European Journal of Orthopaedic Surgery & Traumatology (2019) 29:1473–1479
https://doi.org/10.1007/s00590-019-02469-5

ORIGINAL ARTICLE • KNEE - ARTHROPLASTY

Pre-operative intravenous steroid improves pain and joint mobility after total knee arthroplasty in Chinese population: a double-blind randomized controlled trial

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Received: 26 December 2018 / Accepted: 12 June 2019 / Published online: 20 June 2019

Abstract

Introduction This study aims to investigate the effect of pre-operative intravenous methylprednisolone on post-operative pain control and joint mobility in Chinese patients undergoing single primary total knee arthroplasty.

Methods This is a prospective, randomized, double-blinded, placebo-controlled single-centre trial. Sixty subjects were randomized into intervention and control group. The peri-operative anaesthetic and analgesic regimes were standardized. The intervention group received 125 mg methylprednisolone intravenously on the induction of anaesthesia. Subjects were assessed at 24, 30 and 48 h after surgery and upon discharge for pain scores and range of movement from the operated knee. Change in C-reactive protein level was calculated. Patient's satisfaction was recorded. Adverse reactions were documented. Subjects were followed up at 6 weeks, 4 months and 1 year.

Results Rest pain and pain on movement were significantly reduced in the methylprednisolone group at 24 and 30 h after surgery (ANOVA $p=0.030$, $p=0.003$, $p=0.032$, $p=0.010$). The methylprednisolone group demonstrated a greater range of movement from the operated knee up to 30 h after surgery (ANOVA $p=0.031$). Post-operative C-reactive protein level was significantly less in the methylprednisolone group ($p<0.001$). Methylprednisolone group had a higher patient's satisfaction than the control group ($p<0.01$). No adverse effects were noted at the 1-year follow-up.

Conclusion Pre-operative intravenous methylprednisolone improves post-operative pain and joint mobility after total knee arthroplasty up to 30 h after operation. It results in a higher patients' satisfaction. It can act as an effective adjunct in the multimodal analgesic regime.

Trial registration ClinicalTrials.gov ID: NCT03082092.

Keywords Steroids · Pain · Total knee arthroplasty · Range of movement · Chinese

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Introduction

Compared to conservative management alone, patients with moderate-to-severe knee osteoarthritis treated with total knee arthroplasty showed a better pain relief and functional outcome [1]. However, post-operative pain relief remains an important challenge. In a systematic review, Gunaratne et al. reported that poor peri-operative pain control was a factor for dissatisfaction after total knee arthroplasty [2]. A prospective survey of more than 10,000 patients showed that moderate or severe post-operative pain and severe nausea and vomiting were associated with patients' dissatisfaction [3].

Considering steroid as an adjunct to the multimodal analgesic regime, it can reduce post-operative inflammation and surgical stress response. Inflammatory markers such as IL-6 [4] and C-reactive protein [5] showed significant reduction after the administration of peri-operative steroids. In both orthopaedic and non-orthopaedic operations, a single high-dose of pre-operative systemic steroid was found to be effective in reducing early post-operative pain, nausea and vomiting [6–10].

Focusing on the use of peri-operative intravenous steroids in total knee arthroplasty or total hip arthroplasty, a few meta-analyses showed an improvement in post-operative pain, nausea and vomiting control [11–15]. Yue et al. concluded that peri-operative systemic steroid use could also enhance functional rehabilitation in one of the meta-analyses [11]. To achieve the analgesic effect and reduction in opioid consumption, De Oliverira et al. proved that dexamethasone at doses more than 0.1 mg/kg was required [16]. Liu et al. found that the systemic use of methylprednisolone, instead of local use, can achieve pain reduction in total joint arthroplasty [15].

However, the effect of systemic steroids on post-operative pain control for total knee arthroplasty in Chinese population is yet to be studied. Majority of the randomized controlled trials focused on post-operative control of pain, nausea and vomiting; the data for the improvement in the range of movement in total knee arthroplasty were scarce [4, 5, 17–19]. No studies investigated patient's satisfaction towards post-operative pain control with intravenous steroids in total knee arthroplasty.

Materials and methods

This is a prospective, randomized, double-blinded, placebo-controlled single-centre trial. Prior regional ethic committee approval was obtained. All human studies have been approved by the regional ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patients undergoing elective single primary total knee arthroplasty in our hospital from June 2017 to March 2018 were recruited. Patients who were aged < 18 or > 85, or with American Society of Anaesthesiologist (ASA) grading of ≥ 3 were excluded. Subjects with the diagnosis of rheumatoid arthritis, seronegative arthritis or post-traumatic arthritis were excluded. Patients with an allergy to any medications used in the standard protocol of our hospital for total knee arthroplasty ("Appendix") were excluded. Subjects with chronic opioid use, substance dependence, hepatitis B or deranged liver function, history of peptic ulcer disease, uncontrolled diabetic patients with HbA1c > 7.5% in recent 3 months were excluded. Patients who suffered from psychiatric or neurological conditions that may influence pain perception and reporting were excluded. Subjects that contraindicated to spinal anaesthesia were excluded (Table 1).

Informed consent was obtained from the recruited patients. An independent investigator randomized subjects into intervention group or control group in 1:1 ratio by computer. Allocations were kept in concealed envelopes. Surgeons, anaesthetists, patients, nurses and physiotherapists were all blinded.

All subjects received single total knee arthroplasty using the same implant, NexGen LPS-Flex® high flexion total knee prosthesis (Zimmer Inc., Warsaw, IN, USA) under spinal anaesthesia. All operations were carried out by two orthopaedic fellows specialized in joint arthroplasty. All operations were done with the use of tourniquet. The pre-operative, intra-operative and post-operative analgesic regimes were the same between the groups. Intra-articular multimodal analgesic injection was given, combined with post-operative patient-controlled analgesia for 48 h ("Appendix"). The intervention group received

Table 1 Exclusion criteria

Exclusion criteria
Age < 18 or > 85
ASA (American Society of Anaesthesiologists) grading ≥ 3
Rheumatoid arthritis, seronegative arthritis or post-traumatic arthritis
Allergy to any medications used in the standard protocol
Methylprednisolone, Adrenaline, Ropivacaine, Ketorolac, Heavy Bupivacaine, Tranexamic acid, Cefazolin, Gabapentin, Etoricoxib, Paracetamol, Dihydrocodeine, Morphine, Esomeprazole, Bisacodyl, Metoclopramide
Chronic opioid use
Substance dependence
Psychiatric or neurological condition that may influence pain perception or reporting
Hepatitis B carrier or deranged liver function
History of peptic ulcer disease
Uncontrolled diabetic patients with HbA1c > 7.5% in recent 3 months
Contraindications to spinal anaesthesia

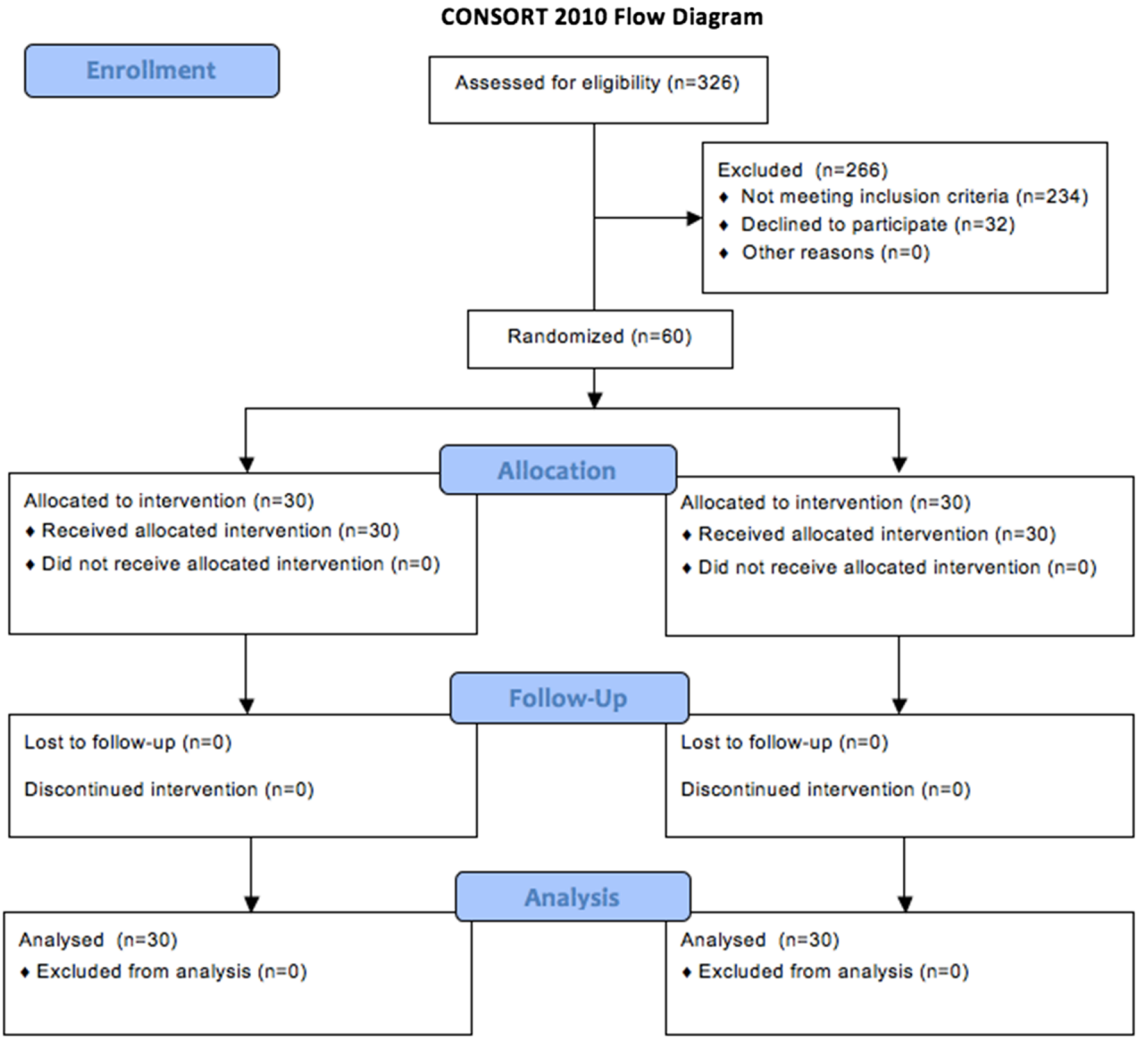

Fig. 1 CONSORT flow diagram

an additional 125 mg methylprednisolone intravenously on the induction of anaesthesia. 10 mg/kg of intravenous tranexamic acid was given before the end of operation to minimize blood loss in both groups.

Subjects were assessed by physiotherapists at 24, 30 and 48 h after surgery and upon discharge. In each assessment, primary outcomes, including rest pain and pain on movement from operated knee, were assessed with 100-mm visual analogue scale (VAS) during patients performing different tasks, including at rest, maximal knee flexion, straight knee raise with 45 degree hip flexion and frame walking for 5 m. Range of movement from the operated knee was also documented in each assessment. Time to achieve independent frame walking for 5 m and length of in-hospital stay were recorded in terms of days.

Blood was taken for C-reactive protein (CRP) in day 1 after surgery and compared with pre-operative CRP. Renal function and blood sugar were monitored to detect any hypokalaemia or hyperglycaemia. Subjects were also asked to rate the sleep quality on the day of operation using a 100-mm VAS (0 = worst sleep; 100 = best sleep). Patient's satisfaction was recorded upon discharge with 100-mm VAS (0 = not satisfied at all; 100 = completely satisfied).

Subjects were followed up at 6 weeks, 4 months and 1 year after the operation to assess the range of movement, pain scores and any prosthetic joint infections.

Sample size was calculated based on Jules-Elysee's study in 2012 on steroid use in bilateral total knee arthroplasty [4]. Considering a difference in pain score of 1.0 at 24 h post-operatively as clinically relevant and specified such an effect to be detected with 80% power and a significant level alpha of 0.05, the sample size was approximately 25 subjects for each group. A 10% exclusion rate was expected; therefore, 60 patients with each arm having 30 subjects were recruited.

For categorical data, Chi-squared test or Fisher's exact test was used. Independent *t* test was performed on continuous

Table 2 Baseline demographics and clinical characteristics of subjects

	Placebo group	Intervention group	*p* value
Age	68.1 ± 4.8	66.7 ± 7.3	0.386
Sex (male/female)	8/22	8/22	1
BMI	26.7 ± 3.5	26.3 ± 3.4	0.653
Side (left/right)	12/18	15/15	0.604
Pre-morbid (unaided/stick)	15/15	18/12	0.604
Rest pain	8.1 ± 14.7	4.5 ± 8.0	0.234
Straight knee raise	19.7 ± 23.3	14.9 ± 23.3	0.431
Maximal knee flexion	23.7 ± 22.1	19.0 ± 19.5	0.383
Frame walking for 5 m	15.3 ± 17.2	8.1 ± 11.7	0.060
Range of movement (°)	109 ± 20.4	106 ± 17.0	0.538
C-reactive protein (mg/L)	2.8 ± 2.1	2.3 ± 2.9	0.417
ASA class (1/2)	3/27	3/27	1
Blood loss (ml)	26.3 ± 20.4	27.8 ± 29.4	0.819
Surgery time (min)	68.1 ± 16.2	65.0 ± 12.5	0.415

ASA American Society of Anaesthesiologists, *BMI* body mass index

data. For continuous data with repeated measures, ANOVA was used. Statistical analysis was performed with SPSS version 20, and the level of significance was set as $p < 0.05$.

Results

Sixty subjects with 30 patients in each arm were analysed. There was no loss of follow-up (Fig. 1). The baseline characteristics between the groups were similar with *p* value > 0.05 (Table 2).

Rest pain and pain on movement, including straight knee raise, maximal knee flexion and walking with frame for 5 m, were significantly reduced in the methylprednisolone group at 24 and 30 h after surgery than the placebo group (ANOVA $p = 0.030$, $p = 0.003$, $p = 0.032$, $p = 0.010$, respectively). The effect was not seen beyond 30 h after surgery (Fig. 2). Analgesic consumption in terms of morphine use in patient-controlled analgesia at post-operative 48 h was not different between the groups ($p = 0.527$, Table 3).

The methylprednisolone group demonstrated a greater range of movement from the operated knee at 24-h and 30-h post-operative assessment (ANOVA $p = 0.031$). Similarly, the effect was not observed beyond 30 h after surgery (Fig. 2).

Patient's satisfaction was higher in the methylprednisolone group than that in the control group upon discharge ($p < 0.01$, Table 3). Post-operative CRP was significantly less in the methylprednisolone group ($p < 0.001$, Table 3).

Time to achieve walking with frame for 5 m was not different between the groups ($p = 0.118$, Table 3). Length of in-hospital stay was not significantly different between the groups ($p = 0.391$, Table 3).

Some subjects in the methylprednisolone group did experience hypokalaemia or hyperglycaemia in the early post-operative period, but statistically it was not significant ($p = 1.0$, $p = 0.103$, respectively, Table 3). Sleep quality on the day of operation between the groups was not different ($p = 0.687$, Table 3).

At 6-week, 4-month and 1 year follow-up, there was no difference in pain scores and range of movement between the groups (Table 4). There were no wound complications or prosthetic joint infections noted in both the groups.

Discussion

Use of systemic steroids in total knee arthroplasty is increasingly popular. Table 5 shows a summary of randomized control trials from previous publications. Five studies were identified, two of them focusing on single total knee arthroplasty [5, 18], another two on bilateral total knee arthroplasty [4, 19], and the remaining one including both unilateral total knee arthroplasty and unilateral total hip arthroplasty [16]. Different types of steroids were involved, including dexamethasone [17, 18], methylprednisolone [5] and hydrocortisone [4, 19]. There was no direct comparison to prove which drug was superior. Dosing regimes ranged from a single pre-operative dose to repeated doses up to three doses at 24 h after operation.

Although the anaesthetic method and peri-operative pain regimes were different between the studies, all studies showed a significant improvement in the post-operative pain control. The duration of pain reduction effect ranged from 24 to 48 h post-operatively. Half-lives of hydrocortisone, methylprednisolone and dexamethasone were around 8–12 h, 18–36 h and 36–54 h, respectively [20]. This may explain why the pain relief effect weaned off after post-operative day 2. Our study showed significant reduction in pain scores up to 30 h, which is comparable with other studies.

Functional outcomes were less reported. Jules-Elysee et al. [4, 19] and Backes et al. [17] showed an improvement in the range of movement on the day of discharge and post-operative day 2, respectively. Backes et al. showed that, with additional dose of dexamethasone at post-operative 24 h, subjects can ambulate further in post-operative day 0–2 and achieved a shorter length of stay [17]. Our study demonstrated a significant improvement in the range of motion up to 30 h after surgery, which is a more objective measurement than pain scores subjectively reported by patients. More intense rehabilitation can be

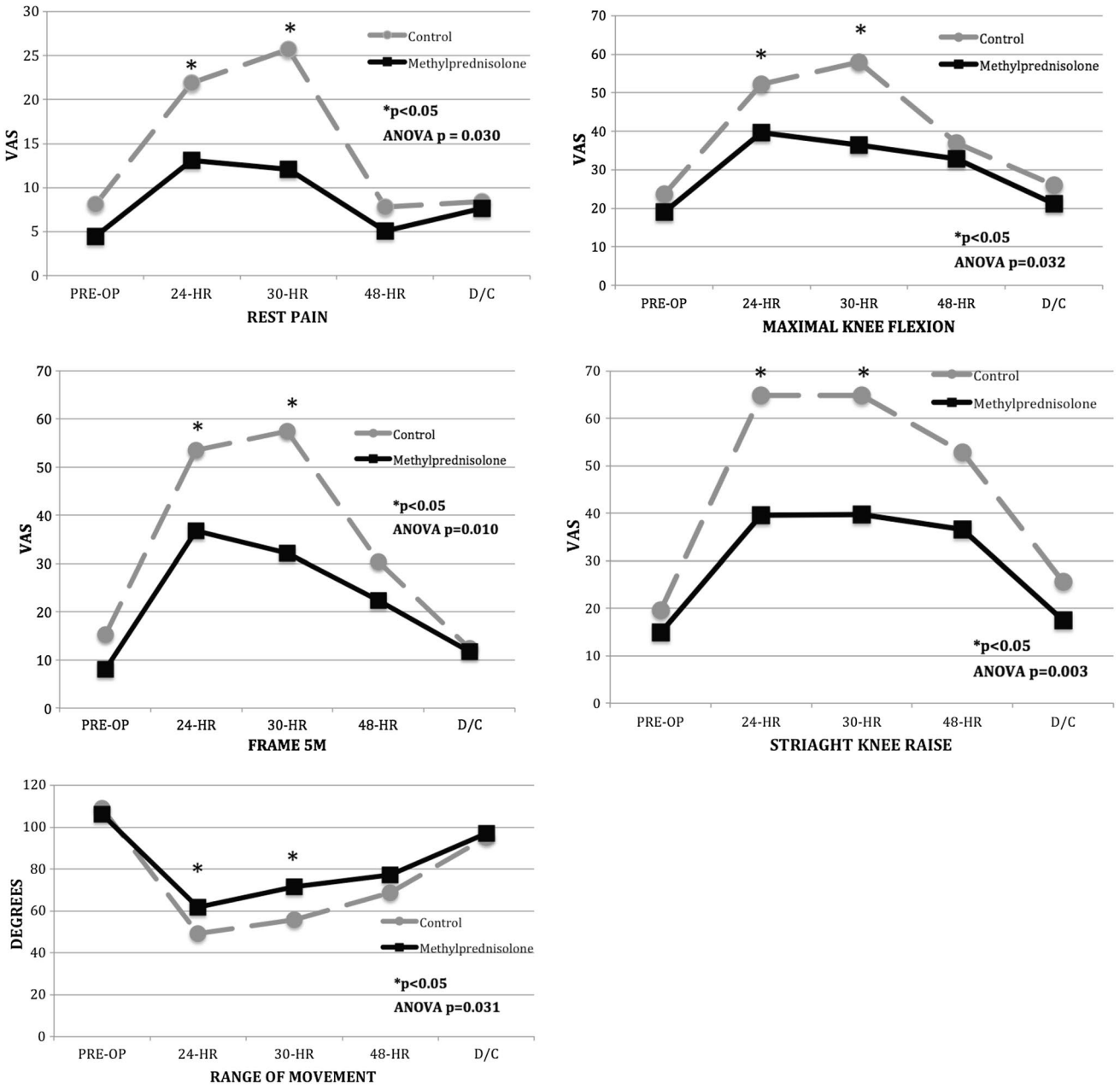

Fig. 2 Range of movement of operated knee, visual analogue scale (VAS) for rest pain and pain on movement (maximal knee flexion, walking with frame for 5 m and straight knee raise) at different assessment time points

started post-operatively with less pain and greater range of the operated knee. Although faster rehabilitation may lead to earlier discharge, other factors such as social problems may hinder discharge from hospital. In this study, the length of stay was similar between both the groups.

None of the above trials or meta-analyses reported patient's satisfaction towards pain control at early post-operative period. In our study, the methylprednisolone group rated a higher patient's satisfaction than the control group.

There were a few limitations in this study. The follow-up period was relatively short with only 1 year. Longer follow-up period may allow investigations on long-term effect of recovery in total knee arthroplasty. The sample size could be increased to detect uncommon adverse effects such as peri-prosthetic infection.

Use of peri-operative steroids raised the concern of safety. In this study, no adverse effects were noted. Yue et al. [11] and Xing et al. [14] found that use of peri-operative systemic steroids in total knee arthroplasty or

Table 3 Outcomes other than pain and range of movement

Outcomes	Placebo group	Intervention group	*p* value
Patient's satisfaction (0 = worst; 100 = best)	67.2 ± 17.0	84.1 ± 13.7	< 0.001
C-reactive protein on day 1 (mg/L)	75.1 ± 28.9	31.1 ± 22.2	< 0.001
PCA morphine use (mg)	8.68 ± 7.62	7.33 ± 8.79	0.527
Sleep quality (0 = worst, 100 = best)	67.7 ± 23.9	64.8 ± 32.8	0.687
Hypokalaemia (K ≤ 3.5) (Y/N)	4/26	3/27	1.0
Hyperglycaemia (H'stix ≥ 14) (Y/N)	1/29	6/24	0.103
Length of in-hospital stay (day)	9.8 ± 3.8	8.9 ± 3.6	0.391
Time to achieve independent frame walking for 5 m (day)	3.8 ± 2.37	3.0 ± 1.41	0.118

H'stix, Hemastix; K, potassium; N, No; PCA, patient-controlled analgesia; Y, yes

Table 4 Pain score and range of movement at 6 weeks, 4 months and 1 year after operation

	Placebo group	Intervention group	*p* value
VAS at 6 weeks	19.2 ± 13.4	13.9 ± 14.8	0.129
ROM at 6 weeks	98.0 ± 11.6	103.8 ± 12.3	0.323
VAS at 4 months	0.7 ± 3.7	1.2 ± 3.3	0.309
ROM at 4 months	104.5 ± 9.1	109.3 ± 8.3	0.239
VAS at 1 year	1.0 ± 2.8	0.7 ± 1.7	0.205
ROM at 1 year	105.5 ± 10.3	111.3 ± 11.7	0.756

VAS visual analogue scale, *ROM* range of movement

total hip arthroplasty was associated with higher level of post-operative serum glucose. Two systemic reviews evaluated the risks and benefits of peri-operative use of methylprednisolone [21] and dexamethasone [22] in both orthopaedic and non-orthopaedic operations. Both papers concluded that peri-operative steroids would not increase complications rates including infection, gastrointestinal bleeding, avascular necrosis of bone, etc.

We believe that the use of pre-operative methylprednisolone is a safe and useful way to improve pain relief and recovery after total knee arthroplasty. Some patients may have contraindications to certain analgesics, for example, the use of non-steroidal anti-inflammatory drugs in patients with renal, gastrointestinal or cardiac problems, the incorporation of steroids into the current multimodal anaesthetic and analgesic regime for joint arthroplasty may help to reduce the dosage of other analgesics which may have more severe side effects.

Conclusions

For unilateral total knee arthroplasty, single dose pre-operative intravenous methylprednisolone significantly reduced rest pain and pain on movement at 24 and 30 h post-operatively. It also increased the range of movement of the operated knee at 24 and 30 h after surgery. Post-operative C-reactive protein level was lower in the methylprednisolone group. Patients had a higher satisfaction towards post-operative pain control with systemic methylprednisolone. There were no adverse effects noted. In conclusion, pre-operative systemic methylprednisolone is a safe and effective measure to improve pain control and range of movement in unilateral total knee arthroplasty.

Table 5 Summary of randomized controlled trials studying on the effect of systemic steroids in total knee arthroplasty

Studies	Sample size (S/C)	Operations	Anaesthesia	Intervention	Follow-up
Lunn et al. [5]	24/24	Unilateral TKR	Spinal anaesthesia	Methylprednisolone 125 mg	30 days
Jules-Elysee et al. [4]	15/15	Bilateral TKR	Spinal/epidural anaesthesia	Hydrocortisone 100 mg 8 h apart for two doses	6 months
Jules-Elysee et al. [4]	17/17	Bilateral TKR	Spinal/epidural anaesthesia	Hydrocortisone 100 mg 8 h apart for three doses	6 months
Koh et al. [18]	135/134	Unilateral TKR	Spinal anaesthesia	Dexamethasone 10 mg	1 year
Backes et al. [17]	40/40/40	Unilateral THR/TKR	General anaesthesia	Dexamethasone 10 mg or dexamethasone 10 mg 24 h apart for two doses	24 weeks

S steroid group, *C* control group, *TKR* total knee arthroplasty, *THR* total hip arthroplasty

Compliance with ethical standards

Conflict of interest All authors declared that they have no potential conflict of interest.

Ethics approval Prior approval from institutional review board was obtained (Research Ethics Committee, Ref: KC/KE-17-0032/FR-4).

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix

See Table 6.

Table 6 List of medications used in our standard protocol for total knee arthroplasty

Oral or intravenous medications	Gabapentin Esomeprazole Paracetamol Cefazolin Tranexamic acid Etoricoxib Bisacodyl Metoclopramide Dihydrocodeine
Patient-controlled analgesia	Morphine
Spinal anaesthesia medications	0.5% Heavy Bupivacaine
Intra-articular injection medications	Ropivacaine Ketorolac Adrenaline

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