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Perineural dexamethasone added to peripheral nerve block in knee surgery: a systematic review with meta-analysis

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Abstract

The objective of the study was to assess the analgesic effects of dexamethasone (DEX) added to peripheral nerve block in knee surgery. We searched for relevant randomized controlled trials (RCTs) in PubMed and the Cochrane Database of Systematic Reviews. The latest search was done on September 11, 2024. Search terms included knee surgery, regional anesthesia, and DEX. Data extraction, statistical analysis, and risk of bias assessment followed established protocols. Seven RCTs with 551 patients were included. In the DEX 4 mg group, no reduction of pain at rest was found. However, for the DEX 8 mg group, pain management at rest was more effective; the mean difference (MD) with 95% CI was –0.34 [–0.50, –0.18]. For pain with movement, the model favors the DEX 4 mg group (MD with 95% CI was –1.03 [–1.84, –0.22]). Only one study reported the differences in pain intensity scores with movement between the DEX 8 mg and control groups. For morphine consumption, the model did not reveal any reduction in the DEX 4 mg group (MD –0.68 [–1.87, 0.5]) or DEX 8 mg group (MD –10.44 [–23.92, 3.03]). Pain with movement may be reduced with a lower dose, and pain without movement with a higher dose of DEX.

Key words: dexamethasone, perineural, knee surgery, morphine consumption, pain intensity, peripheral nerve block, adjuvant, corticosteroids.

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Knee pain is common among individuals around the age of 55 and older. It is often caused by osteoarthritis or trauma, with the most common injury leading to chronic knee pain being anterior cruciate ligament (ACL) injury. Chronic knee pain tends to intensify with movement, especially on jumping or walking, and existing inflammation within the joint can worsen the pain [1]. In severe cases of osteoarthritis of the knee (gonarthrosis), knee arthroplasty (knee replacement) serves as an effective surgical intervention for knee osteoarthritis. During this surgery, the affected joint is replaced with a prosthesis that functions similarly to a natural joint [2]. However, nearly 20% of patients undergoing knee arthroplasty do not fully recover and continue to experience chronic knee pain along with impaired joint function. As many as half of these patients might require revision surgery due to persistent pain or infection [3].

Surgical injury triggers an inflammatory response initially caused by local mediators, which can also have systemic effects. Such inflammation not only leads to increased postoperative pain but can also result in such complications as delirium and a longer recovery period [4]. Furthermore, sleep disruption due to severe pain can contribute to mental problems and worsen outcomes [5].

Adequate perioperative pain management is considered a top research priority for patients undergoing knee replacement surgery, since it plays a crucial role in facilitating early mobilization and rehabilitation. A comprehensive recovery program for knee surgery patients was described in *The Lancet* by Price *et al*. [3]. One important aspect of this program is effective analgesia, including techniques such as regional blocks.

Peripheral nerve blocks (PNBs) serve as an effective and safer alternative to traditional opioid analgesia in knee surgery. PNBs involve the use of local anesthetics [6] and can address concerns around the use of opioids, such as addiction risks and other safety issues [7]. The advantages of PNB include not only fewer side effects but also faster patient reco-

very [8]. The conventional PNBs used in knee surgery include femoral nerve block (FNB) and sciatic nerve block (SNB). Recently there has been a growing interest in using adductor canal block (ACB) [7]. The International Consensus on Anesthesia-Related Outcomes after Surgery (ICAROS) recommends the use of PNBs in total knee arthroplasty to minimize postoperative complications [9].

However, to prolong the effect of PNBs, which generally last a few hours, adjuvants such as dexamethasone (DEX) may be required [10, 11]. Perineural DEX added to a PNB demonstrated decreased rescue analgesia requirements and pain intensity after upper limb surgery [8]. The precise mechanisms by which DEX controls pain are not fully understood. It probably has both local and systemic effects. Locally it acts as a vasoconstrictor, which can reduce the absorption rate of anesthetics [8, 12]. Systemically, it suppresses the release of inflammatory mediators and pain signals by modulating the cyclooxygenase and lipoxygenase pathways [4], as well as affecting C-fibers and nerve cells [8]. These anti-inflammatory effects along with alleviation of nausea and vomiting [13] may contribute to improved patient recovery and longer peripheral block duration [14, 15]. Additionally, some guidelines recommend using steroid injections for knee osteoarthritis treatment. Intra-articular injections were associated with lower pain intensity in such patients [16].

Previous systematic reviews have examined mixed intravenous and perineural routes of DEX administration in total knee reconstruction [17] or perineural DEX in upper limb surgery [8]. Some systematic reviews have studied the effects of DEX in other lower limb procedures, such as hip arthroplasties [11, 18]. However, there is currently no recent review specifically focusing on the analgesic effects of perineural DEX in knee surgery patients.

This systematic review aims to evaluate the analgesic effects of perineural DEX as an adjuvant to regional peripheral block in knee surgery.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. The protocol was registered in Open Science Framework and is publicly available at https://doi.org/10.17605/OSF.IO/AQRZ2.

Search strategy

We searched PubMed and the Cochrane Library for the relevant literature published before September 11, 2024. We used the following search query: ((“knee surgery”) OR (“total knee replacement”)) AND ((“regional anesthesia”) OR (“dexamethasone”) OR (“perineural dexamethasone”)) + randomized controlled trial (PubMed) / trial (Cochrane Library) + English language (please see the supplementary file). We screened the titles and the abstracts against the following inclusion and exclusion criteria:

Inclusion criteria:

1) patient age and gender: without restrictions,
2) type of surgery: knee surgery with PNB,
3) intervention: perineural DEX,
4) comparator: placebo,
5) study types: RCTs to minimize bias,
6) language restrictions: articles written in English.

Exclusion criteria:

1) population: wrong surgery type, no PNB,
2) intervention: epidural, oral, intravenous DEX,
3) comparator: active comparator,
4) study types: ongoing, observational, animal, and *in vitro* studies, secondary analyses, and editor correspondences. These types of studies generally have a higher risk of bias than RCTs.

After selecting eligible studies, duplicates were removed.

Outcomes

The primary outcomes of our meta-analysis are postoperative pain intensity scores at rest and with movement (numerical rating scale (NRS) or visual analogue scale (VAS, 0–10)) for postoperative days (POD) 1 and 2. The secondary outcome is postoperative opioid consumption, converted to morphine equivalents (mg), for the first two POD.

Data extraction and statistical methods

AA extracted data from eligible studies and recorded the citation, country, study design, types of surgery, age and number of participants, comparator, dose and concentration of DEX, peripheral block used, and study conclusions in Table 1. The data from each study were screened against the outcomes of interest to be eligible for the evidence synthesis. Outcome data were extracted to an Excel table and analyzed using the Review Manager (RevMan) computer program, Version 5.4 (The Cochrane Collaboration, 2020). We double-checked the data extracted.

For some studies, we estimated the missing data values of the sample mean and sample standard deviation using existing methods [20, 21]. Heterogeneity was estimated by the I^2 statistic. Subgroup analysis was used to explore the sources of heterogeneity. In the case of high heterogeneity, we explored it by subgroup analysis based on the DEX regimen. We used a random-effects meta-analysis for synthesis of evidence. To express continuous outcomes, we calculated the mean difference (MD) and 95% confidence interval (CI) using an inverse variance method. The sensitivity analysis was per-

TABLE 1. Characteristics of included studies

Author, citation	Country	Study design	Study goals	Types of surgery	Age (mean ± SD, or mean and range, or median and IQR) in the groups	Number of patients: total (intervention; control)	Groups (control; comparators) and specification	Dose and concentration of dexamethasone	What peripheral block was used?	Study conclusions
Aoyama *et al*. 2021	Japan	RCT double-blind study using computer-generated sequence	1S. Whether giving PD together with local anesthetic for sciatic nerve block could increase the period that patients experienced analgesia after receiving quadruple nerve blocks. 2S. To compare the effects of PD given intravenously against oral and assess any differences.	ACLR	Age (mean ± SD): 1S. Group C: 28 ± 15 Group P: 25 ± 11 2S. Group 1: 28 ± 15 Group 2: 26 ± 11 Group 3: 23 ±10	1S. Total number of patients: 18 Group C: 11 Group P: 7 2S. Total number: 45 Group 1: 17 Group 2: 18 Group 3: 10	1S: Group P vs. C 2S: Group 1 vs. 2 vs. 3	1S. PD Group P: "20 ml of 0.5% ropivacaine with dexamethasone sodium phosphate 4 mg" Group C: 1 ml of normal saline for sedation before blockage: "Midazolam 1–2 mg and fentanyl 50 µg" 2S. Intravenously Group 1: Patients who did not receive dexamethasone Group 2: Dexamethasone 4 mg Group 3: Dexamethasone 4 mg along with local anesthetic for subgluteal sciatic nerve block	SNB and CFNB	The duration of analgesia from QNBs for ACL reconstruction was prolonged when PD was delivered together with a local anesthetic, but the effects were the same as those of ID. 1S. PD extended the analgesia by 9.5 hours (median duration: 22.5 and 13.0 h with and without PD). 2S. Compared to no dexamethasone, the duration of analgesia was similarly prolonged with ID and PD.
Chisholm *et al*. 2017	United States	RCT double-blind	To determine whether SSNB "is an effective analgesic alternative to femoral nerve block after ACL reconstruction" by bone-tendon autograft.	ACLR	Age: range of total number of patients 16–65 Mean, SD Control: 27, 10 Treatment group I: 26, 8 Treatment group II: 27, 10	Total number of patients: 186 Control: 62 Treatment group I: 61 Treatment group II: 63	Control vs. treatment group I vs. treatment group II	Control: "SSNB with 13 mL of 0.5% bupivacaine" Treatment group I: "1 mg preservative-free dexamethasone + 0.5% bupivacaine" (10 mg/ml) Treatment group II: "4 mg preservative-free dexamethasone + 0.5% bupivacaine" (10 mg/ml)	SSNB	Both 1 mg and 4 mg of dexamethasone to the block infusion significantly prolonged the "block duration by 8-13 hours". Moreover, patients in the dexamethasone 4 mg group reported lower resting pain scores, improved patient satisfaction, and less sleepiness and confusion, which may indicate a systemic effect of dexamethasone. There was no difference in numerical rating scale pain score measurements during exercise.

TABLE 1. Cont.

Author, citation	Country	Study design	Study goals	Types of surgery	Age (mean ± SD, or mean and range, or median and IQR) in the groups	Number of patients: total (intervention; control)	Groups (control; comparators) and specification	Dose and concentration of dexamethasone	What peripheral block was used?	Study conclusions
Li *et al*. 2024	China	RCT double-blind	To study the effect of PD on rebound pain after SNB and FNB in patients undergoing UKA.	UKA	Age (mean ± SD): Control: 65.2 ± 5.9 Dexamethasone: 65.5 ± 7.0	Control: 34 Dexamethasone: 33	Dexamethasone 5 mg + ropivacaine vs. Control (ropivacaine only)	Dexamethasone: 15 mL of 0.4% ropivacaine + 5 mg dexamethasone Control: 15 mL of 0.4% ropivacaine	SNB, FNB	Dexamethasone increased the duration of nerve block, but elevated the occurrence and intensity of rebound pain, and showed no benefits on the postoperative analgesia.
Morales-Munoz *et al.* 2017	Spain	RCT double-blind	To contrast the analgesia produced by dexamethasone administered intravenously vs perineurally during the femoral nerve block following a total knee replacement vs. control group.	TKR	Median, 95% CI: IV dexamethasone: 68.8 (65.3–72.2) PD: 70.5 (67.8–73.1) Control: 68.8 (65.3–72.6)	Total number of patients: 81 IV Dexamethasone: 27 Perineural dexamethasone: 27 Control: 27	IV dexamethasone vs. PD vs. Control	IV dexamethasone: 8 mg Perineural dexamethasone: PD 8 mg Control: placebo All patients received 20 mL of ropivacaine 0.5%	FNB	Dexamethasone prolongs the sensory block caused by a single dose of ropivacaine-based FNB. With fewer side effects, it also offers superior analgesia and patient satisfaction. Additionally, there were fewer postoperative problems, side effects, and pains in group IV.
Turner *et al.* 2018	United States	RCT double-blind, placebo-controlled	To investigate whether PD prolongs objectively measured PNB. Determine whether 1 mg and 4 mg doses "provide equivalent PNB prolongation compared to PNB without dexamethasone".	UKA	Mean, SD Placebo: 59.2, 9.1 1 mg group: 63.3, 8.9 4 mg group: 62.8, 5.2	Placebo: 12 1 mg group: 36 4 mg group: 36	Placebo vs. 1 mg group vs. 4 mg group	Placebo group: placebo 1 mg group: 1 mg of PD 4 mg group: 4 mg of dexamethasone	PNB	When determined by repeated neurologic pinprick tests, dexamethasone 4 mg but not 1 mg lengthened the ACB. No differences were found in the amount of opioids used or the time taken to request an analgesic; nevertheless, some pain levels were noticeably lower in the dexamethasone groups than the placebo group.

TABLE 1. Cont.

Author, citation	Country	Study design	Study goals	Types of surgery	Age (mean ± SD, or mean and range, or median and IQR) in the groups	Number of patients: total (intervention; control)	Groups (control; comparators) and specification	Dose and concentration of dexamethasone	What peripheral block was used?	Study conclusions
Wang *et al.* 2017	China	RCT	To consider whether the addition of dexamethasone to the ACB ropivacaine can lengthen analgesia and diminish pain.	TKA	Mean ± SD Control: 63 ± 5 Dexamethasone: 62 ± 7	Total number of patients: 186 Control: 93 Dexamethasone: 93	Control vs. dexamethasone	Control: 0.5% ropivacaine + normal saline Dexamethasone: 0.5% ropivacaine + 8 mg dexamethasone	ACB	The period of analgesia and early postoperative pain after TKA can both be reduced by mixing dexamethasone with ropivacaine for ACB.
Veneziano *et al.* 2018	United States	RCT double-blind, placebo-controlled	To determine the effectiveness of the mechanism of action of PDF as an adjuvant in regional anesthesia in children and teens.	AKS	Age: range of total number of patients: 10–18 (mean 14.8) Mean, SD Group R: 14.6, 2 Group D: 15.1, 2 Group M: 14.7, 2	Total number of patients: 73 Group R: 27 Group D: 23 Group M: 23	Group R vs. Group D vs. Group M	Group R: 0.5% ropivacaine and intramuscular saline Group D: 0 5% ropivacaine plus "perineural dexamethasone 0.1 mg/kg (maximum 4 mg) and intramuscular saline" Group M: "ropivacaine 0.5% and intramuscular dexamethasone 0.1 mg/kg (maximum 4 mg)"	FNB	Perineural or intramuscular dexamethasone did not enhance analgesia in the pediatric population following FNB for TKA. It was not possible to determine whether the apparent lack of benefit was a genuine adult-pediatric difference or a study restriction. The authors suggested evaluating dexamethasone for different block types and other types of surgery.

1S – first study, 2S – second study, ACB – adductor canal block, ACLR – anterior cruciate ligament reconstruction, AKS – arthroscopic knee surgery, CFNB – continuous femoral nerve block, FNB – femoral nerve block, ID – intravenous dexamethasone, PD – perineural dexamethasone, PNB – peripheral nerve blockade, QNB – quadruple nerve block, RCT – randomized controlled trial, SNB – sciatic nerve block, SSNB – subsartorial saphenous nerve blockade, TKA – total knee arthroplasty, TKR – total knee replacement, UKA – unicompartmental knee arthroplasty

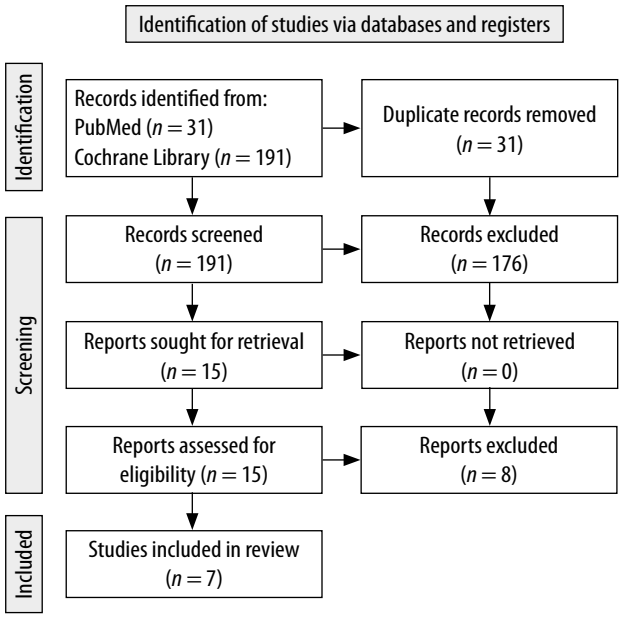

FIGURE 1. PRISMA diagram

formed by repeating the analysis with each individual study removed. The outcomes were shown in forest plots and summarized in a summary of findings table. A reduction in pain of 2 or more points on a VAS scale of 10 was considered to be clinically meaningful [22].

Risk of bias assessment and the certainty of evidence

Each RCT was classified as having a low, unclear, or high risk of bias in the following areas: randomization, allocation concealment, blinding of participants, staff, and investigators, missing data, and selective reporting of outcomes. In the category of "other" bias, we assessed the conflict of interests in the included studies [23]. KT summarized the risk of bias using RevMan. We did not exclude any studies based on our assessments.

We assessed the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [24]. We assessed five outcomes: pain at rest, pain with movement and morphine consumption. Our evaluation considered factors such as risk of bias, imprecision, inconsistency, and indirectness. Each outcome was assigned a level of certainty: "low," "moderate," or "high." We presented our assessments in the summary of findings. For meta-analyses involving more than ten RCTs, we planned to assess publication bias using a funnel plot.

RESULTS

The initial search yielded 160 articles, 153 of which were excluded. The reasons for exclusion are described in Figure 1. Seven RCTs with 551 patients were included in the meta-analysis [25–31] (Table 1). The studies were focused on total knee replacement, total knee arthroplasty, and ACL reconstruction. The doses of DEX ranged from 1 to 8 mg. The regional blocks included sciatic nerve block, single-shot nerve block, FNB, perineural nerve block, and ACB. The age of participants varied from children to seniors. While most of the studies focused on adult populations, Aoyama *et al*. [25] and Veneziano *et al*. [30] investigated the effects of DEX in children, adolescents, and young adults.

Postoperative pain intensity score at rest measured on POD1 and POD2 for DEX 4 mg vs. control (NRS/VAS, 0–10)

The forest plot in Figure 2 presents the comparison of the DEX 4 mg group with the control group on POD1 and POD2. Five studies (DEX = 165, con-

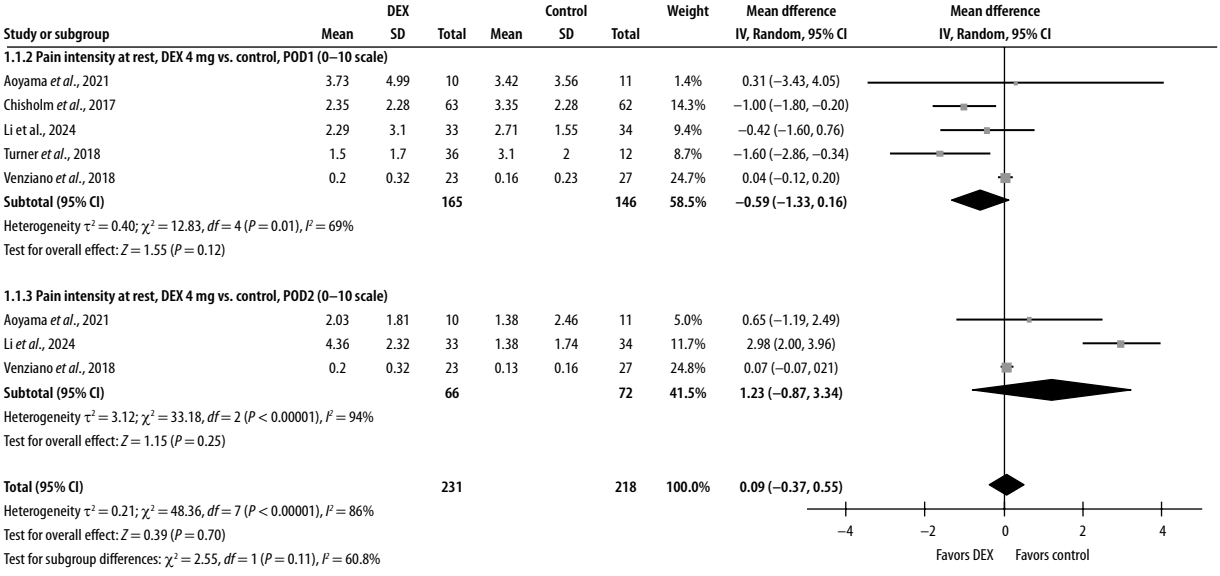

FIGURE 2. Postoperative pain intensity at rest on postoperative days 1 and 2 for DEX 4 mg vs. control (NRS/VAS, 0–10)

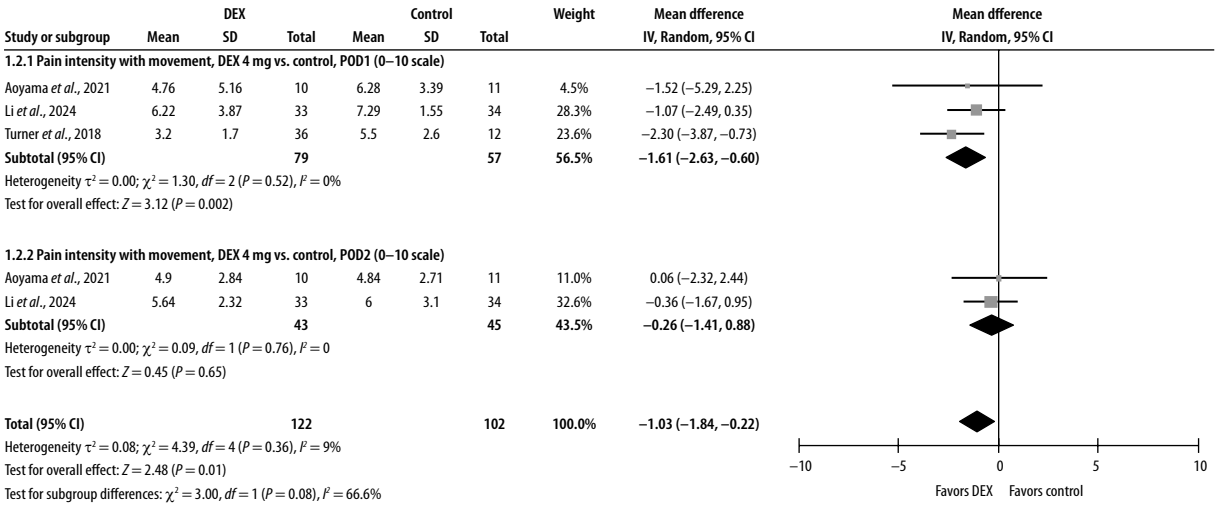

FIGURE 3. Postoperative pain intensity score with movement on postoperative day 1 and 2 for DEX 4 mg vs. control (VAS/NRS, 0–10)

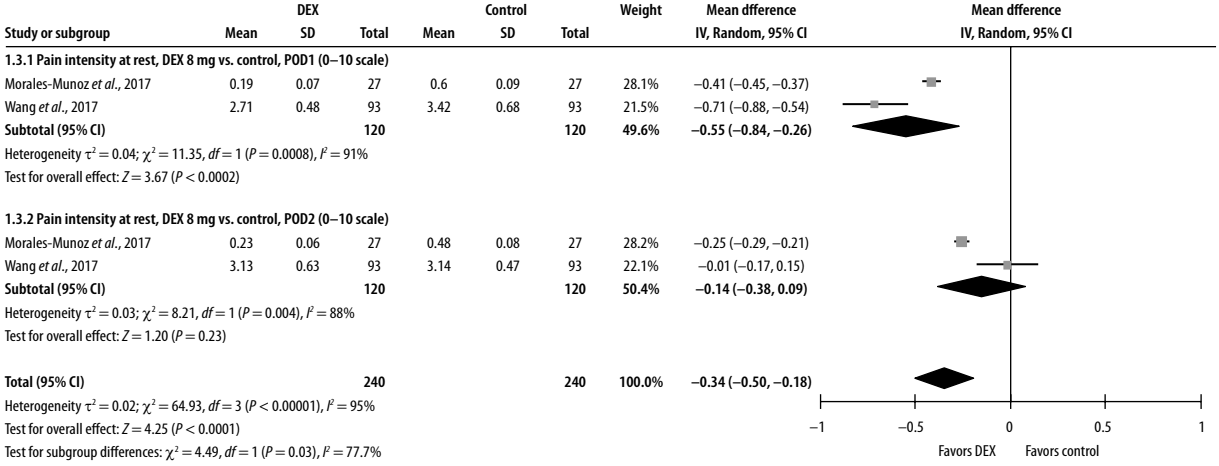

FIGURE 4. Postoperative pain intensity score at rest on postoperative day 1 and 2 for DEX 8 mg vs. control (NRS/VAS, 0–10)

trols = 146) report the results for pain scores at rest on POD1. The model does not favor either group (MD with 95% CI is –0.59 [–1.33; 0.16]; P = 0.12). There is moderate heterogeneity among the included studies (I^2 = 69%). Three studies (DEX = 66, controls = 72) reported pain scores at rest on POD2. On the second POD the model did not favor either group (MD = 1.23 [–0.87; 3.34], P = 0.25); the heterogeneity among the included studies was considerable (I^2 = 94%). Overall, the model does not favor either group (MD with 95% CI is 0.09 [–0.37; 0.55]; P = 0.7).The sensitivity analysis indicates that the model favors the DEX 4 mg group on POD1 when the study by Venziano *et al*. is excluded [30].

Postoperative pain intensity score with movement measured on POD1 and POD2 for DEX 4 mg vs. control (NRS/VAS, 0–10)

The forest plot in Figure 3 below presents the comparison of pain intensity with movement in the DEX 4 mg group versus the control group on POD1 and POD2. Three studies (DEX = 79, controls = 57) report pain scores on movement in the first 24 h after the surgery. The model favors the DEX group over the control group (MD with 95% CI is –1.61 [–2.63, –0.60], P = 0.002, I^2 = 0%). Only two studies (DEX = 43, controls = 45) reported the results of pain intensity with movement on POD2. On the second day after surgery the model did not favor the DEX group (MD with 95% CI is –0.26 [–1.41, 0.88], P = 0.65), with no heterogeneity observed between studies (I^2 = 0%). Overall, the model favors the DEX group in terms of the pain intensity with movement, showing a significant effect (–1.03 [–1.84, -0.22], P = 0.01). The results are sensitive to the exclusion of a study by Turner *et al*. [28], in which case the model does not favor either group.

Postoperative pain intensity score at rest measured on POD1 and POD2 for DEX 8 mg vs. control (NRS/VAS, 0–10)

The forest plot in Figure 4 illustrates the comparison of postoperative pain intensity at rest between the DEX 8 mg and control groups on POD1 and

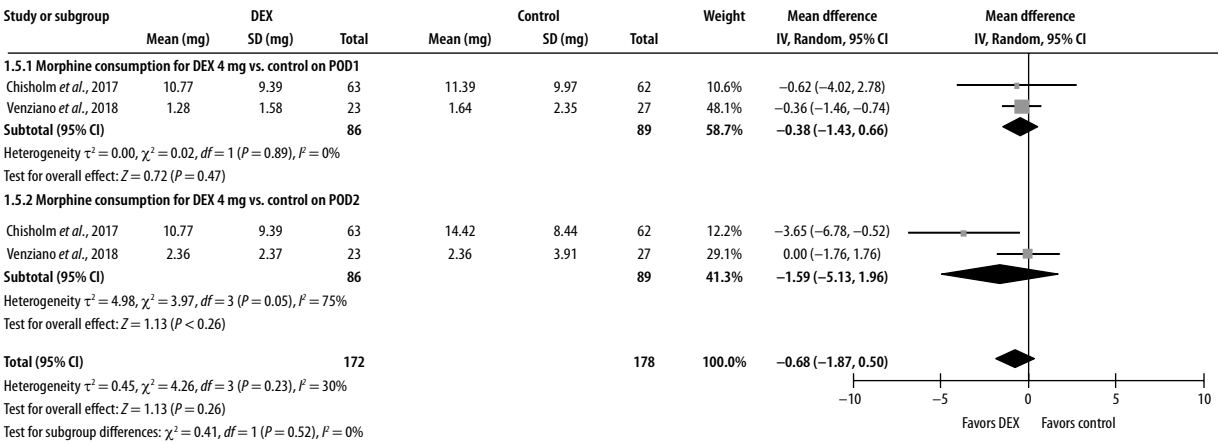

FIGURE 5. Postoperative opioid consumption at postoperative day 1 and 2 in morphine equivalents (mg)

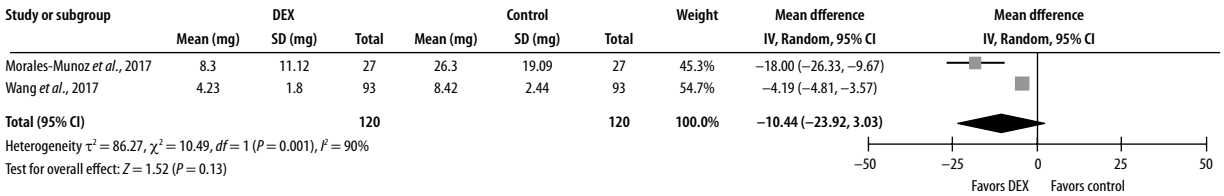

FIGURE 6. Morphine consumption for dexamethasone 8 mg vs. control on postoperative day 1 (mg)

POD2. Only two studies were included in this comparison (DEX = 120, controls = 120). On POD1 the mean difference was –0.55 [95% CI: –0.84, –0.26], indicating a statistically significant lower pain intensity at rest in the DEX group compared to the control group, with considerable heterogeneity, I^2 = 91%. On POD2 the mean difference was –0.14 [95% CI: –0.38, 0.09], indicating no significant difference between the groups, while the heterogeneity remained considerable, I^2 = 88%. The model would favor the DEX 8 mg group over the control if a study by Wang *et al*. [29] were excluded. The overall result of the model favors the DEX 8 mg group over the control group, with MD of –0.34 [–0.50, –0.18], $P < 0.0001$, and considerable heterogeneity, I^2 = 95%. This indicates better pain reduction management with use of DEX 8 mg.

Morphine consumption for DEX 4 mg vs. control

Two studies report the outcome of morphine consumption on POD1 and POD2 (DEX = 86, controls = 89), as shown in Figure 5. The forest plot shows that the model does not favor either group; MD with 95% CI is –0.68 [–1.87; 0.5], P = 0.26. There was low heterogeneity (I^2 = 30%).

Morphine consumption for DEX 8 mg vs. control

Two studies (DEX = 120, control = 120) reported morphine use in those who received a dose of DEX of 8 mg. The overall effect of the model (Figure 6) does not favor the DEX 8 mg group over the control group (MD with 95% CI is –10.44 [–23.92, 3.03], P = 0.13, I^2 = 90%). The sensitivity analysis shows that

TABLE 3. Summary of findings

Outcomes	Mean difference [95% CI]	Number of patients (studies)	Certainty of the evidence (GRADE)
Pain at rest DEX 4 mg POD1	–0.59 [–1.33; 0.16]	311 (5)	⊕⊕⊕◯ Moderate
Pain at rest DEX 4 mg POD2	1.23 [–0.87; 3.34]	138 (3)	⊕⊕◯◯ Low
Pain on movement DEX 4 mg POD1	–1.61 [–2.63, –0.6]	136 (3)	⊕⊕⊕◯ Moderate
Pain on movement DEX 4 mg POD2	–0.26 [–1.41, 0.88]	88 (2)	⊕⊕◯◯ Low
Pain at rest DEX 8 mg POD1	–0.55 [–0.84, –0.26]	240 (2)	⊕⊕⊕◯ Moderate
Pain at rest DEX 8 mg POD2	–0.14 [–0.38, 0.09]	240 (2)	⊕⊕⊕◯ Moderate
Morphine consumption DEX 4 mg POD1-2	–0.68 [–1.87; 0.50]	175 (2)	⊕⊕◯◯ Low
Morphine consumption D DEX ex 8 mg POD1-2	–10.44 [–23.92, 3.03]	240 (2)	⊕⊕◯◯ Low

CI – confidence interval, DEX – dexamethasone, POD – postoperative day

TABLE 2. Cochrane risk of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aoyama *et al*. 2021	+	+	+	+	+	+	+
Chisholm *et al*. 2017	+	+	+	+	+	+	+
Li *et al*. 2024	+	+	+	+	+	+	+
Morales-Munoz *et al*. 2017	+	+	+	+	+	+	+
Turner *et al*. 2018	+	+	+	+	+	+	+
Wang *et al*. 2017	+	+	+	+	+	+	+
Veneziano *et al*. 2018	+	+	+	+	+	+	+

the result is sensitive to the exclusion of either study, in which case the model favors the DEX 8 mg group. Again, given the limited number of included studies, the results should be interpreted with caution.

Risk of bias

All the studies had a low risk of bias (Table 2). All the studies described adequate randomization and allocation concealment techniques. All the studies were double-blind, and outcome measurements were also performed by blinded study team members. The missing data were addressed, and all the primary outcomes were reported in each study.

The certainty of evidence was "low" or "moderate". This is presented in the summary of findings (Table 3). Perineural DEX did not improve postoperative pain at rest. There are moderate and low levels of evidence for POD1 and POD2, respectively, due to inconsistency and imprecision. Administration of DEX 4 mg significantly reduced pain on movement on POD1, supported by moderate evidence. No differences were found in pain alleviation on movement on POD2, though the level of certainty is low. As for morphine consumption, there were no differences between the intervention group and controls for both the DEX 4 mg and DEX 8 mg groups. However, our confidence regarding these results is low due to imprecision and inconsistency. We did not assess publication bias due to the scarcity of studies (less than ten).

DISCUSSION

This meta-analysis involved seven RCTs and a total of 551 patients. Its primary focus was evaluating the effects of DEX as an adjuvant to regional peripheral blocks in knee surgery. The key outcomes considered were pain intensity and opioid requirements within two POD. These outcomes were assessed separately for DEX doses of 4 mg and 8 mg. Almost all the trials, except for one [25], had low or unclear risks of bias.

The findings did not favor the use of DEX at any dose in terms of pain intensity at rest and morphine consumption on POD1. However, administration of 4 mg of DEX showed a reduction in pain with movement by 1.61 points (on a scale out of 10) on POD1. The certainty regarding pain intensity with movement is moderate, given that the result is based only on two studies. There were slight improvements in pain in those who received the 8 mg dose of DEX.

There are several explanations for such results. One study suggested that many patients suffering from chronic knee pain often rely on opioids before surgery. This can lead to the development of opioid tolerance and opioid-induced hyperalgesia [32]. Additionally, pain catastrophizing – where patients excessively focus on and exaggerate their pain – may reduce the perceived analgesic effects of DEX. Finally, there might be differences in the effects of different PNBs [6]. Among the various types of PNBs, Kumar *et al*. [32] suggest the ACB as the preferred choice, as it was associated with reduced length of hospital stay. In contrast, FNB and sciatic nerve block have been observed to negatively affect immediate postoperative knee function, which in turn can extend the recovery period. Our meta-analysis demonstrates somewhat better analgesic effects of perineural DEX in ACB compared to FNB and SNB, according to the sensitivity analyses. However, a Cochrane systematic review of 25 RCTs and 1688 patients did not find any evidence supporting the superiority of ACBs, over sham or FNB [33].

The applicability of these results is relatively broad, extending across various demographic and clinical characteristics. We included studies focused on different age groups, from children and adolescents to adults. The included studies were conducted in different geographical locations, thus covering variations in health systems, postoperative care practices, and patient populations across different regions. In terms of surgical and intervention contexts, our

results include the most common orthopedic procedures, while the diverse regional blocks reflect the variety of anesthesia practices. Almost all the studies reported the primary outcome, namely, pain at rest. However, one of the studies lacked blinding of outcome assessors, which could affect the results.

We have found two systematic reviews that assess perineural DEX in knee surgery. One systematic review [17] was focused only on total knee arthroplasty, and out of eight studies, only two evaluated perineural DEX. A Cochrane systematic review [8] included upper and lower limb operations, with only two studies on lower limbs. Both systematic reviews concluded lower pain scores and opioid use within the first POD in the DEX group. The perineural DEX group experienced lower pain levels than the control group 12 hours after surgery, with a mean reduction of 2.08 on a 10-point scale. However, there was no clinically significant difference in pain intensity between the groups 24 and 48 hours postoperatively. The perineural DEX group required fewer opioids than the placebo group 24 hours after surgery, with a mean difference of 19.25 mg [8].

Two more systematic reviews studied perineural DEX in other types of surgery. One systematic review of four RCTs focused on the use of the DEX in knee and hip arthroplasties. The authors concluded that it reduced pain and opioid use during the first two days after surgery [18]. Another meta-analysis of nine RCTs also found decreased morphine use, with a mean difference of 8.5 mg [11]. It did not find any benefits regarding postoperative pain intensity. The mean difference did not reach one point out of ten for the outcomes of early (several hours postoperatively) and late (after 24 hours) pain.

The results of these systematic reviews are somewhat controversial, probably due to the heterogeneity of the included studies, e.g. differences in DEX administration and types of surgery. More studies, focusing specifically on perineural DEX in knee surgery, are needed to draw more solid conclusions.

Regarding our limitations, the most important one is the modest number of the included trials and low number of participants for each outcome as a result. This affected our level of certainty in evidence. For more definitive conclusions, we need more studies evaluating perineural DEX in knee surgery, particularly assessing postoperative pain on movement. The limited number of trials did not allow us to assess publication bias. However, as we included only articles written in English, there could be a considerable bias in selection of studies. Another limitation of our meta-analysis is the lack of safety assessment of perineural DEX in knee surgery patients. Glucocorticoids are notorious for causing a range of adverse events, the most common of which are infections, delayed wound healing, hyperglycemia, and psychological issues [34].

Implications for further research

Future research should address the adverse events caused by perineural DEX and effects on peripheral block duration. Long-term patient-reported outcomes, including quality of life, would also be of interest. Different PNB and the effects of perineural DEX in each should be compared to choose the block with the most benefits in knee surgery. The effects of perineural DEX should be compared with the effects of convenient intravenous administration, already recommended in guidelines for hip surgery [35].

Implications for practice

Perineural DEX can be used to reduce pain with movement and opioid requirements in knee surgery patients. Thus, it can enhance postoperative rehabilitation.

CONCLUSIONS

In this meta-analysis of seven RCTs involving 551 patients, we assessed the analgesic effects of perineural DEX as an adjuvant to regional peripheral blocks in knee surgery.

The 4 mg dose of DEX did not significantly reduce pain at rest on the first POD, but showed a benefit in reducing pain during movement, suggesting improved postoperative mobility. In contrast, the 8 mg dose provided more effective pain management at rest, indicating its potential for better overall pain management. In terms of morphine consumption, neither dose of DEX demonstrated a reduction in morphine requirements. In knee surgery patients, the use of a higher dose (8 mg vs. 4 mg) of perineural DEX may reduce pain, while a lower dose (under 4 mg DEX) may reduce pain on movement. Despite the positive findings, the evidence is limited by the relatively small number of participants included in the analysis.

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