The estimation of minimum effective volume of 0.5% ropivacaine in ultrasound-guided interscalene brachial plexus nerve block: A clinical trial

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Abstract

**Background and Aims:** Interscalene brachial plexus block (ISB) is the most commonly used mode of anesthesia for upper limb surgeries. Higher volume of local anesthetic used in ISB is associated with increased incidence of side effects, particularly phrenic nerve palsy. The aim of this study was to determine the minimum effective volume of 0.5% ropivacaine in 90% patients (MEV90) in ISB.

**Material and Methods:** With target of 45 successful cases, phase 1 clinical trial was conducted based on the principles of biased coin design up-and-down method. After obtaining Ethical Committee's approval and patient's consent, patients with American Society of Anesthesiologist physical status (ASA PS) I and II, aged 18–60 years of either sex, undergoing upper arm surgery were recruited into the study until 45 successful cases. A 7 ml of 0.5% ropivacaine was used as starting dose, with patients receiving a higher or lower dose depending on previous patient's response. R package, SPSS 23, and Microsoft Excel were used for statistical analysis.

**Results:** MEV90 of 0.5% ropivacaine for ISB was determined as 8.64 ml [confidence interval (CI) 95%, 8.28–9.02 ml]. Time for onset of sensory block and motor block was 5 min (5–15 min) and 10 min (5–20 min), respectively, while duration of analgesia was observed as 8.2 (4.8–12.5) h.

**Conclusions:** This study observes that surgical anesthesia can be accomplished with 8.64 ml (95% CI: 8.28–9.02 ml) of 0.5% ropivacaine with ultrasound-guided ISB with multiple injection technique, without clinical deterioration in block onset and duration of analgesia.

**Keywords:** Interscalene brachial plexus block, ultrasonography, biased coin design

Introduction

Regional anesthesia has been a mainstay of the anesthesiologist’s armamentarium since Hall first reported the use of cocaine to block the brachial plexus in 1884.[1] Interscalene brachial plexus block (ISB) is one such regional block in regular use for upper limb surgeries.

Conventional methods include nerve stimulation (NS) and patient-reported paresthesia, which rely on surface landmark identification in a semi-blind manner. Apart from individual and anatomical variations, the success rate in such cases is dependent on equipment accuracy. The introduction of ultrasonography (USG) made the real-time assessment of drug administration possible around the target nerve, without incurring damage to adjacent vessels and anatomical structures.[2,3] Before the introduction of USG guidance for brachial plexus blockade, larger volumes of...
local anesthetic (LA) were used to improve the success rate of ISB.\textsuperscript{14} Despite continuous efforts to improve the block technique, 20–30 ml of LA remains common in clinical use.\textsuperscript{5} However, this volume is associated with 100% incidence of phrenic nerve palsy, which limits its use in patients with limited pulmonary reserve.\textsuperscript{66}

Various studies have proven that the use of low volume of drug has decreased the severity of reduction in forced expiratory volume in 1 second, forced vital capacity, and peak expiratory flow rate after 30 min of ISB administration and lower fall in postoperative oxygen saturation (SpO\textsubscript{2}) as compared to standard volume group, without hampering pain scores and sleep quality.\textsuperscript{57}

Hence, the current study was conducted to investigate a clinically relevant minimum effective volume of 0.5% ropivacaine required for successful surgical anesthesia with ISB.

Material and Methods

This study was registered with the Clinical Trial Registry of India with registration no. CTRI/2017/05/008603. The prospective study was conducted after approval from the hospital’s ethical committee, over a period of 6 months. A written and informed consent was taken from the patient after explaining the procedure to the patient. Patients with American Society of Anesthesiology physical status (ASA PS) I and II, aged 18–60 years, with BMI <30 kg/m\textsuperscript{2} undergoing surgeries of upper arm were included in the study. Exclusion criteria of the study included patient’s refusal, patients with known hypersensitivity to LA, patients with opioid addiction, bleeding diathesis, any chronic systemic illness, anatomical abnormality, infection at the regional site, neurological deficit involving brachial plexus, and pregnant female.

During preoperative visits, patient’s detailed history, general physical examination, and systemic examination was carried out. Basic demographic data including age, sex, height, and weight were recorded. Routine investigations as per recent guidelines were also recorded. The patient was explained in detail about the anesthesia procedure. After the arrival of the patient in the operating room, intravenous access was established with 18-gauge (G) cannula in the nonoperative upper limb, and standard ASA monitoring was attached. The patient was premedicated with Inj. midazolam 0.05 mg/kg intravenously. Then, the patient was placed in the semi-recumbent position with the shoulder down and head turned toward the opposite side. Brachial plexus was identified by “Traceback approach,” and low ISB approach was preferred for injection.\textsuperscript{88} Needle placement and LA (0.5% ropivacaine) injection were guided by ultrasound (M-Turbo SonoSite), equipped with a 38-mm high-frequency (12 MHz) linear array transducer. 2% Lidocaine was administered locally after disinfecting the site. Afterwards, 50 mm 22G needle (Stimuplex, B. Braun) was introduced percutaneously, from the lateral to medial side, using an in-plane technique. The nerve stimulator was set at 0.5 mA (0.1 ms). The needle was placed beside each trunk in succession, and the 0.5% ropivacaine was injected in three equal aliquots, to the predetermined total volume. Motor response was not deliberately sought, however, when obtained, the current was reduced until the motor response stopped being visible or palpable. Needle insertion and injection were considered intraneural, if NS at a current of 0.2 mA (0.1 ms) or less resulted in an evoked motor response, or if a high resistance to injection was felt or nerve swelling was noticed upon initiating the injection. In case of such an instance, the injection was immediately stopped, and the patient with suspected intraneural injection was excluded from the analysis. To prevent any intravascular spread, the injection was repeatedly aspirated and the drug was immediately stopped if any signs of systemic toxicity appeared.

During the performance of block, the imaging time (time interval between the contact of the ultrasound probe with the patient and the acquisition of a satisfactory image) and the needling time (time interval between the start of skin wheal and the end of ropivacaine injection) were recorded. Thus, the performance time was defined as the sum of imaging and needling time. Duration of surgical procedure and time to first analgesic requirement (duration of analgesia) were also recorded.

An examiner who was blinded to the volume evaluated the presence of motor and sensory blockade in the territory of C5 to C6. Block assessment was performed at 5 min intervals up to 30 min, after completion of the last injection. Simultaneous sensory and motor functions in the contralateral limb were used for comparison purposes. The deltoid area was chosen for testing of the sensory block because axillary nerve territory was considered most relevant to the surgical model used. Sensory function was assessed by pinprick test, using a three-point scale where scores 0, 1, and 2 reflected sharp pain, dull pain (analgesia), and no pain (anesthesia), respectively. Bromage scale was used to assess the motor function by testing abduction of the arm (axillary nerve) and flexion of the forearm at elbow joint (musculocutaneous nerve).\textsuperscript{99} The assessment was terminated on the achievement of surgical anesthesia in the deltoid region or completion of...
30 min, whichever occurred first. A successful block of the brachial plexus was defined as the presence of adequate motor block (motor score of ≤2), absent sensation to cold and pinprick sensation, within 30 min of injection, and no requirement of general anesthesia (GA). Block failure was defined as the absence of surgical anesthesia at 30 min or requirement of GA intraoperatively for completion of surgery.

Adverse effects such as Horner’s syndrome and hemidiaphragmatic paresis were assessed at 30 min, before administration of sedation and starting of surgery. Horner’s syndrome was evaluated clinically. The diaphragmatic movement was assessed by real-time USG of the ipsilateral hemidiaphragm with a 2–5 MHz curvilinear probe at the cephalad border of the zone of apposition of the diaphragm to the costal margin, i.e., between the midclavicular and the anterior axillary lines. All assessments were performed with the patient in the supine position during quiet inspiration, deep inspiration, and forceful sniff as explained by Riazi et al.\(^1\)

Surgery was conducted under ISB as a sole anesthetic technique with intraoperative sedation consisting of intravenous infusion of propofol (25–75 \(\mu\)g/kg/min) which was titrated to the Ramsay sedation score of 4 or 5.\(^1\) Duration of sensory blockade was assessed by asking the patient to record the time of first pain sensation.

The primary objective of the study was to determine the minimum effective volume of 0.5% ropivacaine in 90 patients (MEV90) for surgical anesthesia in upper arm surgery under USG-guided ISB. The secondary outcomes included onset and duration of sensory and motor block, duration of analgesia, and incidence of complications and adverse effects (nausea, vomiting, allergic reaction, respiratory distress, hemidiaphragmatic paresis, Horner’s syndrome, neurovascular injury, etc.).

Minimum sample size required to calculate MEV90 was based on simulations carried out for different scenarios of dose distribution, sample size, and the number of positive responses, as explained by Durham et al.\(^1\) A fixed minimum number of 45 positive responses was estimated for the dose-finding study. Hence, patients were recruited until 45 successful blocks were performed, which was achieved with totally 50 cases, five being unsuccessful. Volume assignment was carried out using a biased coin design up-and-down method (BCD-UDM), where the volume administered to each patient depended on the response of the previous one.\(^1\) A dose of 7 ml of 0.5% ropivacaine was used as a starting dose, as it was found to be sufficient volume for patients with ASAPS I and II, with BMI <40 kg/m\(^2\) in previous studies.\(^1\) In case of block failure, the next subject received a higher volume (defined as the previous volume with an increment of 1.0 ml). If the previous patient had a successful block, the next subject was randomized to receive a lower volume (defined as the previous volume with a decrement of 1.0 ml) or the same volume, with a probability of \(b = 0.11\) and \(1 - b = 0.89\), respectively.

MEV90 with a CI of 95% was calculated using isotonic regression, as derived by bootstrapping, done with R package software. Mean and standard deviations were used to analyze parametric data, whereas median and quartiles were used to analyze nonparametric data. Statistical analysis was performed using the Microsoft Excel, R statistical software, and SPSS 23 software.

### Results

Demographic characteristics of the patients are described in Table 1. Imaging time, needling time, and performance time for the block are described in Table 2. For the group as a whole, the time for onset of sensory block was 5 (5–20) min [median (range)] and the time for onset of motor block for the biceps and the deltoid muscles was 7.5 (5–15) min and 10 (5–15) min, respectively [Table 3 and Figure 1]. The duration of analgesia was 8.9 (3–15) h [Table 4]. MEV90 of 0.5% ropivacaine for ISB was determined as 8.64 ml (CI 95%, 8.28–9.02 ml). There was no relation between the volume used and sensory and motor onset and duration of analgesia.

| Parameter | Mean±standard deviation |
|-----------|-------------------------|
| Age (years)* | 34.68±12.47 |
| Weight (kg)* | 62.82±9.72 |
| Height (cm)* | 166.58±6.34 |
| Gender (male/female) | 39/11 |
| ASA physical status (I/II) | 32/18 |

\(^*\) Data expressed as mean±standard deviation

| Parameter | Mean±standard deviation |
|-----------|-------------------------|
| Imaging time (sec) | 56.06±10.416 |
| Needling time (min) | 3.61±0.611 |
| Performance time (min) | 5.29±0.618 |

| Parameter | Median (min) | Range (min) | Adjusted \(R^2\) |
|-----------|--------------|-------------|-----------------|
| Sensory block | 5 | 5–15 | −0.022 |
| Motor block (biceps) | 10 | 5–20 | 0.033 |
| Motor block (deltoid) | 10 | 5–20 | −0.023 |

\(^*\) \(R^2\): calculated using regression analysis
Side effects related to ISB were comparatively lower as compared to previously conducted studies. The incidence of hemidiaphragmatic paresis was 20%, the incidence of Horner’s syndrome was 11%, while vascular and intraneural injections were nil. 13.33% patients experienced nausea/vomiting, but there was no observed incidence of hypotension/bradycardia/clinically significant pneumothorax [Table 5].

### Discussion

This study was performed to determine the MEV90 of 0.5% ropivacaine for surgical anesthesia in upper arm surgery. A substantial decrease in volume and dose of LA is possible for surgically successful ISB, when NS and USG guidance are used simultaneously. Though large volumes and higher doses of LA are used to ensure rapid onset and effective ISB, lower volume of LA is associated with reduced risk of toxicity. Moreover, there is a decreased incidence of phrenic nerve palsy (C3 to C5) with lower volumes, as it is typically blocked when high volumes of LA are used to block brachial plexus.

In this study, MEV90 of 0.5% ropivacaine for ISB was determined as 8.64 ml (CI 95%, 8.28–9.02 ml) [Figure 2]. This was a little higher when compared to previous studies where comparatively lower dosages have been claimed. Vandepitte et al. had determined that ED95 of 0.75% ropivacaine was 7 ml using catheter-based technique. A similar study conducted by Gautier et al. had found ED50 of 0.75% ropivacaine was 5 ml. Both these studies have undermined the dosage as they had used Dixon and Massey UDM which is considered inferior to BCD-UDM. We used BCD-UDM to determine the MEV90 of 0.5% ropivacaine for USG-guided ISB using isotonic regression [Figure 3]. Furthermore, 95% CI was derived by bootstrapping, as recommended by Pace and Stylianou. BCD-UDM is a relatively new method to approximate MEV of LA for peripheral nerve blocks. It allows the direct investigation of ED or MEV at any quantile.

Using a single-injection technique may be more time efficient and carry less risk for inadvertent injury to the trunks of the brachial plexus, but its adequacy in the accomplishment of surgical anesthesia is not yet determined. Various studies have been conducted previously, which have compared single and multiple injection techniques for various blocks, including ISB and found that multiple injection protocols resulted in the faster onset of anesthesia and that too with comparatively lower volumes. However, data available on the ability of low volume LA to provide surgical brachial plexus anesthesia, particularly with single-injection techniques is limited. Hence, we used the multiple injection technique to accomplish ISB in this study.

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**Table 4: Duration of analgesia (n=45)**

|                   | Median | Range | Adjusted R² |
|-------------------|--------|-------|-------------|
| Duration of analgesia (h) | 8.2    | 4.8-12.50 | -0.003      |

*R²: calculated using regression analysis

**Table 5: Incidence of side effects (n=45)**

| Side effect                     | Incidence | Percentage |
|---------------------------------|-----------|------------|
| Hemidiaphragmatic paresis       | 9         | 20         |
| Horner’s syndrome               | 4         | 11         |
| Vascular puncture               | 0         | 0          |
| Nausea/vomiting                 | 6         | 13.33      |
| Bradycardia                     | 0         | 0          |
| Hypotension                     | 0         | 0          |
| Pneumothorax                    | 0         | 0          |
In our study, we have administered lower ISB for better coverage of analgesia for the upper arm. This was also supported by various studies conducted earlier, which claim better analgesia and lower incidence of phrenic nerve palsy.[23,24]

The median (range) duration of analgesia in our study was found to be 8.2 (4.8–12.5) h, which was similar to the previous studies with ISB. Gautier et al.[17] had also observed similar findings, with a mean duration of 9.9 ± 3.7 h.

Earlier studies have found no correlation between the duration of analgesia and volume of LA.[17,17] But one such study made claims of delay in onset of analgesia with the use of lower concentration of LA.[25] In our study, duration of onset and analgesia were not affected by the decreased volume of LA as determined by regression analysis [Tables 2 and 3].

Urmey et al.[6] had claimed in their study conducted on ISB that hemidiaphragmatic paresis is inevitable with ISB and reported an incidence of 100%. But further advancement of technology and better USG guidance have made possible the reduction of side effects.[17] We observed a similar trend of lower incidence of side effects. In our study, the incidence of hemidiaphragmatic paralysis, Horner’s syndrome, and vascular injury was 20, 11, and 0%, respectively, though even lower incidences have also been claimed by some.[26]

This study was limited by its inability to collect data regarding VAS scores, for which further studies would have to be conducted to properly evaluate the quality of analgesia.

It may be concluded from this study that surgical anesthesia can be obtained with 8.64 ml (95% CI: 8.28–9.02 ml) of 0.5% ropivacaine, when administering ISB under USG guidance, with multiple injection technique, without clinical deterioration in block onset and duration of analgesia. Further dose finding studies are still required for determination of optimum concentration, depending on the different approaches used for ISB in upper arm surgeries.

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Conflicts of interest
There are no conflicts of interest.

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