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Effect of liposomal bupivacaine for sciatic nerve block on opioid use in patients undergoing maxillofacial reconstruction with free fibular flap: a randomized, controlled trial

Hai-Yin Wu[1†], Xiao-Dong Wang[1†], Guo-Li Xiong[1], Xu-Dong Yang[1*] and Li-Kuan Wang[1*]

Abstract

Background We investigated the efficacy and safety of preoperative popliteal sciatic nerve block (PSNB) using liposomal bupivacaine (LB) to reduce perioperative opioid consumption and improve recovery quality in patients undergoing maxillofacial reconstruction with a free fibular flap.

Methods A total of 74 patients were randomly allocated into two groups. The PSNB group received ultrasound guided PSNB using 133 mg of LB after anesthesia induction. In the control group, patients underwent nerve block preparation procedures without puncture or drug injection. The primary endpoint was cumulative opioid consumption during the perioperative period (from anesthesia induction to 48 h post-surgery). The secondary endpoints were the total incidence of moderate to severe pain during the 48 h postoperative period; the incidence of moderate to severe pain during different time periods after surgery; the incidence of PONV within 48 h after surgery; subjective sleep quality within 2 days after surgery; the length of post-surgical hospital stay; all-cause in-hospital mortality; and the incidence of other complications during hospitalization.

Results There was no significant difference in cumulative opioid consumption between the control group (3020.0 [2163.0, 3569.5] μg of remifentanil equivalents) and the PSNB group (2856.0 [2204.0, 3771.0] μg; $p = 0.863$). The incidence of moderate to severe pain at the donor site within 48 h after surgery was significantly lower in the PSNB group (3 [8.1%] of 37 patients) than in the control group (18 [48.6%] of 37 patients; $p < 0.001$). The consumption of rescue opioids was significantly reduced in the PSNB group (0 [0, 50]) compared with that in the control group (50 [0, 100]; $p = 0.007$). The subjective sleep quality numeric rating scale score was significantly lower in the PSNB group than in the control group (day of surgery: 6.0 [5.0, 8.0] vs. 8.0 [6.0, 9.0], $p = 0.029$; postoperative day 1: 5.0 [4.0, 5.0] vs. 7.0

[†]Hai-Yin Wu and Xiao-Dong Wang are co-first authors.

*Correspondence:
Xu-Dong Yang
kqyangxudong@163.com
Li-Kuan Wang
wanglikuan3@163.com

Full list of author information is available at the end of the article

[5.5, 7.5], $p < 0.001$; postoperative day 2: 5.0 [4.0, 5.5] vs. 6.0 [5.0, 7.5], $p = 0.001$). The incidence of postoperative nausea and vomiting was significantly lower in the PSNB group (0 [0.0%]) compared with that in the control group (5 [13.5%]; $p = 0.021$). There was no significant difference in the incidence of adverse events between the two groups.

Conclusion Preoperative administration of PSNB by LB did not spare opioids during the intraoperative period, but significantly relieved postoperative pain at the donor site, reduced rescue opioid consumption, and improved postoperative sleep quality, without additional adverse events.

Trial registration Clinicaltrials.gov. Identifier ChiCTR2400080944, 19 February 2024.

Keywords Liposomal bupivacaine, Popliteal sciatic nerve block, Maxillofacial reconstruction, Free fibular flap, Opioid sparing, Postoperative analgesia

Background

Maxillofacial surgery with free flap transfer reconstruction is a major procedure that has a long operative time, involves multiple surgical fields, is highly invasive, and might cause intense postoperative pain for patients. As an indispensable component of general anesthesia, the use of opioids for analgesia, and to relieve the stress response induced by surgery, is necessary. Despite their effectiveness, opioids are associated with major adverse effects, including an increased risk of respiratory depression, postoperative nausea and vomiting (PONV), constipation, oversedation, delayed mobilization, and opioid-induced hyperalgesia [1, 2]. These adverse effects can significantly impact recovery quality and clinical outcomes.

Based on previous studies, in hemi-mandibulectomy and microsurgical reconstruction, the fibular flap donor site has been reported by most patients to be more painful than the tumor resection area [3]. This might be attributed to the combined effects of extensive trauma from flap harvesting procedures and ischemiareperfusion injury induced by tourniquet use [4, 5]. Preoperative peripheral nerve blocks (PNBs) can reduce the surgical stress response by inhibiting the impulse generation triggered by noxious stimulation. Adjunctive PNBs to general anesthesia have been utilized in a variety of surgical procedures to reduce perioperative opioid use and enhance postoperative pain management [6–8]. Our previous study demonstrated that the use of preoperative trigeminal nerve block in orthognathic surgery led to reduced perioperative opioid consumption, higher analgesia satisfaction, and fewer postoperative adverse events [9].

In hemi-mandibulectomy and microsurgical reconstruction using unilateral free fibular flaps, postoperative popliteal sciatic nerve block (PSNB) has been shown to reduce sufentanil use and improve analgesia satisfaction [3]. However, given the limitation of currently available local anesthetics, administering PSNB preoperatively might not be practical because of the relatively short duration of analgesia, which is typically 24 h or less, and is insufficient to cover the entire intra- and early postoperative period. A relatively new alternative agent for continuous nerve block is liposome bupivacaine (LB), which is a novel local anesthetic comprising water-soluble bupivacaine wrapped in a liposome, allowing for a steady and continuous release of the drug for up to 72 h [10]. In a phase 3 clinical trial, single-shot administration of LB via sciatic nerve block showed reduced pain and opioid use over 4 days after bunionectomy [11]. Safe and effective use of LB has also been described for total ankle arthroplasty surgery [12].

In maxillofacial reconstruction with a free fibular flap, the efficacy of preoperative PSNB combined with general anesthesia for opioid sparing and pain management has not been reported. Therefore, in the current study, we administered LB as a single dose, and under the guidance of ultrasound to block the popliteal sciatic nerve preoperatively, we aimed to determine the effect of this technique on minimizing perioperative opioid consumption and improving postoperative recovery quality. In addition, we also assessed the safety profile when LB was used in ultrasoundguided PSNB procedures.

Methods

This study was a randomized and controlled trial, which was approved by the Peking University Hospital of Stomatology Ethics Committee (PKUSSIRB-202386053, 20 June 2023) and registered with the Chinese Clinical Trial Registry (ChiCTR2400080944, 19 February 2024). The study was conducted in Peking University Hospital of Stomatology (Beijing, China) in accordance with the CONSORT guidelines. Written informed consent was obtained from each participant.

Participants and enrollment

The inclusion criteria comprised: Patients aged 18 to 79, with a prior diagnosis or presumed diagnosis of an oral and maxillofacial tumor, who were scheduled for elective mandibulectomy or maxillectomy and microsurgical reconstruction using unilateral free fibular flaps. The exclusion criteria were: (1) Infection at the puncture site, (2) severe coagulopathy, (3) a history of local anesthetic allergy, (4) a history of psychiatric illness, (5) American

Society of Anesthesiologists (ASA) class ≥ III, and (6) participation in other clinical studies.

Randomization and intervention

Randomization was performed by an independent statistician, and random numbers were generated using STATA 15.0 software (Stata Corp., College Station, TX, USA) in a 1:1 ratio and sealed in sequentially numbered opaque envelopes. The envelopes were opened before anesthesia by an anesthesia nurse who did not participate in the rest of the study.

Patients were randomly allocated into two groups. For patients in the PSNB group, ultrasound guided PSNB with LB at 133 mg was performed after anesthesia induction by the same anesthesiologist, who did not participate in the rest of the study. Briefly, ultrasound images were obtained using a portable ultrasound unit (M9; Mindray, Shenzhen, China) and an 8–12 MHz linear array probe. Patients were placed in the supine position, and their calves and ankles were elevated by an assistant, just to the extent necessary to position the probe beneath the popliteal fossa. Following skin disinfection, the ultrasound probe, covered with a sterile sheath, was used to identify the anatomy of the popliteal fossa. A good landmark to start with was the popliteal artery, which is shallowest precisely at the crease. Superficially to that is the popliteal vein. Above that is the tibial nerve. At this location, the peroneal nerve might be separated by one to two centimeters, laterally and superficially from the tibial nerve. The probe was slid proximally and distally along the back of the distal thigh until the bifurcation between the tibial and common peroneal verves was visualized. A 22-gauge, 100-mm needle (Stimuplex, Braun, Melsungen, Germany) was inserted using in-plane imaging and LB was injected into the small space between the two branches. The needle was repositioned until the separation of the tibial and common peroneal nerves was affirmed, and the surrounding area was infiltrated with local anesthetic.

With regard to ethical considerations, for patients in the control group (general anesthesia (GEA) group), they only experienced skin disinfection, sterile sheath coverage, and ultrasound scanning. They did not receive puncture and drug injection.

The patients, surgeons, the attending anesthesiologist, the nurse who conducted the postoperative follow-up, and all other clinical personnel were kept blind to the group allocation throughout the study. Meanwhile, all nerve blocks were completed by the same anesthesiologist, who had at least 5 years of experience with this operation.

Anesthesia and perioperative management

The drug was prepared as follows: LB (10 ml, 133 mg) was diluted to 30 ml with 20 ml of normal saline. Intraoperative monitoring included electrocardiography (ECG), pulse oximetry (SpO2), invasive blood pressure, body temperature measurement, bispectral index (BIS) monitoring and neuromuscular transmission measurement (TOF; trainoffour (transmission with four stimulators)). General anesthesia was induced using sufentanil (0.15 to 0.2 μg/kg), 1% propofol (1.0 to 2.5 mg/kg) with or without etomidate (0.1 to 0.2 mg/kg), and rocuronium (0.6 mg/kg) or Cis-atracurium (0.2 mg/kg). Intubation was then performed. Anesthesia was maintained by target controlled continuous infusion of propofol (2 to 5 μg/ml) and remifentanil (2 to 6 ng/ml) combined or not combined with 1 to 2% inhalant sevoflurane and with or without dexmedetomidine (0.1 μg/kg/h–0.7 μg/kg/h) at the discretion of the attending anesthesiologists. Mechanical ventilation was established using a mixture of oxygen-air. The BIS values were maintained between 40 and 60. Sufentanil (0.1 to 0.2 μg/kg) and rocuronium (0.3 mg/kg) or Cis-atracurium (0.1 mg/kg) were administered when clinically indicated. At the end of the surgery, tropisetron (5 mg), flurbiprofen (1 mg/kg) and/or Sufentanil (0.1 μg/kg) and/or dezocine (5 mg) and/or morphine (5 mg) were administered when considered necessary and an intravenous analgesia pump with 1 μg/kg sufentanil and 10 mg tropisetron (diluted with normal saline to 100 ml), was attached and initiated at a continuous infusion rate of 2 ml/h for 48 h.

After surgery, the patients were transferred to post-anesthesia care unit (PACU) with tracheal intubation or tracheostomy when they started breathing spontaneously (TOF > 0.9). Dexmedetomidine sedation (0.1 μg/kg/h–0.7 μg/kg/h) was provided to maintain the Richmond Agitation Sedation Scale (RASS) ≥ −2, ≤ 1. When the patients exhibited emergence coughing or agitation (RASS ≥ 2), a rescue bolus of propofol (0.5–1 mg/kg) could be given initially. If it remained unrelieved, one of the following opioid agents was selected and administered as a single intravenous bolus: sufentanil (5 μg), dezocine (5 mg) or morphine (5 mg). This opioid rescue regimen was also utilized for patients who complained of pain. Rescue antiemetics were tropisetron (2 mg) and/or metoclopramide (10 mg). All the drugs administered in the PACU were determined by attending anesthesiologists, with specific records on the case report form (CRF). The patients were maintained in the PACU overnight postoperatively for continuous monitoring of airway stability, free flap viability and systemic condition to ensure both microvascular perfusion integrity and overall clinical safety. Patients exhibiting any signs of clinical instability were promptly transferred to the intensive care unit (ICU) for protocol-driven management. Next morning, for patients with intubation, they were extubated when they regained consciousness, fully recovered from paralysis, and had normal airway protective reflexes and stable

circulatory and respiratory status. The decision to extubate and transfer patients from PACU to general wards or the ICU was made by attending anesthesiologist.

Data collection and outcome assessment

Baseline data included demographic and morphometric characteristics, surgical diagnosis, preoperative comorbidities (Charlson Comorbidity Index), and a history of smoking and drinking. Sleep quality was assessed using the numeric rating scale (NRS; 0 indicates the best sleep and 10 the worst sleep). Pain severity was assessed using the NRS (0 indicates no pain and 10 the worst pain). Intraoperative data included duration of anesthesia, types and doses of medications, type and duration of surgery, and fluid balance.

After surgery, patients were evaluated for postoperative pain intensity at 6, 12, 24, and 48 postoperative hours using NRS. The NRS scores were determined at two sites: The oral and maxillofacial resection area and the flap donor site. Considering the potential impact of anesthetic rescue medications on pain measurements, the windowed worst observation carried forward (wWOCF) method was utilized to accurately document the NRS pain scores [6]. Specifically, if patients received rescue medication within a 2 h "window" before an assessment, we replaced the score for that time point with the highest NRS score recorded before the administration of the initial rescue medication. In addition, we employed a nocturnal recall score to minimize the disruption to the patient's nighttime rest. We did not carry out bedside face-to-face scoring at night (11 pm to 6 am the following day). If the subject was awake within the time window, the subject or their companion was prompted to recollect the pain state the following morning, and if the subject was asleep during the time window, the NRS score was assigned a uniform value of 2. If the pain score was higher than 3, rescue medication with sufentanil 5 μg or dezocine 5 mg or morphine 5 mg could be slowly injected intravenously by the attending anesthesiologist.

Postoperative subjective sleep quality was also assessed using the NRS, whereby "0" indicated the "best" possible sleep and "10" indicated the "worst" possible sleep between 8 am and 10 am on the first, second, and third days after surgery.

Direct questioning was used to evaluate PONV, which was defined as the development of any nausea, retching, or vomiting.

Endpoints

The primary outcome was the cumulative opioid consumption during the perioperative period (from anesthesia induction to postoperative 48 h). Opioid consumption was converted to μg of remifentanil equivalents [13], specifically, 1 μg of sufentanil = 1 mg of dezocine = 1 mg of morphine = 10 μg of remifentanil.

The secondary outcomes included: (1) The total incidence of moderate to severe pain during the 48 h postoperative period. Moderate to severe pain was defined as an NRS score > 3; (2) the incidence of moderate to severe pain during different time periods after surgery (0 to 6 h, 6 to 12 h, 12 to 24 h, and 24 to 48 h); (3) the incidence of PONV within 48 h after surgery; (4) subjective sleep quality within 2 days after surgery; (5) the length of postsurgical hospital stay; (6) all-cause in-hospital mortality; and (7) the incidence of other complications during hospitalization.

Adverse events were monitored until the patients were discharged from the hospital. Potential adverse events included: Paranesthesia, headache, constipation, pruritis, and body temperature disorders.

Sample size calculation

Based on a previous study conducted by our team, the cumulative opioid consumption, when converted to remifentanil equivalents, was 1294 ± 579 μg in maxillofacial tumor resection with fibular free flap reconstructive surgery [14]. We assumed that using ultrasound-guided PSNB could result in a 30% reduction in opioid consumption. Setting a power of 0.8, a 0.05 level of significance, and using 1:1 randomization, we used the Power Analysis & Sample Size (PASS) software (NCSS, LLC, East Kaysville, UT, USA) to calculate that each group needed to include 35 cases. Considering a 5% dropout rate, we decided to enroll a total of 74 patients, with 37 in each group.

Statistical analysis

Statistical analysis was performed using IBM SPSS STATISTICS 25 software (IBM Corp., Armonk, NY, USA). Continuous variables are described as the mean ± SD or the median interquartile range (IQR). Categorical variables are described as a number (percentage). A T test was used for comparisons of normally distributed variables and a Mann–Whitney U test was used for comparisons of abnormally distributed variables. Qualitative variables were compared using either the chi-squared or Fisher's exact test. Two-sided $P < 0.05$ was considered statistically significant.

Results

Subject characteristics

Between March 10, 2024, and November 13, 2024, 108 patients were screened for study participation; of these, 33 patients were excluded because of refusal to participate in the study, and 1 patient was excluded because of participation in other studies. Finally, 74 patients were enrolled into the study and were randomly assigned

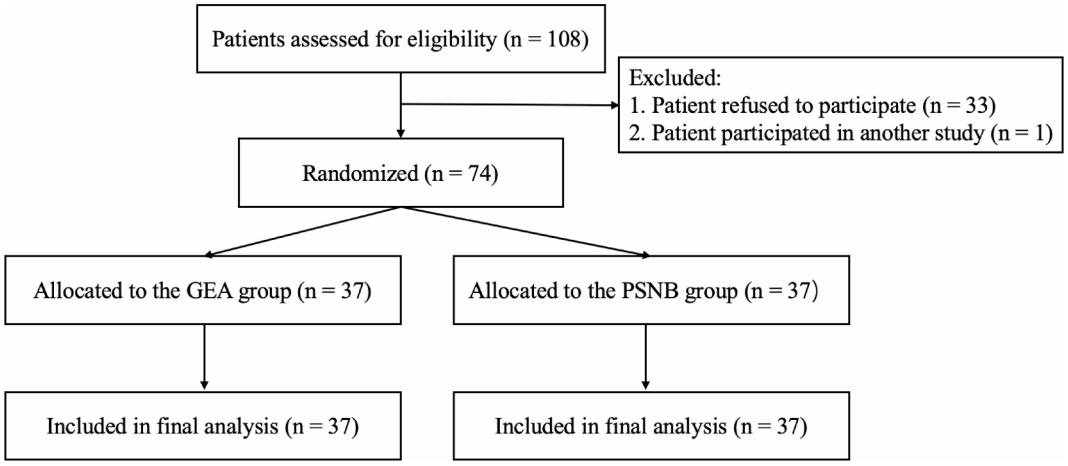

Fig. 1 Flowchart of the study

Table 1 Patient demographics and preoperative variables

	GEA group	PSNB group	*P* value
Age (y)	57.7 ± 11.2	52.1 ± 13.8	0.242
Male sex	24 (64.9%)	26 (70.3%)	0.781
BMI (kg/m^2)	23.2 ± 3.2	23.4 ± 3.5	0.725
ASA classification			0.760
I	7 (18.9%)	6 (16.2%)	
II	30 (81.1%)	31 (83.8%)	
Previous surgery	12 (32.4%)	12 (32.4%)	> 0.999
Drinking history [a]	2 (5.4%)	2 (5.4%)	> 0.999
Smoking history [b]	15 (40.5%)	17 (45.9%)	0.639
Charlson comorbidity index score	1.9 ± 1.2	1.8 ± 1.3	0.524
Sleep NRS score [c]	4 (3,6)	4 (2,6)	0.503
Pain NRS score [d]	1 (0,2)	1 (0,2)	> 0.999

Data are presented as median (interquartile range), mean ± SD, or n (%)

GEA, general anesthesia; PSNB, popliteal sciatic nerve block; BMI, body mass index; ASA, American Society of Anesthesiologists; NRS, numeric rating scales

[a] Daily consumption of the equivalent of 80 g of alcohol for at least 1 year

[b] Smoking history was defined as smoking more than 100 cigarettes in a lifetime

[c] Assessed using the 11-point NRS ranging from 0 (best sleep) to 10 (worst sleep) at 8:00 AM to 10:00 AM on the day of surgery

[d] Assessed using the 11-point NRS ranging from 0 (no pain) to 10 (worst pain) at 8:00 AM to 10:00 AM on the day of surgery

to the GEA group ($n = 37$) or the PSNB group ($n = 37$) (Fig. 1). Overall, the two groups were well matched for baseline and perioperative variables (Tables 1 and 2).

The cumulative opioid consumption

As shown in Table 3, the primary outcome was the cumulative opioid consumption during the perioperative period, which included both the intraoperative and the 48 h postoperative periods. Opioid consumption was converted to μg of remifentanil equivalents. The total opioid consumption showed no significantly differences between the GEA group and the PSNB group: 3020 (2163, 3570) μg vs. 2856 (2204, 3771) μg, respectively; $p = 0.863$. Similarly, the intraoperative opioid consumption also showed no significant differences: 2970 (2163, 3569) μg vs. 2856 (2175, 3746) μg, respectively; $p = 0.931$. However, the consumption of rescue opioids within 48 h after surgery was significantly lower in the PSNB group compared with that in the GEA group: 0 [0, 50] μg vs. 50 [0, 100] μg, respectively; $p = 0.007$.

Table 2 Intraoperative and postoperative variables

	GEA group	PSNB group	*P* value
Intraoperative data			
Surgery for malignant tumor	30 (81.1%)	25 (67.6%)	0.183
Tumor site			0.711
Maxillary	2 (5.4%)	3 (8.1%)	
Mandibular	31 (83.8%)	33 (89.2%)	
Others	4 (10.8%)	1 (2.7%)	
Time from LB administration to the end of surgery (h)	-	5.23±1.28	-
Duration of surgery (min)	272.5 ± 70.2	304.4 ± 80.6	0.655
Tourniquet time (min)	63.4 ± 13.6	64.6 ± 16.8	0.790
Neck dissection	29 (78.4%)	28 (75.7%)	0.589
Tracheotomy	28 (75.7%)	22 (59.5%)	0.136
Duration of anesthesia (min)	330.0 ± 73.6	358.0 ± 89.2	0.948
Intraoperative medications			
Sevoflurane	30 (81.1%)	32 (86.5%)	0.528
Dose of etomidate (mg)	14 (7,20)	12 (0,16)	0.073
Midazolam	21 (56.7%)	20 (54.1%)	0.815
Dose of propofol (mg)	1500 (950, 1999)	1520 (1140, 2073)	0.492
Rocuronium	36 (97.3%)	35 (94.6%)	0.556
Cis-atracurium	1 (2.7%)	2 (5.4%)	0.556
Dexmedetomidine	15 (40.5%)	18 (48.4%)	0.483
Flurbiprofen axetil	14 (37.8%)	17 (45.9%)	0.480
Postoperative data			
Dose of dexmedetomidine in PACU (μg)	160 (144, 184)	160 (140, 186)	0.892
Duration in PACU (min)	906.6 ± 182.4	841.7 ± 184.9	0.133

Data are presented as median (interquartile range), mean ± SD, or n (%)

GEA, general anesthesia; PSNB, popliteal sciatic nerve block; PACU, post-anesthesia care unit

Table 3 Endpoints—Opioid consumption

	GEA group (*n* = 37)	PSNB group (*n* = 37)	*P* value
Primary endpoint			
Total cumulative opioid consumption [a]	3020 (2163, 3570)	2856 (2204, 3771)	0.863
Secondary endpoint			
Intraoperative opioid consumption	2970 (2163, 3569)	2856 (2175, 3746)	0.931
Postoperative opioid rescue consumption within 48 h	50 (0,100)	0 (0,50)	0.007

Data are presented as medians (interquartile range)

GEA, general anesthesia; PSNS, popliteal sciatic nerve block

[a] The cumulative opioid consumption is shown as remifentanil equivalents (μg)

Table 4 Secondary endpoints—Incidence of moderate to severe pain at different site

	GEA group (*n* = 37)	PSNB group (*n* = 37)	*P* value
Moderate to severe pain within 48 h after surgery [a]	21 (56.8%)	10 (27.0%)	*0.010*
Moderate to severe pain at different time points			
0–6 h after surgery	8 (21.6%)	8 (21.6%)	*> 0.999*
6–12 h after surgery	7 (18.9%)	2 (5.4%)	*0.075*
12–24 h after surgery	5 (13.5%)	2 (5.4%)	*0.233*
24–48 h after surgery	5 (13.5%)	0 (0.0%)	*0.021*
Moderate to severe pain at the donor site within 48 h after surgery	18 (48.6%)	3 (8.1%)	*0.000*
Moderate to severe pain at the donor site at different time points			
0–6 h after surgery	7 (18.9%)	1 (2.7%)	*0.025*
6–12 h after surgery	6 (16.2%)	0 (0.0%)	*0.011*
12–24 h after surgery	3 (8.1%)	2 (5.4%)	*0.643*
24–48 h after surgery	5 (13.5%)	0 (0.0%)	*0.021*
Moderate to severe pain in the maxillofacial resection area within 48 h after surgery	4 (10.8%)	7 (18.9%)	*0.327*
Moderate to severe pain in the maxillofacial resection area at different time points			
0–6 h after surgery	3 (8.1%)	7 (18.9%)	*0.174*
6–12 h after surgery	1 (2.7%)	2 (5.4%)	*0.556*
12–24 h after surgery	2 (5.4%)	0 (0.0%)	*0.152*
24–48 h after surgery	0 (0.0%)	0 (0.0%)	-

Data are presented as medians (interquartile range) or n (%)

GEA, general anesthesia; PSNS, popliteal sciatic nerve block; NRS, numeric rating scales

[a] This refers to a postoperative pain score that was higher than 3 regardless of the pain site

Table 5 Other secondary endpoints

	GEA group (*n* = 37)	PSNB group (*n* = 37)	*P* value
PONV within 48 h after surgery	5 (13.5%)	0 (0.0%)	*0.021*
Sleep quality NRS score			
Day of surgery	8 (6,9)	6 (5,8)	*0.029*
Postoperative day 1	7 (6,8)	5 (4,5)	*0.000*
Postoperative day 2	6 (5,8)	5 (4,6)	*0.001*
Length of stay in hospital (d)	8 (7,10)	8 (8,10)	*0.453*
In-hospital mortality	0 (0.0%)	0 (0.0%)	-
Adverse events			
Paranesthesia	0 (0.0%)	1 (2.7%)	*0.314*
Headache	0 (0.0%)	2 (5.4%)	*0.152*
Constipation	0 (0.0%)	0 (0.0%)	-
Pruritis	0 (0.0%)	0 (0.0%)	-
Body temperature disorder	0 (0.0%)	0 (0.0%)	-

Data are presented as medians (interquartile range) or n (%)

GEA, general anesthesia; PSNS, popliteal sciatic nerve block; PONV, postoperative nausea and vomiting; NRS, numeric rating scales

The incidence of moderate to severe postoperative pain

As illustrated in Table 4, the number of patients experiencing moderate to severe pain in both groups progressively decreased over the 48 h postoperative period. The incidence of moderate to severe pain was significantly lower in the PSNB group compared with that in the GEA group (10 [27.0%] vs. 21 [56.8%], $P = 0.010$). Regarding the incidence during different time periods, when compared with that in the GEA group, it was significantly lower in the PSNB group only from 24 to 48 h after surgery. We assessed the pain score at two regions: The oral and maxillofacial resection area and the flap donor site. Specifically, at the resection area, there was no significant difference in the incidence of moderate to severe pain between the GEA group (4 [10.8%]) and the PSNB group (7 [18.9%]; $p = 0.327$), including during the four time periods after surgery. At the flap donor site, the incidence of moderate to severe pain was significantly lower in the PSNB group (3 [8.1%]) than in the control group (18 [48.6%]; $p < 0.001$). Regarding the incidence of pain during different time periods, when compared with that in the GEA group, it was significantly lower in the PSNB group from 0 to 6 h, 6 to 12 h, 24 to 48 h after surgery.

The sleep quality scores

As shown in Table 5, the subjective sleep NRS scores gradually decreased in both groups during the night after surgery and over two subsequent nights. The score was significantly lower in the PSNB group than in the control group (day of surgery: 6 [5, 8] vs. 8 [6, 9], $p = 0.029$; postoperative day 1: 5 [4, 5] vs. 7 [6, 8], $p < 0.001$; postoperative day 2: 5 [4, 6] vs. 6 [5, 8], $p = 0.001$) (Table 6).

Table 6 Other endpoints

	GEA group (*n* = 37)	PSNB group (*n* = 37)	*P* value
Postoperative sleep disturbance [a]			
Day of surgery	29 (78.4%)	21 (56.8%)	*0.047*
Postoperative day 1	28 (75.7%)	9 (24.3%)	*0.000*
Postoperative day 2	22 (59.5%)	9 (24.3%)	*0.002*
Most painful location was the. donor site	28 (75.7%)	4 (10.8%)	*0.000*
Incidence of emergence agitation and coughing	4 (10.8%)	2 (5.4%)	*0.394*
Flap survival during hospitalization	35 (94.6%)	37 (100.0%)	0.152
Need a second surgery	4 (10.8%)	2 (5.4%)	0.394

Data are presented as n (%)

GEA, general anesthesia; PSNS, popliteal sciatic nerve block

[a] Postoperative sleep disturbance was defined as subjective sleep numeric rating scales (NRS) score ≥ 6

Nausea and vomiting, hospital stay, and adverse events (AEs)

As shown in Table 5, the incidence of nausea and vomiting during the 48 h postoperative period exhibited a significant difference between the two groups, with no patient in the PNSB group experiencing PONV (0 vs. 5 [13.5%], $P = 0.021$). The postoperative duration of hospital stay and the incidence of adverse events did not show significant differences between the two groups. In the PSNB group, one case of paranesthesia and two cases of headaches were reported, while no subjects reported constipation, pruritis, or body temperature disorder. Additionally, no subjects died during the current study.

Discussion

Our results showed that the use of LB for preoperative PSNB did not spare the use of opioid agents during the intraoperative period; however, it decreased the consumption of opioids for postoperative rescue analgesia. Patients in the PSNB group exhibited a significantly lower incidence of moderate to severe pain at the flap donor site, higher subjective sleep quality, and a lower rate of PONV. Moreover, administering PSNB by LB appeared to be safe, with only rare and mild potential adverse events observed.

The administration of PNBs before skin incisions is considered an optimal method to reduce opioid use perioperatively and enhance postoperative pain management [6–8]. As one of the most common blocks, PSNB provides complete anesthesia or analgesia to the bone, muscle, and skin of the calf, ankle, and foot, which can theoretically cover the injured area caused by free fibular flap harvest and tourniquet use [15, 16]. It has also been demonstrated that nerve blocks can ensure continuous analgesia and vasodilation, which diminishes the systemic stress response and reduces the incidence of deep vein thrombosis in many reconstructive surgeries using free flaps [17, 18]. Liposomal bupivacaine is an extendedrelease form of bupivacaine, whose efficacy and safety have been proven in a variety of surgical scenarios using blockade of many kinds of peripheral nerves, such as the brachial plexus nerve [19, 20], the femoral nerve [21], and the intercostal nerve [22]. However, some studies have engendered great controversy on this topic. One recent meta-analysis examined nine trials that reported on LB for peripheral nerve blockade [23], which demonstrated that LB did not provide significant clinical advantages over the standard formulation. Moreover, another recent study revealed that LB is not a suitable "sole" drug for intraoperative regional anesthesia because its sensory blockade started later and did not last as long when compared with plain bupivacaine [24]. However, the study results could have been influenced by variations in the study protocols and the locations of the injection sites. Regarding PSNB, in a phase 3 clinical trial, a single shot of 133 mg LB showed reduced pain and opioid use over 4 days after bunionectomy when compared with plain bupivacaine [11]. This study led to FDA approval of LB administered via PSNB in adults for postsurgical regional analgesia. Moreover, it also indicated the potential for reduced opioid use or opioid-free surgery when PSNB was employed as a component of the anesthesia and pain management program.

In the current research, we combined general anesthesia and preoperative PSNB using a single-dose of LB as the study intervention. However, during the surgical period, no difference in the consumption of opioids was observed between the PSNB and GEA groups. Several plausible reasons might account for this result. Firstly, unlike reconstruction using free soft tissue flaps, the shape and size of the free bone flaps were typically predesigned before surgery based on the maxillofacial image data. During the operation, the sequence of the two main surgical procedures, tumor resection and flap harvest, was determined by the surgeons. If these two processes are carried out successively, PSNB would be more likely to show its analgesic efficacy and exhibit an advantage in anesthetic sparing. However, to achieve higher surgical efficiency, surgeons in our hospital typically perform these two procedures simultaneously. Under these conditions, regardless of the extent to which the surgical stress at the donor site has been suppressed, a full dose of narcotics might still be necessary to mitigate the trauma stimulation induced by tumor resection. Secondly, depending on a report from a previous trial, the median time to onset of sensory block using a single dose of 133 mg of LB on PSNB was 0.97 h [11]; however, in the current study, the median time from LB administration to tourniquet inflation was 0.48 h. To accommodate

patient-blinding and ethical requirements, it was necessary to implement the nerve block after anesthetic induction. Moreover, a time gap to wait for LB to take effect should not be set, because it might delay the surgical procedure and prolong the anesthesia time inappropriately. Lastly, the anesthesia and analgesia effect of LB might not be reliable. According to a pharmacodynamic research using LB in volunteers, only 32% of the subjects experienced surgical blockade [24]. Similar results were also reported in another volunteer study using LB: Ilfeld et al. [25] used the drug for bilateral blockade of the femoral nerve but lessthan-complete success in sensory and motor blockade were achieved. Regardless of the specific timing and the exact extent of its efficacy, if PSNB is administered preoperatively and takes effect, this method will alleviate surgical stress, enhance postoperative pain control, and facilitate a smoother recovery process.

As expected, a sciatic nerve block in the popliteal fossa using LB at 133 mg in our study exhibited superior pain control compared with that in the GEA group within 48 h after surgery. The incidence rate of moderate to severe pain at the donor site was significantly decreased, particularly from 0 to 6 h, from 6 to 12 h, and from 24 to 48 h after surgery. It was previously reported that the pain at the donor site was greater than that at the recipient site in patients undergoing head and neck microsurgical reconstruction [3, 26]. Consistent with these data, in the control group of this study, 76% (28/37) of the subjects reported that the donor site was the most painful area within 48 h after surgery. Therefore, special attention should be given towards treating pain at the donor site in patients undergoing microsurgical reconstruction.

Liposomal bupivacaine provides a novel delivery system for the sustained release of local anesthetic. Indeed, LB at 133 mg exhibited a biphasic bupivacaine plasma concentration, with a mean early time to maximum bupivacaine plasma concentration (T_{max}) of 8 h after administration and a mean late T_{max} of 72.32 h after administration [11, 27]. In the current study, the median time from LB administration to the end of the surgery was 5.2 h (Table 2). Despite the implementation of an intravenous analgesia pump, the preventive analgesics administered before the end of surgery might gradually lose their potency, leading to challenging pain management in the early postoperative stage. The early analgesic effect before 12 h after surgery observed in the LB group might be attributed to the release of bupivacaine from the outer surface vesicles of LB during the first tide, at around 8 h after administration. Pain relief observed beyond 24 h after surgery was consistent with the prolonged release profile of LB. Our data suggested that LB at 133 mg exhibited a reliable analgesic effect when administered as a PSNB, at least within the first 48 h of the postoperative period. Moreover, this result provided confidence for the safe use of additional local anesthetics to block multiple nerves. For instance, in the current surgical setting, using LB or plain bupivacaine to block the supraorbital nerve or the inferior alveolar nerve depended on the tumor sites [28]. To the best of our knowledge, this study is the first to demonstrate that administering PSNB using LB can markedly relieve postoperative pain from the early period until at least 48 h after surgery at lower extremity donor sites following free fibular flap harvest.

Based on the significant analgesic effect on the donor site, the consumption of postoperative opioids in the PSNB group was reduced compared with that in the GEA group. In fact, within the current surgical scenario, pain at the donor site was not the sole reason for the requirement of rescue opioids. For example, administration of opioids was a necessary and effective way to prevent and suppress emergence agitation [29] and coughing/bucking [30]. Moreover, the pain caused by tumor resection and neck dissection, and the discomfort related to neck swelling, tracheal tube, tracheostomy, and immobilization, were also contributing factors. It is not easy to isolate the postsurgical opioid sparing effect of PSNB by LB from the distracting factors mentioned above. However, we analyzed the incidence of emergence agitation and coughing, in which cases opioids were given, and there were no significant differences between the two groups (Table 6). After the patients awakened, rescue analgesics were given on an as-needed basis and then recorded and imputed for different reasons. Moreover, we used the wWOCF protocol to record the NRS pain scores in the first 48 h after surgery. This method helped to reduce the influence of opioid rescue medication on the NRS evaluations [6]. Along with postoperative pain, PONV was a major factor that negatively affected the quality of recovery. In the GEA group, the incidence of PONV was 13.5%, which was consistent with the results of a prior study reporting a rate of 19% [31]. In contrast, no patients in the PSNB group experienced PONV. This significant reduction might be attributed to the opioid-sparing effect of PSNB, because the overuse of opioids is associated with a high risk of PONV [32]. Consequently, despite the comparable influences of various distracting factors, the consumption of opioids still showed a reduction in the PSNB with LB group. Therefore, this nerve block method could be regarded as a component of the pain management strategy in the surgical setting in the current study.

Given the bidirectional relationship between sleep and pain, adequate pain control is vital to support sleep after surgery [33]. In our study, sleep quality was markedly improved using PSNB, as evidenced by the comparison of NRS scores between the two groups. On the night of surgery, the sleep NRS scores were lower in the PSNB group, and these scores continued to decrease significantly on the first- and second-nights following surgery.

This improvement could likely be attributed to the superior pain management observed in the PSNB group. However, when considering the incidence of postoperative sleep disturbance (PSD), defined as NRS ≥ 6 [34], especially on the night of surgery, it remained as high as 56.8% (78.4% in the GEA group). Nonetheless, the use of PSNB by LB can be considered as a valuable component of a multimodal strategy aimed at enhancing sleep and recovery quality in patients who have undergone free flap reconstruction following oral tumor resection.

The overall safety profile in the PSNB group was similar to that in the GEA group. One participant in the LB 133 mg group experienced paresthesia and numbness of the shin and foot at nearly 12 h after surgery, for whom we checked the dorsalis pedis arterial pulse, adjusted the bandage pressure, and then monitored the skin color, warmth, and artery pulse for 48 h. This symptom disappeared at approximately 40 h after surgery. Two participants in the LB 133 mg group experienced moderate headache at 6 and 24 h after surgery, separately. The symptom was markedly relieved within 12 h after administering 50 mg of flurbiprofen. Other common adverse events mentioned in the LB instructions, such as constipation, pruritis, and body temperature disorder were not observed in this study.

As an exploratory study, several obvious limitations of this trial were identified. Firstly, in complex major multi-incision surgeries, it was challenging to isolate the specific contribution of a peripheral nerve block administered at a single site, especially when used in combination with analgesics, which is a common issue in pain management studies. Secondly, the success rate of the nerve block was not evaluated using sensomotoric testing, although it was believed that the block was successful if the spread of the local anesthetic could be seen under ultrasound imaging. Thirdly, the pain and sleep NRS were only monitored up to the second day post-surgery, and adverse events were only tracked until patients were discharged from the hospital, further follow-up might need to be carried out. Therefore, in subsequent research, PNBs by LB could be implemented before anesthesia induction, covering both the flap donor and tumor resection sites. The outcomes should not only focus on sparing opioids and early analgesic efficacy, but should also consider the long-term influences on patient recovery quality, including chronic pain, sleep quality during the postdischarge period, ambulation ability, and the incidence of deep vein thrombosis and other rare long-term complications.

Conclusions

Our study discovered that, in contrast to general anesthesia alone, the combination of PSNB by LB and general anesthesia did not decrease the requirements for systemic opioids during the intraoperative period. However, it did successfully provide postoperative analgesia at the donor site, reduced the consumption of rescue opioids, and improved postoperative sleep quality. These data suggest that PSNB by LB should be considered as a valuable component of the anesthesia and pain management strategy for patients undergoing maxillofacial neck reconstruction with free fibular flaps.

Abbreviations

PSNB	Popliteal sciatic nerve block
LB	Liposomal bupivacaine
PONV	Postoperative nausea and vomiting
PNBs	Peripheral nerve blocks
ASA	American Society of Anesthesiologists
GEA group	General anesthesia group
ECG	Electrocardiography
SpO_2	Pulse oximetry
BIS	Bispectral index
TOF	Train-of-four
PACU	Post-anesthesia care unit
RASS	Richmond Agitation Sedation Scale
CRF	Case report form
ICU	Intensive care unit
NRS	Numeric rating scales
wWOCF	Windowed worst observation carried forward
T_{max}	Time to maximum bupivacaine plasma concentration

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Author contributions

HYW: Data acquisition, analysis, interpretation, drafting, and critical revision of the manuscript. XDW: Study conception and design, nerve block administration. GLX: Research drug preparation. LKW: Study conception and design, critical revision of the manuscript. XDY: Study conception and design, critical revision of the manuscript, final approval for submission. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This trial was performed in accordance with the Declaration of Helsinki and the Chinese Clinical Trial Specifications. The study was approved by the Peking University Hospital of Stomatology Ethics Committee (PKUSSIRB-202386053, approved 20 June 2023) and registered with the Chinese Clinical Trial Registry (ChiCTR2400080944, registered 19 February 2024). All participants provided written informed consent before any study-specific screening procedures were performed.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details
[1]Department of Anesthesiology, Peking University School and Hospital of Stomatology, #22 Zhongguancun South Avenue, Haidian District, Beijing 100081, China

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