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A meta-analysis on effect of dexamethasone as an analgesic adjuvant to pain treatment after total knee arthroplasty

Dr Netravathi H

Assistant Professor, Department of Anesthesia, East point college of Medical Sciences Bidarahalli, Avalahalli, Bengaluru 560049, India

Dr M. Shanmugam*

Associate Professor, Department of orthopaedics, Sambhram Institute of Medical Sciences And Research, D. K. HALLI, BEML NAGAR, KGF – 563115, India

*Corresponding author

Dr Shiva Kumar. M. S

Assistant Professor, Department of orthopaedics, East point college of Medical Sciences Bidarahalli, Avalahalli, Bengaluru 560049, India

Abstract--Background: Pain management after a total-knee arthroplasty (TKA) has become an important issue in the field of medicine. Objective: 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 2021 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 I² statistic. Results: A total of 5 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 48hours after TKA. Administering dexamethasone could significantly reduce opioid consumption at 12hours after TKA. However, no significant difference was found in opioid consumption at 24 and 48hours after TKA. There was a decreased risk of adverse effects in dexamethasone groups. A fixed-effects model was adopted when I²<50% and P>.05; otherwise, the random effects model was adopted. We did not perform a publication bias, if there were <10 included articles. 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.

Keywords---meta-analysis, dexamethasone, pain, total-knee arthroplasty, publication bias, forest plot, randomized controlled trial (RCT).

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.[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 management, 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.[3,4]. 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. Previous studies have demonstrated that dexamethasone appeared to be effective and safe for postoperative pain control in arthroplasties.[5,6] Additionally, preoperative administration of dexamethasone has been shown to reduce postoperative nausea and vomiting. Based on its high efficiency and wide application, we chose dexamethasone as the target drug in our study. 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.

Materials and Methods

Author and Co-author searched PubMed, Scopus, Embase, ScienceDirect, and Web of Science for relevant studies. All databases were searched up to December 2021, without restrictions on publication date and language. The terms used to search the databases were: “dexamethasone” 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. If no consensus was reached, a third investigator was consulted on a study’s eligibility.

Inclusion Criteria

Studies searched were considered eligible when they met following criteria: clinical randomized controlled trials (RCTs) published between 1986 and 2021; 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.

Exclusion criteria

Studies excluded from the present meta-analysis were comprised of incomplete data, case reports, conference abstracts, or review articles. 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.

Statistical Analysis

Analysis of data was done by using SPSS software ver. 22. Data were statistically described in terms of mean ($\pm$ SD), frequencies (number of cases) and percentages when appropriate. For comparing categorical data, Chi square test was performed. A probability value (p value) less than 0.05 was considered statistically significant. 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.

Results

Total of 420 potentially relevant studies related to dexamethasone and TKA were reviewed. After the scan of all titles and abstracts, 415 articles were excluded. Five RCTs[7-11] published between 2013 and 2017 satisfied the eligibility criteria for this study. There were 290 participants in the dexamethasone groups and 280 patients in the control groups.

Table 1- Characteristics of the included studies

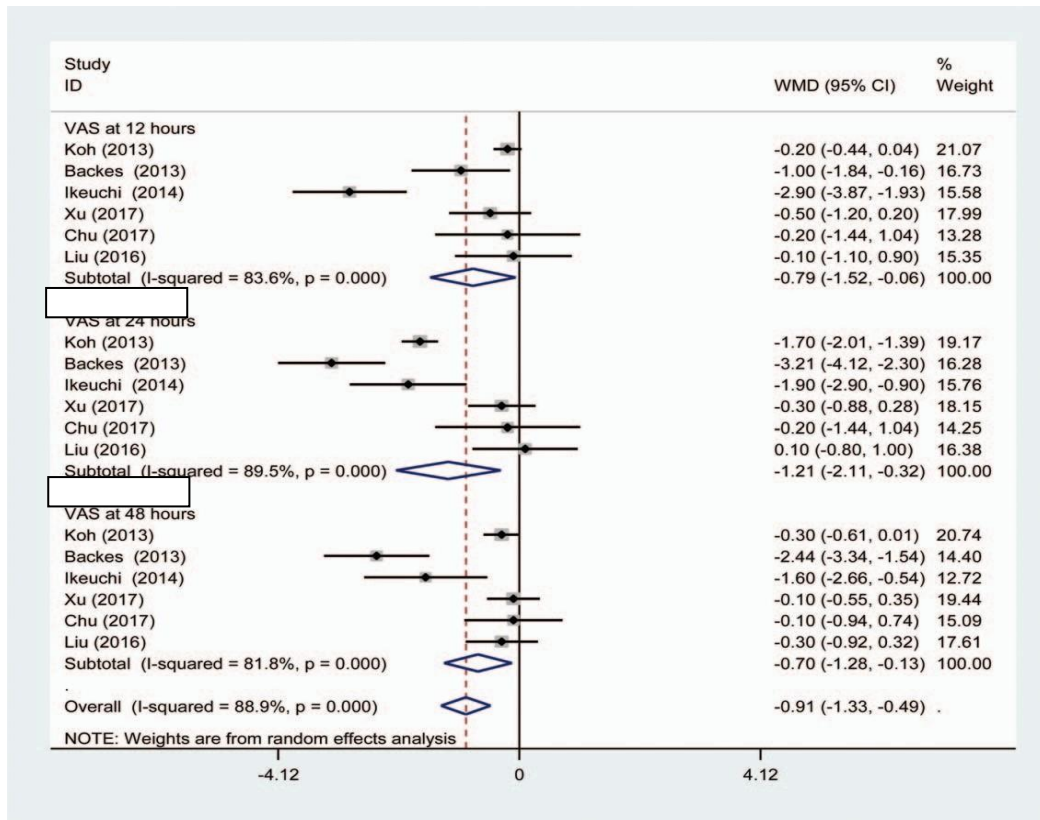
Author country			surg	Cases	Mean age	male	Dexamethasone group	Control	Pain Control	Follow up
Backes (2013) USA			TKA	42/37	66/66	9/8	Intravenous dexamethasone 10 mg immediately	Normal saline	PCA	6 mo
RCT							prior to induction of anesthesia			
Ikeuchi (2014)	Japan	RCT	TKA	20/20	77/76	2/4	Periarticular 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.

As per table 1 the sample size of included trials ranged from 40 to 260, 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.

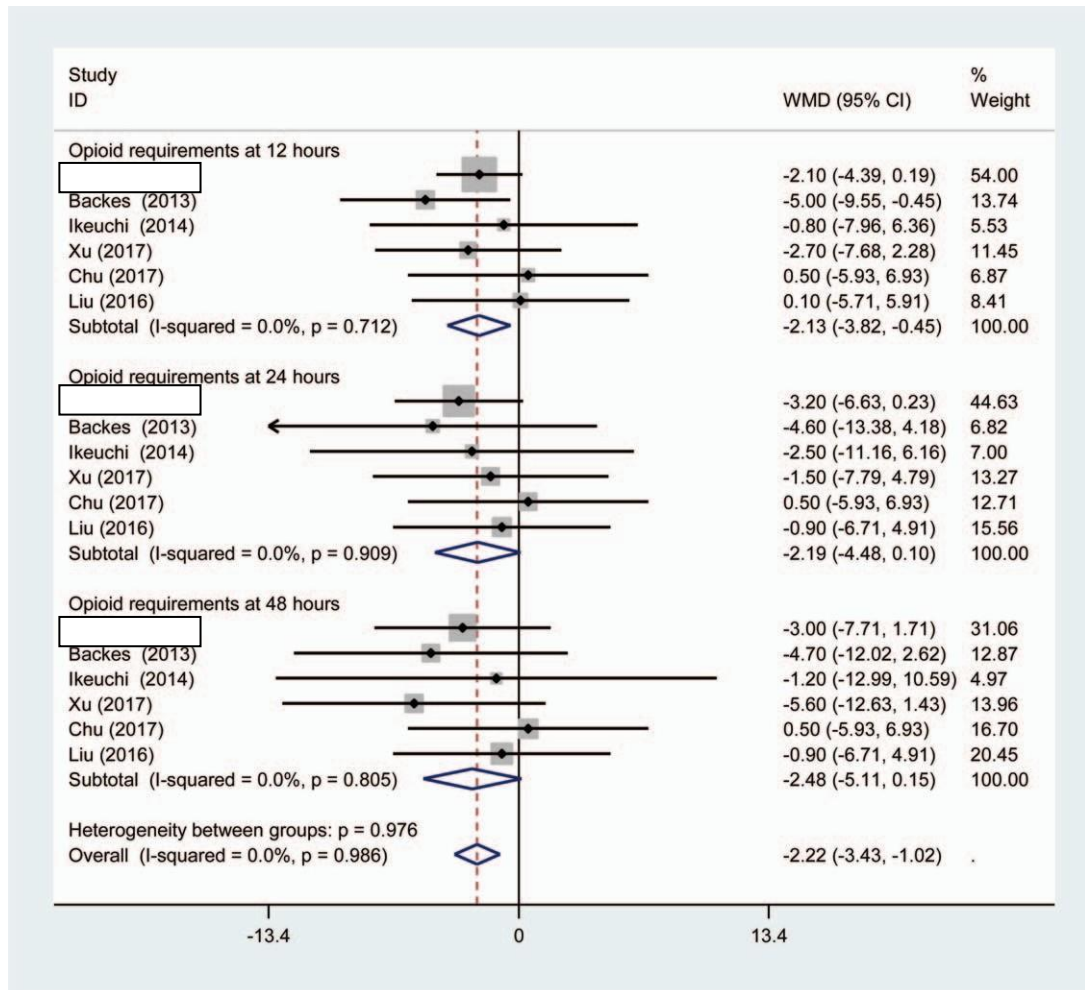
Figure 1- Forest plot showing VAS score after TKA



As per figure 1 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 12hours after TKA. There was

significant difference in terms of postoperative VAS at 48hours after TKA between 2 groups (WMD=0.705, 95% CI:1.283 to 0.126, P=.017).

Figure 2- Forest plot showing Opioid Requirement after TKA



As per figure 2 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 12hours. Opioid requirements at 24hours after TKA were documented in all RCTs. 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 24hours after TKA.

Five RCTs[7-11] reported postoperative adverse effects, including nausea, vomiting, and pruritus. No significant heterogeneity was found across articles.

Meta-analysis revealed that there was no significant difference between the groups regarding to length of a hospital stay. Five studies[7-11] 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 metaanalysis indicated that there was no significant difference between groups regarding the risk of postoperative complications.

Discussion

Recently, a similar metaanalysis has been published.[12] 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 48hours postoperatively, which was contrary to the previous meta-analysis study mentioned. 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.

Although multimodal regimes were applied, postoperative pain, moderate to severe, still occurred in approximately 50% of TKA patients.[13] 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[14] 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[15] demonstrated that glucocorticoids could significantly reduce inflammatory factors such as interleukin-6 and C-reactive protein in total hip arthroplasty.

Opioid treatment was widely applied as pain management after major orthopedic surgery.[16] 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. However, previous studies have indicated that opioids were associated with many adverse effects, including gastrointestinal events, headache, pruritus, consumption, and respiratory depression.[17,18]. 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 12hours after TKA, which could decrease the adverse effects. No significant difference between groups in terms of the risk of thrombotic complications was found.

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.

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Conflict of Interest- None declared

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