CLINICAL ARTICLE

A new cocktail formula with diprospan of local infiltration analgesia in primary total hip arthroplasty: A prospective, randomized, controlled, observer-blinded study

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Objective: This study aimed to observe the analgesic effect of the cocktail formulation with diprospan during total hip arthroplasty (THA).

Methods: From September 2018 to April 2019, 120 patients undergoing primary unilateral THA were included in this prospective, randomized, observer-blinded study. Patients were randomized into three groups, according to the different local infiltration analgesia (LIA) strategies: LIA with ropivacaine (the ropivacaine group, $n = 40$), LIA with a new cocktail containing ropivacaine, diprospan, and morphine (the cocktail group, $n = 40$), and the control group ($n = 40$). The primary outcomes included postoperative pain scores. The resting visual analogue scale (VAS) scores were measured at 2, 6, and 12 h after the surgery (a.m. and p.m.) on postoperative day (POD) 1, POD2, and the day of discharge. Movement VAS scores were assessed at 6 h, 12 h after the operation (a.m. and p.m.) on POD1, POD2, and the day of discharge. The secondary outcomes included opioid consumption, postoperative hospital stay, range of motion of the hip at discharge, patient satisfaction, and the results of the follow-up.

Results: After the screening, 120 patients were randomized into three groups (40 patients in each group). All of the patients completed the trial. The resting VAS scores in the ropivacaine group and cocktail group at 2 h were lower than those in the control group ($P < 0.001$ and $P < 0.001$, respectively, $F = 17.054$), and the same trend was also postoperatively found at 6 h ($p = 0.005$ and $P = 0.002$, $F = 6.212$). Twelve hours after the operation, the pain score in the cocktail group was lower than that in the other two groups, but only the difference between the cocktail group and the control group was statistically significant ($P = 0.018$, $F = 3.144$). From the morning of the first postoperative day to the a.m. on POD 2, the VAS scores in the cocktail group were significantly lower than those in the ropivacaine group and the control group. Furthermore, the movement VAS scores in the ropivacaine group and the cocktail group were better than those in the control group at 6 and 12 h post-operation ($P < 0.05$). The *per capita* opioid consumption in the cocktail group was less than that in the ropivacaine group and the control group within 24 h post-operation. There were no significant differences in the comparison of additional indicators among the three groups.

Conclusion: The new cocktail with diprospan had a better result and longer duration time for early postoperative pain control in primary THA *via* the posterolateral approach under general anesthesia, especially for treating resting pain.

Key words: Local infiltration analgesia; New cocktail formula; Pain control; Prospective randomized controlled trial; Total hip arthroplasty

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Introduction

Total hip arthroplasty (THA) has been broadly recognized as being an effective treatment for end-stage hip disease.[1] With the continuous improvement of surgical techniques and the continuous accumulation of perioperative patient management experience in recent years (especially in the promotion of the concept of accelerated perioperative rehabilitation), an increasing number of Chinese patients have chosen to undergo total hip arthroplasty; however, pain after THA is still a problem that doctors need to focus on.[2] According to the literature, approximately 20% of patients experience moderate-to-severe pain after joint replacement surgery. If postoperative pain cannot be effectively controlled, it will delay the speed of recovery, prolong the length of hospital stay, increase the cost of treatment, lead to chronic pain after operation, and further affect the satisfaction of patients.[3,4] Multimodal analgesia provides an effective scheme for the perioperative pain control of joint replacement and has achieved good results.[5,6] As one of the important measures of perioperative multimodal analgesia, local infiltration analgesia (LIA) has been widely used in total hip arthroplasty.[7] Different drug formulations of local infiltration analgesia have been demonstrated by different researchers. Ropivacaine, morphine, nonsteroidal anti-inflammatory analgesics, and several other drugs are commonly used in the "cocktail" formula. Some researchers believe that glucocorticoids in LIA can inhibit the inflammatory reaction at the surgical site, reduce the production of pain signals, and improve the analgesic effect after total joint arthroplasty. Moreover, other researchers have adopted a wait-and-see attitude, with the belief that the addition of glucocorticoids such as dexamethasone does not affect the actual effect of LIA, which may be related to the regional rapid absorption of glucocorticoids.[8,9]

The question as to whether glucocorticoids in LIA can improve analgesia is debatable, and researchers are attempting to identify methods to make LIA last longer. Diprospan is a compound glucocorticoid preparation made from a mixture of betamethasone disodium phosphate and betamethasone dipropionate, in which betamethasone disodium phosphate can be soluble in water, thus making it easily absorbable and effective, whereas betamethasone dipropionate is slightly soluble in water, temporarily stored in the injection site and slowly absorbed to maintain the effect. This compound glucocorticoid preparation can provide a longer action time. Noskov *et al.* found that diprospan could effectively relieve shoulder pain in patients with shoulder periarthritis.[10] Furthermore, Lara-de la Fuente *et al.* believed that the injection of diprospan at the joint site could effectively relieve joint pain in patients.[11] From this point of view, diprospan should be effective in relieving joint pain, but there is no precedent for the addition of diprospan to LIA for total hip arthroplasty. At the authors' institution, LIA with the use of 0.25% ropivacaine has already achieved good clinical results for pain management in THA, but the researchers still want to find a better cocktail formula. Therefore, they designed this prospective, randomized, controlled trial to answer the following questions: (i) whether LIA is effective in reducing postoperative pain in primary THA; (ii) whether the new cocktail has a better effect than ropivacaine; and (iii) whether this new cocktail can prolong the effective time compared with the use of ropivacaine alone.

Methods and Materials

Inclusion and Exclusion Criteria

From September 2018 to April 2019, the patients who underwent THA were screened for enrollment. The inclusion criteria were as follows: (i) patients aged 18–80 years; (ii) patients with American Society of Anesthesiologists Physical Status I–III; and (iii) patients undergoing primary unilateral THA. The perioperative management of surgery was built on a widely recognized multimodal enhanced recovery strategy, including venous thromboembolism (VTE) prevention, pain control,[12,13] blood loss management,[14] and rehabilitation training.[15]

The exclusion criteria were as follows: (i) patients with diagnoses other than osteoarthritis or osteonecrosis of the femoral head; (ii) patients with a known allergy to the drugs used in this study; (iii) patients with uses of spinal anesthesia; (iv) patients unable to tolerate general anesthesia or the surgery; (v) patients with mental illnesses or an inability to complete the visual analogue scale (VAS); (vi) diabetes patients; (vii) patients with operative side hip joints who had previous surgery history or limb shortening more than 4 cm than the normal side; (viii) patients who could not cooperate with the completion researcher for various reasons; and (ix) for facilitating the recording and statistics of the pain score, patients in which the surgeries were completed after 5 p.m.

Randomization and Blinding

All of the patients were randomized into three groups: LIA with ropivacaine (the ropivacaine group), LIA with a new cocktail (the cocktail group), and the control group. Randomization was based on a computer-generated randomization list, and the results were placed into sequentially numbered, opaque, sealed envelopes by a statistician who did not participate in this clinical trial. The envelope was opened on the day of the operation, and the corresponding LIA drugs were dispensed by a nurse who was not involved in patient care. The patients, anesthesiologists, outcome assessors, and data collectors were blinded to the allocations. The surgeon who performed the LIA could not be blinded, but he did not take part in the data collection or postoperative management of this trial.

Surgery and Perioperative Management

All of the patients received general anesthesia from the same group of anesthesiologists. All of the surgeries were performed by one senior surgeon (Dr. ZkZ) using a posterolateral approach and a single brand of cementless acetabular and femoral components (DePuy Synthes, PINNACLE cup and CORAIL stem, Warsaw, IN, USA). No postoperative drain was used. All of the patients received tranexamic acid (20 mg/kg) intravenously 10 min before the surgery after which they received 1 g of tranexamic acid intravenously

3 and 6 h after the operation. All of the patients received a standardized thromboembolic prophylaxis protocol,[16] which consisted of a subcutaneous injection of 2000 IU enoxaparin sodium (Clexane, Sanofi, Synthelabo, Paris, France) at 8 h post-operation and then one time a day (4000 IU); in addition, 10 mg rivaroxaban (Xarelto, Bayer Pharma Daesung Maref, Gyeonggi-do, korea, republic) was prescribed for 10 days after discharge. The patients received mechanical thromboprophylaxis *via* a portable intermittent inflatable calf pump (Daesung Maref) and lower extremity strength training on the day after surgery. A physiotherapist who did not participate in this study guided the rehabilitation training of all of the enrolled patients, including hip functional training on the bed, walking with the aid of a walker, and daily life training.

Interventions and the Multimodal Analgesia Protocol

The patients were randomized into one of three interventions. Patients in the ropivacaine group received LIA with ropivacaine (Naropin, AstraZeneca) before suturing of the wound; 200 mg ropivacaine was dissolved in saline, and the concentration of ropivacaine was 0.25% in a total of 80 ml. Forty milliliters of solution was injected into the deep tissues, including the tensor fasciae latae and gluteus maximus, and the remaining 40 ml of solution was injected into the superficial tissues, including the superficial fascia and subcutaneous tissues. The cocktail group received LIA with 200 mg ropivacaine (final concentration of 0.25%), 10 mg morphine, 1 ml diprospan (which contained 2 mg betamethasone disodium phosphate), and 5 mg betamethasone dipropionate, in a total of 80 ml. The injection technique was the same as that in the ropivacaine group. Patients in the control group did not receive the LIA procedure.

All of the patients received the same multimodal analgesia protocol except those not receiving the LIA. Education was performed before the surgery by one nurse who was not involved in this study. Patients received 200 mg celecoxib (Celebrex, Pfizer) two times a day for 2 days before the operation until 2 weeks after the surgery. Intraoperative anesthesiologists developed the same anesthesia and analgesic measures for each patient. After the surgery, all of the patients received cold therapy for 12 h. One data collector who was blinded to the allocations assessed each patient's pain score and delivery of analgesic drugs, according to the VAS score. Specifically, patients received 10 mg oral oxycodone hydrochloride prolonged-release tablets (OxyContin, Mundipharma) 10 when the VAS score was between 4 and 6; a subcutaneous injection of 5 mg of morphine was immediately administered if the VAS score was ≥7. Intravenous patient-controlled analgesia (PCA) was abandoned in this study.

Outcome Measures

The primary outcomes included postoperative VAS pain scores. The secondary outcomes included opioid consumption, postoperative hospital stay, range of motion of the hip at discharge, patient satisfaction, complications, and follow-up outcomes.

Visual Analogue Scale

The VAS involved a 10-point self-reported score for the assessment of patients' hip pain. A minimum score of 0 indicates no pain; a score of 1–3 indicates mild pain; a score of 4–6 indicates moderate pain; and a score of 7–10 indicates severe pain. The resting VAS scores were measured at 2, 6, and 12 h after surgery (a.m. and p.m.) on postoperative day (POD) 1, POD2, and the day of discharge. Movement VAS scores were assessed at 6 and 12 h after the operation (a.m. and p.m.) on POD1, POD2, and the day of discharge.

Opioid Consumption

Opioid consumption was converted into oral morphine as follows: 10 mg of subcutaneously injected morphine was equal to 30 mg of oral morphine, and 10 mg of oral oxycontin was equal to 20 mg of oral morphine.[17,18] Opioid consumption was recorded at 24 h PO and at discharge.

Postoperative Hospital Stay

The length of postoperative hospital stay was defined as the number of days from POD1 to the day of discharge.

Range of Motion

The range of motion of the hip included flexion and abduction. The flexion and abduction of the hip were defined as hip flexion or abduction from neutral (0°) to maximum. The range of motion was recorded at the day of discharge.

Patient satisfaction

A questionnaire was used to investigate patient satisfaction, including pain and function satisfaction. Patient satisfaction was recorded as satisfied or dissatisfied at the day of discharge.

Complications

Complications were defined as side effects related to opioids, glucocorticoids, and LIA, including nausea and vomiting, urinary retention, pruritus, superficial and deep infections, hematoma, superficial wound necrosis, and blood sugar fluctuations. Blood sugar fluctuations were defined as fasting blood glucose greater than 8 mmol/L or blood glucose 2 h after a meal greater than 13 mmol/L.

Follow-up Outcomes

The follow-up time points were at 3 and 6 months after surgery. Follow-up outcomes included the resting and movement VAS, Harris hip score (HSS), and the 12-Item Short Form Health Survey (SF-12).

Statistical Analysis and Sample Size

Data were analyzed by using SPSS (version 22.0; IBM). Continuous data are presented as the mean and standard deviation (SD). One-way analysis of variance (ANOVA) with a *post hoc* Bonferroni test was used to analyze the normally

distributed continuous variables, and the Kruskal–Wallis test with the *post hoc* Nemenyi test was used for the skewed continuous variables. Categorical data are reported as the number and percentage. The statistical analysis of categorical variables was performed by using chi-square or Fisher tests. Statistical significance was established at $P < 0.05$.

The postoperative pain scores were selected as the primary outcome. Based upon a pilot study that was previously conducted in 15 patients (five patients in each arm) who underwent unilateral primary total hip arthroplasty, the sample size was calculated *via* G Power Version 3.1.9 (Franz Faul; UniKiel) software, and 35 patients were needed in each group by using a fixed effect, one-way ANOVA design. Assuming a 15% loss to follow-up, 40 patients were enrolled in each group.

Results

Patient Characteristics

From September 2018 to April 2019, 148 patients who underwent primary unilateral THA were assessed for eligibility. Twenty-eight of the patients were excluded: 20 patients violated the inclusion criteria, five patients declined to participate, and three patients were excluded for other reasons. Finally, 120 patients were randomized into three groups (40 patients in each group), and all 120 patients completed the trial (Fig. Fig. 1). No significant differences were identified among the three groups concerning the patients' baseline demographic variables and perioperative characteristics (Table 1).

Primary Outcome

A noteworthy difference in postoperative resting pain intensity (VAS) was found among the three groups beginning at 2 h post-operation and continuing to the a.m. of POD2. The VAS scores in the ropivacaine group and cocktail group at 2 h post-operation were lower than those in the control group ($P < 0.001$ and $P < 0.001$, respectively, $F = 17.054$), and the same trend was also found at PO 6 h ($P = 0.005$ and $p = 0.002$, $F = 6.212$). Twelve hours after the operation, the pain score in the cocktail group was lower than that in the other two groups, but only the difference between the cocktail group and the control group was statistically significant ($P = 0.018$, $F = 3.144$). From the morning of the first postoperative day to a.m. POD2, patients in the cocktail group exhibited lower VAS scores than those in the ropivacaine group and control group, and the differences were statistically significant (a.m. POD1: cocktail group *versus* ropivacaine group, $P = 0.021$; cocktail group *versus* control group, $P = 0.005$; $F = 4.683$. p.m. POD1: cocktail group *versus* ropivacaine group, $P = 0.034$; cocktail group *versus* control group, $P = 0.023$; $F = 3.300$. a.m. POD2: cocktail

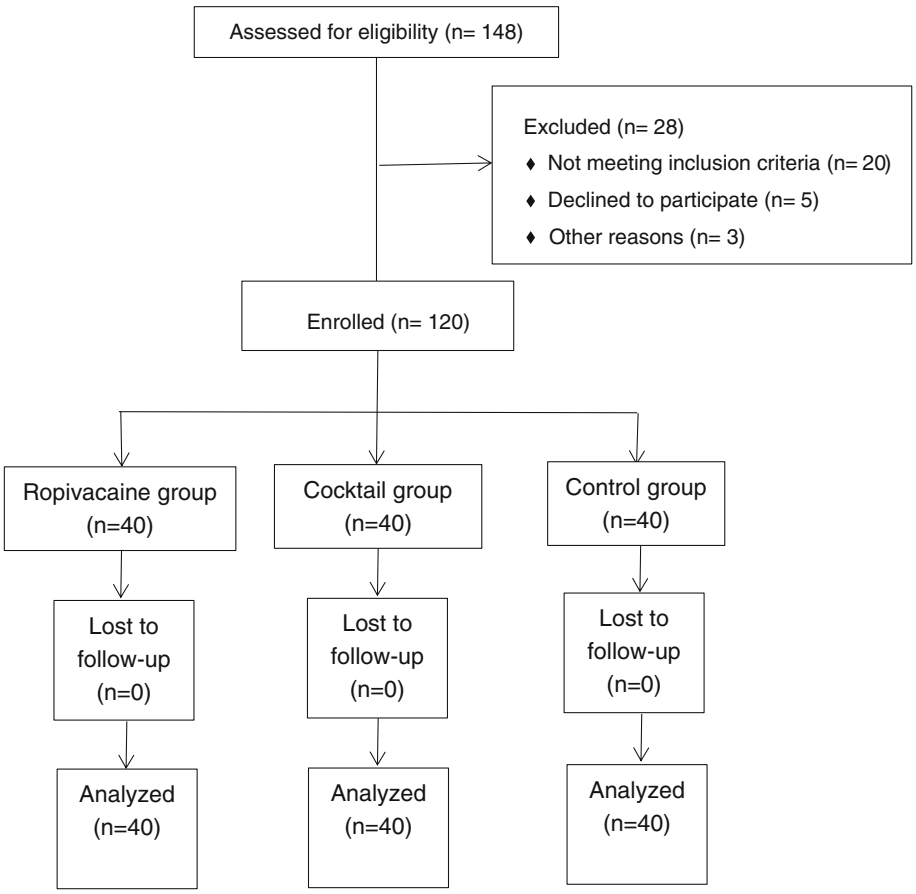

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flowchart of the study

TABLE 1 Demographic variables and preoperative characteristics

Variable	Ropivacaine group ($n = 40$)	Cocktail group ($n = 40$)	Control group ($n = 40$)	Statistic values	P values[a]
Age (year)	56.03 ± 13.22	54.33 ± 12.07	56.95 ± 13.94	$F = 0.413$	0.662
Female sex (no. of patients [%])	18 (45.0%)	22 (55.0%)	24 (60.0%)	$\chi^2 = 1.875$	0.392
Operative side (no. of patients [%])				$\chi^2 = 2.660$	0.264
Right	26 (65.0%)	19 (47.5%)	24 (60%)		
Left	14 (35.0%)	21 (52.5%)	16 (40%)		
Diagnosis				$\chi^2 = 1.290$	0.525
Osteonecrosis of femoral head	15 (37.5%)	20 (50.0%)	17 (42.5%)		
Osteoarthritis	25 (62.5%)	20 (50.0%)	23 (57.5%)		
Height (cm)	160.57 ± 8.61	162.33 ± 8.52	160.05 ± 8.50	$F = 0.774$	0.463
Weight (kg)	61.89 ± 12.32	61.23 ± 12.21	60.91 ± 9.83	$F = 0.075$	0.928
BMI (kg/m^2)	23.91 ± 3.95	23.06 ± 3.09	23.72 ± 3.02	$F = 0.694$	0.502
ASA class (no. of patients [%])				$\chi^2 = 3.498$	0.478
I	3	3	6		
II	29	33	27		
III	8	4	7		
HHS	52.55 ± 14.0	51.58 ± 10.00	51.33 ± 12.92	$F = 0.109$	0.897
Movement VAS	4.10 ± 1.28	4.38 ± 1.00	4.50 ± 0.88	$F = 1.474$	0.233
Resting VAS	0.70 ± 0.69	0.68 ± 0.62	0.68 ± 0.59	$F = 0.023$	0.977
SF-12					
PCS	14.83 ± 2.80	14.35 ± 2.40	14.45 ± 2.15	$F = 0.413$	0.663
MCS	21.35 ± 2.86	21.40 ± 2.62	22.23 ± 1.64	$F = 1.634$	0.200

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; HHS, Harris hip score; MCS, mental component summary; PCS, physical component summary; SF-12, The 12-Item Short Form Health Survey; VAS, visual analogue scale.
[a] The p value represents the result of one-way analysis of variance for independent means for continuous variables and the chi-squared test or Fisher's exact tests for categorical variables among the three groups. The values are given as the mean and the standard deviation or the number of patients.

TABLE 2 VAS scores and morphine equivalents consumption during hospitalization

Variable	Ropivacaine group ($n = 40$)	Cocktail group ($n = 40$)	Control group ($n = 40$)	Statistic values	P values[a]
Resting VAS					
PO 2 h	2.48 ± 0.75	2.35 ± 0.89	3.43 ± 1.05	$F = 17.054$	<0.001[b]
PO 6 h	2.38 ± 0.63	2.33 ± 0.86	2.85 ± 0.69	$F = 6.212$	0.003[b]
PO 12 h	2.25 ± 0.78	2.15 ± 0.66	2.55 ± 0.78	$F = 3.144$	0.047[b]
POD 1					
a.m.	2.13 ± 0.69	1.80 ± 0.52	2.20 ± 0.65	$F = 4.683$	0.011[b]
p.m.	2.08 ± 0.69	1.73 ± 0.55	2.10 ± 0.90	$F = 3.300$	0.040[b]
POD 2					
a.m.	1.60 ± 0.78	1.25 ± 0.44	1.63 ± 0.70	$F = 4.076$	0.019[b]
p.m.	1.83 ± 0.87	1.68 ± 0.80	1.78 ± 0.83	$F = 0.335$	0.555
Discharge	1.55 ± 0.75	1.45 ± 1.01	1.60 ± 0.93	$F = 0.286$	0.752
Movement VAS					
PO 6 h	4.00 ± 0.72	3.78 ± 0.89	4.53 ± 0.85	$F = 8.781$	<0.001[b]
PO 12 h	3.80 ± 0.82	3.60 ± 0.67	4.43 ± 0.98	$F = 10.600$	<0.001[b]
POD 1					
a.m.	3.85 ± 0.83	3.65 ± 0.80	3.80 ± 0.97	$F = 0.572$	0.566
p.m.	3.38 ± 0.67	3.33 ± 0.76	3.45 ± 0.81	$F = 0.280$	0.756
POD 2					
a.m.	3.15 ± 0.70	3.18 ± 0.50	3.20 ± 0.82	$F = 0.053$	0.948
p.m.	3.03 ± 0.69	3.17 ± 0.90	3.25 ± 0.74	$F = 0.850$	0.430
Discharge	2.90 ± 0.98	2.83 ± 0.87	3.05 ± 0.88	$F = 0.631$	0.534
Morphine equivalents (mg)					
PO 0–24 h	11.50 ± 14.42	5.13 ± 7.55	12.38 ± 15.89	$F = 3.631$	0.030[b]
Total during hospitalization	33.25 ± 45.88	34.50 ± 47.55	50.25 ± 58.04	$F = 1.393$	0.252

Abbreviations: a.m., *ante meridiem*; h, hour; p.m., post meridiem; PO, postoperative; POD, postoperative day; VAS, visual analogue scale.
[a] The p value represents the result of one-way analysis of variance or Kruskal–Wallis analysis for independent means for continuous variables among the three groups; [b] Significant. The values are given as the mean and the standard deviation.

TABLE 3 VAS scores *post hoc* test during hospitalization

Variable	Ropivacaine group ($n = 40$)	Cocktail group ($n = 40$)	Control group ($n = 40$)	*P* values[a]			
				P	P1	P2	P3
Resting VAS							
PO 2 h	2.48 ± 0.75	2.35 ± 0.89	3.43 ± 1.05	<0.001[b]	0.536	<0.001[b]	<0.001[b]
PO 6 h	2.38 ± 0.63	2.33 ± 0.86	2.85 ± 0.69	0.003[b]	0.762	0.005[b]	0.002[b]
PO 12 h	2.25 ± 0.78	2.15 ± 0.66	2.55 ± 0.78	0.047[b]	0.548	0.073	0.018[b]
POD 1							
a.m.	2.13 ± 0.69	1.80 ± 0.52	2.20 ± 0.65	0.011[b]	0.021[b]	0.590	0.005[b]
p.m.	2.08 ± 0.69	1.73 ± 0.55	2.10 ± 0.90	0.040[b]	0.034[b]	0.879	0.023[b]
POD 2							
a.m.	1.60 ± 0.78	1.25 ± 0.44	1.63 ± 0.70	0.019[b]	0.019[b]	0.865	0.012[b]
Movement VAS							
PO 6 h	4.00 ± 0.72	3.78 ± 0.89	4.53 ± 0.85	<0.001[b]	0.223	0.005[b]	<0.001[b]
PO 12 h	3.80 ± 0.82	3.60 ± 0.67	4.43 ± 0.98	<0.001[b]	0.287	0.001[b]	<0.001[b]
Morphine equivalents (mg)							
PO 0–24 h	11.50 ± 14.42	5.13 ± 7.55	12.38 ± 15.89	0.030[b]	0.032[b]	0.766	0.015[b]

Abbreviations: a.m., *ante meridiem*; h, hour; p.m., post meridiem; PO, postoperative; POD, postoperative day; VAS, visual analogue scale.
[a] From one-way analysis of variance for independent means for continuous variables among the three groups. *P* values from analysis with use of the *post hoc* Bonferroni test; P, *P* value of Ropivacaine group *vs*. Cocktail group *vs*. Control group; P1, *P* value of Ropivacaine group *vs*. Cocktail group; P2, *P* value of Ropivacaine group *vs*. Control group; P3, *P* value of group Cocktail group *vs*. Control group; [b] Significant. The values are given as the mean and the standard deviation.

TABLE 4 Operative outcomes and follow-up outcomes

Variable	Ropivacaine group ($n = 40$)	Cocktail group ($n = 40$)	Control group ($n = 40$)	Statistic values	*P* values[a]
During hospitalization					
Duration of surgery (min)	69.9 ± 14.36	66.08 ± 19.23	64.93 ± 14.67	$F = 1.007$	0.369
Postoperative hospital stay (day)	2.95 ± 0.71	2.93 ± 0.86	3.10 ± 0.87	$F = 0.536$	0.587
Range of motion at discharged (°)					
Flexion	106.13 ± 7.55	106.63 ± 7.88	104.13 ± 7.67	$F = 1.180$	0.311
Abduction	33.00 ± 3.72	33.25 ± 3.50	32.88 ± 3.63	$F = 0.109$	0.897
Follow-up					
Resting VAS					
PO 3 months	0.25 ± 0.49	0.20 ± 0.46	0.33 ± 0.57	$F = 0.604$	0.548
PO 6 months	0.18 ± 0.38	0.13 ± 0.33	0.23 ± 0.42	$F = 0.683$	0.507
Movement VAS					
PO 3 months	0.75 ± 0.67	0.80 ± 0.65	0.90 ± 0.74	$F = 0.492$	0.613
PO 6 months	0.65 ± 0.62	0.58 ± 0.59	0.78 ± 0.58	$F = 1.142$	0.323
HHS					
PO 3 months	88.90 ± 1.98	89.05 ± 2.28	88.00 ± 2.29	$F = 2.698$	0.072
PO 6 months	92.45 ± 2.23	93.05 ± 2.33	92.40 ± 2.53	$F = 0.934$	0.396
SF-12-PO 3 months					
PCS	22.2 ± 1.29	21.95 ± 1.20	21.60 ± 1.61	$F = 1.916$	0.152
MCS	26.18 ± 1.20	25.85 ± 1.35	25.63 ± 1.37	$F = 1.787$	0.172
SF-12-PO 6 months					
PCS	23.53 ± 1.24	23.60 ± 1.03	23.20 ± 0.82	$F = 1.653$	0.196
MCS	27.10 ± 0.90	27.45 ± 0.91	27.15 ± 0.80	$F = 1.893$	0.155
Pain satisfaction (no. of patients [%])				$\chi^2 = 1.829$	0.456
Satisfied	35 (87.5%)	37 (92.5%)	33 (82.5%)		
Dissatisfied	5 (12.5%)	3 (7.5%)	7 (17.5%)		
Function satisfaction (no. of patients [%])				$\chi^2 = 0.173$	1.000
Satisfied	36 (90.0%)	36 (90.0%)	35 (87.5%)		
Dissatisfied	4 (10.0%)	4 (10.0%)	5 (12.5%)		

Abbreviations: HHS, Harris hip score; MCS, mental component summary; PCS, physical component summary; PO, postoperative; SF-12, The 12-Item Short Form Health Survey; VAS, visual analogue scale.
[a] The *P* value represents the result of one-way analysis of variance for independent means for continuous variables and the chi-squared test or Fisher's exact tests for categorical variables among the three groups. *P*, *P* value of Ropivacaine group *vs*. Cocktail group *vs*. Control group. The values are given as the mean and the standard deviation or the number of patients.

TABLE 5 Complications

Variable	Ropivacaine group ($n = 40$)	Cocktail group ($n = 40$)	Control group ($n = 40$)	Statistic values	P values[a]
Nausea and vomiting	3	2	5	$\chi^2 = 1.527$	0.601
Urinary retention	2	1	3	$\chi^2 = 1.053$	0.870
Pruritus	0	0	1	$\chi^2 = 2.017$	1.000
Aseptic fat liquefaction of wound	1	1	1	$\chi^2 = 0.000$	1.000
Superficial infection	0	0	0	—	—
Deep infection	0	0	0	—	—
Haematoma	1	0	0	$\chi^2 = 2.017$	1.000
Superficial wound necrosis	0	0	0	—	—
DVT	0	0	0	—	—
PE	0	0	0	—	—
Blood glucose fluctuations	1	1	0	$\chi^2 = 1.017$	1.000

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.
[a]The P value represents the result of chi-square or Fisher's test for independent proportions among the three groups. The values are given as the number of patients.

group *versus* ropivacaine group, $p = 0.019$; cocktail group *versus* control group, $P = 0.012$; $F = 4.076$). Although the VAS scores in the ropivacaine group were lower than those in the control group, no meaningful differences were found between the two groups. However, even the cocktail group had a better analgesic effect than the rest of the groups regarding resting pain intensity from p.m. POD2 to discharge, but the differences were not statistically significant (Tables 2 and 3).

When the movement VAS scores were evaluated among the three groups, patients in the ropivacaine group and cocktail group had better results than the patients in the control group in the very early period after surgery (6 and 12 h post-operation, $P < 0.05$). However, from POD1 to the time of discharge, the movement pain scores among the three groups were similar ($P > 0.05$) (Tables 2 and 3).

Secondary Outcomes

The *per capita* opioid consumption in the cocktail group was less than that in the ropivacaine group and control group within 24 h post-operation (5.13 ± 7.55 mg in the cocktail group *versus* 11.50 ± 14.42 mg in the ropivacaine group *versus* 12.38 ± 15.89 mg in the control group, $P = 0.032$ and $P = 0.015$, respectively, $F = 3.631$). However, because 10 mg morphine was used in the cocktail group, the differences in total morphine consumption among the three groups were not statistically significant (Tables 2 and 3).

No significant difference was observed among the three groups when compared with postoperative hospital stay ($P = 0.587$, $F = 0.536$), range of motion of the hip at discharge ($P = 0.311$, $F = 1.180$ for flexion of the hip and $p = 0.897$, $F = 0.109$ for abduction), and patient satisfaction ($P = 0.456$, $\chi^2 = 1.829$ for pain management satisfaction and $P = 1.000$, $\chi^2 = 0.173$ for function satisfaction). Patients in this study were followed up at 3 and 6 months after surgery, and the resting and movement VAS scores and the HSS and SF-12 scores were similar among the groups ($P > 0.05$) (Table 4).

The incidence of complications related to opioids, glucocorticoid use, and LIA were assessed, including the incidences of nausea and vomiting, urinary retention, pruritus, wounds complications, large fluctuations in blood glucose, deep vein thrombosis, and pulmonary embolism, and there was no statistically significant difference among the groups (Table 5).

Discussion

The Effectiveness of the New Cocktail in Reducing Postoperative Pain

In this prospective, randomized, controlled, observer-blinded study, the researchers found that with the LIA and multimodal analgesic protocol, the two groups with LIA had better pain management results than the control group in the early period after THA. However, the cocktail group achieved the most satisfactory analgesic effect. As is known, LIA is an important part of perioperative multimodal analgesia in joint replacement. With the use of a cocktail composed of local anesthetics and analgesics, LIA can block the pain from the source, thus avoiding analgesia-related systemic complications without affecting the muscles around the hip joint. A randomized controlled study conducted by Villatte *et al.* suggested that LIA can effectively reduce pain at 24 h after THA.[19] Titman *et al.* also observed that LIA can effectively decrease early pain after THA in a randomized, placebo-controlled study.[20] Moreover, Ma *et al.* found that LIA can effectively relieve pain after THA and reduce perioperative opioid consumption.[21] In the guidelines of China, South Korea, and other countries, local infiltration analgesia is regarded as an important part of perioperative multimodal analgesia in joint replacement.[22,23] In a survey conducted by the American Association of Hip and Knee Surgeons (AAHKS), 80% of joint surgeons surveyed chose to use local infiltration analgesia as a means of perioperative analgesia in joint replacement.[24] Although some studies believe that under the premise of multimodal analgesia, LIA does not improve the overall analgesic effect, more related research

results have confirmed the role of local infiltration analgesia.[25,26] The results of this study were similar to those of most previous studies showing that LIA could effectively reduce pain after THA.

Advantages of the New Cocktail Local Infiltration Analgesia

There have been different results on the effect of LIA in different studies. Kuchálik *et al.* showed that the postoperative analgesic advantage of LIA was only 6 h,[3] but Liu *et al.* observed that the analgesic effect of LIA could be sustained to approximately 36 h after the operation.[27] The effective time of LIA may be affected by various factors, such as the cocktail formula, injection site, injection manipulation, surgical techniques, and other analgesic strategies in the multimodal analgesia measures. From the literature, the mainstream cocktail formula contains anesthetics, nonsteroidal anti-inflammatory analgesics, and opioids. Some researchers may use glucocorticoids and/or epinephrine in the cocktail.[2,28] Correlated studies have suggested that epinephrine could prolong the effective time of LIA, but the vasoconstrictive effect of epinephrine may cause ischemic necrosis of the skin; thus, it was not suitable for subcutaneous injection. For this reason, epinephrine was not used in this study. Even so, these results showed that LIA with the new cocktail effectively reduced resting pain for nearly 40 h after THA, which is better than what has been reported in most current studies. The question as to whether glucocorticoids are needed in LIA is still controversial. El-Boghdadly *et al.* believed that dexamethasone could not improve the analgesic effect of LIA, and that the use of glucocorticoids may lead to the fluctuation of blood glucose.[8,29] Liu believed that glucocorticoids in LIA could effectively reduce the perioperative dosage of opioids in THA, which was beneficial to pain control and postoperative rehabilitation. The results of a meta-analysis also supported the idea that glucocorticoids could improve the analgesic effect of LIA.[27,30] Some studies have also suggested that betamethasone could improve the analgesic effect of LIA,[27,31] but there has been little research on the effect of diprospan and morphine in the cocktail formula for THA. The results of this study confirmed that the new cocktail worked better than ropivacaine alone. In consideration of the antagonistic effect of glucocorticoids on insulin, this study excluded diabetic patients, and there was no significant difference in the fluctuation of blood glucose among the three groups. However, whether this new cocktail is suitable for patients with diabetes still requires further research. In addition, this study showed that the new cocktail was beneficial to early pain control after THA, but it had little effect on the long-term joint function and quality of life of patients, which was consistent with the results of previous studies.[32,33]

Limitations of the Study

Although the results confirmed that the new cocktail could effectively reduce pain after THA, this study still had limitations. First, the surgeon was not blinded to the group assignment, but patients, anesthesiologists, outcome assessors, and data collectors were blinded, and the surgeon did not participate in the data collection and postoperative management related to this trial. Second, patients in the control group were not injected with normal saline as a placebo, which may bias the results of the study. However, the research team believed that the injection of normal saline into the patient's tissue is not suitable. Third, in this study, all of the patients used the same multimode analgesic measures except for LIA, which may affect the results of the study to some extent. However, the schemes that were adopted by the three groups of patients were consistent, and it can be considered that the difference between the three groups is mainly caused by the unique variable "cocktail" formula. In addition, at present, there is a positive attitude toward the effect of perioperative multimode analgesia in joint replacement surgery. It is inhumane and not in line with ethical requirements for patients to abandon well-known and effective analgesic measures for the sake of clinical research. Therefore, this study did not set up a control group for abandoning the use of multimodal analgesia. Fourth, this study was conducted in a single center, and all of the operations were performed by the same surgeon who had completed more than 3000 THAs and was proficient. Therefore, it is not clear whether the surgical technique will affect the results of the study and whether other surgeons can repeat the results.

Conclusion

In conclusion, for patients undergoing primary THA *via* the posterolateral approach under general anesthesia, the new cocktail with diprospan, morphine, and ropivacaine had a better result and longer time duration for early postoperative pain control than ropivacaine alone, especially for treating resting pain.

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Conflict of Interest

The authors declare that they have no competing interests.

References

1. Shon WY, Park BY, RN R, et al. Total hip arthroplasty: past, present, and future. What Has Been Achieved? Hip Pelvis. 2019;31:179–89.
2. Russo MW, Parks NL, Hamilton WG. Perioperative pain management and anesthesia: a critical component to rapid recovery total joint arthroplasty. Orthop Clin North Am. 2017;48:401–5.
3. Kuchálik J, Magnuson A, Lundin A, Gupta A. Local infiltration analgesia: a 2-year follow-up of patients undergoing total hip arthroplasty. J Anesth. 2017;31:837–45.
4. Zhu S, Qian W, Jiang C, Ye C, Chen X. Enhanced recovery after surgery for hip and knee arthroplasty: a systematic review and meta-analysis. Postgrad Med J. 2017;93:736–42.

5. Sah AP, Liang K, Sclafani JA. Optimal multimodal analgesia treatment recommendations for total joint arthroplasty: a critical analysis review. JBJS Rev. 2018;6:e7.
6. Elmallah RK, Chughtai M, Khlopas A *et al*. Pain control in total knee arthroplasty. J Knee Surg, 2018, 31:504–513.
7. Aso K, Izumi M, Sugimura N, et al. Additional benefit of local infiltration of analgesia to femoral nerve block in total knee arthroplasty: double-blind randomized control study. Knee Surg Sports Traumatol Arthrosc. 2019;27: 2368–74.
8. El-Boghdadly K, Short AJ, Gandhi R, Chan VWS. Addition of dexamethasone to local infiltration analgesia in elective total hip arthroplasty: a double-blind, randomized control trial. Reg Anesth Pain Med. 2019;27:2019–100873.
9. Gurava Reddy AV, Thayi C, et al. Validating the role of steroid in analgesic cocktail preparation for local infiltration in total knee arthroplasty: a comparative study. Anesth Essays Res. 2018;12:903–6.
10. Noskov SM, Fetelego OI, Krasivina IG, Dolgova LN. Alflutop in local therapy of shoulder periarthritis. Ter Arkh. 2005;77:57–60.
11. Lara-de la Fuente R. Steroid infiltrations in orthopedics. Acta Ortop Mex. 2011;25:12–6.
12. Lei YT, Xu B, Xie XW, Xie JW, Huang Q, Pei FX. The efficacy and safety of two low-dose peri-operative dexamethasone on pain and recovery following total hip arthroplasty: a randomized controlled trial. Int Orthop. 2018;42:499–505.
13. Li J, Zhu H, Liao R. Enhanced recovery after surgery (ERAS) pathway for primary hip and knee arthroplasty: study protocol for a randomized controlled trial. Trials. 2019;20:599.
14. Ma J, Huang ZY, Shen B, Pei FX. Blood management of staged bilateral total knee arthroplasty in a single hospitalization period. J Orthop Surg Res. 2014;9:116.
15. Wang HY, Wang L, Luo ZY *et al*. Intravenous and subsequent long-term oral tranexamic acid in enhanced-recovery primary total knee arthroplasty without the application of a tourniquet: a randomized placebo-controlled trial. BMC Musculoskelet Disord, 2019, 20:478.
16. Wang D, Wang HY, Luo ZY, Pei FX, Zhou ZK, Zeng WN. Finding the optimal regimen for oral tranexamic acid administration in primary total hip arthroplasty: a randomized controlled trial. J Bone Joint Surg Am. 2019;101:438–45.
17. Takahashi M, Ohara T, Yamanaka H, Shimada A, Nakaho T, Yamamuro M. The oral-to-intravenous equianalgesic ratio of morphine based on plasma concentrations of morphine and metabolites in advanced cancer patients receiving chronic morphine treatment. Palliat Med. 2003;17:673–8.
18. Curtis GB, Johnson GH, Clark P, et al. Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. Eur J Clin Pharmacol. 1999;55:425–9.
19. Villatte G, Engels E, Erivan R, et al. Effect of local anaesthetic wound infiltration on acute pain and bleeding after primary total hip arthroplasty: the EDIPO randomised controlled study. Int Orthop. 2016;40:2255–60.
20. Titman S, Hommel A, Dobrydnjov I, Johansson A. The efficacy of high volume of local infiltration analgesia for postoperative pain relief after total hip arthroplasty under general anaesthesia—a randomised controlled trial. Int J Orthop Trauma Nurs. 2018;28:16–21.
21. Ma HH, Chou TA, Tsai SW, et al. The efficacy of intraoperative periarticular injection in total hip arthroplasty: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2019;20:269.
22. Shen B, Weng X, Liao R, et al. Expert consensus in enhanced recovery after total hip and knee arthroplasty in China: pain and sleep management. Chin J Bone Joint Surg. 2016;9:91–7.
23. Min BW, Kim Y, Cho HM, et al. Perioperative pain management in total hip arthroplasty: Korean hip society guidelines. Hip Pelvis. 2016;28:15–23.
24. Hannon CP, Keating TC, Lange JK, Ricciardi BF, Waddell BS, Della Valle CJ. Anesthesia and analgesia practices in total joint arthroplasty: a survey of the American Association of hip and Knee Surgeons Membership. J Arthroplast. 2019;34:2872.e2–7.e2.
25. Hofstad JK, Winther SB, Rian T, Foss OA, Husby OS, Wik TS. Perioperative local infiltration anesthesia with ropivacaine has no effect on postoperative pain after total hip arthroplasty. Acta Orthop. 2015;86:654–8.
26. Jimenez-Almonte JH, Wyles CC, et al. Is local infiltration analgesia superior to peripheral nerve blockade for pain management after THA: a network meta-analysis. Clin Orthop Relat Res. 2016;474:495–516.
27. 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: 387–93.
28. 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;22:1638–43.
29. Habib G, Khazin F, Sakas F, Hakim G, Artul S. The impact of intra-articular injection of diprospan at the knee joint on blood glucose levels in diabetic patients. Eur J Rheumatol. 2018;5:96–9.
30. Tran J, Schwarzkopf R. Local infiltration anesthesia with steroids in total knee arthroplasty: a systematic review of randomized control trials. J Orthop. 2015;12:S44–50.
31. Liu P, Guo WS, Zhang QD, Wang WG, Zhang Y, Wang YY. Efficacy and safety of compound betamethasone cocktail therapy in primary unilateral unicompartmental knee arthroplasty. Zhonghua Yi Xue Za Zhi. 2019;99:3100–4.
32. Kuchalik J, Magnuson A, Tina E, Gupta A. Does local infiltration analgesia reduce peri-operative inflammation following total hip arthroplasty? A randomized, double-blind study. BMC Anesthesiol. 2017;17:63.
33. Nassar I, Fahey J, Mitchell D. Rapid recovery following hip and knee arthroplasty using local infiltration analgesia: length of stay, rehabilitation protocol and cost savings. ANZ J Surg. 2020;90:355–9.