■ HIP

Addition of corticosteroid to periarticular injections reduces postoperative pain following total hip arthroplasty under general anaesthesia: a double-blind randomized controlled trial

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Aims

Although periarticular injection plays an important role in multimodal pain management following total hip arthroplasty (THA), there is no consensus on the optimal composition of the injection. In particular, it is not clear whether the addition of a corticosteroid improves the pain relief achieved nor whether it is associated with more complications than are observed without corticosteroid. The aim of this study was to quantify the safety and effectiveness of cortocosteroid use in periarticular injection during THA.

Methods

We conducted a prospective, two-arm, parallel-group, randomized controlled trial involving patients scheduled for unilateral THA. A total of 187 patients were randomly assigned to receive periarticular injection containing either a corticosteroid (CS group) or without corticosteroid (no-CS group). Other perioperative interventions were identical for all patients. The primary outcome was postoperative pain at rest during the initial 24 hours after surgery. Pain score was recorded every three hours until 24 hours using a 100 mm visual analogue scale (VAS). The primary outcome was assessed based on the area under the curve (AUC).

Results

The CS group had a significantly lower AUC postoperatively at 0 to 24 hours compared to the no-CS group (AUC of VAS score at rest 550 ± 362 vs 392 ± 320, respectively; mean difference 158 mm; 95% confidence interval (CI) 58 to 257; p = 0.0021). In point-by-point evaluation, the CS group had significantly lower VAS scores at 12, 15, 18, 21, 24, and 48 hours. There were no significant differences in complication rates, including surgical site infection, between the two groups.

Conclusion

The addition of corticosteroid to periarticular injections reduces postoperative pain without increasing complication rate following THA.

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Introduction

The effective management of postoperative pain following total hip arthroplasty (THA) plays an important role in improving patient satisfaction and enhancing functional recovery.[1,2] There is now good evidence for the effectiveness of periarticular injection as part of a multimodal pain management regimen following THA,[3,4] but there is no consensus on the optimal composition of such injections, with various local anesthetics, corticosteroids, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and adrenaline amongst the agents used.[5] In particular, there is conflicting evidence regarding the inclusion of corticosteroids, with some reports showing better postoperative pain relief when corticosteroids are used within the periarticular injection

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during knee arthroplasty,[6-11] and others showing no benefit.[12-14] No studies exist to examine this question in THA.

We conducted a double-blind randomized controlled trial (RCT) to clarify the role of corticosteroid in promoting pain relief as part of a periarticular injection following THA. Our hypothesis was that the inclusion of corticosteroid in the periarticular injection would result in better pain relief without an increase in rate of complications.

Methods

Study design. The study was a prospective, two-arm, parallel-group, double-blind RCT that was conducted at a single hospital.

The study was approved by the institutional review board (registration no. R0019). All patients provided written informed consent. This trial was registered with University Hospital Medical Information Network (registration no. UMIN000033059) under the title, "The impact of including corticosteroid in a periarticular injection for pain control after total hip arthroplasty: a double blind randomized controlled trial."

We focused on postoperative pain at rest in the first 24 hours after surgery.

Participants. Patients scheduled to undergo unilateral primary THA were recruited between June 2018 and February 2019. We excluded patients scheduled for simultaneous bilateral THA, revision THA, or THA combined with subtrochanteric osteotomy as well as patients with allergies to any of the trial drugs, renal insufficiency, regular narcotic use, or diabetes (HbA1c ≥ 7.0). All participants were informed that we were testing the efficacy of corticosteroids for pain control after THA and that they would be assigned to receive periarticular injection with or without corticosteroid.

Randomization and blinding. A random number sequence from 0 to 99 was generated using R (The R Foundation for Statistical Computing, Vienna, Austria) which was printed and sealed in separate opaque envelopes. Immediately before each surgery, an envelope was selected and opened by a non-blinded member (MY and HY) of the operating room (OR) staff who was not involved in assessment of the trial outcomes. If an odd number was selected, the patient was given a periarticular injection that contained a corticosteroid (CS group); if an even number was selected, the patient was given an otherwise identical periarticular injection without the corticosteroid (no-CS

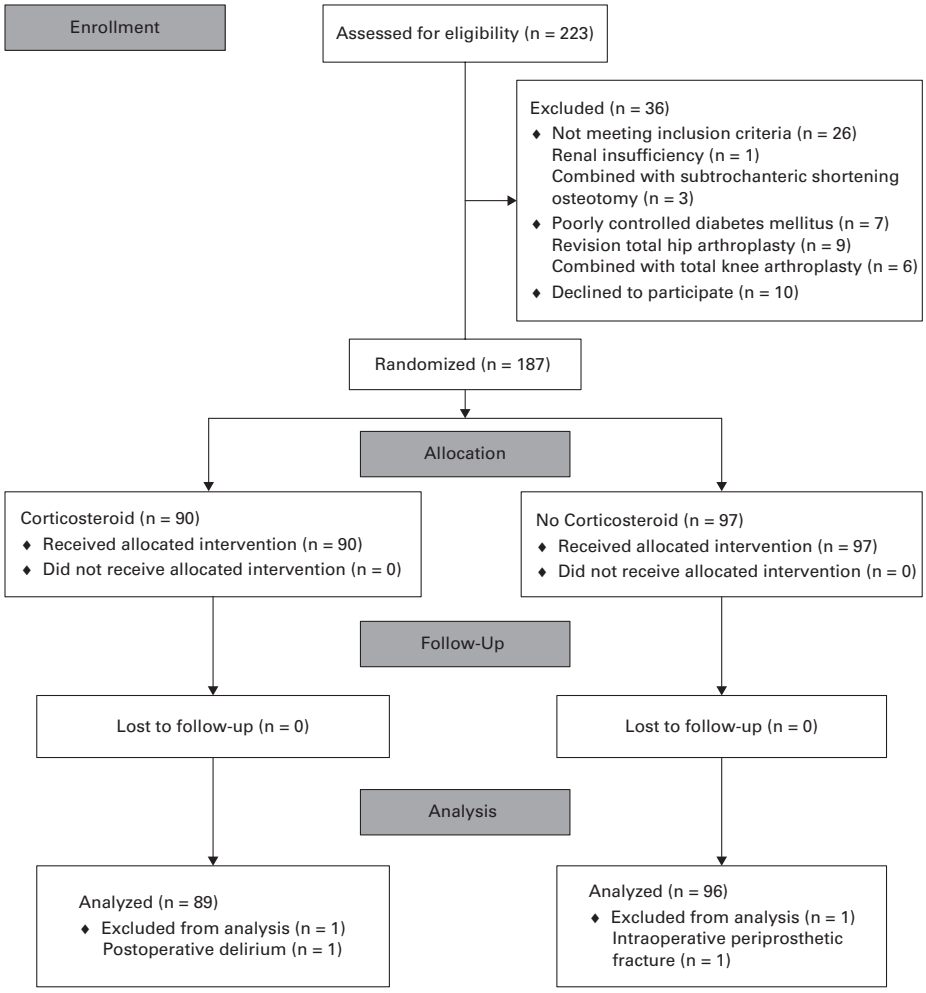

Fig. 1

Flow diagram of patients.

Table I. Patient demographics and baseline clinical characteristics.

Variable	CS group (n = 90)	No-CS group (n = 97)	p-value
Age, yrs (mean ± SD)	64.7 ± 11.8	67.3 ± 11.5	0.129*
Sex, female:male	82:8	80:17	0.129†
Side, right:left	56:34	63:34	0.814†
Height, cm (mean ± SD)	153± 7	154± 8	0.295*
Weight, kg (mean ± SD)	55.8 ± 11.7	59.2 ± 12.3	0.056*
Body mass index, kg/m^2 (mean ± SD)	23.7 ± 4.4	24.8 ± 4.4	0.110*
Diagnosis, OA:ION:RA	89:1:0	96:1:0	1.000†
Preoperative VAS at rest, mm (mean ± SD)	25.6 ± 29.2	28.4 ± 29.4	0.524*
Preoperative VAS during activity, mm (mean ± SD)	50.2 ± 25.5	50.5 ± 25.3	0.942*
Intraoperative blood loss, ml (mean ± SD)	175 ± 83	199 ± 117	0.108*
Duration of surgery, min (mean ± SD)	50 ± 14	53 ± 22	0.294*

CS, corticosteroid; ION, idiopathic osteonecrosis of femoral head; OA, osteoarthritis; RA, rheumatoid arthritis; SD, standard deviation; VAS, visual analogue scale.
*Student's *t*-test.
†Chi-squared test.

group). Patients and all other medical staff (i.e. surgeons, nurses, caregivers, and outcome assessors) were blinded to their intervention during the study period; a non-blinded member (MY and HY) of the OR staff also prepared the injection syringe and covered it with sterile tape.

Interventions. In both groups, the periarticular injection contained 40 ml of 7.5 mg/ml ropivacaine; 0.8 ml of 10 mg/ml morphine hydrochloride hydrate; 2.5 ml of 20 mg/ml ketoprofen; and 0.3 ml of 1 mg/ml adrenaline. In the CS group, 1 ml of 40 mg/ml methylprednisolone (Solu-Medrol, Pfizer, Tokyo, Japan) was added. The solution was injected into the tensor fascia lata (20 ml), gluteus medius (20 ml), and subcutaneous tissue (4 ml) prior to the arthrotomy.

Preoperative and postoperative medications. At induction of anaesthesia, all patients received standardized antibiotic prophylaxis (cefazolin 1 g) and 1 g of tranexamic acid. A second 1 g iv dose of tranexamic acid was given three hours after the first incision.

The day after the operation, patients received regular NSAID (4 mg of lornoxicam three times a day). Diclofenac suppositories (50 mg of diclofenac sodium) were used for rescue analgesia.

Patients received an anticoagulant (15 mg of oral edoxaban tosylate hydrate) for seven days starting on the day after surgery to prevent deep vein thrombosis (DVT).

Surgery and rehabilitation. In all cases, THA was performed under general anaesthesia without any peripheral nerve block or epidural anaesthesia, in the lateral position using the minimally invasive anterolateral approach.[15]

All procedures were performed by one of two surgeons (KK and NH). Cementless acetabular components were used in all cases.

Most femoral components were cementless (173/187) with the remaining 14 being cemented. All patients started range of motion and gait training without restriction on the day after surgery.

Outcome measurements

Primary outcome measure. The primary outcome was postoperative pain at rest during the first 24 hours after surgery. Pain intensity was measured using a 100 mm horizontal visual analogue scale (VAS) from "no pain" (0 mm) to "extreme pain" (100 mm). VAS score was recorded at time zero defined as the time the patient arrived in the recovery room following surgery and every three hours until 24 hours. A further resting VAS score was recorded at 48 hours.

Secondary outcome measure. Postoperative pain during activity was measured on the first and second days after surgery. The worst pain experienced by the patient during rehabilitation was recorded, along with the number of suppositories used as postoperative rescue analgesia and intraoperative consumption of fentanyl and remifentanil citrate.

Any postoperative complications, such as postoperative surgical site infections, DVT, wound complications, and opioid-related side effects, were recorded.

Sample size calculation. We considered a ten-point decrease in VAS score as the minimal clinically important difference based on previous studies on pain associated with corticosteroid use in TKA.[11] Using preliminary data before the start of the trial, power analysis indicated a recommended sample size of 76 for each trial arms (standard deviation (SD) 23, $\alpha = 0.05$, $\beta = 0.80$). We decided on a minimum sample size of 85, assuming a drop-out rate of 10%.

Statistical analyses. The primary outcome was resting pain in the first 24 hours after THA, as assessed using area under the curve (AUC) analysis by plotting VAS score against time and approximating the integral using the trapezoidal rule.[16] AUC was compared between the two groups using an independent samples *t*-test. Missing primary outcome data were replaced with the median score at the same time point.

The chi-squared test and independent samples *t*-test were used to compare categorical and continuous variables between the two groups, respectively. All tests were two-sided and $p < 0.05$ was taken to indicate statistical significance.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[17]

Results

Patient characteristics. The trial outline is illustrated as a flowchart in Figure 1. Of the 223 patients assessed for eligibility, 36 were excluded, with the remaining 187 patients being included in the trial. These patients were randomly assigned to the CS or no-CS group as described above (n = 90 and 97, respectively). Two cases were excluded after allocation: one due

Table II. Visual analogue scale score for postoperative pain at rest.

Duration after surgery	CS group (n = 89), mean ± SD	No-CS group (n = 96), mean ± SD	Difference (95% CI)	p-value*
Recovery room	33.5 ± 31.2	28.4 ± 30.0	7.1 (-13 to 4)	0.303*
3 hours after surgery	19.4 ± 19.7	20.6 ± 22.4	1.2 (-5 to 7)	0.678*
6 hours after surgery	16.7 ± 18.7	16.7 ± 17.9	0 (-5 to 5)	0.990*
9 hours after surgery	14.0 ± 15.7	17.7 ± 18.3	3.7 (-1 to 9)	0.157*
12 hours after surgery	10.8 ± 15.1	20.1 ± 21.4	9.3 (3 to14)	0.003*
15 hours after surgery	11.7 ± 14.4	21.5 ± 21.0	9.8 (5 to 15)	< 0.001*
18 hours after surgery	13.9 ± 17.4	27.1 ± 22.9	13.2 (7 to 19)	< 0.001*
21 hours after surgery	17.4 ± 17.7	31.5 ± 24.5	14.1 (8 to 21)	< 0.001*
24 hours after surgery	19.8 ± 18.6	28.6 ± 22.7	8.8 (3 to 15)	0.004*
48 hours after surgery	16.7 ± 18.0	27.0 ± 22.3	10.3 (5 to 16)	0.001*

Visual analogue scale score was rated using a 100 mm horizontal scale.
CS, corticosteroid; SD, standard deviation; CI, confidence interval.
*Student's *t*-test.

to a periprosthetic fracture and the other due to postoperative delirium.

As shown in Table I, there were no significant differences in patient characteristics between the two groups.

Primary outcome. Table II and Figure 2 show the pain VAS scores at rest. The CS group had a significantly lower AUC postoperatively at zero to 24 hours compared with the no-CS group (AUC of VAS score at rest 550 ± 362 vs 392 ± 320; mean difference 158 mm; 95% confidence interval (CI) 58 to 257; p = 0.0021). In the point-by-point evaluation, the CS group had significantly lower VAS scores than the no-CS group at 12, 15, 18, 21, 24, and 48 hours (Table II and Figure 2).

Secondary outcome. The VAS score during activity was significantly better in the CS group on the first and second days after surgery (Table III).

The consumption of diclofenac sodium was not significantly different between the two groups (Table IV).

The total volumes of fentanyl and remifentanil administered intraoperatively were similar in the two groups (Table V) and there were no significant differences in the rate of complications between the two groups (Table VI).

Discussion

In this prospective randomized trial, the CS group had significantly better pain relief than the no-CS group during the first 24 hours after THA. The CS group also had better pain relief during activity until day two after surgery. There were no significant differences in complication rates between the two groups.

To our knowledge, this is the first RCT to demonstrate the efficacy of including corticosteroid, in periarticular injection, during THA. Six previous RCTs on periarticular injection after unicompartmental and total knee arthroplasty (TKA) reported significantly lower pain scores at rest in patients given

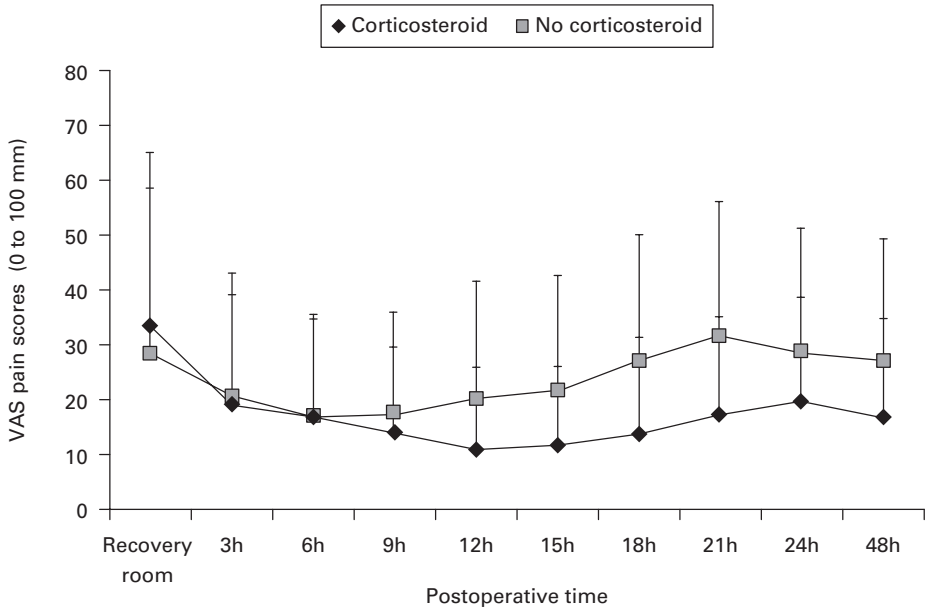

Fig. 2

The pain scores at rest (mean and standard deviation) following total hip arthroplasty as rated on a 100 mm horizontal visual analoge scale (VAS). The corticosteroid group showed significantly lower VAS scores 12, 15, 18, 21, 24, and 48 hours after surgery (p = 0.003, p = 0.0003, p = 0.00002, p = 0.00001, p = 0.004, and p = 0.0007 respectively).

Table III. Visual analogue scale score for postoperative during activity.

Duration after surgery	CS group (n = 89), mean ± SD	No-CS group (n = 96), mean ± SD	Difference (95% CI)	p-value*
1 day	38.9 ± 23.1	47.3 ± 23.7	8.4 (2 to 17)	0.009*
2 day	26.6 ± 18.5	34.7 ± 21.7	8.1 (2 to 14)	0.008*

Visual analogue scale score was rated using a 100 mm horizontal scale.
CS, corticosteroid; SD, standard deviation; CI, confidence interval.
*Student's *t*-test.

Table IV. Number of suppositories used as rescue analgesia.

Postoperative period	CS group (n = 89), mean (SD)	No-CS group (n = 96), mean (SD)	Difference (95% CI)	p-value*
On the night of surgery	0.4 (0.6)	0.4 (0.6)	0 (-0.2 to 0.2)	0.917*
Postoperative day 1	0.7 (0.7)	0.9 (0.8)	0.2 (-0.04 to 0.4)	0.105*
Postoperative day 2	0.5 (0.7)	0.6 (0.7)	0.1 (-0.1 to 0.3)	0.511*
Postoperative day 3	0.2 (0.5)	0.3 (0.6)	0.1 (-0.1 to 0.2)	0.334*
Total	1.8 (1.7)	2.2 (2.0)	0.4 (-0.2 to 0.9)	0.225*

CI, confidence interval; CS, corticosteroid; SD, standard deviation.
*Student's *t*-test.

Table V. The total consumption of fentanyl and remifentanil during surgery.

Variable	CS group (n = 89), mean ± SD	No-CS group (n = 96), mean ± SD	Difference (95% CI)	p-value*
Remifentanil, mg	1.3 ± 0.5	1.3 ± 0.6	0 (-0.1 to 0.2)	0.530*
Fentanyl citrate, μg	61 ± 60	76 ± 60	15 (-2 to 33)	0.082*

CI, confidence interval; CS, corticosteroid; SD, standard deviation.
*Student's *t*-test.

Table VI. Postoperative complications.

Condition	CS group (n = 89), n (%)	No-CS group (n = 96), n %)	p-value*
Nausea	16 (18)	28 (29)	0.107*
Delayed wound healing	1 (1)	1 (1)	1.000*
Surgical site infection	0 (0)	0 (0)	N/A
Nerve palsy	0 (0)	0 (0)	N/A
Deep vein thrombosis	0 (0)	0 (0)	N/A
Dislocation	0 (0)	0 (0)	N/A

CS, corticosteroid; N/A, not available.
*Chi-squared test.

periarticular injection with steroid than without.[6-11] However, three RCTs indicated no significant differences in postoperative pain scores in patients receiving periarticular injection with or without corticosteroid following TKA.[12-14] These conflicting results may have been due to differences in other variables, such as non-corticosteroid drugs, surgical procedures, and/or anaesthesia methods used.

The analgesic effect of periarticular injection compared with placebo or no injection after THA is controversial.[3,4,18-23] However, in all published studies where a corticosteroid is included in the periarticular injection, the study group has shown better pain relief than the placebo/no injection group.[3,4,19] This suggests that the corticosteroid may be an important component of such injections.

Although not statistically significant, the very early (recovery room) mean VAS score was slightly worse in the CS group; this may or may not be a genuine result and if so, it may be related to a flare of pain related to the corticosteroid.[24]

The strengths of this study were the double-blinded randomized trial design and strict standardization of perioperative treatment regimens other than interventions.

There were several limitations in this study. Firstly, this study was conducted at a single centre and all procedures were performed by only two surgeons. Further prospective multi-centre trials are required to determine the generalizability of our findings. Secondly, all patients were managed under general anaesthesia in this study. As THA is more commonly performed under neuraxial anaesthesia in Europe and North America, further investigation is needed in patients managed under neuraxial anaesthesia.[25] Thirdly, although postoperative pain in the first 24 hours after surgery was significantly different between groups, we did not quantify the actual benefit to patients during the course of hospitalization. Further studies are needed to confirm whether the addition of corticosteroid to periarticular injection would be of benefit for patients.

Take home message

- Administration of periarticular injections including corticosteroid showed strong analgesic effects in the first 24 hours after THA without increases in complication rates.

References

1. **Brokelman RB**, **van Loon CJ**, **Rijnberg WJ**. Patient versus surgeon satisfaction after total hip arthroplasty. *J Bone Joint Surg [Br].* 2003;85(4):495–498.
2. **Parvataneni HK**, **Shah VP**, **Howard H**, **et al**. Controlling pain after total hip and knee arthroplasty using a multimodal protocol with local periarticular injections: a prospective randomized study. *J Arthroplasty.* 2007;22(6):33–38.
3. **Busch CA**, **Whitehouse MR**, **Shore BJ**, **et al**. The efficacy of periarticular multimordal drug infiltration in total hip arthroplasty. *Clin Orthop Relat Res.* 2010;468(8):2152–2159.
4. **Hirasawa N**, **Kurosaka K**, **Nishino M**, **et al**. No clinically important difference in pain scores after THA between Periarticular analgesic injection and placebo. *Clin Orthop Relat Res.* 2018;476(9):1837–1845.
5. **Tsukada S**, **Wakui M**, **Hoshino A**. The impact of including corticosteroid in a periarticular injection for pain control after total knee arthroplasty: a double-blind randomised controlled trial. *Bone Joint J.* 2016:194–200.
6. **Ikeuchi M**, **Kamimoto Y**, **Izumi M**, **et al**. Effects of dexamethasone on local infiltration analgesia in total knee arthroplasty: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc.* 2014;22(7):1638–1643.
7. **Kwon SK**, **Yang IH**, **Bai SJ**, **Han CD**. Periarticular injection with corticosteroid has an additional pain management effect in total knee arthroplasty. *Yonsei Med J.* 2014;55(2):493–498.
8. **Ng YCS**, **Lo NN**, **Yang KY**, **et al**. Effects of periarticular steroid injection on knee function and the inflammatory response following Unicondylar Knee Arthroplasty. *Knee Surg Sports Traumatol Arthrosc.* 2011;19(1):60–65.
9. **Pang HN**, **Lo NN**, **Yang KY**, **Chong HC**, **Yeo SJ**. Peri-articular steroid injection improves the outcome after unicondylar knee replacement: a prospective, randomised controlled trial with a two-year follow-up. *J Bone Joint Surg [Br].* 2008;90(6):738–744.

10. **Sean VW**, **Chin PL**, **Chia SL**, **et al**. Single-dose periarticular steroid infiltration for pain management in total knee arthroplasty: a prospective, double-blind, randomised controlled trial. *Singapore Med J*. 2011;52:19–23.
11. **Tsukada S**, **Wakui M**, **Hoshino A**. The impact of including corticosteroid in a periarticular injection for pain control after total knee arthroplasty: a double-blind randomised controlled trial. *Bone Joint J*. 2016:194–200.
12. **Chia SK**, **Wernecke GC**, **Harris IA**, **et al**. Peri-articular steroid injection in total knee arthroplasty: a prospective, double blinded, randomized controlled trial. *J Arthroplasty*. 2013;28(4):620–623.
13. **Christensen CP**, **Jacobs CA**, **Jennings HR**. Effect of periarticular corticosteroid injections during total knee arthroplasty. A double-blind randomized trial. *J Bone Joint Surg [Am]*. 2009;91:2550–2555.
14. **Yue DB**, **Wang BL**, **Liu KP**, **Guo WS**. Efficacy of multimodal cocktail periarticular injection with or without steroid in total knee arthroplasty. *Chin Med J (Engl)*. 2013;126:3851–3855.
15. **Bertin KC,Röttinger H**. Anterolateral mini-incision hip replacement surgery: a modified Watson-Jones approach. *Clin Orthop Relat Res*. 2004;429:248–255.
16. **Felker GM**, **Lee KL**, **Bull DA**, **et al**. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797–805.
17. **Kanda Y**. Investigation of the freely available easy-touse software 'EZR' for medical statistics. *Bone Marrow Transpl Bone Marrow Transplant*. 2013;48(3):452–458.
18. **Dobie I**, **Bennett D**, **Spence DJ**, **Murray JM**, **Beverland DE**. Periarticular local anesthesia does not improve pain or mobility after THA. *Clin Orthop Relat Res*. 2012;470(7):1958–1965.
19. **Hofstad JK**, **Winther SB**, **Rian T**, **et al**. Perioperative local infiltration anesthesia with ropivacaine has no effect on postoperative pain after total hip arthroplasty. *Acta Orthop*. 2015;86(6):654–658.
20. **Liu W**, **Cong R**, **Li X**, **Wu Y**, **Wu H**. Reduced opioid consumption and improved early rehabilitation with local and intraarticular cocktail analgesic injection in total hip arthroplasty: a randomized controlled clinical trial. *Pain Med*. 2011;12(3):387–393.
21. **Murphy TP**, **Byrne DP**, **Curtin P**, **Baker JF**, **Mulhall KJ**. Can a periarticular levobupivacaine injection reduce postoperative opiate consumption during primary hip arthroplasty? *Clin Orthop Relat Res*. 2012;470(4):1151–1157.
22. **Nakai T**, **Nakamura T**, **Nakai T**, **Onishi A**, **Hashimoto K**. A study of the usefulness of a periarticular multimodal drug cocktail injection for pain management after total hip arthroplasty. *J Orthop*. 2013;10(1):5–7.
23. **Zoric L**, **Cuvillon P**, **Alonso S**, **et al**. Single-Shot intraoperative local anaesthetic infiltration does not reduce morphine consumption after total hip arthroplasty: a double-blinded placebo-controlled randomized study. *Br J Anaesth*. 2014;112(4):722–728.
24. **Berger RG**, **Yount WJ**. Immediate "steroid flare" from intraarticular triamcinolone hexacetonide injection: case report and review of the literature. *Arthritis Rheum*. 1990;33(8):1284–1286.
25. **Hannon CP**, **Keating TC**, **Lange JK**, **et al**. Anesthesia and Analgesia Practices in Total Joint Arthroplasty: A Survey of the American Association of Hip and Knee Surgeons Membership. *J Arthroplasty*. 2019;34(12):2872–2877.

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