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RESEARCH ARTICLE

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Prolonged effects of dexamethasone following total knee arthroplasty: A pre-planned sub-study of the DEX-2-TKA trial

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Abstract

Objectives: The DEX-2-TKA trial demonstrated that one and two doses of 24 mg intravenous dexamethasone reduced opioid consumption and pain after total knee arthroplasty (TKA). We aimed to investigate the prolonged effects of dexamethasone after the 48-h intervention period.

Design: This was a prospective, pre-planned questionnaire follow-up on postoperative days 3–7 of patients in the DEX-2-TKA trial that randomly received: DX1 (dexamethasone 24 mg + placebo), DX2 (dexamethasone 24 mg + dexamethasone 24 mg), and placebo (placebo + placebo) perioperatively and 24 h later.

Setting: A multicenter trial performed at five Danish hospitals.

Participants: We analyzed 434 of 485 adult participants enrolled in the DEX-2-TKA trial.

Outcome Measures: Primary outcome was difference between groups in average of all numerical rating scale (NRS) pain scores reported in the morning, at bedtime, and

the daily average pain on postoperative days 3–7. Secondary outcomes were sleep quality and patient satisfaction.

Results: The median (interquartile range) pain intensity levels for postoperative days 3–7 were: DX2 3.2 (2.1–4.3); DX1 3.3 (2.3–4.1); and placebo 3.3 (2.5–4.7). Hodges–Lehmann median differences between groups were: 0 (95% confidence interval − 0.54 to 0.2), P = 0.38 between DX1 and placebo; 0.1 (−0.47 to 0.33), $p = .87$ between DX1 and DX2; and 0.1 (−0.6 to 0.13), $p = .20$ between DX2 and placebo. We found no relevant differences between groups on sleep quality on postoperative days 3–7 nor for patient satisfaction with the analgesic treatment.

Conclusions: We found that neither one nor two doses of 24 mg intravenous dexamethasone demonstrated prolonged effects on overall pain or sleep quality on postoperative days 3–7 after total knee arthroplasty. We also found that dexamethasone had no effect on patient satisfaction.

Trial registration number: Clinicaltrials.gov NCT03506789 (main result trial).

KEYWORDS
dexamethasone, pain, total knee arthroplasty

Editorial Comment

In this exploratory substudy of a previous RCT, no additional analgesic effect on overall pain from two doses of 24 mg dexamethasone was observed beyond 48 h after total knee arthroplasty. Although no differences in overall sleep quality were observed, a higher occurrence of very bad sleep was observed in patients with repeated dexamethasone dosages.

1 | INTRODUCTION

Total knee arthroplasty (TKA) is one of the most frequently performed major orthopedic procedures with more than 1,000,000 procedures performed annually worldwide.[1] A multitude of postoperative pain treatments have been investigated in relation to total knee arthroplasty, but currently, the literature does not present a gold standard.[2]

The DEX-2-TKA trial investigated one and two doses of 24 mg intravenous dexamethasone as part of multimodal pain treatment for total knee arthroplasty.[3] The trial showed that both one and two doses of 24 mg intravenous dexamethasone compared with placebo resulted in reduced morphine consumption at 48 h postoperatively, in relevant reductions in pain at 24 h, and furthermore in reduced pain at 48 h for the group receiving two doses of dexamethasone.

Dexamethasone has a half-life of 36–72 h in relation to the anti-inflammatory properties.[4] Based on this, we found it relevant to investigate if dexamethasone would demonstrate a prolonged analgesic effect lasting beyond the intervention period of 48 h in the DEX-2-TKA trial. To account for this, all participants in the DEX-2-TKA trial received a supplemental diary questionnaire on pain for postoperative days 3–7. In addition, the diary contained questions on quality of sleep and satisfaction with the instituted pain treatment.

It is a common concern that quality of sleep may be affected by perioperative steroids.[5] The natural sleep-wake cycle is primarily regulated by the pineal hormone melatonin directly influenced by environmental cues, especially light.[6] Previous studies have shown that steroids decrease plasma levels of melatonin resulting in diminished circadian rhythm.[5] Moreover, it is believed that steroids provoke a state of hyperarousal due to the inhibitory effect on GABA causing restlessness and insomnia.[5] Furthermore, it is described that dexamethasone administered after chemotherapy causes insomnia in patients during the first week.[7]

With this sub-study of the DEX-2-TKA trial, we aimed to investigate if one and two doses of 24 mg intravenous dexamethasone given perioperatively and at 24 h after surgery would reduce pain on postoperative days 3–7. Furthermore, we aimed to investigate the impact on quality of sleep and patient pain treatment satisfaction. We hypothesized that one dose of dexamethasone would show prolonged analgesic effects and that two doses of dexamethasone would demonstrate even more prolonged effects.

2 | METHODS

This was a pre-planned sub-study of the DEX-2-TKA trial. A protocol synopsis with a statistical analysis plan was made publicly available on the trial website (www.appraz.dk, https://appraz.dk/projects/dex-2-tka/substudies) on the March 15, 2021 before outcome data from the patient diaries was explored. All outcomes were chosen prior to exploration of data.

2.1 | DEX-2-TKA trial overview

The DEX-2-TKA trial was a randomized, blinded, placebo-controlled, three-group, multicenter trial investigating the effects of one and two doses of dexamethasone as part of multimodal pain treatment on morphine consumption, pain intensity levels, and harm in patients who underwent total knee arthroplasty.[3] The methodology of the DEX-2-TKA trial is described in detail in the published protocol[8] and in the main results article.[3]

The DEX-2-TKA trial was approved by the Regional Committee on Health Research Ethics (SJ-695), Region Zealand, the Danish Medicines Agency (2018-001099-39), and the Danish Data Registration Agency (REG-034-2018) and registered at ClinicalTrials.gov (2018-001099-39). All participants provided written informed consent prior to enrolment. The consent also included the data presented in this article.

Patients having a primary, TKA were randomly allocated to one of three groups: DX1 (single dose of 24 mg intravenous dexamethasone + matching placebo (isotonic saline)), DX2 (two consecutive doses of 24 mg intravenous dexamethasone), or placebo (two doses of matching placebo [isotonic saline]). Trial medications were administered perioperatively and at 24 h postoperatively. All patients had local infiltration analgesia during surgery and paracetamol and ibuprofen were administered with 6 h intervals during the intervention period of 48 h.

All participants had patient-controlled analgesia with morphine the first 24 h postoperatively, followed by oral morphine administered on demand 24–48 h postoperatively. After the intervention period, the analgesic treatment followed local guidelines at the participating sites, (Table S1).

The main findings were that one and two doses of 24 mg intravenous dexamethasone in addition to paracetamol, ibuprofen and local infiltration anesthesia reduced postoperative morphine consumption in DX1 and DX2 compared with placebo, and with concomitant clinically relevant reductions of pain in DX1 and DX2 at 24 h postoperatively, and furthermore that clinically relevant reductions of both opioid and pain was found with two doses of dexamethasone in DX2 at 48 h postoperatively. Dexamethasone did not alter the incidence of adverse events.

2.2 | The methodology of this sub-study

This prospective, pre-planned diary sub-study was made in continuation of the DEX-2-TKA trial. All participants of the DEX-2-TKA trial received a supplemental diary with questions for postoperative days 3–7. The questionnaire was to be returned by mail. In the diary, the participants were asked to report on pain and quality of sleep postoperative days 3–7, and satisfaction with the pain treatment received after hospitalization on postoperative day 7. Pain was measured using a numeric rating scale (NRS, score range 0 [no pain] to 10 [worst imaginable pain]), and reported in the morning, before bedtime and as a daily average. Quality of sleep and satisfaction was measured on a categorical scale (very good, reasonably good, reasonably bad, very bad). In addition, the participants were asked about whether or not they had experienced sleep disturbance on postoperative days 3–7. If yes, they were asked to report the cause based on multiple options (pain, nausea, vomiting, restlessness, external disturbance and other causes).

The patient-reported outcomes were registered by a third party in an electronic case report form created in EasyTrial in connection to the DEX-2-TKA trial. This was done prior to data being explored by the investigators. The full version of the patient diary can be seen in Appendix 1.

2.3 | Outcomes

The primary outcome was the average of all the reported pain intensity levels using the numeric rating scale during postoperative days 3–7.

The secondary outcomes were quality of sleep for each night between postoperative days 3–7, and overall satisfaction with the pain treatment after postoperative day 7.

2.4 | Statistical analysis

The DEX-2-TKA trial was powered to investigate morphine consumption 0–48 h postoperatively. Therefore, this sub-study was exploratory by nature. The primary and secondary analysis were conducted on participants from the DEX-2-TKA trial who returned the patient diary for postoperative days 3–7 (Figure 1).

In the primary analysis of pain intensity levels, we predefined 1 point as a meaningful clinical difference using a numeric rating scale.

For comparing quality of sleep and patient satisfaction, numerical values were assigned to the scores from each participant (score range 0–3: 0 [very good], 1 [reasonably good], 2 [reasonably bad], 3 [very bad]).

All outcomes were assessed in pairwise comparison and stratified by site by using the nonparametric Van Elteren test. Group differences were calculated as Hodges–Lehmann median difference and presented with 95% confidence intervals. For all outcomes, we used a significance level of $p < .05$.

We used STATA, R and Microsoft Excel for the analyses.

3 | RESULTS

A total of 485 participants were enrolled in the DEX-2-TKA trial between October 2, 2018 and March 9, 2020. Of these, 434 (89.5%) returned the patient diary for postoperative days 3–7 and were included in this follow-up study (Figure 1). Demographics and baseline characteristics for the total cohort and those responding for this sub-study are presented in Table 1.

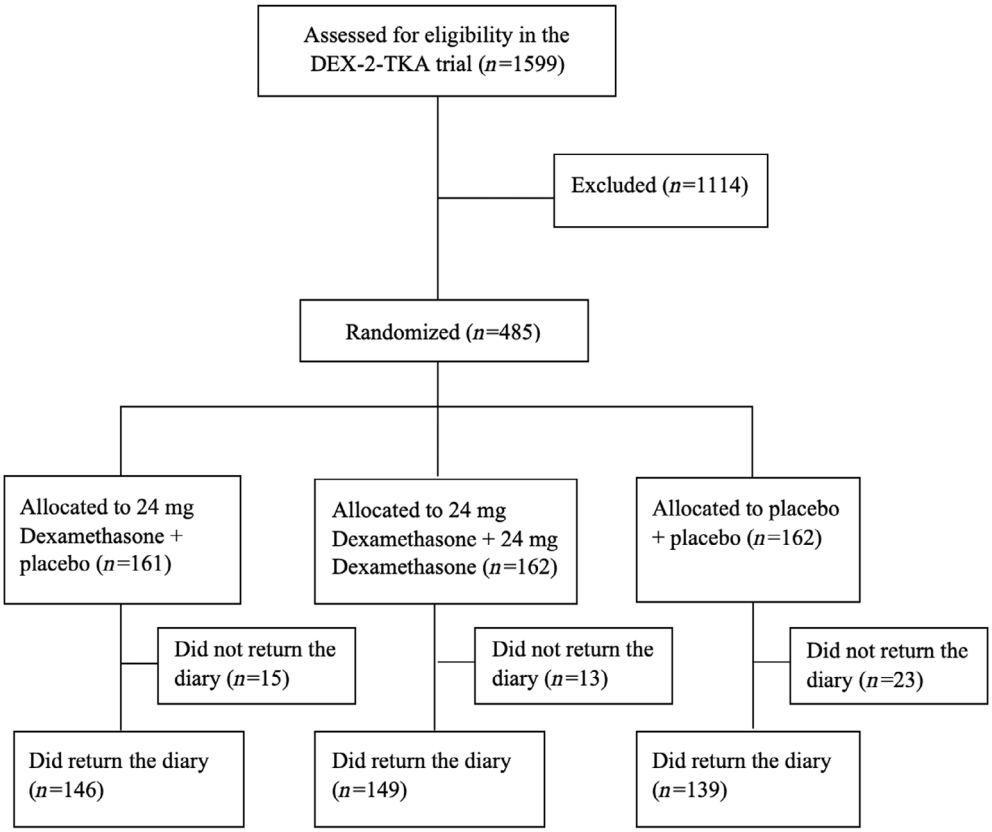

FIGURE 1 Screening and randomization of the DEX-2-TKA trial, and number of participants who did and did not return the diary.

3.1 | Primary outcome

The median pain intensity level was 3.2 (interquartile range 2.1–4.3) in DX2, 3.3 (2.3–4.1) in DX1, and 3.3 (2.5–4.7) in placebo. The van Elteren test showed no difference between DX1 and placebo (Hodges-Lehmann median difference − 0.2; 95% confidence interval − 0.54 to 0.2; $p = .3757$), between DX1 and DX2 (−0.07; −0.47 to 0.33; $p = .869$), and between DX2 and placebo (−0.27; −0.6 to 0.13; $p = .2019$) (Table 2).

Profile plot showing the mean pain intensity levels in the morning, before bedtime, and as daily average postoperative days 3–7 are presented in Figure 2. Profile plot showing the mean of the combined pain intensity levels on postoperative days 3–7 are presented in Figure S1.

3.2 | Secondary outcomes

On postoperative day 4 the median quality of sleep was 1 (1–1) in DX2, 1 (0–1) in DX1 and 1 (1–2) in placebo. No difference was found between DX1 and DX2 or between DX2 and placebo. The van Elteren test showed a difference between DX1 and placebo (Hodges–Lehmann median difference 0; 95% confidence interval 0–0; $p = .0311$) (Table 3).

No differences were found between the groups on postoperative days 3, 5, 6, or 7 (Table 3).

Table S2 and Figure S2 present the distribution of quality of sleep on postoperative days 3–7. Profile plot showing the mean quality of sleep postoperative days 3–7 is presented in Figure S3.

The distribution of sleep disturbances is presented in Table S3. Numerically, the three most frequent causes of sleep disturbance were "pain," "restlessness," and "other causes" on postoperative days 3–7 regardless of the intervention group, with pain being the most frequent cause.

No difference was found in patient satisfaction between groups after postoperative day 7 (Table 3).

4 | DISCUSSION

4.1 | Principal findings

In this pre-planned sub-study of participants enrolled in the DEX-2-TKA trial we did not find a prolonged analgesic effect of neither one or two doses of dexamethasone compared to placebo given before and 24 h after total knee arthroplasty. The median pain intensity levels for postoperative days 3–7 were low and did not differ between the groups. The profile plots displaying daily pain intensity levels also did not indicate a relevant effect on any single day. However, pain studies in patients without significant pain is challenging due to low assay sensitivity. Thus, our findings might not exclude a potential prolonged effect of dexamethasone but rather be a result of low pain intensity levels

We did not find that dexamethasone affected participants sleep except for postoperative day 4, which was most likely a chance finding. The most frequent cause of sleep disturbance was pain on

postoperative days 3–7 in all groups. Thus, the potential adverse effect of dexamethasone regarding sleep was not overrepresented in the groups receiving dexamethasone, as we hypothesized. However, it is noticeable that participants who received two doses of dexamethasone had more scores of "very bad sleep" overall. Restlessness was the second or third most common cause to sleep disturbance postoperative days 3–7 in all groups.

We did not find that participants receiving dexamethasone were more satisfied with the analgesic treatment than those who did not. Patient satisfaction with a given treatment may however depend on a number of things other than pain treatment per se. A systematic review suggests certain patient- and hospital-related predictors of patient satisfaction, for example, the quality of communication with nurses and physicians, the environment of the hospital and length of stay, with shorter stay positively associated to patient satisfaction.[9] Another review found important influence on patient satisfaction from demographic status like age, gender, ethnicity, socioeconomic status, and health status.[10] Also patient expectations and resolution of symptoms were found to be associated with patient satisfaction.[10] However, although other factors may have a significant impact on patient satisfaction, we could not detect any effect of the intervention on this matter.

TABLE 1 Demographics, baseline and perioperative characteristics.

Intervention group	The DEX-2-TKA trial	This sub-study
Baseline characteristics	($n = 485$)	($n = 434$)
Sex—no. (%)		
Male	229 (47)	206 (47)
Female	256 (53)	228 (53)
Mean age (SD)—year	68.4 (9.1)	68.4 (9.1)
ASA Score—no. (%)		
Healthy	75 (15)	70 (16)
Mild systemic disease	336 (69)	306 (71)
Severe systemic disease	74 (15)	58 (13)
Mean height (SD)—cm	172 (10)	172 (9)
Mean weight (SD)—kg	88 (17)	87 (16)
Mean body mass index (SD)—kg/m^2	29 (5)	29 (5)
Pre-operative use of opioids—no. (%)		
None	451 (93)	405 (93)
As needed	18 (4)	17 (4)
Daily	16 (3)	12 (3)
Perioperative characteristics		
Type of prothesis—no. (%)		
Uncemented	11 (2)	11 (3)
Hybrid	187 (39)	161 (37)
Cemented	287 (59)	262 (60)
Other	0 (0)	0 (0)
Type of anesthesia—no. (%)		
Spinal	391 (81)	354 (82)
General anesthesia	84 (17)	72 (17)
Conversion from spinal to general anesthesia	10 (2)	8 (2)

Abbreviations: ASA, American Society of Anaesthesiologists Score; SD, standard deviation.

4.2 | Comparison with other studies

The analgesic effect of glucocorticoids beyond 48 h after surgery has been investigated in a few other studies. These studies are, however, limited to a single and/or lower dose of glucocorticoids, and mainly a maximum of 72 h follow-up.[11,12] Nevertheless, one trial evaluated pain in a questionnaire for postoperative days 2–10 in patients undergoing total knee arthroplasty and found no prolonged analgesic effect of a single dose of 125 mg methylprednisolone (equivalent to 24 mg dexamethasone).[13] Conversely, another trial found a prolonged analgesic effect of a single dose of 8 mg dexamethasone in patients undergoing laparoscopic cholecystectomy during the first postoperative week.[7] However, in this present sub-study, we did not find a prolonged analgesic effect of neither a larger nor a repeated dose of 24 mg dexamethasone on postoperative days 3–7, which to our knowledge has not been reported previously.

TABLE 2 Primary outcome.

Intervention group	DX1 ($n = 146$)	DX2 ($n = 149$)	Placebo ($n = 139$)
Median pain intensity levels POD 3–7 (IQR)–NRS	3.3 (2.3–4.1)	3.2 (2.1–4.3)	3.3 (2.5–4.7)
DX2 and PBO compared with DX1			
Difference (95% CI)	NA	−0.07 (−0.47 to 0.33)	−0.2 (−0.54 to 0.2)
p-value	-	.87	.38
PBO compared with DX2			
Difference (95% CI)	NA	NA	−0.27 (−0.6 to 0.13)
p-value	-	-	.20

Abbreviations: CI, confidence interval; Group DX2, two doses of DXM 24 mg; Group DX1, one dose of DXM 24 mg + one dose of matching placebo (isotonic saline); Group PBO, two doses of matching placebo (isotonic saline); IQR, interquartile range; NRS, numeric rating scale (score range 0 [no pain] to 10 [worst imaginable pain]); POD, postoperative day.

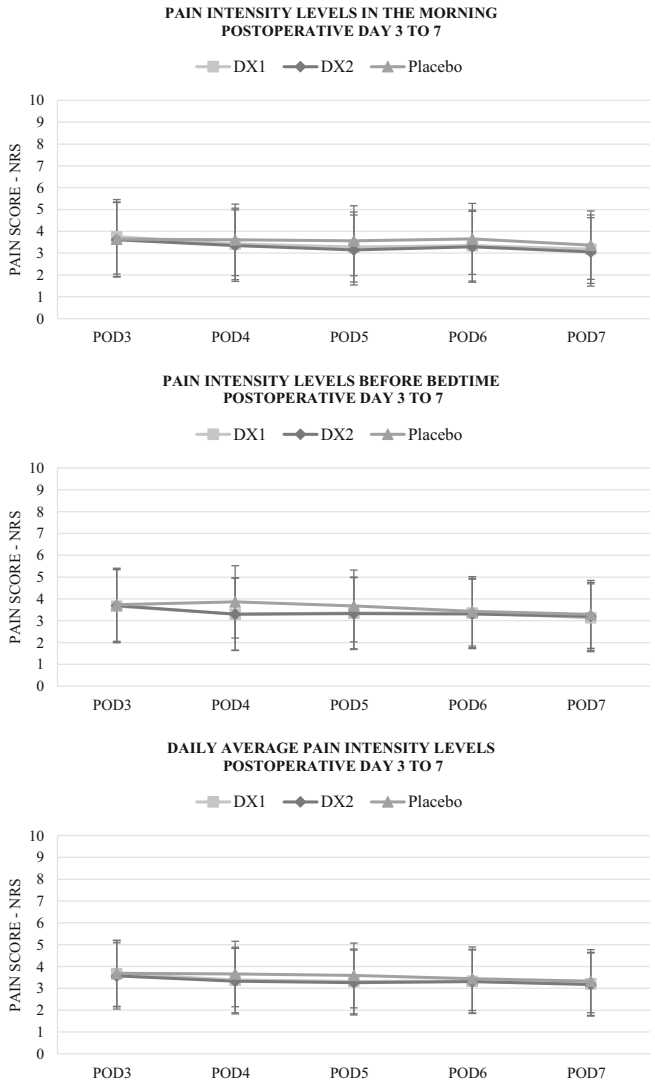

FIGURE 2 Profile plots showing the mean of the (NRS)-pain intensity levels in the morning, before bedtime, and of the daily average for each intervention group postoperative days 3–7 including standard deviations. Group DX2: two doses of DXM 24 mg. Group DX1: one dose of DXM 24 mg + one dose of matching placebo (isotonic saline). Group placebo: two doses of matching placebo (isotonic saline). POD: postoperative day.

4.3 | Strengths and limitations

It is a strength that our data arise from a randomized population with overall low-risk of bias including a few missing data. High response rates on questionnaires are often considered important for study validity. There is no established cut-off regarding an acceptable percentage of missing data, but statistical guidance articles have asserted, that missing data of 5% or less is insignificant, whereas missing data of more than 10% increases the risk of bias.[14] However, this sub-study had an encouraging response rate of 89.5%, and since the baseline characteristics of the DEX-2-TKA trial and this sub-study were very similar, we found no reason to believe that missing data was a confounder for our results, although this cannot be absolutely established. Moreover, the diaries were completed by a sample population representative for the population of interest due to the pragmatic design of the trial, contributing to the most accurate reflection of the reality as possible. Also, a protocol with a statistical analysis plan was made publicly available prior to the exploration of the data from the diary to avoid data-driven analyses and selective outcome reporting.[15]

It is a general limitation of our results that this study was not powered for the analyses, and therefore the results can only be hypothesis-generating. However, data were very unambiguous, and it is therefore unlikely that more participants would have changed the outcome. Type 1 errors are another risk typically arising from sub-studies due to multiple testing. However, to minimize the risk of type 1 error in the primary outcome the number of analyses on pain were reduced by calculating one mean pain intensity level for each participant. Data could have been further explored by longitudinal analyses. We chose not to do so in order to avoid increasing the risk of spurious significant findings by limiting a number of analyses.

A major limitation of our results is that we did not standardize the postoperative pain treatment in the investigated period as the participants were discharged with different pain treatments according to local tradition at the five participating hospitals. The major constituents were however paracetamol, NSAID and opioids at all hospitals. It can also be considered a limitation that the diary did not include questions about analgesics and how it was used in relation to the pain assessment in the diary. This could have been of value to the interpretation of the reported pain scores and to fully evaluate the analgesic effect of dexamethasone. Conversely, this pragmatic design mimics the clinical reality and possibly supports our findings.

Additionally, we did not differentiate between pain during activity and rest in the diary. Due to this, we are not able to present detailed information on type of pain but only the aggregated load of pain experienced by the participants in the morning and evening, and as an average during the day which was combined to one average pain score on POD 3–7. However, it can also be considered a strength that participants were not biased to relate to type of pain and answered according to their actual individual experience of pain in general.

Finally, it can be considered a limitation that the ordinal data concerning sleep quality and satisfaction were converted to numerical values. It is a frequently used method, but it is important to emphasize that the assumption of "reasonably good" is twice as good as "reasonably bad" may not be fully illustrated in this sub-study. In this line, it may also be considered a limitation that no meaningful difference in sleep was determined before interpretation of data. This study might have provided more detailed information on sleep by using validated questionnaires as, for example, Pittsburg Sleep Quality Index (PSQI). On the other hand, the minimal important difference of PSQI is currently unknown which makes PSQI results difficult to interpret. The diary was a hypothesis-generating study and by converting ordinal data to using a simple 0–3 numerical value, we simply aimed to see if we were able to detect any protracted effect of one or two doses of dexamethasone. However, we only detected a marginal difference that was most likely a chance finding in this study. If such were experienced, this would have to be addressed in future and more detailed studies.

TABLE 3 Secondary outcomes.

Intervention group	DX1 ($n = 146$)	DX2 ($n = 149$)	Placebo ($n = 139$)
Median sleep quality POD 3 (IQR), (0–3)	1 (1–2)	1 (1–1)	1 (1–2)
DX2 and PBO compared with DX1			
Difference (95% CI)	NA	0 (0–0)	0 (0–0)
p-value	-	.36	.17
PBO compared with DX2			
Difference (95% CI)	NA	NA	0 (0–0)
p-value	,18	-	.60
Median sleep quality POD 4 (IQR), (0–3)	1 (0–1)	1 (1–1)	1 (1–2)
DX2 and PBO compared with DX1			
Difference (95% CI)	NA	0 (0–0)	0 (0–0)
p-value	-	.29	.03
PBO compared with DX2			
Difference (95% CI)	NA	NA	0 (0–0)
p-value	-	-	.18
Median sleep quality POD 5 (IQR), (0–3)	1 (0–1)	1 (1–1)	1 (1–2)
DX2 and PBO compared with DX1			
Difference (95% CI)	NA	0 (0–0)	0 (0–0)
p-value	-	.69	.01
PBO compared with DX2			
Difference (95% CI)	NA	NA	0 (0–0)
p-value	-	-	.01
Median sleep quality POD 6 (IQR), (0–3)	1 (1–2)	1 (1–2)	1 (1–2)
DX2 and PBO compared with DX1			
Difference (95% CI)	NA	0 (0–0)	0 (0–0)
p-value	-	.95	.62
PBO compared with DX2			
Difference (95% CI)	NA	NA	0 (0–0)
p-value (van Elteren Test)	-	-	.61
Median sleep quality POD 7 (IQR), (0–3)	1 (1–2)	1 (1–2)	1 (1–2)
DX2 and PBO compared with DX1			
Difference (95% CI)	NA	0 (0–0)	0 (0–0)
p-value	-	.59	.97
PBO compared with DX2			
Difference (95% CI)	NA	NA	0 (0–0)
p-value	-	-	.58
Median satisfaction after POD 7 (IQR), (0–3)	1 (0–1)	0 (0–1)	1 (0–1)
DX2 and PBO compared with DX1			
Difference (95% CI)	NA	1 (0–0)	0 (0–0)
p-value	-	.65	.52
PBO compared with DX2			
Difference (95% CI)	NA	NA	0 (0–0)
p-value	-	-	.22

Note: Quality of sleep and satisfaction was ranged from 0 to 3: 0 [very good], 1 [reasonably good], 2 [reasonably bad] and 3 [very bad].
Abbreviations: CI, confidence interval; IQR, Interquartile range; POD = postoperative day.

It is a common concern that the administration of glucocorticoids might cause adverse events such as infection and delayed wound healing. We did not investigate this in this 7-day follow-up, but such information could have been interesting to collate in this follow-up diary. The results, however, of the 90-day follow-up on serious adverse events were reported in the main trial, and a 1-year follow-up on such adverse events are further planned in a future study.

Larger and longer-term follow-up studies may be necessary to address possible advantages and disadvantages of perioperative glucocorticoid. However, this had already been investigated in several large cohorts and randomized controlled trials.[16–19] One study reported a minor increase in blood sugar in nondiabetic patients[16] but otherwise no association was found between glucocorticoids and concerns such as extended length of stay, readmission and infection.

5 | CONCLUSION

In conclusion, this hypothesis-generating study does not suggest a prolonged analgesic effect of neither one or two doses of dexamethasone in relation to total knee arthroplasty. We found no reductions in overall pain on postoperative days 3–7 in groups receiving dexamethasone compared to placebo. In addition, we found no clinically relevant differences between groups on quality of sleep postoperative days 3–7. Lastly, we did not find that dexamethasone had any impact on patient satisfaction.

AUTHOR CONTRIBUTIONS

Cecilie Bauer Derby, Kasper Smidt Gasbjerg, and Ole Mathiesen had full access to all data in the study, took responsibility and acted as guarantors for the integrity of the data and the accuracy of the data analysis. Janus Christian Jakobsen conducted, and is responsible for, the data analysis. Cecilie Bauer Derby, Kasper Smidt Gasbjerg, and Ole Mathiesen contributed to the conception of the work and data interpretation. Cecilie Bauer Derby drafted the manuscript. Kasper Smidt Gasbjerg and Ole Mathiesen contributed to critical revision of the manuscript. All authors helped conceive the study, contributed to

editing the manuscript, and finally approved the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Researchers wishing to access data from this sub-study should contact cebm@regionsjaelland.dk in the first instance.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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