Heliyon 10 (2024) e28304

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Intravenous injection of dexamethasone is non-inferior to perineural administration for popliteal sciatic nerve and saphenous nerve blocks: A randomized, controlled, triple-blind study

Guiyu Lei [a], Siliu Yang [a,b], Lili Wu [a], Yue Yin [a], Shu Zhang [c], Guyan Wang [a,*]

[a] Department of Anesthesiology, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China
[b] Department of Anesthesiology, Beijing Dongcheng Maternal and Child Health Care Hospital, Beijing, 100007, China
[c] Center of Foot and Ankle Surgery, Beijing Tongren Hospital, Capital Medical University, Beijing, China

ARTICLE INFO

Keywords:
Foot and ankle surgery
Dexamethasone
Nerve block
Perineural
Intravenous

ABSTRACT

Background: The aim of this study was to assess whether intravenous dexamethasone was non-inferior to perineural dexamethasone as an adjuvant to ropivacaine for a combination of saphenous and sciatic nerve blocks in patients undergoing foot and ankle surgery.
Methods: This was a prospective, blinded, randomized noninferiority study. Seventy-five patients, aged 18–75 years, with an American Society of Anesthesiologists (ASA) physical status I-III who underwent foot and ankle surgery were involved. Patients scheduled for ultrasound-guided popliteal sciatic nerve block and saphenous nerve block were randomized to receive 0.375% ropivacaine with 7.5 mg of dexamethasone perineurally (Dex-PN), 10 mg of dexamethasone intravenously (Dex-IV) or neither (Placebo). The primary outcome was the duration of analgesia. The major secondary outcomes were the composite pain intensity and opioid consumption score at 0–48 h intervals after anesthesia.
Results: The mean analgesic duration was 26.2 h in the Dex-IV group and 27.9 h in the Dex-PN group (duration difference, −1.7; 95% CI, −3.8 to 0.43; $P = 0.117$), and both durations were significantly longer than that in the placebo group (17.6 h, $P < 0.001$). Conditions for establishing non-inferiority were met.
Conclusions: Our findings indicate that a single 10-mg intravenous dose of dexamethasone was noninferior to the combined dose of ropivacaine plus deaxmethasone in terms of duration of analgesia for foot and ankle surgery.

1. Introduction

Severe pain within the first 24–48 h after major foot and ankle surgery is common [1,2], triggering several adverse effects. These effects include delayed postoperative mobility, chronic pain, and a notable increase in opioid consumption. Additionally, the use of opioids can result in various dose-dependent side effects, such as sedation, nausea, cough suppression, and constipation, and may also foster both physical and psychological dependency [3,4]. Peripheral nerve block (PNB) with local anesthetics has revolutionized distal

* Corresponding author.
E-mail address: guyanwang2006@163.com (G. Wang).

https://doi.org/10.1016/j.heliyon.2024.e28304
Received 16 December 2023; Received in revised form 6 March 2024; Accepted 15 March 2024
Available online 24 March 2024

extremity surgery due to advantages such as pain relief and an overall reduction in opioid consumption [5–7]. One drawback of single-shot peripheral nerve blockade is its limited duration of analgesia, which has been reported as 8–14 h [2,8]. In addition, rebound pain can also offset peripheral nerve blockade [9–12].

Anesthesiologists have sought strategies to extend the analgesic duration peripheral blocks, and different adjuncts have been used previously, of which dexamethasone is described as being highly effective with few side effects [13–15]. The perineural administration was initially tested, which led to systemic administration becaming an increasingly common route. Numerous studies have investigated the differences between the two routes [16–20]. Nevertheless, the results have been inconsistent. In addition, most of the studies were of brachial plexus blocks [8,21–23], lacking representativeness of the lower extremities. Whether perineural or IV. dexamethasone provides superior, prolonged analgesia duration PNB with minimal side effects remaining a topic debate.

The aim of our study was to test whether the efficacy of dexamethasone administrated intravenously was non-inferior to that of dexamethasone administered perineurally for ultrasound-guided popliteal sciatic nerve block and saphenous nerve block for foot and ankle surgery in terms of analgesic duration, postoperative pain and adjunctive opioid demand.

2. Methods

2.1. Trial design and participants

Our trial was a prospective, randomized, single-center clinical study conducted at Tongren Hospital in Beijing. This study was approved by the Ethics Committee of Tongren Hospital (No. TRECKY2021-007) and was registered in the Chinese Trials registry (https://www.chictr.org.cn/showproj.html?proj=122097) before patient enrollment (identifier: ChiCTR2100043561, Principal investigator: Wang Guyan, Date of registration: Feb 21, 2021, Dates of enrollment: March 1, 2021–Dec 31, 2021). Written informed consent was obtained from all patients before randomization. This manuscript adheres to the applicable CONSORT guidelines. The study included patients aged between 18 and 75 years with American Society of Anesthesiologists (ASA) physical status I-III who were scheduled for foot and ankle surgery and was conducted between March 2021 and July 2022. The exclusion criteria included contraindications to anesthesia (coagulation disorder, puncture site infection, potential for allergic reaction to anesthetics), BMI <18 kg/m^2 or $>$ 35 kg/m^2, reduced sensation or neuropathy involving the sciatic or femoral nerve, pregnancy or currently breastfeeding, abnormal kidney function (serum creatinine >1.2 mg/dL), diabetes that was not satisfactorily controlled (fasting glucose >11 mmol/L) during the screening period, Charcot osteoarthropathy, history of daily steroid use for 10 days or longer anytime during the past year or systemic glucocorticoid therapy within 24 h of surgery, and chronic opioid use. Chronic opioid use was defined as having taken opioids daily for 10 days or longer immediately preceding surgery, 3 times a week for more than 3 months anytime in the past year, or currently useing for pain.

2.2. Randomization and blinding

Patients were randomly allocated to the control group, perineural dexamethasone (Dex-PN) group or intravenous dexamethasone (Dex-IV) group at a 1:1:1 ratio. Block randomization with blocks of nine generated by SPSS software was used to allocate participants to one of the groups; the grouping information was put in sealed, opaque, and numbered envelopes that were kept in a secure location. Randomization and treatment allocation were performed by a clinical investigator who was not involved in the data collection or analysis. Eligible participants were randomized prior to surgery using the next numbered envelope in sequence. Medication was prepared by an anesthesiologist who was not involved in the study and delivered in unidentifiable syringes, according to the group assignment specified in the envelope. The anesthesiologists performing all nerve blocks, orthopedists, patients, research assistants, and investigators collecting data and assessing outcomes were blinded to group assignment.

2.2.1. Group assignments

The control group received 28.5 ml ropivacaine 0.375%+1.5 ml of perineural saline solutio + 2 ml of systemic saline solution. The Dex-PN group received 28.5 ml ropivacaine 0.375% + perineural dexamethasone 7.5 mg (1.5 ml) + 2 ml of systemic saline solution. The Dex-IV group received 28.5 ml of ropivacaine 0.375% +1.5 ml of perineural saline solution +systemic dexamethasone 10 mg (2 ml)."

2.2.1.1. Anesthesia and monitoring. After establishing the IV access and commencing standard monitoring (electrocardiograph, noninvasive blood pressure, continuous oxygen saturation, bispectral index), participants were sedated with 1 mg of midazolam before the regional anesthesia procedure. A study team consisting of three anesthesiologists with more than 5 years of experience in administering regional anesthesia performed the block. All regional anesthesia procedures were guided by ultrasound (SonoSite Export, 8–12 MHz linear probe; SonoSite, Bothell, Washington) using a 100-mm needle (Ultraplex; B. Braun, Melsungen, Germany). A sensory pinprick test was performed on all patients before block, before surgery and postoperatively using a standard pressure of 40 g (Neuropen with 40 g Neurotips; Owen Mumford Ltd, Oxford, United Kingdom), and the results were graded on a 3-point scale (0 = no sensation, 1 = reduced sensation, and 2 = normal sensation to pinprick compared with the opposite side). The superficial peroneal nerve was tested on the dorsal side of the third toe, the deep peroneal nerve was tested on the dorsal side in the first web space, and the tibial nerve was tested on the plantar side of the first toe. The saphenous nerve branches were tested at the midpoint of a line connecting the medial femoral condyle and the tibial tuberosity (the infrapatellar branch of the saphenous nerve) a few centimeters

proximal to the medial malleolus (the sartorial branch of the saphenous nerve).

The popliteal sciatic nerve block was performed while the patient was in the prone position. After the sciatic nerve bifurcation was identified with a 6–15 MHz high-frequency linear array transducer, the needle was inserted in-plane from the lateral end of the probe, and 20 ml of local anesthetic was injected just distal to the bifurcation and constantly visualized to confirm circumferential spread. The needle tip was finally positioned between the tibial and common peroneal nerves within the paraneural sheath.

Saphenous nerve block was performed with the patient in the supine position. The probe was placed at the midthigh level, the saphenous nerve was identified as a rounded, hyperechoic structure anterolateral to the femoral artery, and 10 ml of local anesthetic was injected [24].

All patients were operated on under general anesthesia via a laryngeal mask airway and total intravenous anesthesia. Intravenous anesthesia was induced with sufentanil (0.1–0.3 μg/kg), propofol (1–2 mg/kg), and rocuronium (0.6 mg/kg). Anesthesia was maintained by total intravenous anesthesia with propofol and remifentanil to maintain the sedation level within the range of 40–60 under a bispectral index (BIS) monitor. The fluctuation of mean atrial pressure (MAP) was maintained within 20% of the preoperative values of the patients. All patients received IV lactated Ringer's solution at a rate of 5–7 ml/kg. All surgical procedures were conducted by a fixed group of surgical team members. After surgery, all patients were transferred to the post-anesthesia care unit (PACU) for at least 30 min until they met the discharge criteria. Block success was defined as no sensation of cold or touch in the sciatic and saphenous nerve dermatomes and no requirement for analgesia for pain in the PACU. No opioids or other analgesics were allowed until patients reported the first onset of pain. The postoperative supplemental analgesia protocol was standardized as follows: the mode of patient-controlled analgesia (PCA) system was a bolus of 2 ml, a lockout time of 15 min, and a continuous infusion of 0.5 ml/h (total regimen 12 mg ondansetron and sufentanil 1.5 μg/kg/100 ml). Both the start time of the PCA and cumulative opioid dose were recorded automatically by the pump. All patients received flurbiprofen axetil (100 mg twice a day) once the first PCA bolus was initiated. Five milligrams of oxycodone was administered as rescue analgesia if necessary (NRS>5).

2.2.1.2. Outcomes. Patients were asked to report their pain at rest on a numeric rating scale (NRS) of ranging from 0 to 10. Pain scores were evaluated at the following time points by blinded principal investigator: 0.5, 2, 6, 12, 24, 36, and 48 h after surgery. At 48 h, the patients answered the International Pain Out questionnaires on quality of recovery, overall satisfaction, and opioid side effects, and at 14 days, one month and six months after the surgery, patients were contacted by a blinded investigator to evaluate pain and adverse effects such as persistent numbness or motor deficit. Opioid consumption at 24 and 48 h was automatically registered by the PCA pump, recorded for each participant and converted to intravenous morphine equivalents (IMEs).

The primary outcome was the duration of analgesia defined as the time from the end of block performance until the first sensation of pain at the surgical site (NRS >1 score). The major secondary outcome was the composite pain intensity and opioid consumption (PIOC) score at 0–48 h after anesthesia. This was calculated by ranking both the NRS area under the curve (AUC) pain score and the total morphine consumption at 0–48 h across groups, totaling −200% to +200% for each patient [25,26]. Other secondary outcomes were separate PIOC components, NRS-AUC pain scores and opioid consumption 0–48 h after anesthesia and quality of recovery (the International Pain Outcome Questionnaire, comprising key outcomes of postoperative pain management including pain intensity, physical and emotional functional interference, side effects, and perceptions of care) [27,28]. Additional secondary outcomes were the time to first opioid request and postoperative NRS scores at 30 min, 2 h, 6 h, 12 h, 24 h, 36 h, 48 h, 14 days, 1 month and 6 months after surgery. Neural injury is defined as a sensory deficit.

2.2.1.3. Statistical analysis. Based on our experience with 0.375% ropivacaine, we assumed a duration of analgesia of 24.8 h with an SD of 4.8 h in the Dex-PN group. A difference of 4 h between the Dex-PN group and Dex-IV group was considered clinically relevant [23], and a sample size (power = 0.90 and $\alpha = 0.05$) of 23 patients per group was calculated. An additional 6 patients were recruited to allow for an 8% dropout rate.

Blinded data were analyzed according to the intention-to-treat principle using the statistical software SPSS (version 25; SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to present the baseline characteristics of the three groups. The normality of the quantitative data was verified using a Shapiro–Wilk test and expressed as the mean (standard deviation) or median [interquartile] (range) according to their distribution. Quantitative variables were compared using one-way ANOVA or the Kruskal–Wallis test according to the normality of their distribution. Nonparametric analyses, including the Friedman analysis, were used as appropriate. Intergroup comparisons were performed using the Mann–Whitney *U* test. Categorical variables were assessed using the Pearson chi-square test or Fisher's exact test when appropriate. The interval between the performance of the ankle block and the initial use of rescue analgesia was analyzed by Kaplan–Meier survival analysis in accordance with the censured nature of the dependent variable and proportionality of the hazard ratio and compared between groups with the log-rank test or Tarone–Ware test if appropriate. Bonferroni correction ($P < 0.017$) was applied for three comparisons to maintain the overall type 1 error rate at <5%. Significance was defined as a P value < 0.05 (two-sided).

3. Results

3.1. Participants

A flow chart of patient selection and exclusion is shown in Fig. 1. Recruitment began in Feb 2021, and the final follow-up examination was completed on July 30, 2022. Of the 178 patients who were screened for eligibility, 94 agreed to participate and

underwent randomization. A total of 75 patients were prospectively assigned and successfully enrolled in the study. There were no clinically important differences in the baseline or intraoperative characteristics among the three groups (Table 1 and Table S1). No block-related harm or adverse effects, including falls, were noted in any of the groups.

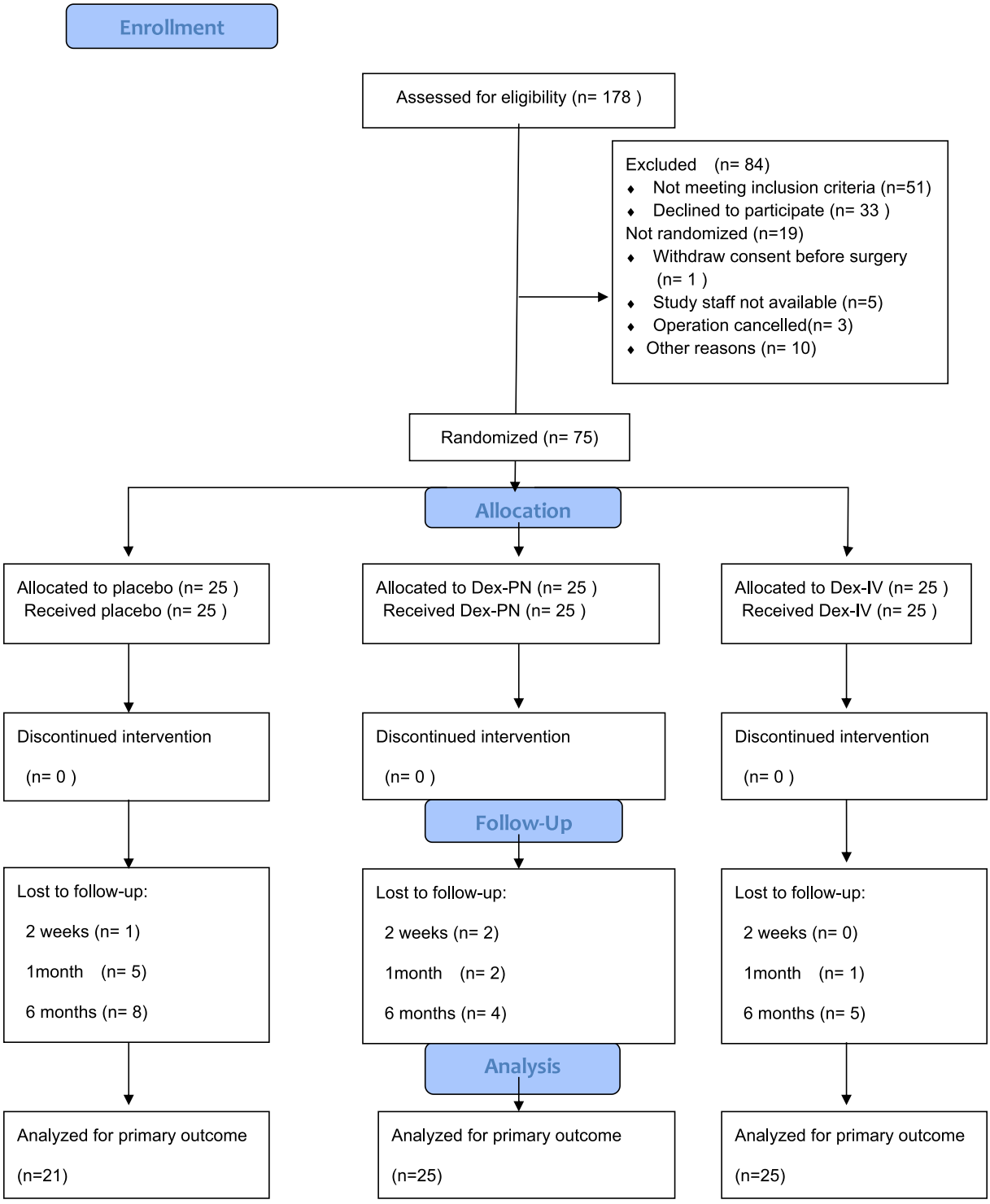

Fig. 1. Study flow diagram Enrollment, randomization, and follow-up of all participants.

3.2. Primary outcome

The primary outcomes were recorded for 25 subjects in the Dex-IV and Dex-PN groups and for 21 subjects in the placebo group because the blocks wore off during sleep. The mean analgesic duration was 26.2 (2.9) hours in the Dex-IV group and 27.9 (4.1) in the Dex-PN group (duration difference, −1.7; 95% CI, −3.8 to 0.43; $P = 0.117$) (Fig. 2), and both durations were significantly longer than that in the placebo group (17.6 (3.5) hours, $P < 0.001$). Because the lower bound of the 95% CI did not cross 4 h, the conditions for establishing noninferiority were met. The Kaplan–Meier curves for the first reported patients are presented in Fig. 3.

3.3. Secondary outcomes

The secondary outcomes are shown in Table 2. The mean duration of the first analgesic effect was 21.5 (5.4) hours in the placebo group, 30.4 (4.4) hours in the Dex-PN group, and 30.1 (5.4) hours in the Dex-IV group [mean (SD)]. The mean difference between the Dex-PN group and the Dex-IV group was 3.5 h (95% CI, 0.8–3.5 h) ($P = 0.212$). Both were significantly longer than those in the placebo group ($P < 0.001$).

The PIOC scores, based on both IV morphine consumption and AUC-NRS pain scores were similar in the Dex-IV group and Dex-PN group for both the first 24 h and 48 h but were significantly lower in both groups than in the placebo group for the first 24 h ($P < 0.001$). The AUC-NRS pain score at 48 h was not significantly different between the groups. The AUCs of the individual PIOC PIOC components for pain scores at 0–48 h after morphine consumption are listed in Table S2.

For the first 24 h, opioid consumption was significantly lower in both the Dex-IV group (0 mg [0–1]) and the Dex-PN group (0 mg [0–1.8]) than in the placebo group (2.4 mg [1.1–7.1]) ($P < 0.001$). Opioid consumption did not differ among the three groups at 24 and 48 h ($P = 0.795$). Five patients (20%) in the Dex-IV group and 6 patients (24%) in the Dex-PN group did not require opioid analgesics for 48 h.

The modified rebound pain score (MRPS), the worst pain score during the first 24 h after surgery minus the lowest score in the PACU, was similar between the two dexamethasone groups but significantly higher in the placebo group ($P < 0.001$) (Table 2). The maximum pain reported during the first 48 h was similar among the three groups ($P = 0.183$) (Table 3). Regarding other profiles in the International Pain Outcome Questionnaire, such as the percentage of time in severe pain, percent pain relief, interference of pain, pain

Table 1
Demographic and peri-operative characteristics by randomization group.

Baseline characteristics	Placebo Group	Dex-PN Group	Dex-IV Group	*p*-values
Number, n	25	25	25	
Female	17 (68%)	19 (76%)	18 (72%)	0.772
Age, y	49.79 (18.31)	49.58 (16.45)	56.57 (16.61)	0.281
Weight, kg	63.9 (10.7)	65.5 (12.2)	66.3 (10.7)	0.797
Height, cm	164.1 (6.9)	164.6 (8.0)	163.7 (9.6)	0.906
BMI, kg/m^2	23.6 (3.1)	24.2 (5.5)	24.7 (2.9)	0.561
ASA physical status				0.520
I	13 (52%)	12 (48%)	8 (32%)	
II	11 (44%)	11 (44%)	16 (64%)	
III	1 (4%)	2 (8%)	1 (4%)	
Comorbidities				
Asthma/COPD	0	1 (4%)	0	0.612
Hypertension	5 (19.2%)	4 (16%)	6 (24%)	0.594
Coronary artery disease	0	1 (4%)	2 (8%)	0.272
Diabetes mellitus	1 (4%)	1 (4%)	2 (8%)	0.053
Smoker	1 (4%)	0	0	0.416
Hyperlipidemia	1 (4%)	1 (4%)	2 (8%)	0.653
Anxiety	1 (4%)	1 (4%)	3 (12%)	0.315
Chronic pain	3 (12%)	6 (24%)	6 (24%)	0.166
Block parameters				
Failed blocks	0	0	0	1
Duration of block procedure, min	6.5 [5,8]{4,10}	6.5 [5,10]{3,13}	8 [5,10]{4,11}	0.392
Duration between the completion of block and induction, min	21.4 (10.1)	22.7 (12.7)	19.1 (10.6)	0.553
Duration between the completion of block and incisure, min	31.8 (10.6)	34.4 (11.5)	31.1 (10.1)	0.549
Operative parameter				
Type of surgery				0.294
Ankle arthroplasty	2 (8%)	1 (4%)	2 (8%)	
Ankle arthrodesis	3 (12%)	5 (20%)	2 (8%)	
Hallux valgus	15 (60%)	11 (44%)	13 (52%)	
Subtalar arthrodesis	3 (12%)	4 (16%)	4 (16%)	
Triple arthrodesis	5 (60%)	7 (28%)	7 (28%)	
History of affected limb surgery	3 (12%)	1 (4%)	4 (16%)	0.289
Length of surgery, min	77.5 [55,93]{30,227}	75 [51.5,98.8]{20,187}	67.8 [45,80]{30,180}	0.525

Values are expressed as mean (standard deviation), median [interquartile range]{range}, or count (percent).
Dex-PN, dexamethasone perineurally; Dex-IV, dexamethasone intravenously; BMI, Body mass index; ASA, American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease.

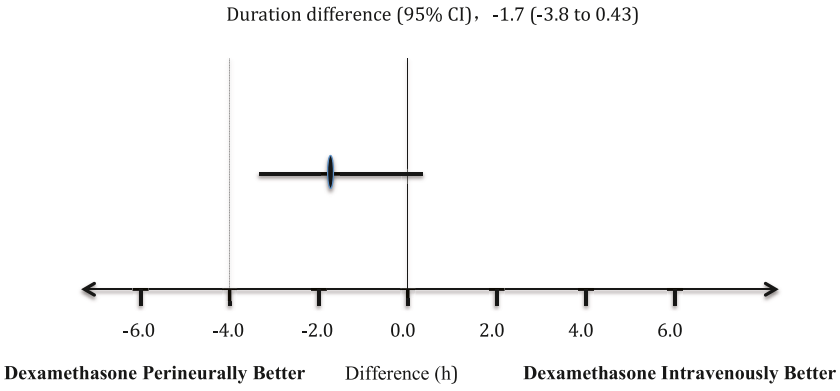

Fig. 2. Ninety-five percent confidence interval of mean block duration.

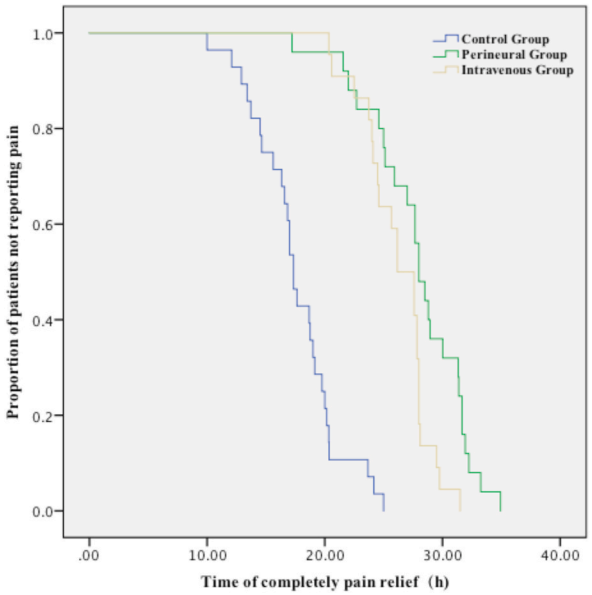

Fig. 3. Kaplan–Meier survival curve Kaplan–Meier survival plot representing the complete pain relief time in the three groups. $p < 0.001$ between the control and other groups. $p = 0.012$ between IV and PN group.

effect on emotions and side effects, no significant difference existed within the three groups (Table 3).

The satisfaction score was higher in the Dex-IV and Dex-PN groups than in the placebo group for the first 24 h and 48 h. Eight patients in the Dex-PN group complained of longstanding numbness; therefore, the satisfaction score was lower in the Dex-PN group than in the Dex-IV group between 24 and 48 h. No differences were observed between the groups in terms of proportion of patients exhibiting a sensory deficit.

4. Discussion

In this randomized clinical trial of patients undergoing major foot and ankle surgery under PNB with 30 ml of 0.375% ropivacaine, a single intravenous administration of dexamethasone was found to be noninferior to its perineural administration as an adjuvant in terms of the duration of analgesia.

Many adjunct medications, including opioids, epinephrine, corticosteroids, α-2 adrenergic receptor agonisits, and magnesium sulfate, have been tested in peripheral regional anesthesia analgesia. However, none of these medications meet all the criteria for an ideal local anesthetic adjunct. Among them, dexmedetomidine and dexamethasone have shown the most promising evidence [11,15]. Dexmedetomidine's use is constrained by its adverse side effects compared to dexamethasone. It remains unclear whether perineural or systemic route of administration is superior. Our findings contrast with those of several earlier meta-analyses and randomized trials [8,18,20–23,29]. These discrepancies may be due to several factors. First, we performed the block procedure in the lower extremities,

Table 2
Primary and secondary outcomes data by study group.

	Placebo Group	Dex-PN Group	Dex-IV Group	*p*-value
Time to first pain, h	17.6 (3.5)	27.9 (4.1)	26.2 (2.9)	<0.001*
Time to first analgesic request, h	21.2 (5.4)	30.4 (4.4)	30.1 (5.4)	<0.001**
PIOC score				
$PIOC_{0–24hrs}$	76.9 [22.4, 130.6] {-119.7, 189.5}	−18.7 [22.4, 130.6] {-119, 189.5}	−26.3 [-119.7, 20.1] {-119.7, 94.7}	<0.001[@]
$PIOC_{0–48hrs}$	−9.8 [-77, 33.6] {-146, 186}	23.7 [-71.1, 75.5] {-146.1, 171.2}	−33.6 [-90.7, 72.5] {-161.8, 157.9}	0.704
NRS profile				
AUC- $NRS_{0–24\ h}$	42 [24, 57]{0,144}	0 [0,12]{0,96}	0 [0,39] {0,96}	<0.001[&]
AUC- $NRS_{0–48\ h}$	72 [24, 72]{0,264}	72 [48, 120]{24,192}	72 [42, 96] {0,168}	0.533
MRPS	3.5 [2, 5] {0,10}	0 [0,1] {0,8}	0 [0, 2.3] {0,8}	<0.001[☆]
Postoperative opioid consumption				
IME 0–24 h total, mg	2.4 [1.1, 7.1]{0,16}	0 [0, 1.6]{0,2.4}	0 [0, 1.8]{0,2.4}	<0.001[✣]
IME 0–48 h total, mg	8.1 [4, 13.1]{0.8,30.4}	7.2 [4,14.4]{0.8,28.8}	4.8 [3.2,11.4]{0.8,34.4}	0.795
Patients not requiring analgesic request during the 0–24 h	8 (32%)	23 (92%)	22 (88%)	<0.001[§]
Patients not requiring analgesic request during the 0–48 h	5 (20%)	3 (12%)	6 (24%)	0.466

Values are expressed as mean (standard deviation), median [interquartile range]{range}, or count (percent).
Abbreviations: Dex-PN, dexamethasone perineurally; Dex-IV, dexamethasone intravenously; NRS, numeric rating scales; PACU, post-anesthesia care unit; AUC, area under the curve; MRPS, modified rebound pain score, equals the highest NRS pain score reported in first 24 h after peripheral nerve block minus the lowest NRS score in PACU[1]. PIOC, pain intensity and opioid consumption, represented as % difference; IME, intravenous morphine equivalents, represented as mg; IME, intravenous morphine equivalents, opioid consumption during the period was recorded for each participant and converted to intravenous morphine equivalents (IME).
*Statistically significant difference: Dex-PN vs Placebo group ($p < 0.001$), Dex-IV vs Placebo group ($p < 0.001$).
**Statistically significant difference: Dex-PN vs Placebo group ($p < 0.001$), Dex-IV vs Placebo group ($p < 0.001$).
& Statistically significant difference: Dex-PN vs Placebo group ($p < 0.001$), Dex-IV vs Placebo group ($p = 0.007$).
☆Statistically significant difference: Dex-PN vs Placebo group ($p < 0.001$), Dex-IV vs Placebo group ($p < 0.001$).
✣ Statistically significant difference: Dex-PN vs Placebo group ($p < 0.001$), Dex-IV vs Placebo group ($p < 0.001$).
§Statistically significant difference: Dex-PN vs Placebo group ($p < 0.001$), Dex-IV vs Placebo group ($p < 0.001$).

whereas previous studies mainly performed the procedure in the brachial plexus, in which the vasculature is abundant. Earlier reviews reporting the disproportionately pooling of upper and lower extremity blocks together reached inconsistent conclusions [2,13,15,19,30]. Sehmbi et al. [18] conducted a post hoc analysis of the studies included in these reviews according to block location and found that perineural dexamethasone was superior to IV administration when used in lower extremity blocks but was similar in upper extremity blocks. This finding further substantiated the theory that dexamethasone predominantly acts through systemic absorption. We are aware of only one randomized trial comparing perineural and systemic administration of dexamethasone with 0.375% ropivacaine for foot and ankle surgery [20]. Nevertheless, two-thirds of the patients in their studies did not require tramadol after the block wore off, which meant that there was no case of the primary endpoint; hence, their conclusions were significantly underpowered. In our study, we adopted a more accurate assessment, the patient's impression of when the block began to wear off, as the primary objective. Second, we compared the supposed optimal ceiling doses of both perineural and systemic dexamethasone that extend the duration of analgesia based on the literature at the time the study was designed. A ceiling dose of 4 mg for perineural administration was reported in a meta-analysis of 33 trials and including 2138 participants. Systemically administered dexamethasone induces analgesic effects at a dose of 0.1 mg/kg or above, which was confirmed by a recent study. Kim et al. [16] found that, compared to 5 mg of intravenous dexamethasone and placebo, only 10 mg of intravenous dexamethasone increased the duration of postoperative analgesia. In particular, previous randomized double-blind trials with lower doses (<8 mg) showed the superiority of the perineural route. A plausible explanation was that intravenously administered low-dose dexamethasone did not reach therapeutic serum levels to induce analgesic effects. Tuerner et al. [31] reported that neither intravenous administration of 4 mg nor 8 mg of dexamethasone prolonged PNB, yet they adopted an objective rather than the commonly used and more clinically relevant surrogate endpoints. Furthermore, the time to first analgesic request was longer in the 8 mg dexamethasone group than in the 4 mg dexamethasone and placebo groups included in their secondary endpoints. Two other randomized trials also failed to show sensory or analgesic block duration prolongation with dexamethasone whether administered perineurally or intravenously, regardless of dosage [21,23]. However, these results were derived from healthy volunteers without surgical stimuli and cannot reflect clinical practice because one possible mechanism of dexamethasone is its anti-inflammatory effects.

Our results showed no difference in PIOC scores nor longitudinal pain measures or opioid consumption between the Dex-IV group and the Dex-PN. By integrating the pain score with opioid consumption, the PIOC score was clinically relevant and provided increased statistical strength when compared with separate analyses of the inherent endpoints [21,26]. However, our design was not sufficient for PIOC comparisons, and additional studies with larger samples are needed.

Rebound pain was defined as a transition from well-controlled pain in the PACU (NRS≤3 or patient report of satisfactory pain control) to severe pain (NRS≥7) within 48 h of block performance, and occurred in half of the patients who underwent foot and ankle surgery managed with a single-shot popliteal sciatic nerve block in the early postoperative period [12,32]. We found that the dexamethasone groups exhibited lower modified rebound pain scores (the highest NRS score minus the lowest score in the PACU) and

Table 3
Descriptive statistics of items from the International Pain Outcomes questionnaire.

Baseline characteristics	Placebo Group	Dex-PN Group	Dex-IV Group	*p*-value[c]
Postoperative day 2 Pain Outcomes questionnaire score[c]				
Intensity				
Worst pain[a]	5.2 (3.8,6.54)	6.1 (5.1,7.2)	4.8 (3.7,5.8)	0.183
Percent time in severe pain[b]	20 [10,30]{10,50}	20 [10,30]{5,50}	10 [10,37]{5,70}	0.907
Interference of pain				
With activities in bed[a]	0 [0,2]{0,6}	1 [0,4]{0,8}	0 [0,1.75]{0,3}	0.213
With breathing/coughing[a]	0 [0,0]{0,3}	1 [0,1.5]{0,8}	0 [0,0.75]{0,3}	0.835
With sleep[a]	0 [0,4]{0,8}	1 [0,5]{0,9}	0 [0,1]{0,2}	0.157
Effect on emotions				
Anxiety[a]	0 [0,2]{0,5}	0 [0,3]{0,9}	0 [0,1.75]{0,3}	0.166
Helpless[a]	0 [0,2]{0,9}	0 [0,1]{0,3}	0 [0,1]{0,4}	0.028
Side effects				
Nausea[a]	0 [0,1]{0,9}	0 [0,1]{0,4}	0 [0,1]{0,2}	0.970
Vomiting	5 (20%)	2 (8%)	2 (8%)	0.038
Drowsiness[a]	0 [0,2.5]{0,9}	0 [0,0.5]{0,6}	0 [0,75]{0,2}	0.774
Itching[a]	0 [0,0]{0,1}	0 [0,0]{0,1}	0 [0,0]{0,1}	0.435
Dizziness[a]	0 [0,4]{0,9}	0 [0,1]{0,9}	0 [0,1]{0,2}	0.821
Percent pain relief[b]	80 [30,50]{70,90}	90 [55,30]{10,90}	80 [70,90]{50,90}	0.989
Allowed to participate in decision about pain treatment as much as wanted				
	13 (52%)	16 (64%)	16 (64%)	0.781
Wish for more treatment	13 (52%)	4 (16%)	3 (12%)	0.093
Overall satisfaction for pain management[a]	9 [7,9]{7,10}	9 [8,10]{5,10}	9 [9,10]{8,10}	0.057
Satisfied with results of pain treatment 0–24 h[a]	9 [8.5,10]{7,10}	10 [9.5,10]{8,10}	10 [10,10]{9,10}	0.002[d]
Satisfied with results of pain treatment 24–48 h[a]	9 [8,9]{7,10}	9 [9,10]{5,10}	10 [9,10]{7,10}	0.009[e]
Patients reporting chronic pain and receipt of opioids before admission to hospital				
How severe was the chronic pain most of the time?				
	5.3 (3.2,8.1)	4.7 (2.1,7.4)	6.3 (4.4,8.3)	0.819
Worst pain after surgery	7.1 (4.9,8.8)	7.5 (5.2,9.1)	5.6 (3.5,5.8)	0.236
Patients with no report chronic pain and no receipt of opioids before admission to hospital				
Worst pain after surgery	5.9 (4.6,7.3)	5.3 (4.1,6.5)	5.5 (4.2,6.7)	0.752
Sensory deficit				
2 week	4 (16%)	8 (32%)	6 (24%)	0.591
1month	3 (18%)	5 (20%)	4 (16%)	0.804
6th month	3 (12%)	4 (16%)	2 (8%)	0.343

Data are expressed as median [IQR]{range}, mean (95% CI), or count (percent).
Dex-PN, dexamethasone perineurally; Dex-IV, dexamethasone intravenously.
95% CI, 95% confidence interval; AUC, area under the curve.
[a] Assessed using a 0–10 numerical rating scale scale.
[b] Assessed using a percentage scale.
[c] Two group comparisons only performed if overall three group comparison p-value <0.017.
[d] Statistically significant difference: Placebo Group vs Dex-IV Group ($p = 0.004$). Placebo Group vs Dex-IV Group ($p = 0.013$).
[e] Statistically significant difference: Placebo Group vs Dex-IV Group ($p = 0.010$).

consumed less opioids during the first 24 h than the placebo group consumed. This finding indicates that rebound pain may be reduced by adding dexamethasone to PNB despite the administration route, which is consistent with former studies [10,33] and may be due to the effect of dexamethasone on PNB duration, as both the Dex-IV and Dex-PN groups had an extended duration of single-shot PNB, more than 26 and 17 pain-free hours, respectively.

The International Pain Outcomes Questionnaire revealed no significant intergroup differences. This questionnaire has been thoroughly validated [27,34] and has focused on mainly on postoperative pain management; thus, it is suitable for assessing patient satisfaction with PNBs. Patient satisfaction was very high, with no intergroup difference in dexamethasone for the first 24 h. Interestingly, the satisfaction score was somewhat higher in the Dex-IV group than in the Dex-PN group between 24 and 48 h, although the difference did not reach statistical significance. From a clinical perspective, the pain-free duration extended by I dexamethasone is long enough to allow patients to sleep the entire night without waking during the first night. Patients prefer to experience a diminishing block and earlier ambulation after restful sleep rather than longstanding numbness.

Few studies have reported the long-term incidence of nerve complications. A retrospective cohort study [35] that included 26,251 PNBs revealed that transient postoperative neurological symptoms (<10 days) occurred in 14.4% of patients and that 56% of these patients fully recovered. Gagne et al. [36] demonstrated that nerve injury was more likely to persist without full recovery in the perineural dexamethasone group than in the ropivacaine-only group (47.65% vs. 32.41%); nevertheless, this study was retrospective, and the nerve injury rates were inconceivably high. Noori et al. [37] reported that 10% of patients experienced neuropathic complications 1year after popliteal block, and there was no difference between the dexamethasone group and the placebo group. In our study, we found a similar incidence of sensory deficit among the three groups at 6 months after surgery (12%,16% and 8%), yet our sample size was relatively small and not large enough to elucidate the differences in the safety profiles between the two routes of dexamethasone; thus, studies including larger patient samples are needed.

We did not monitor postoperative blood glucose even though dexamethasone is associated with increased blood glucose. Patients with uncontrolled diabetes were excluded from our study. Furthermore, two large well-designed randomized controlled trials have specifically addressed the perioperative safety profile of dexamethasone and provided reassurance [38,39]. Cocoran et al. [38] included 8725 patients and demonstrated that a single 8 mg dose of dexamethasone dose was not associated with a risk of surgical-site infection within 30 days after surgery. Another multicenter trial including 1184 patients treated with 0.2 mg/kg dexamethasone also revealed consistent results.

Our study design has several limitations. First, our primary outcome, the time of onset of pain, was based on patient recall. However, patients were well educated before surgery and could coordinate with the investigators to note the exact time when they first sensed the pain at the surgical site, and most of the block receded in the daytime due to the extended duration. Second, our study was a single-center trial of a small sample of patients who underwent major foot and ankle surgery, limiting the generalizability of its findings to all populations. Hence, large-scale, multicenter investigations are warranted to validate and strengthen the results.

In conclusion, this study demonstrated that 10 mg of intravenous dexamethasone is non-inferior to perineural dexamethasone in terms of the analgesic duration of popliteal sciatic nerve and saphenous nerve blocks with 0.375% ropivacaine. Given the concerns related to off-label use, we recommend administering 10 mg of systemic dexamethasone as a local anesthetic adjunct to patients undergoing foot and ankle surgery.

5. Ethics declarations

This study was reviewed and approved by the ethics committee of Beijing Tongren Hospital, Capital Medical University, with the approval number: TRECKY2021-007.

All participants provided informed consent for the publication of their anonymised case details and images.

Funding

This work was supported by Beijing Hospitals Authority Clinical Medicine Development of Special Funding Support (No. ZYLX202103) & Beijing Hospitals Authority's Ascent Plan (No. DFL20220203).

The present study was registered at the Chinese Trials registry (ChiCTR2100043561).

Data availability statement

Data associated with this study has not been deposited into a publicly available repository. All data are included in article and/or supplementary material and are referenced in this article.

CRediT authorship contribution statement

Guiyu Lei: Writing – original draft, Conceptualization. **Siliu Yang:** Formal analysis, Data curation. **Lili Wu:** Investigation, Funding acquisition. **Yue Yin:** Software, Resources, Project administration. **Shu Zhang:** Visualization, Validation, Supervision. **Guyan Wang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28304.

References

[1] C. Stiegelmar, Y. Li, L.A. Beaupre, et al., Perioperative pain management and chronic postsurgical pain after elective foot and ankle surgery: a scoping review, Can. J. Anaesth. 66 (2019) 953–965.

[2] A.J. Short, M. Ghosh, R. Jin, et al., Intermittent bolus versus continuous infusion popliteal sciatic nerve block following major foot and ankle surgery: a prospective randomized comparison, Reg. Anesth. Pain Med. (2019), https://doi.org/10.1136/rapm-2018-100301.

[3] H.M.D.D. Merrill, J.L. Mottla, Opioid consumption following foot and ankle surgery, Foot Ankle Int. 39 (2018) 649–656.

[4] S. Saini, E.L. McDonald, R. Shakked, et al., Prospective evaluation of utilization patterns and prescribing guidelines of opioid consumption following orthopedic foot and ankle surgery, Foot Ankle Int. 39 (2018) 1257–1265.

[5] N. Vadivelu, A.M. Kai, B. Maslin, et al., Role of regional anesthesia in foot and ankle surgery, Foot Ankle Spec. 8 (2015) 212–219.

[6] M.C. Kir, G. Kir, Ankle nerve block adjuvant to general anesthesia reduces postsurgical pain and improves functional outcomes in hallux valgus surgery, Med. Princ. Pract. 27 (2018) 236–240.

[7] K. Korwin-Kochanowska, A. Potie, K. El-Boghdadly, et al., PROSPECT guideline for hallux valgus repair surgery: a systematic review and procedure-specific postoperative pain management recommendations, Reg. Anesth. Pain Med. 45 (2020) 702–708.
[8] A. Holmberg, S.S. Hassellund, T. Draegni, et al., Analgesic effect of intravenous dexamethasone after volar plate surgery for distal radius fracture with brachial plexus block anaesthesia: a prospective, double-blind randomised clinical trial, Anaesthesia 75 (2020) 1448–1460.
[9] D.L. Hamilton, Rebound pain: distinct pain phenomenon or nonentity? Br. J. Anaesth. 126 (2021) 761–763.
[10] G.S. Barry, J.G. Bailey, J. Sardinha, et al., Factors associated with rebound pain after peripheral nerve block for ambulatory surgery, Br. J. Anaesth. 126 (2021) 862–871.
[11] H. Hui, H. Miao, F. Qiu, et al., Adjunctive dexamethasone palmitate use for intercostal nerve block after video-assisted thoracoscopic surgery: a prospective, randomized control trial, Heliyon 9 (2023) e19156.
[12] T.T.H. Jen, J.X.C. Ke, K.J. Wing, et al., Development and internal validation of a multivariable risk prediction model for severe rebound pain after foot and ankle surgery involving single-shot popliteal sciatic nerve block, Br. J. Anaesth. 129 (2022) 127–135.
[13] C. Xuan, W. Yan, D. Wang, et al., The facilitatory effects of adjuvant pharmaceutics to prolong the duration of local anesthetic for peripheral nerve block: a systematic review and network meta-analysis, Anesth. Analg. 133 (2021) 620–629.
[14] E. Albrecht, M. Reynvoet, N. Fournier, et al., Dose-response relationship of perineural dexamethasone for interscalene brachial plexus block: a randomised, controlled, triple-blind trial, Anaesthesia 74 (2019) 1001–1008.
[15] N. Desai, K.R. Kirkham, E. Albrecht, Local anaesthetic adjuncts for peripheral regional anaesthesia: a narrative review, Anaesthesia 76 (Suppl 1) (2021) 100–109.
[16] B.G. Kim, W. Lee, J.H. Song, et al., Effect of intravenous dexamethasone on the duration of postoperative analgesia for popliteal sciatic nerve block: a randomized, double-blind, placebo-controlled study, Korean J. Anesthesiol. 74 (2021) 317–324.
[17] V. Martinez, D. Fletcher, Dexamethasone and peripheral nerve blocks: on the nerve or intravenous? Br. J. Anaesth. 113 (2014) 338–340.
[18] H. Sehmbi, R. Brull, K.R. Ceballos, et al., Perineural and intravenous dexamethasone and dexmedetomidine: network meta-analysis of adjunctive effects on supraclavicular brachial plexus block, Anaesthesia 76 (2021) 974–990.
[19] A. Zorrilla-Vaca, J. Li, Dexamethasone injected perineurally is more effective than administered intravenously for peripheral nerve blocks: a meta-analysis of randomized controlled trials, Clin. J. Pain 34 (2018) 276–284.
[20] P. Marty, O. Rontes, C. Chassery, et al., Perineural versus systemic dexamethasone in front-foot surgery under ankle block: a randomized double-blind study, Reg. Anesth. Pain Med. 43 (2018) 732–737.
[21] A. Short, K. El-Boghdadly, H. Clarke, et al., Effect of intravenous dexamethasone on the anaesthetic characteristics of peripheral nerve block: a double-blind, randomised controlled, doseeresponse volunteer study, Br. J. Anaesth. 124 (2020) 92–100.
[22] P.G. McHardy, O. Singer, I.T. Awad, et al., Comparison of the effects of perineural or intravenous dexamethasone on low volume interscalene brachial plexus block: a randomised equivalence trial, Br. J. Anaesth. 124 (2020) 84–91.
[23] P. Marhofer, M. Columb, P.M. Hopkins, et al., Dexamethasone as an adjuvant for peripheral nerve blockade: a randomised, triple-blinded crossover study in volunteers, Br. J. Anaesth. 122 (2019) 525–531.
[24] S. Bjorn, W.Y. Wong, J. Baas, et al., The importance of the saphenous nerve block for analgesia following major ankle surgery: a randomized, controlled, double-blind study, Reg. Anesth. Pain Med. 43 (2018) 474–479.
[25] R. Sort, S. Brorson, I. Gogenur, et al., Peripheral nerve block anaesthesia and postoperative pain in acute ankle fracture surgery: the AnAnkle randomised trial, Br. J. Anaesth. 126 (2021) 881–888.
[26] L.P.K. Andersen, I. Gogenur, H. Torup, et al., Assessment of postoperative analgesic drug efficacy: method of data analysis is critical, Anesth. Analg. 125 (2017) 1008–1013.
[27] A.L. Garduno-Lopez, V.M. Acosta Nava, Garces L. Castro, et al., Towards better perioperative pain management in Mexico: a study in a network of Hospitals using quality improvement methods from pain out, J. Pain Res. 14 (2021) 415–430.
[28] R. Zaslansky, J. Rothaug, C.R. Chapman, et al., Pain out: the making of an international acute pain registry, Eur. J. Pain 19 (2015) 490–502.
[29] J.D. Turner, S.W. Dobson, R.S. Weller, et al., Intravenous dexamethasone fails to prolong psoas compartment block when assessed by objective pinprick sensory testing: a prospective, randomised, dose-dependent, placebo-controlled equivalency trial, Br. J. Anaesth. 120 (2018) 308–316.
[30] M. Heesen, M. Klimek, G. Imberger, et al., Co-administration of dexamethasone with peripheral nerve block: intravenous vs perineural application: systematic review, meta-analysis, meta-regression and trial-sequential analysis, Br. J. Anaesth. 120 (2018) 212–227.
[31] J.D. Turner, D.S. Henshaw, R.S. Weller, et al., Perineural dexamethasone successfully prolongs adductor canal block when assessed by objective pinprick sensory testing: a prospective, randomized, dose-dependent, placebo-controlled equivalency trial, J. Clin. Anesth. 48 (2018) 51–57.
[32] N. Touil, A. Pavlopoulou, O. Barbier, et al., Evaluation of intraoperative ketamine on the prevention of severe rebound pain upon cessation of peripheral nerve block: a prospective randomised, double-blind, placebo-controlled study, Br. J. Anaesth. 128 (2022) 734–741.
[33] J. Fang, Y. Shi, F. Du, et al., The effect of perineural dexamethasone on rebound pain after ropivacaine single-injection nerve block: a randomized controlled trial, BMC Anesthesiol. 21 (2021) 47.
[34] J. Rothaug, R. Zaslansky, M. Schwenkglenks, et al., Patients' perception of postoperative pain management: validation of the International Pain Outcomes (IPO) questionnaire, J. Pain 14 (2013) 1361–1370.
[35] K.K. Lam, N. Soneji, H. Katzberg, et al., Incidence and etiology of postoperative neurological symptoms after peripheral nerve block: a retrospective cohort study, Reg. Anesth. Pain Med. 45 (2020) 495–504.
[36] O.J. Gagne, A. Cheema, M. Abuhantash, et al., Effect of dexamethasone in peripheral nerve blocks on recovery of nerve function, Foot Ankle Int. 42 (2021) 23–30.
[37] N.A.-O. Noori, K. Anand, G. Pfeffer, et al., Dexamethasone addition to popliteal nerve blocks: effects on duration of analgesia and incidence of postoperative nerve complication, Foot Ankle Spec. 14 (2021) 39–45.
[38] T.B. Corcoran, P.S. Myles, A.B. Forbes, et al., Dexamethasone and surgical-site infection, N. Engl. J. Med. 384 (2021) 1731–1741.
[39] K.A.-O. Asehnoune, C. Le Moal, G. Lebuffe, et al., Effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery: multicentre, double blind, randomised controlled trial, BMJ 373 (2021) n1162.