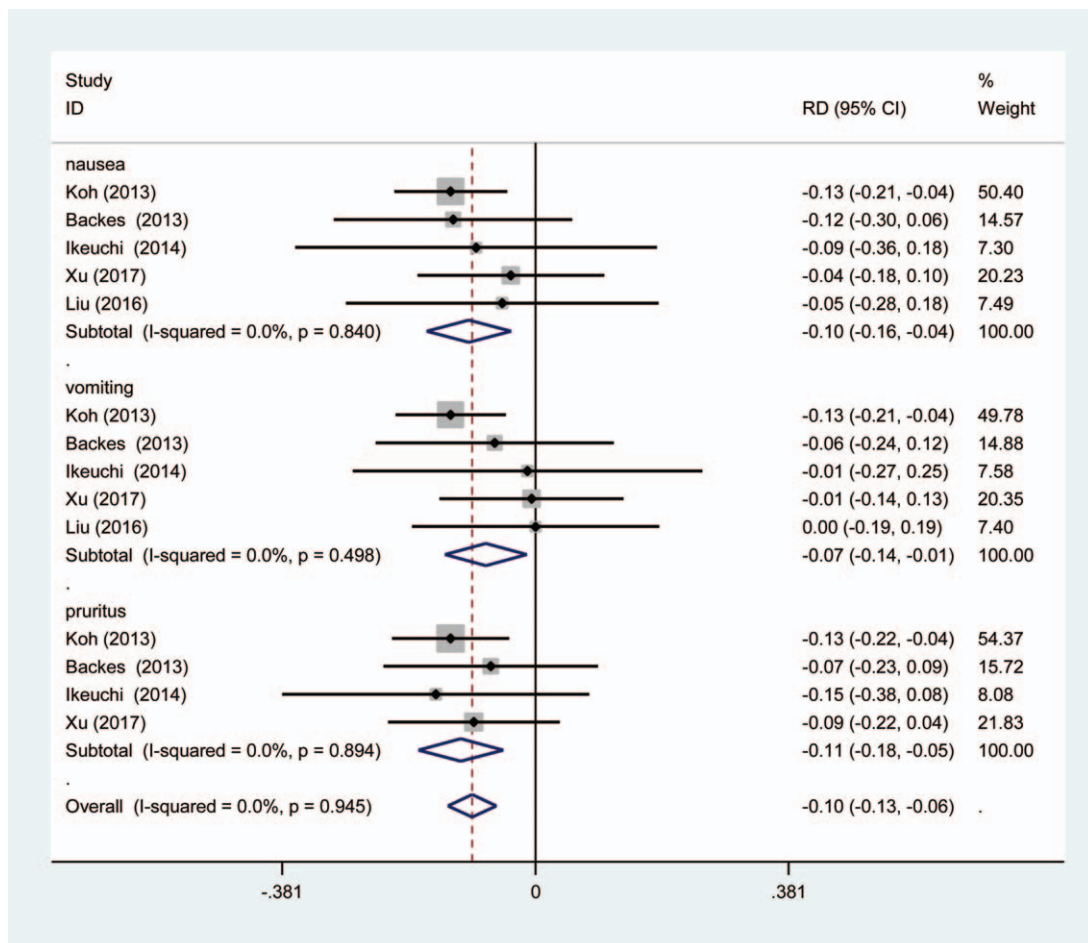


Figure 7. Forest plot diagram showing the risk of opioid-related adverse effects.

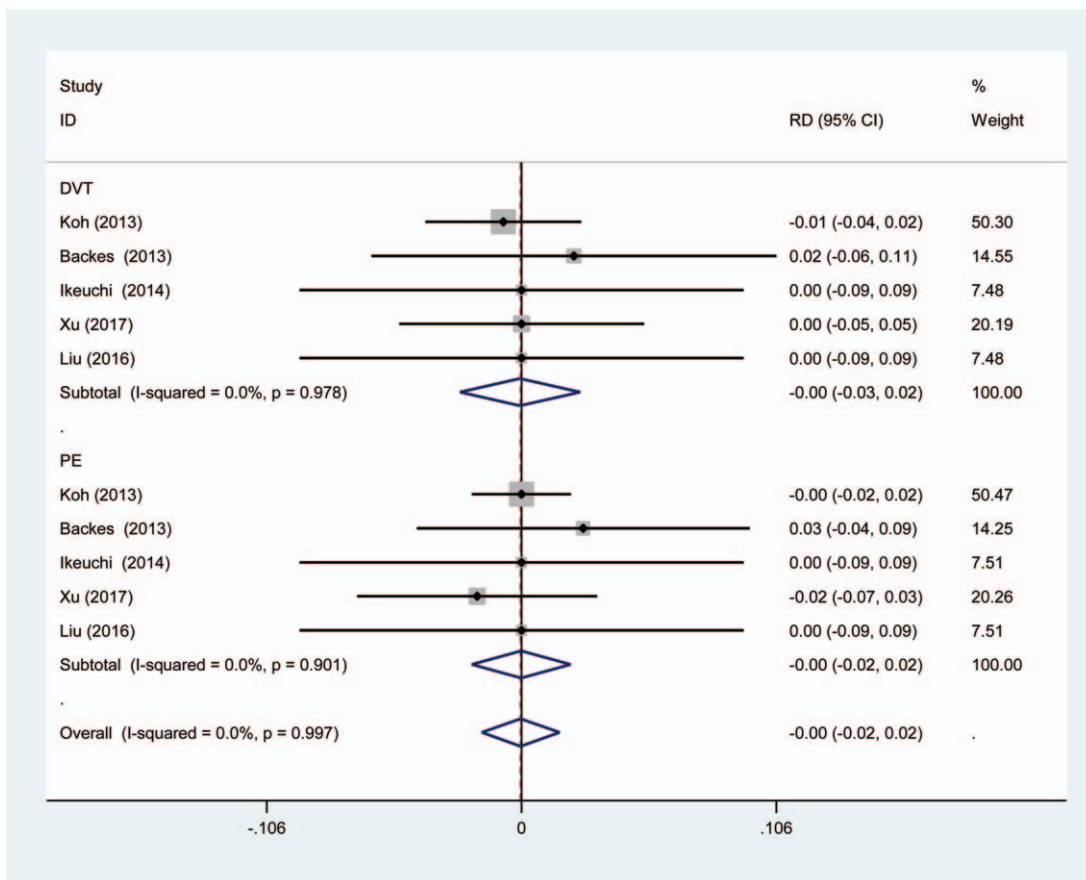


Figure 8. Forest plot diagram showing the risk of postoperative complications.

patients. However, previous studies have indicated that opioids were associated with many adverse effects, including gastrointestinal events, headache, pruritus, consumption, and respiratory depression.^[25-27] Drug dependence as a result of prolonged

opioid usage is a major concern for surgeons and anesthesiologists. Reducing narcotic consumption is crucial to enhance early mobilization and reduce postoperative complications. Previous articles have showed that the opioid-sparing effect was enhanced

Table 2

The Grading of Recommendations, Assessment, Development, and Evaluation evidence quality for main outcome.

No of studies	Design	Limitations	Quality assessment			No of patients		Effect	Quality	Importance
			Inconsistency	Indirectness	Imprecision	Dexamethasone groups	Control groups			
VAS at 12 h										
6	RCT	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	291	285	WMD = -0.793, 95% CI: -1.522 to -0.064	Low	Critical
VAS at 24 h										
6	RCT	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	291	285	WMD = -1.215, 95% CI: -2.109 to -0.321	Low	Critical
VAS at 48 h										
6	RCT	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	291	285	WMD = -0.705, 95% CI: -1.283 to -0.126	Low	Critical
Opioid requirements at 12 h										
6	RCT	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	291	285	WMD = -2.131, 95% CI: -3.816 to -0.447	Low	Critical
Opioid requirements at 24 h										
6	RCT	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	291	285	WMD = -2.192, 95% CI: -4.484 to 0.099	Low	Critical
Opioid requirements at 48 h										
6	RCT	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	291	285	WMD = -2.221, 95% CI: -3.427 to -1.016	Low	Critical

CI = confidence interval, RCT = randomized controlled trial, VAS = visual analog scale, WMD = weighted mean difference.

Variables	Studies (n)	Patients (n)	I ²	Heterogeneity P-value (I ²)	
VAS score at 12 hours			5	840	
Intravenous of dexamethasone	(455	% .011	-0.283[-0.501, -0.064]	0.165 (44.6%)
VAS score at 24 hours					
Intravenous of dexamethasone	(455	% .000	-1.539[-1.1, -1.272]	0.000 (93.7%)
VAS score at 48 hours					
Intravenous of dexamethasone	(455	% .001	-0.4029[-0.648, -0.155]	0.000 (90.9%)
Length of a hospital stay					
Intravenous of dexamethasone	(455	% .260	0.0529[0.0, 0.143]	0.002 (83.7%)

Figure 9. Results of subgroup analysis.

by the addition of dexamethasone to the multimodal analgesic regimen.^[28,29] Currently, the use of dexamethasone for decreasing narcotic use after TKA remains controversial. Meta-analysis could strengthen statistical power and reach reliable conclusions about its efficacy and safety. The present meta-analysis has indicated that use of dexamethasone could significantly decrease the requirements for opioid administering at 12 hours post-TKA. However, no significant difference was found in opioid consumption at 24 and 48 hours after TKA, which is contrary to previous meta-analysis by Fan et al.^[18] Further investigation is still in demand as only 6 RCTs have been included.

Gastrointestinal discomfort, such as nausea and vomiting, is common adverse effects postoperatively. Our study showed that dexamethasone treatment could significantly decrease postoperative nausea and vomiting. This is because anti-inflammation effect made it possible to lessen the postoperative rise of serum markers of systemic inflammation; dexamethasone was associated with a reduced opioid consumption at 12 hours after TKA, which could decrease the adverse effects. No significant difference between groups in terms of the risk of thrombotic complications was found.

The limitations of this study were as follows:

Only 6 RCTs were included and the sample sizes were small. If more studies had been contained, the statistical efficacy of our analysis would have increased.

Subgroup analysis was performed, but there was still significant heterogeneity among studies. Numerous factors may cause heterogeneity, including the doses of dexamethasone, characters of included patients, surgical approach, and postoperative medication. Overall, 6 studies were included in our study. Further investigation is still needed to minimize the heterogeneity and enhance statistical power.

Short-term follow-up caused the underestimation of complications.

Publication bias was unavoidable.

5. Conclusion

Use of dexamethasone could result in a significant reduction in postoperative pain while minimizing adverse effects after TKA. Based on the current evidence available, more RCTs are needed for further investigation.

Author contributions

Hao Jiang conceived of the design of the study. Huihai Jing and Liping Ma performed and collected the data. Guanghong Zhou

finished the manuscript. All authors read and approved the final manuscript.

Conceptualization: Hao Jiang.

Data curation: Liping Ma, Hao Jiang.

Formal analysis: Junhai Jing.

Writing – original draft: Guanghong Zhou.

References

- Canovas F, Dagneaux L. Quality of life after total knee arthroplasty. *Orthop Traumatol Surg Res* 2017.
- Sinatra RS, Torres J, Bustos AM. Pain management after major orthopaedic surgery: current strategies and new concepts. *J Am Acad Orthop Surg* 2002;10:117–29.
- Runge C, Borglum J, Jensen JM, et al. The analgesic effect of obturator nerve block added to a femoral triangle block after total knee arthroplasty: a randomized controlled trial. *Reg Anesth Pain Med* 2016;41:445–51.
- Thorsell M, Holst P, Hyldahl HC, et al. Pain control after total knee arthroplasty: a prospective study comparing local infiltration anesthesia and epidural anesthesia. *Orthopedics* 2010;33:75–80.
- Lee RM, Lim Tey JB, Chua NH. Postoperative pain control for total knee arthroplasty: continuous femoral nerve block versus intravenous patient controlled analgesia. *Anesth Pain Med* 2012;1:239–42.
- Dysart S, Snyder MA, Mont MA. A randomized, multicenter, double-blind study of local infiltration analgesia with liposomal bupivacaine for postsurgical pain following total knee arthroplasty: rationale and design of the pillar trial. *Surg Technol Int* 2016;30:261–7.
- Lewis C, Gunta K, Mitchell K, et al. Effectiveness of multimodal pain management protocol in total knee arthroplasty patients. *Orthop Nurs* 2012;31:153–9.
- Meftah M, Wong AC, Nawabi DH, et al. Pain management after total knee arthroplasty using a multimodal approach. *Orthopedics* 2012;35:e660–4.
- Mathiesen O, Jacobsen LS, Holm HE, et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. *Br J Anaesth* 2008;101:535–41.
- Samona J, Cook C, Krupa K, et al. Effect of intraoperative dexamethasone on pain scores and narcotic consumption in patients undergoing total knee arthroplasty. *Orthop Surg* 2017;9:110–4.
- Lei YT, Xu B, Xie XW, et al. The efficacy and safety of two low-dose perioperative dexamethasone on pain and recovery following total hip arthroplasty: a randomized controlled trial. *Int Orthop* 2017.
- Backes JR, Bentley JC, Politi JR, et al. Dexamethasone reduces length of hospitalization and improves postoperative pain and nausea after total joint arthroplasty: a prospective, randomized controlled trial. *J Arthroplasty* 2013;28:11–7.
- Koh IJ, Chang CB, Lee JH, et al. Preemptive low-dose dexamethasone reduces postoperative emesis and pain after TKA: a randomized controlled study. *Clin Orthop Relat Res* 2013;471:3010–20.
- Ikeuchi M, Kamimoto Y, Izumi M, et al. Effects of dexamethasone on local infiltration analgesia in total knee arthroplasty: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2014;22:1638–43.
- Xu B, Ma J, Huang Q, et al. Two doses of low-dose perioperative dexamethasone improve the clinical outcome after total knee arthro-

- plasty: a randomized controlled study. *Knee Surg Sports Traumatol Arthrosc* 2017;1–8.
- [16] Chu W, Li WZ. Effect of dexamethasone used in periarticular infiltration analgesia for total knee arthroplast. *J Clin Orthop* 2017;20:568–71.
- [17] Liu DM, Zhou XS. A study of dexamethasone used in periarticular infiltration analgesia for total knee arthroplasty. *Chin J bone Joint Injury* 2016;31:1161–3.
- [18] Fan Z, Ma J, Kuang M, et al. The efficacy of dexamethasone reducing postoperative pain and emesis after total knee arthroplasty: a systematic review and meta-analysis. *Int J Surg* 2018;52:149–55.
- [19] Centers for Disease Control and Prevention. Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2012–2014. *MMWR Morb Mortal Wkly Rep* 2013;62:869–73.
- [20] Delanois RE, Mistry JB, Gwam CU, et al. Current epidemiology of revision total knee arthroplasty in the United States. *J Arthroplasty* 2017;32:2663–8.
- [21] Elmallah RK, Chughtai M, Khlopas A, et al. Pain control in total knee arthroplasty. *J Knee Surg* 2018;31:504–13.
- [22] Mattila K, Kontinen VK, Kalso E, et al. Dexamethasone decreases oxycodone consumption following osteotomy of the first metatarsal bone: a randomized controlled trial in day surgery. *Acta Anaesthesiol Scand* 2010;54:268–76.
- [23] Bjornsson GL, Thorsteinsson L, Gudmundsson KO, et al. Inflammatory cytokines in relation to adrenal response following total hip replacement. *Scand J Immunol* 2007;65:99–105.
- [24] Palmer PP, Miller RD. Current and developing methods of patient-controlled analgesia. *Anesthesiol Clin* 2010;28:587–99.
- [25] Kane-Gill SL, Rubin EC, Smithburger PL, et al. The cost of opioid-related adverse drug events. *J Pain Palliat Care Pharmacother* 2014;28:282–93.
- [26] Funk RD, Hilliard P, Ramachandran SK. Perioperative opioid usage: avoiding adverse effects. *Plast Reconstr Surg* 2014;134:32S–9S.
- [27] Redan JA, Wells T, Reeder S, et al. Reducing opioid adverse events: a safe way to improve outcomes. *Surg Technol Int* 2016;28:101–9.
- [28] Lim SH, Jang EH, Kim MH, et al. Analgesic effect of preoperative versus intraoperative dexamethasone after laparoscopic cholecystectomy with multimodal analgesia. *Korean J Anesthesiol* 2011;61:315–9.
- [29] Rasmussen ML, Mathiesen O, Dierking G, et al. Multimodal analgesia with gabapentin, ketamine and dexamethasone in combination with paracetamol and ketorolac after hip arthroplasty: a preliminary study. *Eur J Anaesthesiol* 2010;27:324–30.