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Lack of Sex Difference in Minimum Local Analgesic Concentration of Ropivacaine for Ultrasound-Guided Supraclavicular Brachial Plexus Block

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Sex differences, which may be an important variable for determining anesthetic requirements, have not been well investigated in the aspect of local anesthetic. This investigation aimed to compare the minimum local analgesic concentration (MLAC) of ropivacaine for ultrasound-guided supraclavicular brachial plexus block (US-SCB) between men and women.

Material/Method: Patients aged 18–45 years undergoing elective forearm, wrist, or hand surgeries under US-SCB were divided into 2 groups according to sex. The initial concentration was 0.375% ropivacaine 20 mL and the concentration for the next patient was determined by the up-down technique at 0.025% intervals. Success was defined as the absence of any pain in response to a pinprick in the region of all 4 terminal nerves and the skin incision within 45 min. The primary outcome was the MLAC of ropivacaine, which was estimated by the Dixon and Massey method. The analgesia duration, which was defined as the time from the end of the US-SCB injection to the time of feeling discomfort and need for additional analgesics, was observed for each patient.

Results: The MLAC of ropivacaine 20 mL for US-SCB was 0.2675% (95% confidence interval [CI], 0.2512–0.2838%) in men and 0.2675% (95% CI, 0.2524–0.2826%) in women. There was no significant difference in MLAC or the analgesia duration between the 2 groups ($P>0.05$).

Conclusions: We found no significant sex-related differences in MLAC or analgesia duration of ropivacaine for US-SCB.

MeSH Keywords: Analgesics • Concentration Camps • Sound

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Background

Supraclavicular brachial plexus block (SCB), which has most compact arrangement at this level, can provide good anesthesia for the forearm and hand surgery, including tourniquet coverage. Moreover, the introduction of ultrasonography to guide needle placement and visualize the pattern of local anesthetic spread has led to a resurgence in the popularity of SCB [1,2]. Ultrasound-guided SCB (US-SCB) enables the localization of the brachial plexus and avoidance of the blood vessels, lung, pleura, and other vulnerable structures. The relatively superficial path of the needle allows for good visualization of the needle and accurate real-time injection of local anesthetics. The use of US-SCB is more appropriate for dose-finding studies.

Sex may be an important variable for determining anesthetic requirements since women are more sensitive to opioid receptor agonists than men, whereas men are more sensitive than women to propofol [3–7]. However, sex differences in local anesthetics have not been well investigated [3,7]. Our previous study demonstrated that the minimum local analgesic concentration (MLAC) of ropivacaine for caudal anesthesia in women was 31% greater than that in men [8]. The current study was designed to investigate whether sex influences the potency of ropivacaine for US-SCB using the up-down sequential allocation model to estimate the MLAC in young men and women [9]. The secondary outcome was the duration of analgesia of ropivacaine for US-SCB in young men and women.

Material and Methods

Study objects

After we obtained approval from the Ethics Committee of the Zhejiang University (Hangzhou, People's Republic of China) and written informed consent from each patient, those with an American Society of Anesthesiology (ASA) physical status I/II and who were 18–45 years of age undergoing elective forearm, wrist, or hand surgery were enrolled between April 2012 and December 2013 in this prospective observational study. Exclusion criteria were local infection at the injection site, allergy to local anesthetics, bleeding diathesis, body mass index (BMI) ≤18 kg/m^2 or ≥30 kg/m^2, pre-existing neuralgic disease, currently taking contraceptives or preoperative opioids, presence of alcohol/drug abuse, or current pregnancy.

Patients were divided into 2 groups according to sex: men (Group M) and women (Group F), all patients were blinded to the local anesthetic solution administered (Figure 1). Sample size estimations were based on the SD 0.08%. Power was set at 0.9 and a minimal difference of 0.1% in potency was considered significant. Therefore, 30 participants were required for each group. Because the present study used an up-down method to estimate the threshold for an all-or-none response, we additionally applied a modified Dixon's up-down method to calculate the sample size [9,10]. The study design required recruitment to continue until at least 6 evaluable patients were recruited in each group [9,10].

Based on previous investigations [11], especially in Chinese populations, the initial concentration of ropivacaine used was 0.375%, and the concentration was changed at 0.025%

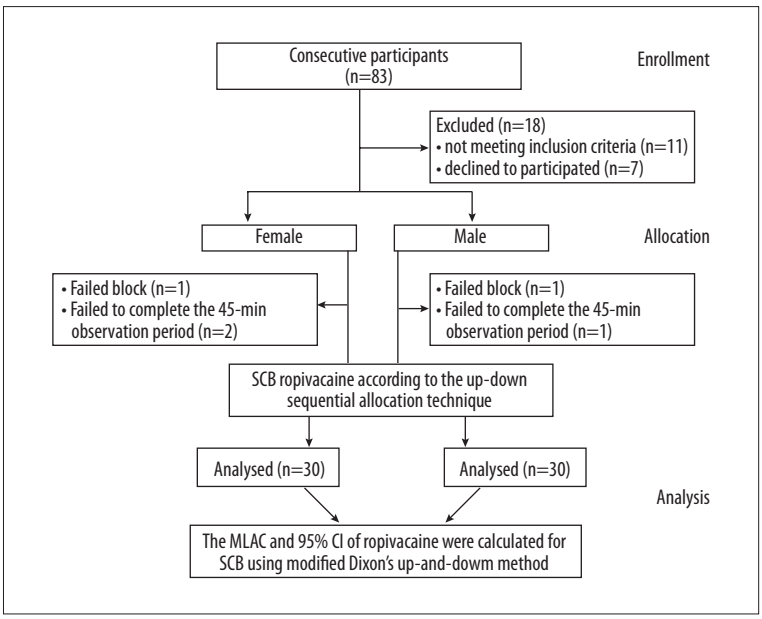

Figure 1. In each group, participants were consecutively enrolled according to the up-down sequential allocation method. The exclusion criteria are described in the text and the study was terminated when the experimental effective case load reached 30 in each group. SCB – supraclavicular brachial plexus block; MLAC – minimal local anaesthesia concentration.

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intervals. The concentration of ropivacaine received by the subsequent patient was determined as ineffective or effective of the block 45 minutes after local anesthetic injection according to Dixon's up-down sequential method [9].

SCB

No sedatives or analgesic agents were administered prior to block placement. After each patient arrived in the operating room, an 18- or 20-gauge intravenous catheter was placed in the upper limb contralateral to the surgical site with an infusion of lactated Ringer's solution administered at a maintenance rate. Supplemental oxygen (oronasal mask at 4 L/min) and standard monitoring (noninvasive arterial blood pressure, electrocardiography, and pulse oximetry) were applied throughout the procedure [8].

SCB was performed under ultrasound guidance with a SonoSite MicroMaxx (Sonosite®, Micromaxx, Bothell, WA, USA) with no electrical stimulation. The patient's ipsilateral neck was prepped with Betadine prior to the procedure and they were positioned supine with the head turned 45° to the nonoperative side. A high-frequency (6–13 MHz) linear-array US probe covered with a sterile dressing was placed in the supraclavicular fossa in a coronal oblique plane posterior to the clavicle. The supraclavicular brachial plexus was identified as a compact group of nerves located lateral and cephalic to the subclavian artery above the first rib [12]. Confirmation imaging was performed using anatomical landmarks and color Doppler sonography to prevent confusion of the nerves with small blood vessels [13]. A pulsating hypoechoic subclavian artery, the first rib, and the pleura were identified in all patients. Using an in-plane technique and a lateral-to-medial direction, a 2-inch Stimuplex needle (B. Braun, Melsungen, Germany) was inserted through the skin. No subcutaneous local anesthetic infiltration was used prior to the block needle insertion. The needle tip was positioned in the corner bordered by the subclavian artery medially and the first rib inferiorly [12]. If the needle tip was not satisfactory, a small amount (1–2 mL) of ropivacaine with testing concentration solution was injected with "color mode" to demonstrate the needle position [14]. If the needle tip was not oriented toward the "corner pocket," then the patient was excluded from the study. If the needle position was satisfactory and negative aspiration was confirmed, a total of 20 mL of ropivacaine (Naropin; AstraZeneca, Sodertalje, Sweden) was diluted with 0.9% saline to achieve the desired concentration and was injected under direct sonographic visualization within 2 min of the local anesthetic spreading. All blockages were performed by the same 2 anesthesiologists who were blinded to the ropivacaine concentration. All local anesthetic solutions were prepared by another investigator.

Blockage assessment and data collection

The assessment was performed by another observer who was blinded to the concentration tested. The effectiveness of the US-SCB was determined at 5-min intervals for 45 min after the administration of the local anesthetic by pinprick testing of the 4 terminal nerve distributions as described below [12]. Sensory block of the musculocutaneous, median, radial, and ulnar nerves was assessed on the lateral aspect of the forearm, volar aspect of the thumb, lateral aspect of the dorsum of the hand, and volar aspect of the fifth finger, respectively. The blockade was considered effective if patients had analgesia in all 4 (median, radial, ulnar, and musculocutaneous) nerve distributions distal to the elbow, and there was an absence of pain in response to operation in the forearm and hand area within 45 min after the ropivacaine injection. All surgical procedures began at 45 min after the blockade. Effective blockade directed a decreased ropivacaine concentration of 0.025% for the next patient. The blockade was considered ineffective if any nerve distributions failed to achieve complete loss of pain sensation at 45 min after ropivacaine injection or the patient complained of pain at the start of surgery despite feeling no pain during the assessment. General or local anesthesia was delivered if the SCB ineffective. Ropivacaine concentration was increased 0.025% for the next patient. If the needle tip was not satisfactorily placed, even after injecting a small amount of ropivacaine with testing concentration solution with "color mode" [15], or did not complete the 45-min observation period, then the participant was identified as having blockage failure and the subsequent patient in this group received the same concentration of ropivacaine.

The range and extent of sensory blockade was tested using pinprick (25-gauge hypodermic needle) according to a 3-point scale: 0=analgesia (no pain, with/without touch sensation), 1=decreased sensation, or 2=normal sensation. The number of nerves (musculocutaneous, median, radial, and ulnar nerves) with analgesia (no pain, with/without touch sensation) was recorded 45 min after SCB injection. The duration of the analgesia, which was defined as the time from the end of the US-SCB injection to the time of filling discomfort and the need for additional analgesics, was also observed for each effective patient. Noninvasive systemic arterial blood pressure, measured with an automatic cycling device (Cardiocap; Datex-Ohmeda), and heart rate on electrocardiography were recorded during and after the SCB and throughout the operation. The incidence of accidental vascular puncture, suspected diaphragmatic paresis resulting in dyspnea, the appearance of Horner syndrome, and symptoms suggestive of local anesthetics toxicity were also noted. In the event of clinical suspicion of pneumothorax, a chest radiograph was obtained.

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Table 1. Baseline characteristics of the participants receiving ultrasound-guided SCB using ropivacaine.

	Group M (n=30)	Group F (n=30)	*p*
Age (years)	33.5±8.3	35.2±7.5	>0.05
BMI (kg·m^{-2})	21.8±2.2	22.1±3.0	>0.05
ASA I/II(n)	27/3	26/4	>0.05
Hypertension (n)	1	1	>0.05
History of alcohol (n)	2	0	>0.05
Hepatitis (n)	2	3	>0.05
Procedure (forearm/wrist/hand surgery)	9/6/15	12/8/10	>0.05
Surgical time (minutes)	57.7±32.6	53.2±37.2	>0.05

Results are expressed as (n) or mean ± standard deviation. BMI – body mass index; ASA – American Society of Anesthesiologists.

All patients were interviewed at 48 h postoperatively. Complications such as bruises and swelling at the block site, chest pain, breathing difficulty, and dysesthesia were recorded and managed until the patients recovered fully.

Statistical analysis

Demographic and hemodynamic data were collected. Data were initially analyzed by normal distribution and homogeneity of variances tests. Data conforming to the normal distribution and exhibiting homogeneity of variance are presented as mean (SD); otherwise, data are presented as median (range/interquartile range). Mean (SD) values were analyzed using the independent-samples *t*-test for different variances; median (interquartile) values were analyzed using the Mann-Whitney *U* test.

The modified Dixon's up-down method was used to calculate the ropivacaine MLAC (EC_{50}), which was determined by calculating the mean of the midpoint concentrations of some specific patient pairs, in which an ineffective response of the ropivacaine concentration was followed by an effective response [9,10,16]. MLAC are expressed as EC_{50} and 95% confidence interval (CI). Analyses were performed using Excel 2007 (Microsoft) and GraphPad Prism software (version 5.0; GraphPad Software Inc.). Statistical significance was defined at $P<0.05$ (2-sided).

Results

Demographic characteristics

This study was conducted from April 2012 to December 2013. There were 83 patients evaluated for eligibility, among which 65 were enrolled and divided into 2 groups by sex. There were 2 cases of failed blockage and 3 cases of failure to complete the 45-min observation period. Ultimately, the complete outcome data were collected for 60 patients (Figure 1). All patient demographic information is summarized in Table 1. The 2 groups were comparable in age, BMI, ASA status, surgical procedures, and surgical duration. The differences in weight and height between the men and women were significant; however, there was no difference in BMI between the 2 groups. There were no significant differences in alcohol consumption, hypertension, or hepatitis preoperatively between the groups (Table 1).

The individual responses to ropivacaine at corresponding effect concentrations in both groups are shown in Figure 2. The MLAC of ropivacaine for US-SCB was 0.2675% (95% CI, 0.2512–0.2838%) in men and 0.2675% (95% CI, 0.2524–0.2826%) in women (Figure 2). There was no significant difference in MLAC between the 2 groups.

A comparative study was conducted in 9 men and 9 women who received 0.25% ropivacaine 45 min after SCB. Of the 9 blocks in group M, 4 were effective. Of the 5 ineffective blocks, all of the nerves were partially blocked: in 3 patients, the median and ulnar nerves were completely blocked, whereas the musculocutaneous and radial nerves were partially blocked; in the other 2 patients, the median, ulnar, and radial nerves were completely blocked whereas the musculocutaneous nerve was partially blocked. Of the 9 blocks in group F, 5 were effective. Of the 4 ineffective blocks, all of the nerves were partially blocked: in 3 patients, the median and ulnar nerves were completely blocked and the musculocutaneous and radial nerves were partially blocked; in the other patient, the median, ulnar, and radial nerves were completely blocked and the musculocutaneous nerve was partially blocked. There was no difference in the number of blocked nerves between the 2 groups.

The duration of the analgesia was reported in all 18 male patients and 17 female patients who had an effective block with

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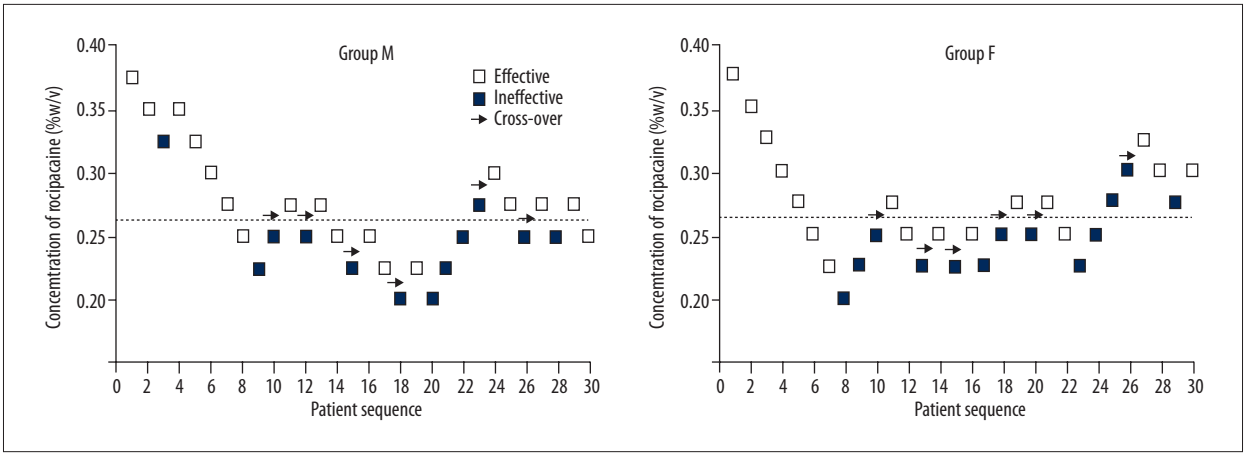

Figure 2. Individual responses to US-SCB at corresponding ropivacaine concentrations. Unfilled squares represent effective responses to the corresponding ropivacaine concentration for achieving a US-SCB. Filled squares represent ineffective responses to the corresponding ropivacaine concentration for achieving US-SCB. Arrows represent the midpoint concentration when crossing from an ineffective to an effective response for US-SCB. The average ropivacaine concentration crossing is represented by the horizontal dashed line.

Table 2. The analgesia duration of different effective ropivacaine concentrations for US-SCB in the two groups.

Concentration (%)	Group M		Group F	
	Number of patients	Mean analgesia duration (range) (h)	Number of patients	Mean analgesia duration (range) (h)
0.375	1	11.6	1	12.5
0.35	2	10.25 (9–11.5)	2	9.45 (8.25–10.3)
0.325	1	8.6	1	8.25
0.3	2	8.375 (7.25–9.5)	3	8.71 (6.75–10.0)
0.275	**6**	**9.73 (6.1–11.45)**	**4**	**9.51 (6.5–12.5)**
0.25	**4**	**9.25 (6.5–11.5)**	**5**	**8.07 (5.5–11.15)**
0.225	2	8.73 (7–10.45)	1	9.15
	18		17	

difference concentration of ropivacaine (Table 2). We found that the duration did not differ significantly between group M and group F in 0.25% concentration and 0.275% concentration ($P>0.05$), which had many more samples in each group.

No statistical difference was found between the men and women with respect to baselines mean arterial blood pressure or heart rate for 60 min after the SCB (Figure 3). Three patients (1 man, 2 women) experienced Horner's syndrome, and 1 man experienced hoarseness. No further treatment was required for any of these complications. One woman (1.4%), whose pulse oximetry gradually decreased until 92% 20 min after the block, experienced temporary dyspnea that resolved within 15 min after the administration of 100% oxygen through a mask. There were no symptoms suggestive of local anesthetic toxicity or other complications. All patients received postoperative follow-up at 24 and 48 h after the SCB, and no adverse events or neurological complications were reported in any of the patients.

Discussion

Ropivacaine is a local anesthetic drug that is frequently used for nerve blocks with well-reported safety and efficacy, and it is thought to be less cardiotoxic and have a greater separation of sensory and motor effects than bupivacaine [8,17,18]. MLAC in local anesthetics is the same as minimum alveolar concentration, which is the most widely used measurement of potency of volatile anesthetics. Using the up-down method described by Dixon, we confirmed that there was no sex

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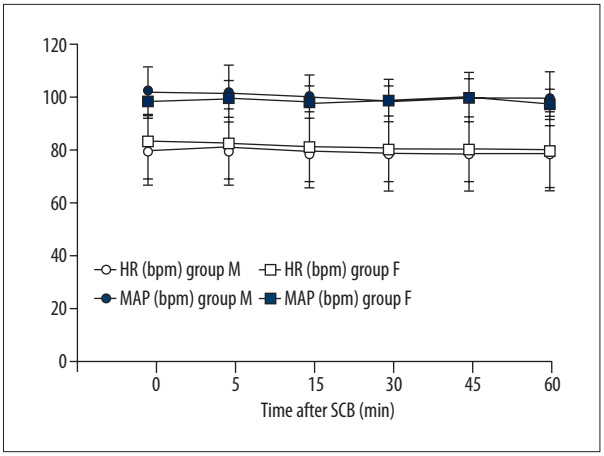

Figure 3. There was no significant difference between the group M and group F in hemodynamic changes before and after US-SCB. Values are expressed as mean ±SD. MAP – mean arterial blood pressure; HR – heart rate; US-SCB – ultrasound-guided supraclavicular brachial plexus block.

difference in MLAC or analgesia duration of 20 mL of ropivacaine for US-SCB between young men and women. This is the first investigation to assess sex differences in the MLAC of ropivacaine for patients with US-SCB.

There has been increasing interest in both basic and clinical science in investigating sex-related influences on analgesia and anesthetics [3,4,6,19–21]. Growing evidence indicates that sex is an independent factor influencing drug responses in terms of efficacy and safety of opioids, sedatives, and non-depolarizing neuroblocking agents [3,17,22,23]. However, unlike the above anesthetics, data on the effect of sex on local anesthetic efficacy is sparse, and such differences have not been consistently demonstrated to date [3,7,22]. Camorcia et al. [24] reported that motor fibers appear to be less sensitive to bupivacaine in men than in women. Our previous investigation demonstrated that the MLAC of ropivacaine for caudal anesthesia in women is 31% higher than that in men [8].

Our current investigation found no significant difference in ropivacaine MLAC in men and women for US-SCB in forearm surgeries. It is not clear why our current results differ from those of our prior study [8]. However, the different results mentioned above may be related to the use of different local anesthetics, differences in pharmacodynamics or pharmacokinetics of local anesthetics after different nerve blocks, or the use of different pain models, which can produce different results [19,20,25]. Rettig et al. [25] demonstrated differences in spread and absorption of ropivacaine when used for brachial plexus nerve block using 4 different approaches (lateral interscalene, posterior interscalene, axillary, and vertical infraclavicular). To the best of our knowledge, no investigation has compared the pharmacokinetics between caudal anesthesia and brachial plexus block, and different nerve block sites may have different results in men and women. Different pain models may induce different results as well. Compared with men, women display enhanced sensitivity to most forms of experimentally-induced pain with the exception of ischemic pain [19]. Studies have shown that women exhibit greater sensitivity to morphine but failed to detect sex differences in the analgesic effect of pentazocine in experimentally-induced pain models [20]. Investigations of local anesthetics used different pain models, making it impossible to draw any meaningful conclusions regarding sex-based differences in the efficacy of local anesthetics [8,24,25]. Finally, there were significant differences in weight, height, or BMI measurements in some prior studies, which may account for some of the local anesthetic differences between men and women, as the effect of weight, height, or BMI on the efficacy of local anesthetics could not be ruled out [8,12,24,26]. In our study, there was no difference in BMI. This is obviously a complex topic, and it is difficult to make any definitive conclusions on any differences between men and women on minimum local analgesic concentrations or other analgesic medications due to multiple "biological" and "psychosocial" mechanisms that might influence the final results [3,5,6,24–26].

A secondary aim of our study was to investigate the difference in the number of nerves with no pain and the duration of analgesia between the young men and women. With the limited data available, we found no difference between the 2 groups. Further studies specifically designed to investigate this aspect are required. The analgesia duration in our study was shorter than that in Liu's investigation [27]. This may be due to differences in drug and volume used.

There has been some variability in the effective local anesthetic volume or concentration for US-guided nerve blockage. In reports of ultrasound-guided techniques, the volume used was 10–40 mL [28,29]. Gupta et al. [12] found that median effective volume was 10.8 mL (95% CI, 5.9–19.7) using the Dixon-Massey formula. The concentration of ropivacaine used in brachial plexus block is 0.75% to 0.25% [8,30,31]. Gupta [12] also found that the median effective volume for 0.25%, 0.375%, and 0.5% bupivacaine for supraclavicular block was 26.8 (18.6–38.4), 18.1 (12.1–26.0), and 12.0 (8.4–17.3) mL, respectively. We chose 20 mL of ropivacaine 0.375% as the first concentration, which in our experience provides a complete block in all patients in our department and from another investigation [11], expect for Chinese patients. Cruvinel et al. [11] demonstrated that the 3 different volumes (20 mL, 30 mL, and 40 mL of 0.375% ropivacaine, respectively) promoted similar analgesia. Moreover, the greater extension of the blockage with larger doses did not translate into better analgesia. We also aimed to minimize the adverse effects of SCB. The results still showed that

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4.3% of patients experienced Horner syndrome. In some studies, Horner syndrome was observed in up to 37.5% of cases under US guidance [32]. Systemic local anesthesia toxicity is still frequently reported in anesthesia studies [33], and local anesthetic volume reduction is preferred whenever possible.

There are several limitations to our work. In an attempt to eliminate bias and increase comparability, we tried to keep the external conditions and procedures identical between the 2 groups. In our study, we used a single injection technique to accomplish the nerve block and increase comparability. Using more than 1 injection technique may result in a faster onset of action, but this perspective is under debate [30,31,34]. The observation time in our study was 45 min, which may have influenced or prolonged the interval between the 2 operations, and 30 min may have been more appropriate. Another limitation of our study is that no premedication was administrated before the nerve block, in an attempt to eliminate the influence of drugs on the result, so sedatives and other drugs administrated after the beginning of the operation could not relieve patients' preoperative anxiety or pain. Anatomical variability exists within the brachial plexus, which may be related to nerve block failures [30,35]. We are not able to distinguish the actual reason of failure (anatomical versus ropivacaine concentration) for the nerve block. More studies, especially multicenter studies in larger and different populations, are needed to further investigate sex differences in response to local anesthetics administered for regional nerve blocks with or without ultrasound.

Conclusions

In conclusion, there was no significant difference in MLAC and duration of analgesia of 20 mL of ropivacaine in young men and women undergoing US-SCB. Since previous studies have no consensus on the sex differences in the response to local anesthetics, further studies are needed to investigate sex differences in MLAC in other peripheral nerve blocks and to explore the possible mechanisms.

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Competing interests

The authors declare no conflicts of interest regarding the publication of this paper

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