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ORIGINAL ARTICLE

Analgesic effect of a single dose of betamethasone after ambulatory knee arthroscopy: a randomized controlled trial

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Abstract
Purpose Glucocorticoids are reported to improve postoperative analgesia. The purpose of the study was to investigate whether a preoperative, single dose of betamethasone could reduce pain after ambulatory arthroscopic knee surgery.
Methods This was a randomized, double-blind, placebo-controlled trial including patients scheduled for knee arthroscopy. The intervention was an intravenous injection of betamethasone 8 mg or placebo. The primary outcome was pain day 1 evaluated by a verbal descriptor scale (VDS).
Results In total, 74 patients (betamethasone = 34; placebo = 40) were randomized. One patient in each group was excluded from analysis. During activity day 1 following surgery, the proportion with no or minor pain was significantly ($p = 0.030$) higher in the betamethasone group (22 of 33; 67 %) compared with the placebo group (17 of 39; 44 %). At rest, the corresponding figures were 26 of 33 (79 %) for betamethasone and 24 of 39 (62 %) for placebo ($p = 0.062$). After 3 months of follow-up, no patient receiving betamethasone experienced adverse events while six receiving placebo did (postoperative nausea and vomiting in five and delayed wound healing in one).
Conclusions An analgesic benefit was seen day 1 following surgery. This indicates that betamethasone has a place in ambulatory arthroscopic knee surgery.
Trial registration https://www.clinicaltrialsregister.eu/ (identifier 2009-014717-27).

Keywords Betamethasone · Pain · Arthroscopy · Randomized controlled trial

Introduction

The prevention of pain, postoperative nausea, and vomiting (PONV) is crucial for recovery and a return to normal activity after day surgical procedures [1, 2]. Evidence exists that as many as 30 % of day surgery patients suffer from moderate-to-severe postoperative pain [3]. Glucocorticoids block the cyclooxygenase and lipoxygenase pathways in the inflammatory chain reaction and can thereby contribute to a reduced pain level [4]. Several studies have confirmed the significant analgesic benefit of a single dose of dexamethasone in patients undergoing a variety of surgical procedures including orthopedic surgery, cholecystectomy, hysterectomy, tonsillectomy, and thyroidectomy [5, 6]. Preoperative administration of the drug is reported to produce a more consistent analgesic effect compared with intraoperative administration [7]. In orthopedic surgery, glucocorticoids have demonstrated an analgesic effect, however, the optimal dose has not been determined and side effects need to be addressed [8]. In addition, there is scarce information on postoperative pain following discharge after ambulatory orthopedic surgery. The advantage of administering a glucocorticoid in a multimodal approach analgetic strategy

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seems to be beneficial and improves recovery on a procedure specific basis. The fear of glucocorticoids causing increased risk of infection and gastrointestinal bleeding seems unwarranted if they are administered in a single dose in surgical patients.

The aim of the present study was to investigate whether a single dose of the long-acting corticosteroid betamethasone administered immediately prior to arthroscopic knee surgery could reduce postoperative pain in ambulatory patients. The primary endpoint was pain day 1 following surgery evaluated by a verbal descriptor scale (VDS) during both rest and activity [9]. Secondary endpoints were postoperative pain before discharge and on day 3.

Methods

Patients and study design

This was a randomized, double-blind, placebo-controlled, two-group parallel trial conducted at a tertiary center in Stockholm, Sweden. The trial was registered at https://www.clinicaltrialsregister.eu/ (identifier 2009-014717-27), approved by the regional ethics committee (no. 2009/888-31/4) and the Swedish Medical Products Agency (EU-no. 2009-014717-27). CONSORT recommendations were followed for the reporting of randomized controlled clinical trials [10] (Fig. 1).

Consecutive patients planned for elective outpatient arthroscopic knee surgery with an American Society of Anesthesiologists (ASA) physical status classification I–II were assessed for eligibility. Exclusion criteria were: age <18 years, an inability to provide informed consent due to linguistic problems or cognitive dysfunction, planned cruciate ligament repair, locked knee due to a torn meniscus with a subsequent planned meniscus reinsertion, use of a tourniquet, diabetes mellitus, bleeding disorder, atrial fibrillation, ongoing corticosteroid medication, intake of non-steroidal anti-inflammatory drugs within 2 days prior to surgery, pregnancy, and an Apfel score >II. The Apfel score is a prediction score for nausea and vomiting and includes four variables and assigns one point for each. The variables are female sex, history of motion sickness, and postoperative nausea and vomiting, non-smoker, and planned postoperative opioid treatment [11].

Intervention, randomization, and blinding

Patients were included by an anesthesiologist. All patients gave their informed written consent. Individual case report forms (CRFs) were established with consecutive subject numbers. Eligible patients were randomized to receive an intravenous injection of either betamethasone 8 mg or a placebo (sodium chloride injection 9 mg/ml) before the induction of anesthesia. Randomization was performed with a 1:1 ratio using a computer-generated, random allocation sequence concealed in consecutively numbered sealed envelopes. At the time of inclusion, an envelope was opened and a syringe with the intervention substance was prepared by a nurse not otherwise involved in data collection or care of the patients. The patients, care providers, and data collectors were blinded to the drug in use.

Standard protocol for anesthesia and surgery

Premedication was given with 1 g of paracetamol and 50 mg of diclofenac (patient numbers 1–45) or 400 mg of ibuprofen (patient numbers 46–75). General anesthesia was induced with fentanyl 0.1 mg and propofol (2–3 mg/kg), and a laryngeal mask was inserted. Anesthesia was maintained with sevoflurane and opioid supplementation (morphine in patient numbers 1–47 and oxycodone in 48–75).

The procedure performed was arthroscopic partial meniscus resection. The arthroscopic unit consisted of a standard 30° 4.5-mm arthroscopic camera and a pressurized pump unit FMS DUO®+ system (DePuy Synthes Mitek Sports Medicine, Raynham, MA, USA). The fluid pressure was set to 50 mmHg. All patients were positioned supine on a flat operating table. A side poll was used proximal to the knee on the side of the affected leg to manipulate the leg into a varus position. The figure of fourth position was used to obtain access to the lateral compartment. All surgery was performed through standardized anteromedial and anterolateral portals. Meniscus resection was performed with arthroscopic meniscal biters and a motorized shaver unit. Three experienced surgeons with skills in advanced arthroscopic surgery performed all the procedures.

Data collection

All baseline characteristics and study parameters were recorded in the CRFs. The primary outcome measure was pain day 1 following surgery recorded by a VDS during both rest and activity. Secondary endpoints were postoperative pain before discharge and postoperative pain on day 3. A VDS consists of seven phrases of pain intensity: “no pain”, “minor pain”, “moderate pain”, “strong pain”, “severe pain”, “extreme pain”, and “the most intense pain imaginable”. Additionally, a VDS allows for follow-up by telephone as it is a verbal scale.

Preoperative pain at rest and during activity was recorded using both a VDS and a visual analogue scale (VAS). At the postoperative ward, the pain level was recorded at rest and during activity using both a VDS and a VAS. Time points for recording pain were 1, 2, 3, and 4 h

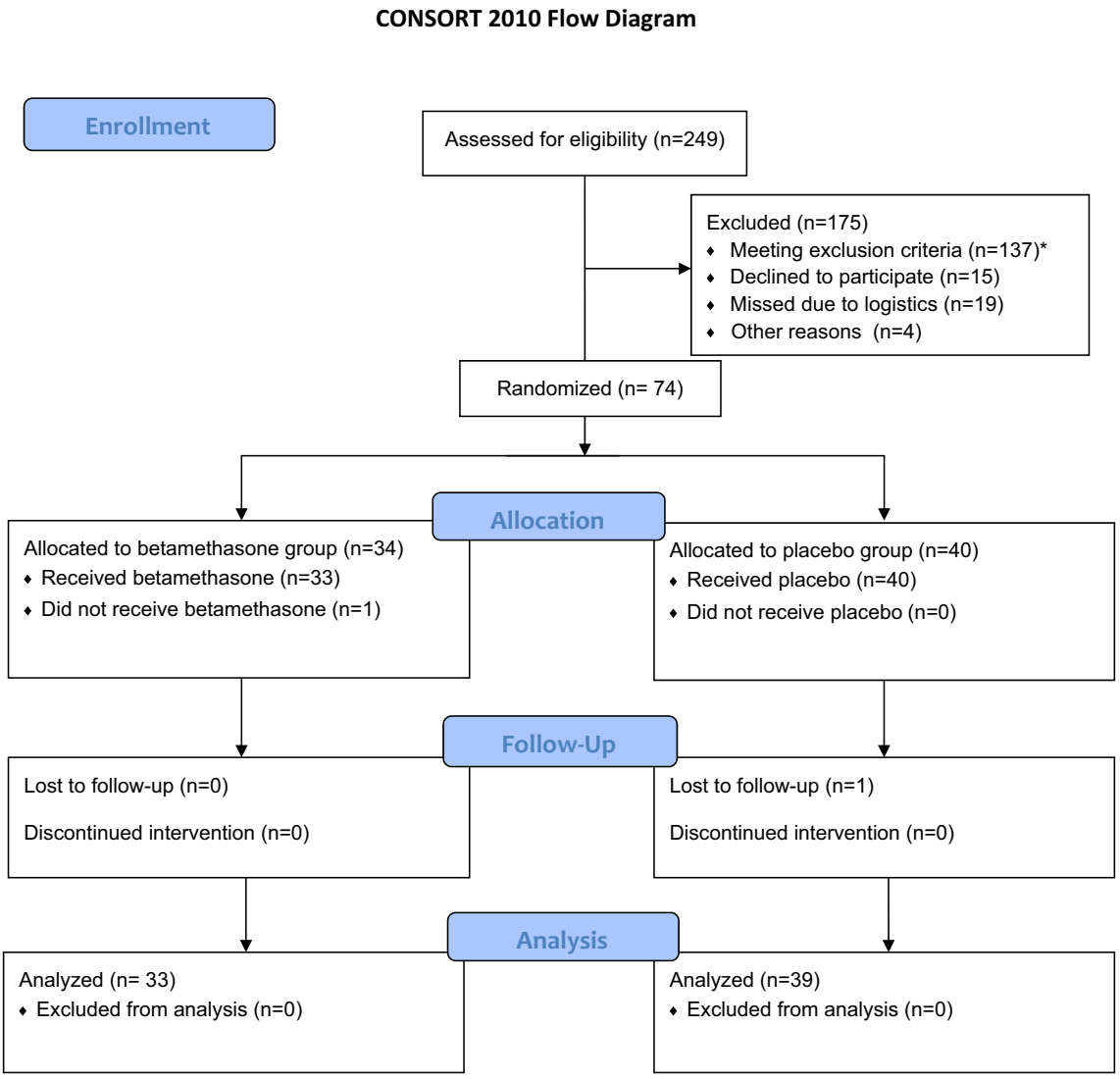

Fig. 1 Consort diagram of the inclusion and exclusion of patients. *Asterisk* locked knee due to a torn meniscus with planned meniscus reinsertion (78 patients), expected postoperative nausea and vomiting (Apfel score >II) (19 patients), age <18 years (12 patients), intake of non-steroidal anti-inflammatory drugs within 2 days prior to surgery (seven patients), ongoing corticosteroid medication (six patients), perioperative use of tourniquet (five patients), planned cruciate ligament repair, bilateral arthroscopy or other operative procedure (five patients), inability to leave informed consent due to linguistic problems or cognitive dysfunction (three patients), diabetes mellitus (one patient), contraindication for glucocorticoids (one patient)

postoperatively or until discharge, whichever came first. Prior to discharge, the patients were given a protocol for the recording of their VDS and consumption of analgesics at home. The patients were instructed to record their pain levels at rest and activity in the morning on days 1 and 3 after surgery. Intake of analgetics (drug and dose) within 4 h of pain registration and any possible adverse events were recorded. The patients were contacted on day 3 by the research nurse or the attending anesthesiologist and were then asked to present their results. The patients were informed by the surgeon before discharge what the findings were during surgery and subsequent recommendations for rehabilitation. All patients received a printed self-exercise programme recommended by the clinic, and were instructed how to follow it by a physiotherapist before discharge. After this type of procedure, there is no routine follow-up but all patients were advised to contact the clinic in case of any complications and not to consult other hospitals or general practitioners. The information supplied to the patients included a list of complications they were encouraged to assess. Three months after surgery, the medical records were scrutinized for any late adverse events.

Table 1 Clinical characteristics and operative data on randomized patients

Variable	Betamethasone group, $N = 34$	Placebo group, $N = 40$
Age (years)[a]	44.2 (13.0)	38.9 (12.0)
Gender		
Male	23 (68 %)	26 (65 %)
Female	11 (32 %)	14 (35 %)
Preoperative verbal descriptor scale at rest		
0–1	19 (56 %)	26 (65 %)
2–7	11 (32 %)	11 (28 %)
Missing	4	3
Preoperative verbal descriptor scale during activity		
0–1	7 (21 %)	14 (35 %)
2–7	23 (68 %)	22 (55 %)
Missing	4	4
Duration of surgery (min)[a]	25.5 (16.0)	24.5 (21.8)
Missing	2	1
Morphine or oxycodone use during surgery (mg)[a]	3.5 (2.6)	3.3 (1.6)
Missing	7	2

[a] Values are mean (SD)

Statistics

We estimated that a sample of 91 patients in each group would be needed to provide a statistical power of 80 % to detect an absolute difference of 20 percentage points in the proportion with no or minor pain (VDS 0–1) 1 day following surgery. We dimensioned the study to detect a clinically relevant difference by assuming a rate of 20 % with placebo and 40 % with betamethasone. The calculations were performed in SamplePower 2.0 and based on the Casagrande and Pike formula (Fisher approximation), with a two-sided alpha value of 0.05. In addition, we assumed that 10 % of the patients would be lost to follow-up and the recruitment goal was therefore set to a total of 203 patients [182/(1 − 0.1)].

To compare VAS differences at rest and during activity at different time points (i.e., preoperatively, and 1, 2, 3, and 4 h after operation) between the groups who received placebo or betamethasone we used the independent *t* test. To study the differences between the groups regarding the proportion with no or minor pain (VDS 0–1) on day 1, (i.e., primary outcome) and day 3 we used Fisher's exact test.

We used multiple logistic regression to study whether the association between the intervention groups and no or minor pain remained after adjustment for differences in preoperative VDS (rest and activity), and age and gender.

All tests were two-sided and considered significant if the p value <0.05.

Results

From May 2011 to February 2013, 74 patients were included in the study, with a follow-up period of 3 months. Unfortunately, the study was closed prematurely due to several reasons. Firstly, the inclusion rate was slower than anticipated. The main reason for this was that more patients than expected were scheduled for reinsertion of the meniscus due to changes in surgical decisions (Fig. 1). Secondly, the number of orthopedic surgeons increased and there was a policy switch regarding the choice of analgetics for pre-medication. The decision to close the study was taken before the results of the randomization were known.

In total, 249 patients were assessed for eligibility (Fig. 1); 175 were excluded, of which 137 met at least one exclusion criterion. Fifteen patients declined to participate. Nineteen patients were not included due to a lack of qualified research personnel on site.

Thus, 74 patients were randomized. All patients were operated with an arthroscopic partial meniscus resection without any perioperative complications. The clinical characteristics are presented in Table 1. Thirty-three patients received betamethasone and 40 received placebo. One patient randomized to the betamethasone group did not receive the study drug due to the start of surgery being delayed. Follow-up was possible for all patients except for one in the placebo group. In total, 33 patients in the betamethasone group and 39 in the placebo group were analyzed.

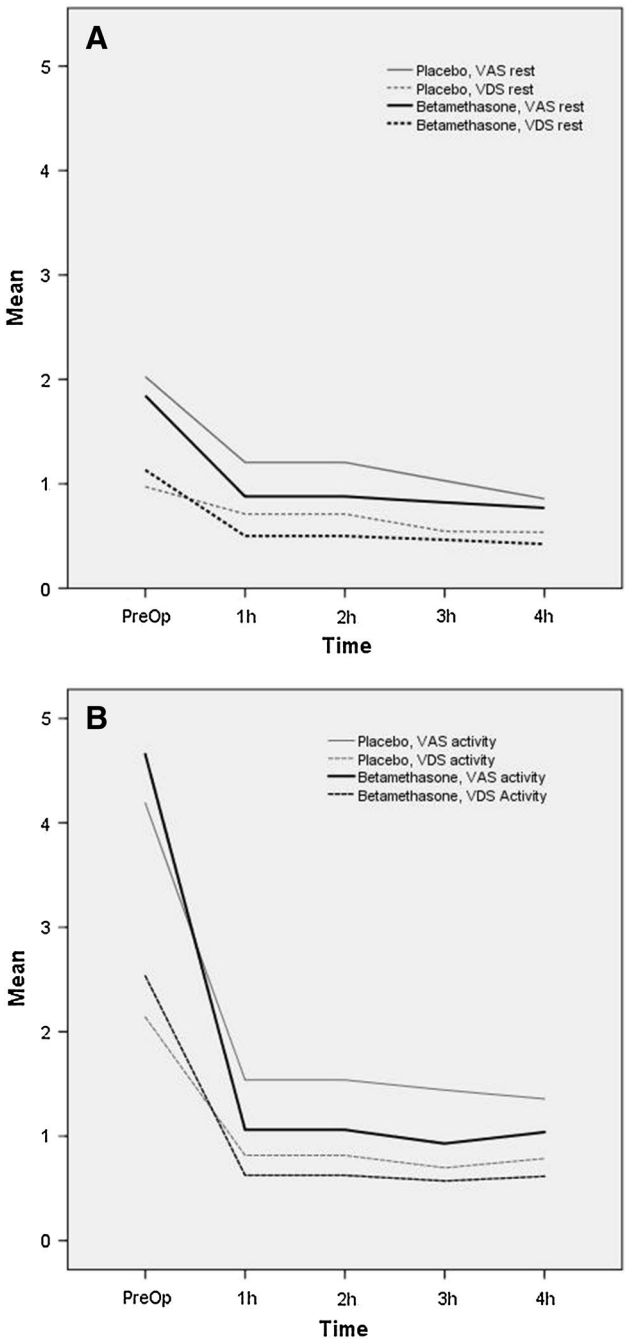

Fig. 2 Pain at rest (**a**) and during activity (**b**) preoperatively and 1, 2, 3, and 4 h postoperatively in patients undergoing ambulatory knee arthroscopy, reported as mean values of the visual analogue scale (VAS) and verbal descriptor scale (VDS), for the placebo and betamethasone groups

Postoperative pain 1–4 h following surgery is reported in Fig. 2. There were no significant differences between the placebo and betamethasone groups.

Postoperative pain on day 1 following surgery is reported in Fig. 3. For day 1, at rest, the proportion with no or minor pain (VDS 0–1) was not significantly ($p = 0.062$) higher among patients who received betamethasone (26 of 33; 79 %) compared with the placebo group (24 of 39; 62 %), although mean VDS in the betamethasone group (0.71 ± 1.01 SD) was significantly lower compared with the placebo group (1.54 ± 1.57 SD) ($p = 0.009$).

For day 1, during activity, the proportion with no or minor pain (VDS 0–1) was significantly higher ($p = 0.030$) among patients who received betamethasone (22 of 33; 67 %) compared with the placebo group (17 of 39; 44 %). Moreover, mean VDS in the betamethasone group (1.23 ± 1.15 SD) was significantly lower compared with the placebo group (2.15 ± 1.68 SD) ($p = 0.008$).

The multiple logistic regression analysis is presented in Table 2. The effect of betamethasone on the outcome of no or minor pain (VDS 0–1) day one at rest remained significant (OR 3.7, 95 % CI 1.1–12.8) after adjustment for preoperative no or minor pain (VDS 0–1), age and gender. In contrast, the effect of betamethasone on the outcome of no or minor pain (VDS 0–1) day one during activity was not significant after adjustment (OR 2.9, 95 % CI 1.0–8.7).

On day 3 after surgery, no significant differences were found between the groups. At rest, mean VDS was 0.52 (±0.81 SD) in the placebo group and 0.68 (±0.87 SD) in the betamethasone group ($p = 0.411$). During activity, the corresponding figures were 1.03 (±1.17 SD), 1.05 (±1.01 SD), and $p = 0.939$.

Adverse side effects

Overall, no patient receiving betamethasone experienced adverse events while six patients receiving placebo did: PONV occurred in five and delayed wound healing in one. One patient in the betamethasone group experienced euphoria on day 1 after surgery.

Discussion

This was a randomized controlled trial where a preoperative single dose of 8 mg of betamethasone was associated with reduced pain on the first postoperative day following outpatient arthroscopic knee surgery. The primary endpoint, pain on day 1 after surgery both at rest and during activity, was lower in the betamethasone compared with the placebo group. In the logistic regression analysis, preoperative no or minor pain (VDS 0–1) and the intervention of 8 mg of betamethasone were significant predictors for no or minor pain (VDS 0–1) at rest on day 1 after surgery.

These findings are in line with other studies reporting a reduction of pain when systemic corticosteroids are administered [12]. Kardash et al. reported that dexamethasone reduced pain after hip surgery although the dose was as high as 40 mg [13]. Romundstad et al. gave a large dose of

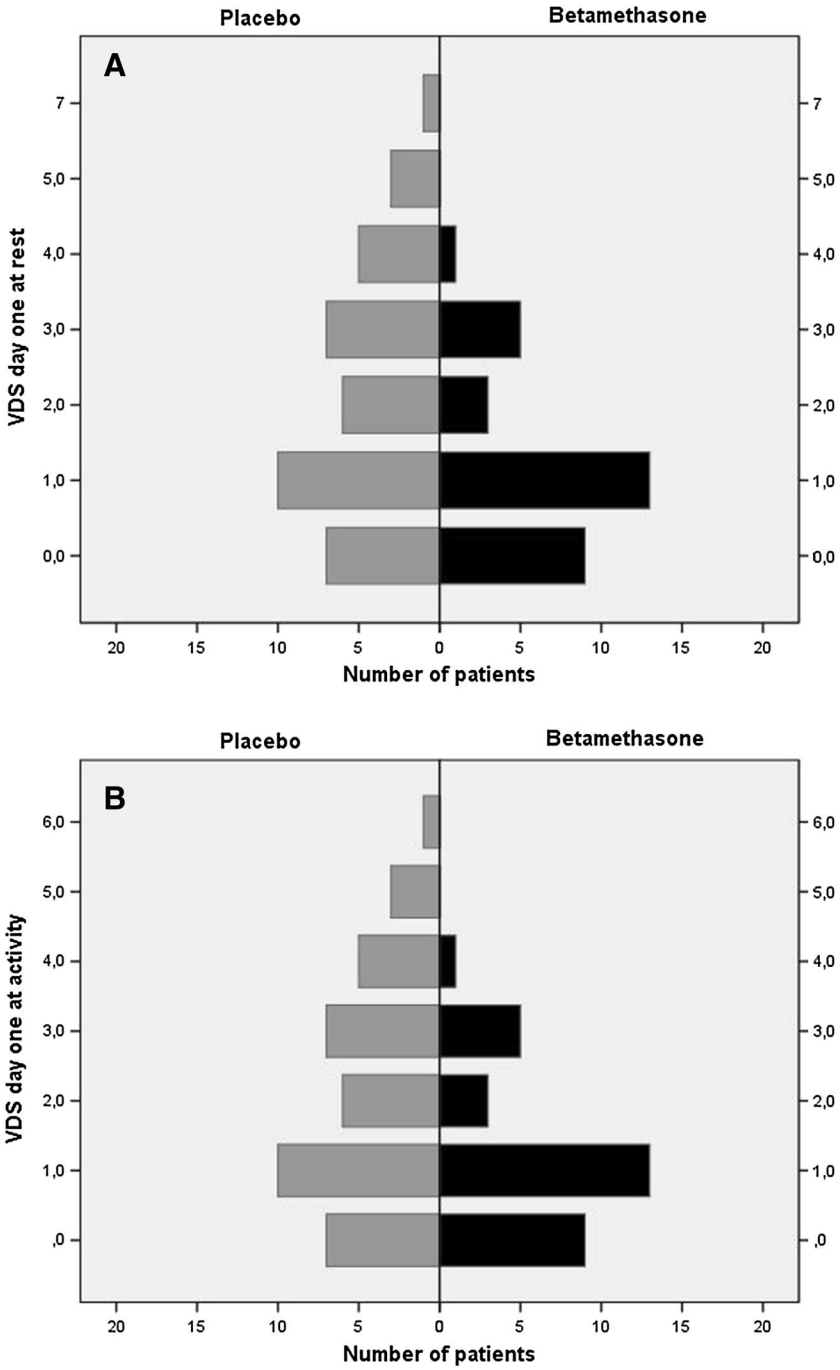

Fig. 3 Pain at rest (**a**) and during activity (**b**) 1 day following ambulatory knee arthroscopy, according to the verbal descriptor scale (VDS), for the placebo and betamethasone groups

methylprednisolone postoperatively and obtained reduced pain following orthopedic surgery [14]. Aasboe et al. gave betamethasone to patients undergoing surgery for hallux valgus or hemorrhoids and found a significant reduction in both nausea and pain postoperatively in an outpatient setting, although this study was limited by a small sample size [15].

Glucocorticoids have powerful anti-inflammatory properties and several synthetic agents have been developed from the primary corticosteroid hydrocortisone. It is desirable to avoid unwanted mineralocorticoid side effects. Dexamethasone and betamethasone lack these effects and are also more long acting and cause less inhibition on the hypothalamic–pituitary–adrenal axis [16]. It has been shown previously that non-genomic, non-inflammatory linked effects on membrane receptors of pain transmission neurons and anti-hyperalgesic effects might be important as an explanation of the analgesic effects of cortisone why a more appropriate way of administering glucocorticoids as a component in a multimodal analgesic approach would be pre-operatively [2]. An increased risk of infection and

Table 2 Multiple logistic regression analysis of predictors for the primary outcome verbal descriptor scale 0–1 (no to mild pain) at rest and during activity on day 1 following knee arthroscopy. $N = 70$

Predictor	Level	Verbal descriptor scale 0–1 on day 1 at rest				Verbal descriptor scale 0–1 on day 1 during activity			
		Total number	Number with verbal descriptor scale 0–1 on day one at rest (%)	OR (95 % CI)	*p*	Total number	Number with verbal descriptor scale 0–1 on day 1 during activity (%)	OR (95 % CI)	*p*
Age	<40	29	21 (72 %)	1		29	15 (52 %)	1	
	≥41	41	29 (71 %)	0.6 (0.2–2.1)	0.422	41	24 (59 %)	1.1 (0.4–3.5)	0.829
Gender	Female	23	13 (57 %)	1		23	12 (52 %)	1	
	Male	47	37 (79 %)	2.2 (0.7–7.2)	0.183	47	27 (57 %)	1.2 (0.4–3.4)	0.772
Preoperative verbal descriptor scale at rest	2–7	22	12 (55 %)	1	–	–	–	–	–
	0–1	43	33 (77 %)	3.7 (1.1–12.8)	0.039	–	–	–	–
Preoperative verbal descriptor scale during activity	2–7	–	–	–	–	43	23 (53 %)	1	
	0–1	–	–	–	–	21	11 (52 %)	1.1 (0.4–3.5)	0.806
Intervention	Placebo	39	24 (62 %)	1		39	17 (44 %)	1	
	Betamethasone	31	26 (84 %)	4.6 (1.2–17.6)	0.027	31	22 (71 %)	2.9 (1.0–8.7)	0.062

OR odds ratio, *CI* confidence interval

gastrointestinal bleeding seems unwarranted if glucocorticoids are administered in a single dose in surgical patients.

In the rather short perspective of this study, we found no negative side effects. Complications were mainly related to PONV problems in the placebo group. One patient in the betamethasone group experienced euphoria on day 1 after surgery. There is always a trade-off between the possible side effects and the actual beneficial analgesic effects of a drug. It has been speculated that corticosteroids do not produce changes in pain parameters when there is not enough pain, edema, and trauma. This may explain the conflicting results from several different studies, particularly in the orthopedic area [16].

The present study has both strengths and limitations. It was designed as a prospective, randomized, controlled trial. The staff and patients were unaware of the intervention drug administered. The group of patients was homogenous, only one patient was lost to follow-up, and there were few missing data. The main limitation was that the study was prematurely terminated. However, despite this, our main hypothesis with pain reduction day 1 was confirmed. Although one possible explanation is that this was the result of a type I error, another explanation is that the true effect of betamethasone in reducing pain might be higher than the 20 % points that we dimensioned the study to detect, and that we therefore were able to find a difference with a smaller sample size.

Conclusions

This was a randomized controlled trial investigating the analgesic effects of a preoperative, systemic, single dose of 8 mg of betamethasone after ambulatory arthroscopic knee surgery. Despite early closure of the study, a significant benefit was seen regarding the primary endpoint, pain on day 1 following surgery. This indicates that betamethasone has a place in ambulatory arthroscopic knee surgery.

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References

1. Simsa J, Magnusson N, Hedberg M, Lorentz T, Gunnarsson U, Sandblom G. Betamethasone in hernia surgery: a randomized controlled trial. Eur J Pain (Lond, Engl). 2013;17(10):1511–6.
2. Lunn TH, Kehlet H. Perioperative glucocorticoids in hip and knee surgery—benefit vs. harm? A review of randomized clinical trials. Acta Anaesthesiol Scand. 2013;57(7):823–34.

3. McGrath B, Elgendy H, Chung F, Kamming D, Curti B, King S. Thirty percent of patients have moderate to severe pain 24 hr after ambulatory surgery: a survey of 5,703 patients. Can J Anaesth. 2004;51(9):886–91.
4. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. N Engl J Med. 2005;353(16):1711–23.
5. Glasser RS, Knego RS, Delashaw JB, Fessler RG. The perioperative use of corticosteroids and bupivacaine in the management of lumbar disc disease. J Neurosurg. 1993;78(3):383–7.
6. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2013;110(2):191–200.
7. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. J Am Coll Surg. 2002;195(5):694–712.
8. Bjornholdt KT, Monsted PN, Soballe K, Nikolajsen L. Dexamethasone for pain after outpatient shoulder surgery: a randomised, double-blind, placebo-controlled trial. Acta Anaesthesiol Scand. 2014;58(6):751–8.
9. Herr KA, Spratt K, Mobily PR, Richardson G. Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. Clin J Pain. 2004;20(4):207–19.
10. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357(9263):1191–4.
11. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91(3):693–700.
12. 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.
13. Kardash KJ, Sarrazin F, Tessler MJ, Velly AM. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. Anesth Analg. 2008;106(4):1253–7 **(table of contents)**.
14. Romundstad L, Breivik H, Niemi G, Helle A, Stubhaug A. Methylprednisolone intravenously 1 day after surgery has sustained analgesic and opioid-sparing effects. Acta Anaesthesiol Scand. 2004;48(10):1223–31.
15. Aasboe V, Raeder JC, Groegaard B. Betamethasone reduces postoperative pain and nausea after ambulatory surgery. Anesth Analg. 1998;87(2):319–23.
16. 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.