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Analgesic effect of ropivacaine combined with methylene blue in fascia Iliaca block for patients undergoing hip arthroplasty

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Abstract

Background The duration of a single fascia iliaca compartment block (FICB) with ropivacaine is limited. This study investigated whether methylene blue as an adjuvant anesthetic in FICB can enhance the postoperative analgesic effect following total hip arthroplasty (THA).

Methods Patients who planned to undergo THA were recruited for this randomized clinical trial from June 2023 to February 2024. Ninety elderly patients undergoing THA were randomly divided into two groups that received ultrasound-guided FICB with either ropivacaine and methylene blue (MB + R group, $n = 45$) or ropivacaine only (R group, $n = 45$) before induction of general anesthesia. The primary outcomes were postoperative Visual Analog Scale (VAS) scores. Secondary outcomes included inflammatory factor levels, heart rate (HR), mean arterial pressure (MAP), postoperative analgesic use, postoperative activity, and adverse events.

Results The MB + R group had significantly lower VAS scores at both rest and with activity at 24 and 48 h postoperatively than the R group ($P < 0.001$). Additionally, the hypersensitive C-reactive protein, procalcitonin, and neutrophil-to-lymphocyte ratio values were significantly lower in the MB + R group than in the R group on the first and second days after surgery ($P < 0.05$). The number of patients requiring supplemental analgesia postoperatively was significantly lower in the MB + R group ($P = 0.020$). Additionally, the MB + R group had a significantly longer walking distance on the first time out of bed and a higher number of out-of-bed activities within 48 h postoperatively ($P < 0.001$).

Conclusion Compared to ropivacaine alone, the combination of ropivacaine and methylene blue in FICB provided better analgesic effects over a longer duration. Additionally, the addition of methylene blue reduced the postoperative production of inflammatory markers and promoted patients' functional recovery.

Trial registration ClinicalTrials.gov, Registration number: NCT06284941, Retrospectively registered, Date of registration: February 04, 2024.

Keywords Analgesia, Fascia Iliaca compartment block, Methylene blue, Ropivacaine, Total hip arthroplasty

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Background

Total hip arthroplasty (THA) is currently the most effective method for treating many hip conditions and improving patients' quality of life, but severe pain is a common postoperative complication [1]. Persistent acute pain not only impairs patient mobility but also prolongs hospitalization, promotes deep vein thrombosis [2], and can even develop into chronic pain [3]. Therefore, effective postoperative analgesia is needed to support optimal patient recovery.

Although opioids are the mainstay drugs used for postoperative analgesia, they are associated with systemic adverse effects. Accordingly, in recent years, peripheral nerve blocks have been investigated and shown clinical benefit as postoperative analgesia after THA. Specifically, fascia iliaca compartment block (FICB) is recommended as the preferred nerve block for pain management after THA [4]. The advantages of FICB include being simple and safe to administer, avoiding vascular nerve damage, rapid onset of action, clear analgesic efficacy, reduction of opioid use, and shortened hospital stay [5]. However, the duration of a single FICB is limited, and although increasing the concentration or volume of local anesthetic delivered can prolong the duration of analgesia, the risk of drug-related toxicity also increases [6]. Research suggests that continuous fascia iliaca block methods can achieve longer analgesia but pose risks associated with leakage of local anesthetic, catheter detachment, and infection [7].

Therefore, the need persists for safer and more effective drugs and methods for postoperative analgesia in patients undergoing THA. The use of methylene blue as a local anesthetic adjuvant has gradually been adopted in clinical practice, including after surgical treatment of hemorrhoids, perianal intractable pruritus, etc. In patients undergoing hemorrhoidectomy, methylene blue was shown to significantly prolong the block time of local anesthetics [8]. However, few clinical studies on the use of methylene blue in nerve block procedures have been reported, but one study on its application specifically in paravertebral nerve blocks indicated that its addition extended the duration of the nerve block and achieved this analgesic effect without damaging neurons [9]. To date, no study on the application of methylene blue in FICB has been reported. Therefore, the present study investigated the application of methylene blue in combination with ropivacaine under ultrasound guidance to achieve FICB in patients undergoing THA, examining its ability to prolong the analgesic time, reduce complications, and promote postoperative recovery relative to traditional methods.

Methods

Study design

This randomized clinical trial was approved by the Ethics Committee of Taizhou Jiangyan Hospital of Traditional Chinese Medicine in April 2023 (ethics number: KY 2023-001-001; registered on May 05, 2023) and registered at clinicaltrials.gov (registration number: NCT06284941; registered on February 04, 2024). The study was performed in compliance with the Declaration of Helsinki and adheres to CONSORT guidelines. Written informed consent for surgery and anesthesia was obtained from each patient or a family member.

Study population

For inclusion in this study, patients of either sex had to meet the requirements for hip replacement surgery, be in the elderly age range of 65–85 years, have a body mass index (BMI) in the range of 18–28 kg/m^2, be categorized as American Society of Anesthesiologists (ASA) grade II to III, have no history of analgesic or local anesthetic allergies, and have no history of alcoholism or narcotic drug abuse. Patients were excluded if they met any of the following criteria: refusal by patient or family member to participate in the study, having a serious mental illness or inability to communicate clearly with researchers, severe coagulopathy, allergy to local anesthetics, severe psychiatric illness or other communication disorder, history of neurological disease such as Guillain-Barré syndrome, infection at the puncture site, delay in awakening post-surgery for more than 60 min, post-surgical use of an analgesic pump, and inability to follow-up at the required time points.

Randomization and blinding

Using a computer-generated random sequence, a person who was not involved in the experimental operation divided the patients into two groups in which FICB was achieved with either methylene blue and ropivacaine (MB + R group) or ropivacaine only (R group). All serial numbers were encoded sequentially, kept, and scheduled for each experiment by someone other than the researcher. Because methylene blue is a blue liquid, exposure to the color could expose the experimental group. Thus, blinding was achieved by having different researchers perform different steps in the study to avoid the color affecting the experiment. The steps of the experimental procedure, including the extraction of the liquid medicine, performance of the nerve block, and postoperative follow-up, were performed by different anesthesiologists, who were only responsible for independent experimental procedures, did not know the information about the patient outside the experiment, and did not communicate with each other about the patient and the experiment. Catheterization was not performed for any patient

to prevent the color of the urine from exposing the experimental group.

Operative procedures

Nerve block

Before general anesthesia induction, FICB was performed under ultrasound guidance using the Edge II ultrasound device (Sonosite, USA). With the patient in supine position and the surgical area disinfected, the high-frequency ultrasound probe was placed perpendicular on the inguinal ligament. The probe was slowly moved until the "bowtie sign" created by the internal oblique and sartorius muscles was observed. This sign corresponds to the confluence of the fascia lata and fascia iliaca, which represents the fascia iliaca compartment. With an in-plane technique in the caudal to cranial direction, the needle tip was inserted deep to the fascia iliac. After confirming it could be withdrawn without blood, local anesthetic drugs in a volume of 30 ml were injected [10]. Patients in the MB + R group received 0.25% ropivacaine (Product Batch Number: EE2344, Zhejiang Xianju Pharmaceutical Co., Ltd.) and 0.05% methylene blue (Product Batch Number: 2310032, Jichuan Pharmaceutical Group Co., Ltd.), and those in the R group received only 0.25% ropivacaine (same batch number). Methylene blue was used at a dose of 15 mg, while ropivacaine was used at a dose of 75 mg in both groups. The effect of the nerve block was evaluated 30 min after injection, and effective block was defined as the loss of pinprick sensation in the innervated area of the femoral nerve and lateral thigh cutaneous nerves 30 min after injection [11].

Induction and maintenance of anesthesia

After successful nerve block, all patients were transferred to the operating room where they received routine monitoring of blood pressure (BP), electrocardiogram (ECG), oxygen saturation (SpO_2), etc. Radial artery puncture catheterization was performed under local anesthesia for invasive arterial pressure monitoring. For anesthesia induction, patients received an intravenous injection of propofol 1.0–2.0 mg/kg, rocuronium bromide 0.6 mg/kg, and sufentanil 0.2–0.3 μg/kg. The specifications of mechanical ventilation after endotracheal intubation were: tidal volume (VT) 6–8 ml/kg, respiratory rate (RR) 10–12 times/min, positive end expiratory pressure (PEEP) 3–5 cmH_2O, and end-expiratory carbon dioxide partial pressure ($PETCO_2$) 35 ~ 45 mmHg. Anesthesia was maintained by inhalation of 1.5–2.0% sevoflurane along with intravenous infusion of remifentanil at 0.05–0.2 μg/kg/min and intermittent administration of rocuronium bromide 5–10 mg according to the intraoperative situation to maintain muscle relaxation. MAP and HR fluctuation within 20% of baseline values was allowed according to the intraoperative situation. If BP dropped by > 20% of the baseline value or if systolic BP was < 90 mmHg, ephedrine 6 mg was given. If the HR was < 50 beats/minute, an intravenous bolus of atropine 0.5 mg was given. All operations among included patients were performed by the same surgical team with the same surgical method, and the surgical method was hip replacement with posterolateral approach in the lateral decubitus position. The inhalation of sevoflurane and infusion of remifentanil was stopped 5 min before the end of the operation. After surgery, the patient was transferred to a recovery room, and the endotracheal tube was removed once the patient was awake and spontaneous breathing had resumed. According to our pre-test experience, many patients refuse the use of analgesic pumps due to the relatively high cost, certain drug-related side effects, and the option of FICB. Thus, we did not include cases with post-surgical use of an analgesic pump in this study. In this study, fascia iliaca block was used to administer postoperative analgesia to patients. If the patients were dissatisfied with the effect of the fascia iliaca block and requested additional analgesic medication, oral Tramadol sustained-release tablets 0.1 g per dose might be used for supplementary analgesia. The frequency of Tramadol use was determined by the guidelines for the drug's prescription and the patient's subjective needs. To avoid the effect of drugs on the level of patients' inflammatory factors, the use of non-steroidal analgesic drugs was prohibited.

Study outcomes

Primary outcomes

As a measure of pain, Visual Analog Scale (VAS) scores at both rest and with activity (passive straight leg raise at 45°) were recorded at the following time points: before block and at 2, 6, 12, 24, and 48 h postoperatively [12]. The VAS score at 48 h after surgery was set as the primary outcome. The VAS score is a common way to assess pain using a sliding ruler about 10 cm long, marked with 10 scales on one side and "0" and "10" at each end. A score of 0 indicates no pain; a score of 10 indicates the most severe pain that is unbearable. The higher the score, the greater the degree of pain. In this study, a dedicated anesthesiologist assessed the pain of each included participant at different time points before and after surgery.

Secondary outcomes

As indicators of inflammation, the values of hypersensitive C-reactive protein (hs-CRP), procalcitonin (PCT), and the neutrophil-to-lymphocyte ratio (NLR) also were recorded on postoperative days 1 and 2.

HR and MAP values were recorded at the following time points: operating room entry (T1), immediately before skin incision (T2), 1 min after skin incision (T3), skin suture (T4), and 30 min after extubation (T5).

The requirement of supplemental analgesia was noted within 48 h postoperatively, along with the number of times patients got out of bed to perform activities within 48 h postoperatively and the distance walked after the patient's first attempt to get out of bed. As long as the patient took oral analgesics, of any dose and frequency, they were classified as using supplemental analgesics. Any occurrence of adverse reactions such as nausea, vomiting, and arrhythmia within 48 h postoperatively also was recorded. Any drug-related nerve damage after surgery was noted. Nerve deficits were defined according to sensory findings: 0—no nerve damage, 1—minor sensory paresthesia, 2—complete sensory parasthesia, 3—complete motor defect with or without sensory paresthesia, and 4—complex regional pain syndrome. Two researchers who were blinded to the group allocation assessed these outcomes.

Sample size

The sample size was calculated using PASS 15.0. A total of 22 patients were selected for preliminary evaluation of VAS scores in a resting state at 48 h after surgery. Based on the results of our preliminary evaluations, the mean VAS scores (± standard deviation [SD]) of the MB + R group and the R group were 2.64 ± 0.505 and 3.18 ± 0.603, respectively. With a bilateral α and β set to 0.05, a minimum of 29 patients was required for each group. Considering a 20% loss to follow-up rate and the availability of sufficient experimental samples, a total of 90 patients were finally included.

Statistical methods

SPSS 25.0 software was used for statistical analysis. Due to the relatively small sample size, the Shapiro–Wilk test was applied to test the normality of data distributions. Normally distributed data were expressed as mean ± SD, and group comparisons were performed using independent samples *t*-test. Data with a skewed distribution were expressed as median (*M*) and interquartile range (IQR), and the Mann–Whitney U test was used for comparisons between groups. Friedman's test was used for intra-group comparisons. Count data were expressed as number (%), and comparisons between groups were performed using the χ^2 test. $P < 0.05$ was considered statistically significant.

Results

For this randomized clinical trial, 97 elderly patients with planned THA were initially included. After application of the exclusion criteria, 7 patients were excluded from the study, including 1 patient due to communication barriers, 2 patients due to the use a pain pump postoperatively, and 4 patients due to postoperative loss to follow-up. Ultimately, 90 cases were included (Fig. 1).

The 90 included patients were assigned to either the MB + R group ($n = 45$ patients) or the R group ($n = 45$ patients). No statistically significant differences in gender, age, BMI, ASA grade, operation time, intraoperative sufentanil dosage, and remifentanil dosage were observed between the MB + R and R groups (Table 1).

Compared with values in the R only group, the VAS scores at rest and with activity at 24 and 48 h postoperatively in MB + R group were significantly lower ($P < 0.05$; Table 2). The median difference between the two groups at rest and while active at 24 h after surgery was – 1, (95% confidence interval was – 1~-1; -1 ~ 0, respectively). The median difference between the two groups at rest and while active at 48 h after surgery was – 1, (95% confidence interval – 2~-1; -1 ~ 0, respectively). The VAS scores at rest and with activity in the MB + R group did not differ significantly among the 2-, 6-, and 12-h time points. In the resting state, the VAS scores of the MB + R group were significantly lower at 2, 6, 12, 24, and 48 h postoperatively than before block (all $P < 0.05$), and those in the R group were significantly lower at 2, 6, 12, and 48 h postoperatively than before block ($P < 0.05$). In the R group, the VAS scores at 12 and 48 h postoperatively were significantly lower than at 24 h postoperatively ($P < 0.05$). In the active state, compared with those before the block, the scores of the two groups at different times postoperatively were consistent with the results in the resting state ($P < 0.05$). Also, in both groups, the VAS scores at 12 and 48 h postoperatively were significantly lower than those at 24 h postoperatively ($P < 0.05$).

Throughout the surgical process, the HR and MAP values of patients were highest at the time of operating room entry and decreased after anesthesia induction to values significantly lower than those at the time of entry ($P < 0.001$; Table 3). The HR and MAP values did not differ significantly between the two groups at any time point during the surgical procedure.

Measurements of inflammation markers showed that the values of hs-CRP, PCT, and NLR in the MB + R group were significantly lower than those in the R only group on the first and second days after surgery ($P < 0.05$; Table 4).

As indicators of patients' postoperative condition, the number of times patients got out of bed for activities within 48 h after surgery and the distance walked on the first time out of bed postoperatively were significantly greater in the MB + R group than in the R group ($P < 0.05$). The number of patients requiring supplemental analgesia postoperatively was significantly lower in the MB + R group than in the R group ($P < 0.05$; Table 5).

With respect to adverse events postoperatively, no statistically significant differences were observed in the incidence of nausea and vomiting, arrhythmia, dizziness and headache, chest tightness, and abdominal pain between the MB + R and R groups within 48 h postoperatively

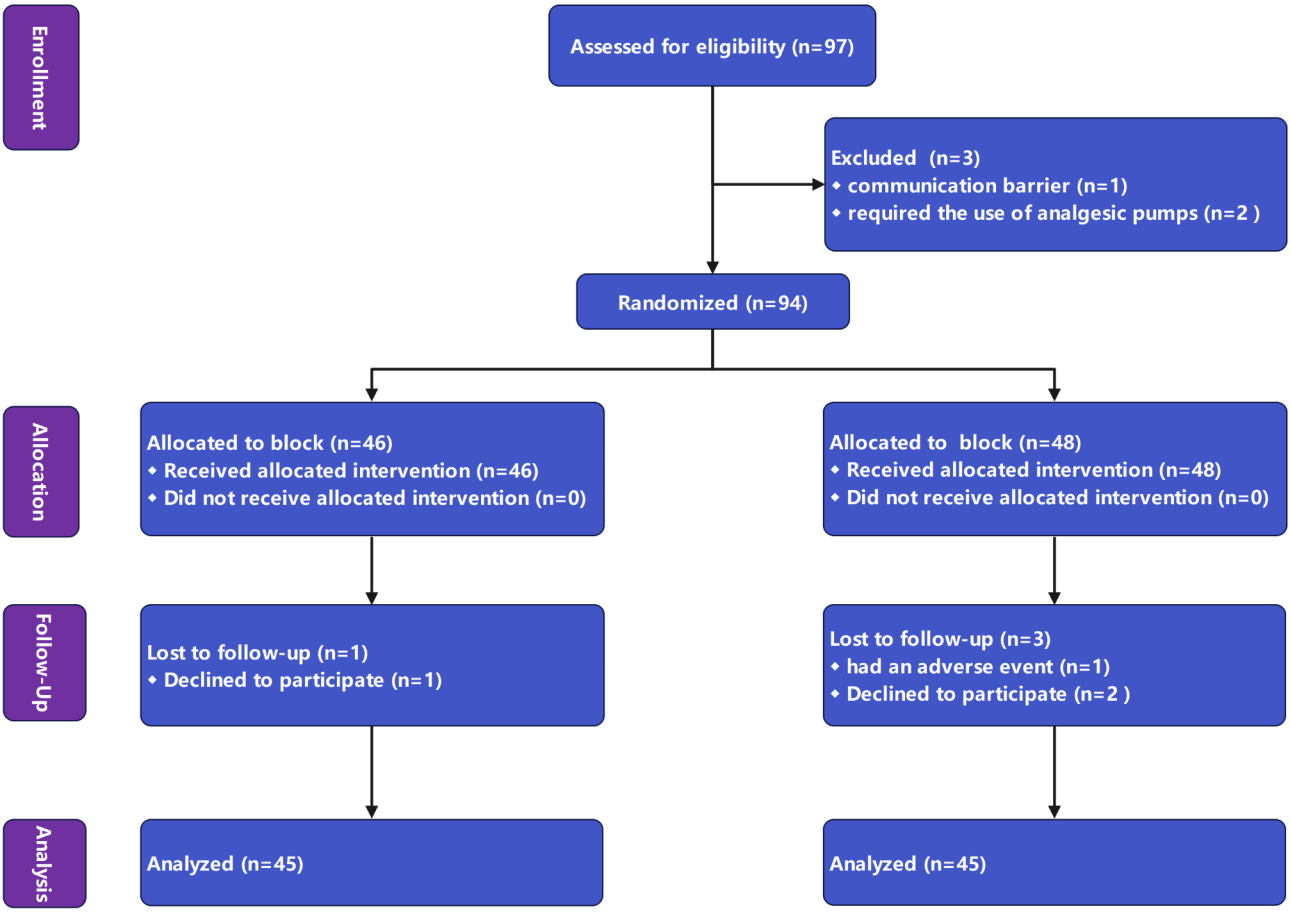

Fig. 1 Flow chart of patient enrollment. Seven patients were excluded from the study, and ultimately, 90 elderly patients were included

Table 1 Characteristics and intraoperative conditions of patients in both groups

Group	Male/ Female (*n*)	Age (years)	BMI (kg/m^2)	ASA II/III (*n*)	Operation time (min)	Intraoperative sufentanil dose (μg)	Remifentanil dose (μg)
MB + R (*n* = 45)	13/32	73.93 ± 5.61	22.69 ± 2.57	7/38	84.44 ± 21.09	30.44 ± 5.31	608.76 ± 234.01
R (*n* = 45)	15/30	75.47 ± 5.54	22.73 ± 2.37	6/39	90.89 ± 19.29	29.67 ± 5.16	661.56 ± 189.13
t/χ^2 value	0.207	-1.305	-0.064	0.090	-1.513	0.705	-1.177
P value	0.649	0.195	0.949	0.764	0.134	0.483	0.242

Data are expressed as n or mean (SD). BMI, body mass index; ASA, American Society of Anesthesiologists; MB, methylene blue; R, ropivacaine; SD, standard deviation

(Table 6). No complications associated with FICB, such as nerve injury, puncture site infection, and drug poisoning, occurred in either group. No drug-related nerve damage was observed.

Discussion

The findings of this study indicate that the use of ropivacaine combined with low-concentration methylene blue for fascia iliaca block can be a safe and reliable technique for postoperative analgesia in hip replacement surgery. This method reduced postoperative pain scores statistically and provided longer-lasting analgesia, thereby facilitating early functional rehabilitation for patients. Additionally, methylene blue decreased the release of inflammatory factors, resulting in a milder stress response and a reduction in surgery-related adverse effects. Furthermore, while the study did not observe a significant effect of low-dose methylene blue on stabilizing hemodynamics, the use of low-dose methylene blue also did not increase the incidence of postoperative adverse reactions.

Activation of the inflammatory response directly correlates with the degree of surgical trauma [13], and effective analgesia is known to be able to reduce both. Methylene blue is a peripheral nerve depressant, as well as an antioxidant and anti-inflammatory molecule, several properties that make it to a useful analgesic [14]. In the present study, hs-CRP, PCT, and the NLR [15] were measured

Table 2 VAS scores at rest and with activity at different time points postoperatively

Group	Resting VAS scores						Z_a value	P_a value
	Before block	2 h after surgery	6 h after surgery	12 h after surgery	24 h after surgery	48 h after surgery		
MB + R (*n* = 45)	5.0 (4.0–6.0)	0.0 (0.0–1.0)[b]	1.0 (1.0–2.0)[b]	2.0 (1.0–2.0)[b]	3.0 (2.0–3.5)[ab]	3.0 (2.0–3.0)[ab]	205.942	< 0.001
R (*n* = 45)	5.0 (4.0–5.0)	0.0 (0.0–1.0)[b]	1.0 (1.0–2.0)[b]	2.0 (2.0–2.5)[bc]	4.0 (4.0–5.0)	3.0 (3.0–4.0)[bc]	203.748	< 0.001
Z_b value	-1.042	-0.424	-0.307	-1.352	-5.861	-4.312	-	-
P_b value	0.289	0.671	0.759	0.176	< 0.001	< 0.001	-	-
MB + R (*n* = 45)	7.0 (6.0–8.0)	1.0 (0.0–1.0)[b]	2.0 (1.5–3.0)[b]	3.0 (3.0–4.0)[bc]	5.0 (4.0–5.0)[ab]	4.0 (3.0–4.0)[abc]	209.60	< 0.001
R (*n* = 45)	7.0 (6.0–8.0)	1.0 (0.0–1.0)[b]	2.0 (2.0–2.5)[b]	3.0 (2.5–4.0)[bc]	6.0 (6.0–6.0)	4.0 (4.0–5.0)[bc]	216.199	< 0.001
Z_b value	-0.903	-0.519	-0.000	-0.374	-6.300	-4.268	-	-
P_b value	0.366	0.603	1.000	0.709	< 0.001	< 0.001	-	-

Notes: [a]*P*<0.05 compared with the R group; [b]*P*<0.05 compared with before block; [c]*P*<0.05 compared with 24 h after surgery; Z_a and P_a values are for intra-group comparisons; Z_b and P_b values are for inter-group comparisons. Data are presented as median [Q1, Q3]. VAS, Visual Analog Scale; MB, methylene blue; R, ropivacaine

Table 3 HR and MAP value at different time points during the surgical procedure

Group	HR (beats/min)					Z_a value	P_a value
	Operating room entry (T1)	Before incision (T2)	One minute after incision (T3)	Skin suture (T4)	Thirty minutes after extubation (T5)		
MB + R (*n* = 45)	72.0 (68.0–77.0)	63.0 (60.0–66.0)[a]	66.0 (62.0–70.0)[a]	62.0 (59.0-67.5)[a]	68.0 (65.0–70.0)[a]	76.263	< 0.001
R (*n* = 45)	74.0 (68.0–78.0)	64.0 (60.5–67.0)[a]	67.0 (62.5–69.5)[a]	62.0 (59.0–68.0)[a]	69.0 (65.0–73.5)[a]	98.800	< 0.001
Z_b value	-0.846	-0.385	-0.854	-0.150	-0.920	-	-
P_b value	0.389	0.700	0.393	0.881	0.358	-	-
MB + R (*n* = 45)	106.0 (101.5–110.0)	84.0 (79.5–88.0)[a]	90.0 (84.5–93.0)[a]	82.0 (79.0–84.0)[a]	92.0 (89.0-95.5)[a]	138.167	< 0.001
R (*n* = 45)	105.0 (101.0–111.0)	83.0 (80.0–88.0)[a]	87.0 (82.5–92.0)[a]	82.0 (78.5–86.0)[a]	91.0 (87.5–96.0)[a]	126.865	< 0.001
Z_b value	-0.113	-0.089	-0.918	-0.214	-0.279	-	-
P_b value	0.910	0.929	0.359	0.830	0.780	-	-

Note: [a]*P*<0.05 compared with value at T1; Z_a and P_a values are for intra-group comparisons; Z_b and P_b values are for inter-group comparisons. Data are presented as median [Q1, Q3]. HR, heart rate; T, time; MB, methylene blue; R, ropivacaine; MAP, mean arterial pressure

Table 4 Levels of inflammation markers at different postoperative time points

Group	hs-CRP (mg/L)		PCT (ng/ml)		NLR (%)	
	1 day after surgery	2 days after surgery	1 day after surgery	2 days after surgery	1 day after surgery	2 days after surgery
MB + R (*n* = 45)	41.6 (30.0–55.1)[a]	73.2 (50.7–92.3)[a]	0.10 (0.06–0.12)[a]	0.10 (0.08–0.13)[a]	5.6 (4.8–8.5)[a]	5.0 (3.9–7.0)[a]
R (*n* = 45)	56.1 (41.7–80.5)	92.6 (67.9–120.4)	0.15 (0.12–0.21)	0.16 (0.11–0.24)	8.3 (5.8–11.7)	6.6 (4.9–8.8)
Z Value	-2.816	-2.336	-4.515	-4.007	-2.982	-3.030
P Value	0.005	0.019	< 0.001	< 0.001	0.003	0.002

Note: [a]*P*<0.05 compared with the R group. Data are presented as median [Q1, Q3]. hs-CRP, hypersensitive C-reactive protein; PCT, procalcitonin; NLR, neutrophil-lymphocyte ratio; MB, methylene blue; R, ropivacaine

Table 5 Post-operative conditions

Group	Number of times patients got out of bed to perform activities within 48 h after surgery (*n*)	Distance walked on first time out of bed after surgery (m)	Patients who required postoperative salvage analgesics (*n*)
MB + R (*n* = 45)	6.16 ± 1.02	28.67 ± 5.40	8
R (*n* = 45)	4.98 ± 1.16	23.56 ± 4.93	18
t/χ^2 value	5.117	4.690	5.409
P value	< 0.001	< 0.001	0.020

Note: *P* < 0.05 compared with the R group. Data are presented as n or mean (SD). MB, methylene blue; R, ropivacaine

Table 6 Postoperative adverse reactions

Group	Nausea and vomiting, *n* (%)	Arrhythmia, *n* (%)	Dizziness and headache, *n* (%)	Chest tightness, *n* (%)	Abdominal pain, *n* (%)
MB + R (*n* = 45)	6 (13.3)	4 (8.9)	5 (11.1)	4 (8.9)	0 (0.0)
R (*n* = 45)	7 (15.6)	6 (13.3)	7 (15.6)	6 (13.3)	1 (2.2)
χ^2 value	0.090	0.450	0.385	0.450	-
P value	0.746	0.502	0.535	0.502	1.000

Data are presented as n (%). MB, methylene blue; R, ropivacaine

as inflammatory markers. The levels of these inflammatory factors in the first and second days postoperatively were significantly lower in the MB + R group than in the R group, indicating a reduction in inflammation with the addition of methylene blue. This effect may be associated with the fact that methylene blue can inhibit inflammasome production and interrupt inducible nitric oxide synthase (iNOS)/NO conduction, and triggering of these mechanisms can achieve an analgesic effect [16]. In addition, Zheng et al. [17] found that methylene blue modulates the inflammatory response in arthritis by targeting the long intergenic noncoding RNA CILinc02, ultimately inhibiting osteoarthritis-related inflammation. These findings also support that methylene blue has an anti-inflammatory effect.

With regard to the primary outcome of the present study, postoperative pain, no significant differences in VAS scores at rest and with activity were observed between the MB + R and R groups at 2, 6, and 12 h postoperatively. The comparable analgesic effects in the two groups at these time points may be due to the fact that ropivacaine is effective for 9–14 h after injection [18]. These results do show that the administration of ropivacaine alone or with methylene blue could meet patients' analgesic requirements within 12 h postoperatively. Notably, methylene blue has a slow onset of action because of its incubation period of 2–4 h [19]. Therefore, use of methylene blue alone cannot meet the early analgesic requirements of patients, and a block with methylene blue only causes the problem of burning pain due to stimulation of the nerve myelin [8]. Conversely, ropivacaine has a rapid onset of effect. Therefore, the use of ropivacaine combined with methylene blue can not only address the limitation of methylene blue for early analgesia but also avoid the problem of burning pain caused by methylene blue. The VAS scores of the two groups reached their peak values at 24 h postoperatively, and these findings are consistent with the results of Liang et al. [20] and associated with the known peak of pain 24 h postoperatively. In addition, on comparison of the VAS scores at 24 h postoperatively to those at 12 and 48 h postoperatively, no significant differences were observed in the resting state for only the MB + R group, which demonstrates the sustainability of the postoperative analgesic effect of methylene blue and its ability to compensate for the lack of analgesia after 12 h postoperatively with ropivacaine only. The VAS scores of the MB + R group at 24 and 48 h postoperatively were statistically significantly lower than those of the R group. While the significant but small decrease in VAS score may not represent a clinically significant improvement in pain, our findings indicate that ropivacaine combined with methylene blue achieved a longer duration of postoperative analgesia for THA patients, both at rest and with activity. This may be related to the fact that methylene blue can change the internal and external acid–base balance and membrane potential of nerve endings for a long time, causing them to be desensitized [9]. Deng et al. [21] also believe that methylene blue can block sodium channels to change the potential to achieve an analgesic effect. Previous research has shown that methylene blue directly inhibits nerve connections to reduce pain, and this process is called denervation [22]. At the same time, a previous study in rats showed that methylene blue can achieve a longer analgesic effect by eliminating nerve firing rates [23]. These findings are consistent with the results of Guoyu et al. [19], who also showed that the combination of ropivacaine with methylene blue can prolong analgesia. Notably, many patients who received the ropivacaine only block still reported a certain blocking effect at 24 h after surgery. Also, some patients even exhibited a block time of much longer than 24 h, which may be attributable to the amount of time required for absorption of the high-dose local anesthetic solution in the narrow fascia iliaca space, which could mean that the nerves of the lower limbs were continuously blocked. This clinical phenomenon is worthy of further study.

The goal of Enhanced Recovery After Surgery (ERAS) is to reduce postoperative complications and facilitate patient mobility as soon as possibly within 24 h postoperatively [24]. In the present study, the first walking distance of the MB + R group was much longer than that of the R group, and the number of times patients got out of bed to perform activities within 48 h was greater in the MB + R group than in the R group, which may indicate that the postoperative analgesia experienced in the MB + R group increased these patients' pain threshold, thereby increasing their desire to be active. Moreover,

the number of patients who required postoperative salvage analgesics was lower in the MB + R group than in the R group, which also suggests that the analgesic effect of ropivacaine combined with methylene blue was better than that of ropivacaine alone.

The HR and MAP values showed no significant differences between the two groups at different time points during surgery, which may be related to the long incubation period of methylene blue [19] and its inability to take effect by the end of surgery. These findings are consistent with the results of Wei [25], suggesting that at these time points, only ropivacaine was responsible for the nerve block. However, the intraoperative HR and MAP values were significantly lower than the preoperative HR and MAP values, and the significantly higher values before anesthesia may be due to pain and anxiety experienced by the patients before surgery. While the HR and MAP decreased rapidly with the onset of anesthetic drugs after induction, only small increases were observed due to the stress response during skin incision. Liu [26] showed that the HR and MAP values before surgery increase as the operation time approaches, and the HR and MAP at 10, 20, and 30 min before anesthesia differ significantly. Thus, the HR and MAP at the time that patients enter the operating room are at peak values among all observation time points. However, THA is mostly performed for elderly patients, who have poor vascular elasticity and greater sensitivity to analgesic drugs. The blood supply to the surgical area for THA is abundant, and because the tourniquet method is not used, extensive bleeding occurs [27], which may explain the significant difference in preoperative and intraoperative HR and MAP. In addition, although the patient is awake after extubation, the HR and MAP after extubation may remain lower than those upon entry into the operating room due to the residual effect of anesthetic drugs caused by the prolonged half-life of the drugs in elderly patients [28] as well as the analgesic effect of the fascia iliaca block.

The common complications of methylene blue include nausea and vomiting, arrhythmia, dizziness and headache, etc. In the present study, no differences in the frequencies of these complications were observed between the two groups, which also confirmed the safety of methylene blue at low concentrations for FICB. As the present study represents the first application of methylene blue in FICB, to avoid unpredictable nerve damage caused by high concentrations of methylene blue [8], a low concentration of 0.05% was selected in reference to the dose used by Guoyu et al. [19]. However, this was lower than the previous 0.2% methylene blue nerve block concentration used by Ji et al. [9]. Whether a higher concentration of methylene blue affects intraoperative hemodynamic stability and can provide a more durable analgesic effect beyond 48 h remains to be studied. In addition, because all patients in this study were elderly, the recovery time after inhalation anesthesia may be prolonged, but the main observation index in this study was the pain response. Considering that the extubation time may still be within the methylene blue incubation period, comparisons at the time of extubation were not performed, and this is a shortcoming of the present study. Because the purpose of this study was to provide a comparative analysis of analgesia, only the intraoperative HR and BP were monitored. Although these results were consistent with those of similar studies, comparative analyses of bleeding volume and infusion volume were not included, which also is a shortcoming of this study. These parameters will be compared in subsequent studies.

Conclusions

In summary, ropivacaine alone and ropivacaine combined with methylene blue for FICB both exhibited a certain analgesic effect after THA. Compared with ropivacaine alone, ropivacaine combined with methylene blue provided a longer postoperative analgesic effect and reduced inflammation, which can significantly reduce the use of postoperative opioids and is more conducive to the rapid postoperative recovery of patients.

Abbreviations

THA	Total hip arthroplasty
FICB	Fascia iliaca compartment block
BMI	Body mass index
ASA	American Society of Anesthesiologists
HR	Heart rate
ECG	Electrocardiogram
SpO_2	Oxygen saturation
VT	Tidal volume
RR	Respiratory rate
PEEP	Positive end expiratory pressure
$PETCO_2$	End-expiratory carbon dioxide partial pressure
BP	Blood pressure
VAS	Visual Analog Scale
hs-CRP	Hypersensitive C-reactive protein
PCT	Procalcitonin
NLR	Neutrophil-to-lymphocyte ratio
MAP	Mean arterial pressure
SD	Standard deviation
M	Median
IQR	Interquartile range
ERAS	Enhanced Recovery After Surgery

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Author contributions

YZ: Contributed to clinical research design, conducted clinical research, collected data, performed statistical analysis, and wrote the manuscript. SY: Contributed to clinical research design and conducted clinical research. ZRL: Conducted clinical studies and analyzed data. FZ: Participated in clinical research. MYL: Contributed to the design of clinical research, provided technical support, and revised the manuscript. All authors read and approved the final version of the manuscript.

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Data availability
The datasets generated and analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This clinical study was approved by the Ethics Committee of Taizhou Jiangyan Hospital of Traditional Chinese Medicine in April 2023 (ethics number: KY 2023-001-001) and registered at clinicaltrials.gov (registration number: NCT06284941; registered on February 04, 2024). The study was performed in compliance with the Declaration of Helsinki and adheres to CONSORT guidelines. Written informed consent for surgery and anesthesia was obtained from the patient or a family member.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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