REVIEW

acta orthopaedica belgica, 2024, 90, 335-342

doi.org/10.52628/90.2.11791

Perioperative systemic corticosteroids in primary unilateral total knee arthroplasty: a systematic review

J. C. VAN EGMOND[1], F. W. VAN DE GRAAF[2], C. D. NIEHOT[3], H. VERBURG[1], N. M.C. MATHIJSSEN[1]

[1]Department of Orthopedics, Reinier Haga Orthopedisch Centrum, Toneellaan 2, 2725 NA Zoetermeer, the Netherlands; [2]Department of Surgery, Erasmus University Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands; [3]Medical library, Erasmus University Medical Center, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.

Correspondence at: J.C. van Egmond, Reinier Haga Orthopedisch Centrum, Toneellaan 2, 2725 NA Zoetermeer, the Netherlands.
Phone: +316 - 232 700 73 - E-mail: j.vanegmond@rhoc.nl

Main reasons for prolonged hospital stay after total knee arthroplasty (TKA) are postoperative nausea and vomiting (PONV) and pain. Having a positive effect on both PONV and pain, perioperative administration of corticosteroids might improve rehabilitation and reduce length of hospital stay (LOS) after TKA. Aim of this review is to determine the effect of different corticosteroid dosages on PONV, pain, and LOS in TKA.

A systematic search for articles comparing dosage effects of corticosteroids regarding PONV, pain, and LOS after primary unilateral TKA was conducted using EMBASE, PubMed publisher, MEDLINE, Cochrane, Google scholar, and Web-of-Science for articles published from inception to March 17, 2022.

16 studies were included involving 2352 TKA procedures. Most studies showed reduced pain scores in corticosteroid groups and some described better pain reduction in high-dose groups. All studies showed reduced PONV in the corticosteroid groups. LOS was similar in most studies comparing placebo and perioperative corticosteroids. Only one study reported increased infection rates and intramuscular venous thrombosis in the corticosteroid group.

Concluding, current literature on corticosteroids use in TKA is highly variable in type, dosage, and timing of administering medication. Overall, corticosteroids mostly reduce pain and PONV with limited effects on LOS after TKA. Only minimal statistically significant and clinically relevant benefits were found in perioperative high-dose corticosteroids compared to low-dose. Given the short follow-up in most studies, it is not possible to evaluate safety of high-dose corticosteroids.

Keywords: Total Knee Arthroplasty, Dexamethasone, Fast-track, Steroids, Enhanced recovery, Systematic review.

INTRODUCTION

During the last decades fast-track protocols have been implemented to optimize rehabilitation after total knee arthroplasty (TKA). As a result, length of hospital stay (LOS) has been decreased and even TKA in an outpatient setting is feasible in selected patients[1]. However, optimizing analgesia and rehabilitation after TKA is challenging[2].

Main reasons for prolonged hospital admission after TKA are postoperative nausea and vomiting (PONV), orthostatic intolerance, fatigue, and pain[3,4]. These symptoms are the result of multiple factors including the surgical stress respons[1]. Adequately managing of these symptoms will lead to reduced LOS, improved patient satisfaction, and will further optimize fast-track rehabilitation[1,6-8].

One of the most potent pharmacological interventions in reducing the surgical stress response are corticosteroids[7,9]. Corticosteroids have an anti-inflammatory effect by inhibiting the cyclooxygenase-2 (COX-2) signaling pathway which lead to a reduced local and systemic inflammatory response[10]. Corticosteroids have a proven beneficial effect on PONV and pain[11-13]. Therefore, interest has been raised for the use of corticosteroids in arthroplasty surgery.

However, despite the promising results of corticosteroids on pain and PONV, there are still concerns regarding the possible side effects of corticosteroids, including hyperglycemia, gastrointestinal hemorrhage, and particularly the risk of infection, preventing further implementation in daily clinical use. Moreover, uncertainty remain concerning the optimal timing, frequency, and dosage of corticosteroids[12].

We hypothesized that the effect of corticosteroids is dose-depended, therefore high-dose of corticosteroids would improve early recovery and reduce LOS, pain, and PONV to a larger extend than low-dose corticosteroids in primary unilateral TKA. Consequently, high-dose corticosteroids might also have more side effects compared to low-dose.

The purpose of this systematic review was investigating the dose-effect relationship of perioperative systemic corticosteroids administration with PONV, pain, and LOS after primary unilateral TKA, as well as the occurrence of adverse events.

MATERIALS AND METHODS

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/prospero), prior to the start of the systematic review, with registration number CRD42021235773. All data were handled according to the Helsinki Declaration (version 64, October 2013).

Search strategy

This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and the PRISMA-S extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews[14,15]. A systematic search was developed in Embase.com and then translated to other databases. The search was carried out on March 17, 2022 in the databases Embase.com, MEDLINE ALL via Ovid, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials via Wiley. Additionally, a search was performed in Google Scholar from which the 200 most relevant references were downloaded using the software Publish or Perish. Detailed search strings are presented in appendix 1.

The following elements were used: 1) total knee arthroplasty, 2) corticosteroids, and 3) perioperative.

The searches in EMBASE, MEDLINE, and Web of Science were limited to exclude conference papers and animal-only articles. The results were deduplicated using the Bramer method[16]. No study registries were searched, but Cochrane Central retrieves the contents of ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform.

Inclusion and exclusion criteria were defined a priori. Studies comparing dose-effect relationship of corticosteroids and placebo vs. corticosteroids (dexamethasone, methylprednisolone, hydrocortisone, betamethasone) regarding PONV, pain, and LOS after primary unilateral TKA were included. Manuscripts were required to report one or more of the following outcomes: LOS, pain, PONV, or adverse events. Non-English written articles were excluded. Further exclusion criteria were local or intra-articular injection of corticosteroids, revision arthroplasty, unicompartmental knee arthroplasty, and bilateral TKA.

Article selection and data extraction

Potential eligible articles were reviewed independently by two investigators (JE and FG) according to pre-agreed criteria. Discrepancies were resolved by consensus or by consulting a third reviewer (NM). Finally, citation tracking was performed by manually screening the reference lists of eligible studies by one reviewer (JE). No authors were contacted to provide full-text articles, since all included articles were obtained full-text.

The following data were extracted from the included studies: number of participants, duration of follow-up, type of corticosteroid used, corticosteroid dosages used, LOS, postoperative pain, PONV, and adverse events.

Risk of bias assessment

The Cochrane Collaborations Risk of Bias Tool 2 was used to assess the methodological quality of the included studies[17]. All domains were independently assessed for possible bias by two reviewers (JE and FG).

Data analysis

Quantitative synthesis was not realized due to the presence of conceptual heterogeneity among the included studies. A narrative synthesis was therefore performed.

RESULTS

The initial search resulted in 3134 articles. After removal of duplicate studies, 1879 were screened based on title and abstract, resulting in 31 eligible studies for full-text review. Finally, 16 articles were included for analysis[18-33]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for systematic reviews is presented in Fig. 1[34].

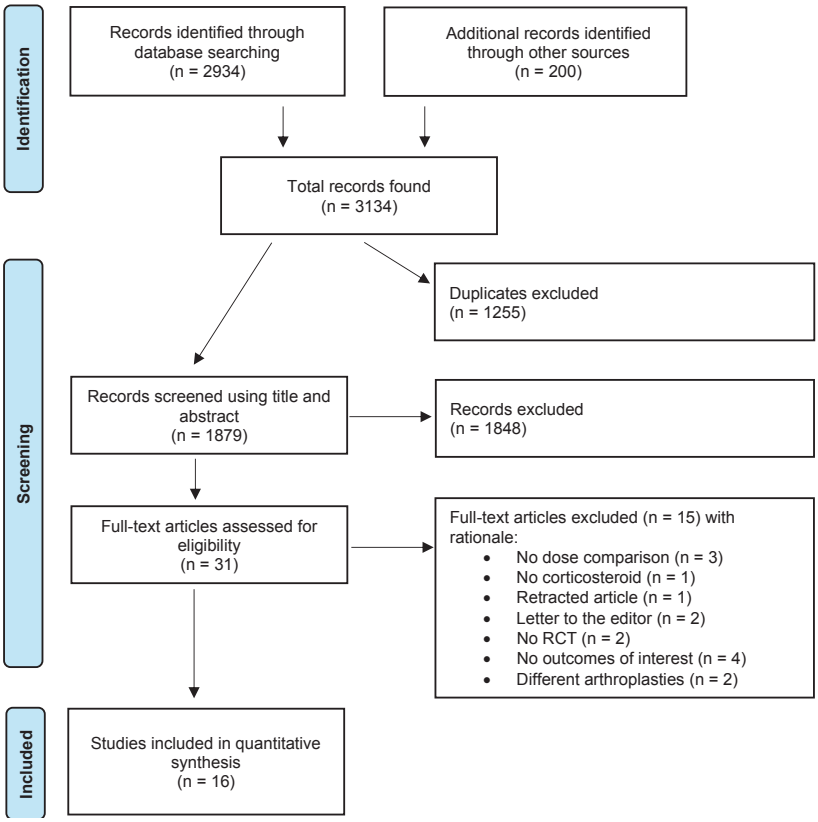

Fig. 1. — PRISMA flowchart.

Citation tracking was performed by manually screening the reference lists of eligible studies and no additional studies were identified as relevant.

Description of included studies

The 16 included studies contained 2352 TKA. Table 1 presents an overview of all included studies. In two studies both TKA and THA were included of which we only analyzed TKA outcomes in this systematic review[18,21]. Pain was reported in all studies,[18-33] PONV in 12 studies,[18,21-26,28,30-33] and LOS in 11 studies[18,20,21,26-33]. Adverse events were reported in all studies with varied length of follow-up from 3 days up to 1 year[18-33].

All, except one study, included a placebo group and compared placebo to one or two intervention groups[18-28,30-33]. In nine studies low-dose and high-dose corticosteroids were compared[18,19,22,23,25,26,29,31,33]. In 12 studies dexamethasone was used in the intervention group[18,19,21-25,29-33]. Three studies used methylprednisolone[20,27,28] and one study used hydrocortisone[26]. Since all corticosteroids have their own specific potential, the equivalent dose of dexamethasone was calculated to assist in the interpretation of the results. The following calculation was used: methylprednisolone 125mg has a dose equivalent of 25mg dexamethasone and hydrocortisone 100mg has a dose equivalent of 4mg dexamethasone.

Primary outcomes

Pain

All studies utilized a visual analogue scale (VAS) to evaluate pain scores. Moreover, some studies used morphine consumption as outcome measurement. In 14 studies a reduction of postoperative pain was found[18-20,22-26,28-33]. In two studies, Lindberg et al. and Dissanayake et al., no difference in postoperative pain was found between placebo and corticosteroids[21,27]. In six of the nine studies which compared high-dose and low-dose corticosteroids, a better pain relief was found in high-dose corticosteroids groups[19,22,26,29,31,32].

PONV

Various ways were used to report PONV in different studies. Most studies used self-reported outcomes. In 12 studies PONV was analyzed[18,21-26,28,30-33]. In all studies reduced PONV was reported in the intervention groups. In one study, the group receiving high-dose corticosteroid had significantly less PONV

Table I. — Detailed description of included studies.

Author, Year	Surgery	Patients	Control	Intervention(s)	Primary outcome	Follow-up
Backes et al., 2013[18]	TKA/THA	73/47	Placebo	10mg dexamethasone i.v. pre-operative 10mg dexamethasone i.v. pre- and postoperative	LOS, length of ambulation, ROM, cumulative hydromorphone PCA use, daily hydrocodone consumption, patient pain scores, daily rescue anti-emetic consumption, and nausea/ vomiting scores	6 months
Chan et al., 2020[19]	TKA	138	Placebo	16mg dexamethasone i.v.	postoperative pain score	1 year
Cheng et al., 2019[20]	TKA	60	Placebo	125mg methylprednisolone i.v.	rest pain and pain on movement	1 year
Dissanayake et al., 2018[21]	TKA/THA	81/83	Placebo	8mg dexamethasone i.v. pre- and postoperative	length of stay	6 weeks
Gasbjerg et al., 2022[22]	TKA	485	Placebo	24mg dexamethasone preoperative 24mg dexamethasone pre- and postoperative	total opioid consumption in milligrams of intravenous morphine equivalents 0-48 hours after the end of surgery.	90 days
Kim et al., 2020[23]	TKA	184	Placebo	10mg dexamethasone i.v. pre-operative 0.1mg/kg^{-1} dexamethasone i.v. preoperative 0.2mg/kg^{-1} dexamethasone i.v. preoperative	pain and nausea visual analogue scale	1 week
Koh et al., 2013[24]	TKA	269	Placebo	10mg dexamethasone	incidence of PONV	1 year
Lei et al., 2022[25]	TKA	192	Placebo	20mg dexamethasone i.v. pre-operative 10mg dexamethasone i.v. pre- and postoperative	postoperative pain level	3 months
Li et al., 2019[26]	TKA	112	Placebo	100mg hydrocortisone i.v. pre- and postoperative 100mg hydrocortisone i.v. pre- and 4x postoperative	level of IL-6 and CRP at 12 hours, 24 hours, 48 hours, and 72 hours after operation	30 days
Lindberg et al., 2017[27]	TKA	70	Placebo	125mg methylprednisolone i.v.	change in knee-extension strength from baseline to 48 hours postoperatively	2 days
Lunn et al., 2011[28]	TKA	48	Placebo	125mg methylprednisolone i.v.	pain during walking 24 hours after surgery	30 days
Nielsen et al., 2022[29]	TKA	88	-	0.3mg/kg^{-1} dexamethasone i.v. preoperative 1.0mg/kg^{-1} dexamethasone i.v. preoperative	proportion of patients experiencing moderate-to-severe pain (VAS >30) during a 5 m walk 24 h postoperatively	90 days
Tammachote et al., 2020[30]	TKA	100	Placebo	0.15mg/kg^{-1} dexamethasone i.v. preoperative	pain level determined by a visual analog scale, and the amount of morphine consumption (mg) 48 hours post-TKA	12 weeks
Wu et al., 2018[31]	TKA	150	Placebo	10mg dexamethasone i.v. pre-operative 10mg dexamethasone i.v. pre- and postoperative	n.a.	3 months
Xu B. et al., 2018[32]	TKA	120	Placebo	10mg dexamethasone i.v. pre- and postoperative	n.a.	3 days
Xu H. et al., 2018[133]	TKA	182	Placebo	20mg dexamethasone i.v. pre-operative 20mg dexamethasone i.v. preoperative and 2x 10mg dexamethasone postoperative	n.a.	3 months

Abbreviations: TKA total knee arthroplasty, THA total hip arthroplasty, LOS length of hospital stay, ROM range of motion, PONV postoperative nausea and vomiting, n.a. not applicable; Dose equivalents: 125mg methylprednisolone = 25mg dexamethasone, 100mg hydrocortisone = 4mg dexamethasone.

compared to low-dose and placebo[31]. In two studies no difference was found between dosage and effect of corticosteroids on PONV[25,33]. Although dexamethasone is a first-line anti-emetic agent, no difference was found between dexamethasone and other steroids in reduction of PONV.

Length of stay

In two studies LOS was a primary outcome, in which Backes et al. found a dose depended significant reduction of LOS[18], and Dissanayake et al. found no difference between placebo and corticosteroid groups[21]. In the study of Li et al. a significant reduced LOS was described; however, this was not dose depended[26]. In the other eight studies reporting LOS no difference was detected[20,27-33].

Secondary outcome

Adverse events

Length of follow-up varied widely between the included studies with follow-up periods ranging from 3 days up to 1 year. No adverse events were found for gastrointestinal bleeding. In one study, increased infection rates and intramuscular venous thrombosis were found in the corticosteroid groups[31]. In seven studies blood glucose levels were reported[18,19,21,23,25,26,33] and in three of these seven studies increased blood glucose levels were found postoperative in the corticosteroid group[18,19,21].

Risk of bias assessment

The results for the assessment of risk of bias can be found in Figure 2. Three studies had an overall low risk of bias[22,27,29]. Twelve studies (75%) were assessed with a moderate risk of bias[18-20,23-26,28,30,33]. This was mainly due to a lack of prespecified outcomes and analysis plan, Cochrane Risk of Bias domain[5]. One study was rated as high risk of bias for excluding 52 of the 218 patients after randomization[21].

DISCUSSION

In this systematic review we provided a critical analysis of perioperative intravenous corticosteroid use in primary unilateral TKA in relation to LOS, postoperative pain, PONV, and adverse events. In general, studies showed that corticosteroids reduce mostly pain and PONV after primary TKA with limited effects on LOS. Furthermore, only minimal statistically significant and clinically relevant benefits were found in perioperative high-dose corticosteroids compared to low-dose as well as in multiple doses compared to single preoperative dose.

In the past years, a number of systematic reviews regarding the perioperative use of systemic corticosteroid administration in arthroplasty have been published[2,35,36]. Most of these systematic reviews included RCTs with both THA and TKA and analyzed these as one group[35,36]. However, it is undesirable to investigate these two different types of arthroplasty

Fig. 2. — Cochrane traffic light risk of bias plot by individual domains for all included studies.

as a single group considering the fact that recovery for THA and TKA are clearly different[37]. Sufficient analgesic treatment is challenging in TKA[2] and functional improvement is less and more slowly in the first year after TKA compared to THA[37]. Therefore, and in contrast to other systematic reviews, we included only studies providing separate data for TKA.

Risk of bias assessment of the included studies was generally moderate, which is in line with previous systematic reviews[2,35]. The quality of this systematic review is naturally limited by the included studies. Despite methodological impairment, limited follow-up impedes strong conclusions regarding implementation of high-dose corticosteroids in fast-track arthroplasty recovery.

The use of corticosteroids in arthroplasty has two major concerns

First is the presumed high risk of periprosthetic joint infections due to the immunosuppressive effects of corticosteroids. As stated in the article of Backes et al. the absence of proof does not prove absence of risk[18]. Recent literature showed no increased infection risk in low-dose and high-dose corticosteroids[38-40]. One of these studies contained over 18 thousand arthroplasties with low-dose corticosteroids and showed no increased infection risk[38]. Furthermore, high-dose corticosteroids in arthroplasty does not result in higher complication rates[39]. However, most studies have a lack of statistical power and follow-up to determine uncommon adverse events as the risk of infection.

Secondly is the risk of hyperglycemia in diabetic patients[41]. Hyperglycemia has been frequently described after administrating corticosteroids even in non-diabetic patients. Interestingly in the study of Backes only an increase in blood glucose was found in diabetic patients[18]. It remains unclear what effects transient hyperglycemia might have on the postoperative outcomes and complications. Remarkably, Diabetes Mellitus (DM) is an exclusion criterion in most studies examining corticosteroids in an arthroplasty setting. Since DM is relatively common in patients with osteoarthritis an advice regarding corticosteroids in these patients or an alternative for corticosteroids is needed, otherwise these patients are treated insufficiently[42].

Inflammatory mediators are involved in nociceptive processing and PONV[43]. Corticosteroids reduce the CRP peak after TKA[44]. The study of Wasko et al. reported increased levels of C-reactive protein (CRP) after TKA, up to 96 hours postoperatively[45]. The half-life of Dexamethasone is 36-54 hours and the maximum effect is to be expected in the first 24-48 hours[12]. Consequently, a single dose of dexamethasone will not be sufficient in reducing CRP levels during the first 4 postoperative days. This is illustrated by the non-randomized study of Samona et al. in which 8mg dexamethasone showed effective pain control only in the first 24 hours postoperative compared to placebo[46]. Therefore, the reasoning to investigate multiple doses at different times in the perioperative phase, as was utilized by several included studies, is valid.

Interestingly, we found that high-dose corticosteroids compared to low-dose corticosteroids had better pain reduction. However, in two studies comparing corticosteroids with placebo no difference in postoperative pain was found between placebo and corticosteroids. These finding, might be partially explained by possible underpowered studies, since pain was a secondary outcome measure in both studies. Moreover, the study of Dissanayake et al. was rated as high risk of bias[21]. Therefore these findings must be interpreted with caution.

Even though most studies demonstrated statistically significant improvement in terms of pain scores (VAS) it is more important to interpret these outcomes in terms of clinical relevance. To achieve this some articles searched for a minimal clinically important difference. A far more clinically relevant outcome of pain reduction is the reduction of postoperative opioids.

Recently Jørgensen et al. described an increased opioid use in TKA and THA and high usage of opioids after one year in 17.6% and 10.2% respectively[47]. The use of opioid-sparing pain medication should be further improved due to the negative side effects of opioids and to prevent long-term opioid dependence[48]. In the RCT of Gasbjerg et al. significant reduction in morphine consumption was found by two doses of 24 mg dexamethasone in TKA[22]. However, in this study only the first 48 hours after surgery were analyzed, therefore no long-term effects of corticosteroids on opioid consumption were presented.

Despite improvement in pain and PONV, which are both symptoms that prolong hospital stay, most included studies showed no reduced LOS. We presume this might be due to the fact that LOS is dependent to multiple factors including factors which are not influenced by corticosteroids. Therefore, LOS might not be a valid outcome measure to determine the effectiveness of corticosteroids.

Although insomnia is less frequent described, it is a common side effect of corticosteroids. Lunn et al. demonstrated significant increase of insomnia the first

night after high-dose methylprednisolone[28]. However, this is not found in other studies[20,26,29].

There are some limitations of this study. First, quality of the included studies was moderate. A high risk of bias was found in one study and the remaining studies had some concerns which might affect their validity. Secondly, outcomes were difficult to compare since dosing, type, and timing regimens for the administered corticosteroids varied greatly. Since different types of corticosteroids have been used with all their own specific potency and half-life, this might cause varying dosing regimens between studies[12]. Finally, with the short follow-up of most of the included studies we were unable to determine safety aspects of high-dose corticosteroids in TKA.

CONCLUSION

Current literature on perioperative use of systemic corticosteroids in TKA is highly variable in type, dosage, and timing of administration. Overall, corticosteroids reduce mostly pain and PONV with limited effects on LOS after TKA. Only minimal statistically significant and clinically relevant benefits were found in perioperative high-dose corticosteroids compared to low-dose. Moreover, in multiple doses compared to a single preoperative dose only minimal benefits were found. Given the short follow-up in most studies, it is difficult to conclude that high-dose corticosteroids are safe in use. Further research is needed regarding the effect and safety aspects before implementation of high-dose corticosteroids in fast-track TKA protocols.

Authors contribution: JE designed the study, supported data collection and data analysis and he wrote and critically reviewed the manuscript. FG supported data analysis and critically reviewed the manuscript. CN supported formulating and executing the search strategy and critically reviewed the manuscript. HV designed the study and critically reviewed the manuscript. NM designed the study, supported data analysis and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Conflict of interest: Each author certifies that there are no funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article related to the author or any immediate family members.

Funding: this research received no external funding.

REFERENCES

1. Vehmeijer SBW, Husted H, Kehlet H. Outpatient total hip and knee arthroplasty. Acta Orthop. 2018;89(2):141-4.
2. Kehlet H, Joshi GP. The systematic review/meta-analysis epidemic: a tale of glucocorticoid therapy in total knee arthroplasty. Anaesthesia. 2020;75(7):856-60.
3. Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? Acta Orthop. 2011;82(6):679-84.
4. Coenders MJ, Mathijssen NMC, Vehmeijer SBW. Three and a half years' experience with outpatient total hip arthroplasty. Bone Joint J. 2020;102-B(1):82-9.
5. Brekke AC, Amaro EJ, Posey SL, Engstrom SM, Polkowski GG, Schoenecker JG. Do Corticosteroids Attenuate the Peri-Operative Acute Phase Response After Total Knee Arthroplasty? J Arthroplasty. 2019;34(1):27-35.
6. Si HB, Yang TM, Zeng Y, Zhou ZK, Pei FX, Lu YR, et al. Correlations between inflammatory cytokines, muscle damage markers and acute postoperative pain following primary total knee arthroplasty. BMC Musculoskelet Disord. 2017;18(1):265.
7. Steinthorsdottir KJ, Kehlet H, Aasvang EK. Surgical stress response and the potential role of preoperative glucocorticoids on post-anesthesia care unit recovery. Minerva Anestesiol. 2017;83(12):1324-31.
8. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. Br J Anaesth. 2000;84(1):6-10.
9. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med. 2005;353(16):1711-23.
10. Falkenstein E, Tillmann HC, Christ M, Feuring M, Wehling M. Multiple actions of steroid hormones--a focus on rapid, nongenomic effects. Pharmacol Rev. 2000;52(4):513-56.
11. Sculco PK, Pagnano MW. Perioperative solutions for rapid recovery joint arthroplasty: get ahead and stay ahead. J Arthroplasty. 2015;30(4):518-20.
12. Salerno A, Hermann R. Efficacy and safety of steroid use for postoperative pain relief. Update and review of the medical literature. J Bone Joint Surg Am. 2006;88(6):1361-72.
13. De Oliveira GS, Jr., Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115(3):575-88.
14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
15. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews(). J Med Libr Assoc. 2021;109(2):174-200.
16. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc. 2016;104(3):240-3.
17. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
18. Backes JR, Bentley JC, Politi JR, Chambers BT. Dexamethasone reduces length of hospitalization and improves postoperative pain and nausea after total joint arthroplasty: a prospective, randomized controlled trial. J Arthroplasty. 2013;28(8 Suppl):11-7.
19. Chan TCW, Cheung CW, Wong SSC, Chung AYF, Irwin MG, Chan PK, et al. Preoperative dexamethasone for pain relief after total knee arthroplasty: A randomised controlled trial. Eur J Anaesthesiol. 2020;37(12):1157-67.

20. Cheng BLY, So EHK, Hui GKM, Yung BPK, Tsui ASK, Wang OKF, et al. Pre-operative intravenous steroid improves pain and joint mobility after total knee arthroplasty in Chinese population: a double-blind randomized controlled trial. Eur J Orthop Surg Traumatol. 2019;29(7):1473-9.
21. Dissanayake R, Du HN, Robertson IK, Ogden K, Wiltshire K, Mulford JS. Does Dexamethasone Reduce Hospital Readiness for Discharge, Pain, Nausea, and Early Patient Satisfaction in Hip and Knee Arthroplasty? A Randomized, Controlled Trial. J Arthroplasty. 2018;33(11):3429-36.
22. Gasbjerg KS, Hagi-Pedersen D, Lunn TH, Laursen CC, Holmqvist M, Vinstrup LO, et al. Effect of dexamethasone as an analgesic adjuvant to multimodal pain treatment after total knee arthroplasty: randomised clinical trial. BMJ. 2022;376:e067325.
23. Kim JK, Ro DH, Lee HJ, Park JY, Han HS, Lee MC. Efficacy of Systemic Steroid Use Given One Day After Total Knee Arthroplasty for Pain and Nausea: A Randomized Controlled Study. J Arthroplasty. 2020;35(1):69-75.
24. Koh IJ, Chang CB, Lee JH, Jeon YT, Kim TK. Preemptive low-dose dexamethasone reduces postoperative emesis and pain after TKA: a randomized controlled study. Clin Orthop Relat Res. 2013;471(9):3010-20.
25. Lei Y, Huang Z, Huang Q, Pei F, Huang W. Dose optimization of intravenous dexamethasone for total knee arthroplasty: when two is not better than one. Arch Orthop Trauma Surg. 2022;142(4):665-72.
26. Li D, Zhao J, Yang Z, Kang P, Shen B, Pei F. Multiple Low Doses of Intravenous Corticosteroids to Improve Early Rehabilitation in Total Knee Arthroplasty: A Randomized Clinical Trial. J Knee Surg. 2019;32(2):171-9.
27. Lindberg-Larsen V, Bandholm TQ, Zilmer CK, Bagger J, Hornsleth M, Kehlet H. Preoperative methylprednisolone does not reduce loss of knee-extension strength after total knee arthroplastyA randomized, double-blind, placebo-controlled trial of 61 patients. Acta Orthop. 2017;88(5):543-9.
28. Lunn TH, Kristensen BB, Andersen LO, Husted H, Otte KS, Gaarn-Larsen L, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. Br J Anaesth. 2011;106(2):230-8.
29. Nielsen NI, Kehlet H, Gromov K, Troelsen A, Husted H, Varnum C, et al. High-dose steroids in high pain responders undergoing total knee arthroplasty: a randomised double-blind trial. Br J Anaesth. 2022;128(1):150-8.
30. Tammachote N, Kanitnate S. Intravenous Dexamethasone Injection Reduces Pain From 12 to 21 Hours After Total Knee Arthroplasty: A Double-Blind, Randomized, Placebo-Controlled Trial. J Arthroplasty. 2020;35(2):394-400.
31. Wu Y, Lu X, Ma Y, Zeng Y, Bao X, Xiong H, et al. Perioperative multiple low-dose Dexamethasones improves postoperative clinical outcomes after Total knee arthroplasty. BMC Musculoskelet Disord. 2018;19(1):428.
32. Xu B, Ma J, Huang Q, Huang ZY, Zhang SY, Pei FX. Two doses of low-dose perioperative dexamethasone improve the clinical outcome after total knee arthroplasty: a randomized controlled study. Knee Surg Sports Traumatol Arthrosc. 2018;26(5):1549-56.
33. Xu H, Zhang S, Xie J, Lei Y, Cao G, Pei F. Multiple Doses of Perioperative Dexamethasone Further Improve Clinical Outcomes After Total Knee Arthroplasty: A Prospective, Randomized, Controlled Study. J Arthroplasty. 2018;33(11):3448-54.
34. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
35. Lex JR, Edwards TC, Packer TW, Jones GG, Ravi B. Perioperative Systemic Dexamethasone Reduces Length of Stay in Total Joint Arthroplasty: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Arthroplasty. 2021;36(3):1168-86.
36. Yue C, Wei R, Liu Y. Perioperative systemic steroid for rapid recovery in total knee and hip arthroplasty: a systematic review and meta-analysis of randomized trials. J Orthop Surg Res. 2017;12(1):100.
37. O'Brien S, Bennett D, Doran E, Beverland DE. Comparison of hip and knee arthroplasty outcomes at early and intermediate follow-up. Orthopedics. 2009;32(3):168.
38. Vuorinen MA, Palanne RA, Makinen TJ, Leskinen JT, Huhtala H, Huotari KA. Infection safety of dexamethasone in total hip and total knee arthroplasty: a study of eighteen thousand, eight hundred and seventy two operations. Int Orthop. 2019;43(8):1787-92.
39. Jorgensen CC, Pitter FT, Kehlet H, Lundbeck Foundation Center for Fast-track H, Knee Replacement Collaborative G. Safety aspects of preoperative high-dose glucocorticoid in primary total knee replacement. Br J Anaesth. 2017;119(2):267-75.
40. Toner AJ, Ganeshanathan V, Chan MT, Ho KM, Corcoran TB. Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery: A Systematic Review and Meta-analysis. Anesthesiology. 2017;126(2):234-48.
41. Wasfie TJ, Groton J, Cwalina N, Hella JR, Barber K. Efficacy of Preoperative Usage of Dexamethasone in Diabetic Patients Undergoing Total Hip or Knee Arthroplasty for Control of Nausea and Vomiting. Am Surg. 2021;87(3):336-40.
42. Capozzi JD, Lepkowsky ER, Callari MM, Jordan ET, Koenig JA, Sirounian GH. The Prevalence of Diabetes Mellitus and Routine Hemoglobin A1c Screening in Elective Total Joint Arthroplasty Patients. J Arthroplasty. 2017;32(1):304-8.
43. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin. 2007;45(2):27-37.
44. Smith C, Erasmus PJ, Myburgh KH. Endocrine and immune effects of dexamethasone in unilateral total knee replacement. J Int Med Res. 2006;34(6):603-11.
45. Wasko MK, Bobecka-Wesolowska K, Tomasiuk R, Kowalczewski J. Measurement of the inflammatory response in the early postoperative period after hip and knee arthroplasty. Clin Chem Lab Med. 2015;53(11):1785-92.
46. Samona J, Cook C, Krupa K, Swatsell K, Jackson A, Dukes C, et al. Effect of Intraoperative Dexamethasone on Pain Scores and Narcotic Consumption in Patients Undergoing Total Knee Arthroplasty. Orthop Surg. 2017;9(1):110-4.
47. Jorgensen CC, Petersen M, Kehlet H, Aasvang EK. Analgesic consumption trajectories in 8975 patients 1 year after fast-track total hip or knee arthroplasty. Eur J Pain. 2018.
48. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The Opioid Crisis: a Comprehensive Overview. Curr Pain Headache Rep. 2018;22(3):16.