INTRODUCTION

Diabetic peripheral neuropathy (DPN), a complication affecting peripheral nerves is present in around 50% of adults with diabetes during their lifetime. [1] Usually, it is accompanied by ailments like foot ulcers and may even worsen to land up in lower limb amputations. [2] These patients are of significant clinical importance to anaesthesiologists as they may have other comorbidities due to micro and macrovascular damage. Any anaesthetic technique which is being contemplated must provide stable haemodynamics and a postoperative period with fewer morbidities. Within the available options, the popliteal sciatic nerve block (PSNB) under...
ultrasound is a widely used anaesthetic technique for many of these patients scheduled for below-knee surgical procedures. The special advantages of this technique include better visualisation of the sciatic nerve and the concomitant precise deposition of the local anaesthetic (LA). In patients with DPN, the characteristics of such blocks are quicker onset time for both sensory and motor blockade with better postoperative pain relief. The established data from diabetic rat models have demonstrated a prolonged block by a mean increase in the block duration by a significant 25–50% over healthy rats. Despite these findings, the incidence of nerve injuries following regional anaesthesia in such patients is not significant, and the reported complications are inconsequential. Hence, conclusions based on such studies regarding whether LAs are extra toxic to these neuropathic nerves remains elusive to the scientific community. Expert recommendations suggest that a diminished LA dose needs to be provided for these patients. The possible presumption is that there is an increased sensitivity of these nerves to LAs. These changes may be the consequence of chronic ischaemic insult and a possible diminished blood flow. To date, there is no data available on minimum effective local anaesthetic volume (MELAV) in this population. Therefore, we designed this prospective study to identify the MELAV of 0.5% bupivacaine for ultrasound guided subparaneural PSNB in 90% DPN patients undergoing below knee surgery (MELAV90).

**METHODS**

This prospective dose-finding study was conducted after obtaining approval from the institutional ethics committee and registered in the Clinical Trials Registry – India (CTRI/2020/05/025251). The study followed the rules of the declaration of Helsinki. Consecutive DPN patients of American Society of Anesthesiologists (ASA) physical status II-IV, above 18 years of age, and presenting for surgery involving the leg, ankle and foot under PSNB were included after obtaining written informed consent. The study was conducted between June 2020 and August 2021 in a tertiary care hospital in south India. Exclusion criteria were pregnancy, coagulopathy, diabetic ketoacidosis, known allergy to local anaesthetic, ongoing dual anti-platelet therapy, open ankle or vascular injury, difficult popliteal sciatic sonoanatomy and patient refusal. DPN was diagnosed using the United Kingdom screening test (UKST) and Biothesiometer (Bio Medical, Newbury, Ohio, USA). UKST is a two-part diagnostic test consisting of symptom-based and physical finding score. The symptom-based screening test consists of five questions about the type, severity and location of symptoms with a maximum score of 9 points. The physical findings-based quantitative score has four questions with a maximum score of 10 points. Peripheral polyneuropathy is defined as the occurrence of moderate to severe signs (score ≥6), even without symptoms, or in the presence of mild signs (≥3) with moderate symptoms (≥5). Biothesiometer assesses the vibratory perception quantitatively by applying the probe to a specific bony point on a limb supported by a pillow. The biothesiometer dial was then gradually increased from 0 to 50 volts until the patient first sensed the vibration, and it was defined as the vibration perception threshold (VPT). After checking for electrical safety, all the patients were assessed with a recently calibrated biothesiometer. VPT between 0 to 15 volts was taken as normal, and values above 15 were graded as neuropathy.

All the patients received ultrasound-guided subparaneural PSNB at the level of nerve bifurcation in the anaesthesia side room approximately 1 hour before the proposed surgery. After establishing 18 G intravenous access and standard monitoring in the procedure room, all the patients received 0.5 µg/kg fentanyl bolus. PSNB was given by the anaesthesiologist who had considerable expertise (>1-year experience) in peripheral nerve block procedures under ultrasound assistance. The procedure was performed with the patient lying prone and the performer sitting on the side of the limb to be blocked and the ultrasound image screen in front of the performer [Figure 1]. A high-frequency broadband linear array transducer probe (HFL15-6 MHz, X-Porte, FUJIFILM Sonosite, Inc, Bothel, USA) was placed in a sterile manner over the popliteal fossa to detect the tibial nerve with popliteal vessels, and the nerve was traced above until it combines with the common peroneal nerve. This point was ascertained as neural bifurcation, where both branches were located closely, giving a bilobular pattern [Figure 2a]. At this point of the out-of-plane approach, a skin-wheat was created using 2 ml of 2% lignocaine to facilitate needle insertion. A 23G Quincke type spinal needle was then advanced in an out-of-plane technique to position its tip inside the paraneural sheath. The correct position of the needle tip was ensured by performing hydro-dissection with saline (<2 mL) to demonstrate the circumferential expansion of the paraneural sheath [Figure 2b]. On
ensuring the appropriate needle tip placement, the predetermined volume of 0.5% bupivacaine was given. The PSNB was supplemented with saphenous nerve block if the medial side of the foot and ankle were involved in the anticipated surgery. The saphenous nerve block was given under ultrasound guidance at the level of mid-thigh in the adductor canal.

An initial LA volume of 10 ml was used in the first patient. Subsequent LA volume was decided based upon the previous patient’s response (success or failure) using a Biased coin up-and-down design (BCD). In block failure, the next patient received a higher volume (an increment of 2 ml from the previous volume). On the other hand, a successful block demanded the subsequent patient receive either a lower volume (a decrement of 2 ml from the previous volume), with a probability of 1/9, or remain the same volume, with a probability of 8/9. It was also decided not to exceed a maximum volume of 20 ml and a minimum of 4 ml as presupposed by our clinical experience. If any patient developed block failure with maximum volume, the subsequent patient would also receive the same volume.

A blinded observer did the motor and sensory assessment of sciatic nerve blockade every 10 min until 30 min after the injection of LA. Sensory block assessment was done by performing a pinprick test using a 22G blunted hypodermic needle in the common peroneal and tibial nerve territories of the foot (both plantar and dorsal side).

Sensory perception was graded on a 3-point scale: 0 = no block (perceives both touch and pain); 1 = analgesia (perceives only touch and not pain); 2 = anaesthesia (perceives neither touch nor pain). Motor block assessment was done by assessing plantar and dorsiflexion movement of the foot on a 3-point quantitative scale: 0 = no block (Power 4/5, 5/5); 1 = paresis (Power 3/5, 2/5); 2 = paralysis (Power 0/5, 1/5).

A composite score of 6 out of 8 must be obtained in 30 min of LA injection to define the block as successful. In addition, the onset times of sensory and motor blockade were also measured. In the event of an inadequate block, the block was considered failure, and further management was with an additional bolus of 0.5% bupivacaine. This additional volume was decided by deducting the total volume used for the block from 20 ml of bupivacaine. Despite these measures, if the block was not adequate or failed, either spinal or, general anaesthesia or monitored anaesthesia care with ketamine boluses was provided depending on the patient’s status and attending anaesthesiologist’s decision. Surgery was performed only after successful blocks or after the management of block failure by the attending anaesthesiologist. In the postoperative period, the time taken to first perception of pain [visual analogue scale (VAS) score >4] requiring analgesic intervention was noted, and it was defined as the duration of the block. The attending anaesthesiologist decided on the postoperative analgesia. Patients were followed up in the postoperative period for any noted complications.

The primary outcome variable is the minimum effective local anaesthetic volume (MELAV) of 0.5% bupivacaine providing sensory and motor blockade for surgical anaesthesia in 90% of patients. The isotonic regression method and 95% confidence interval (CI) derived by bootstrapping were used to determine the MELAV in 90% of patients. The sample size was calculated following the method by Styliano et al.[11] The minimum sample size required to stabilise the minimum effective volume calculation was obtained after performing several simulations, and a predetermined value of 45 successful blocks was estimated to terminate the study.[12] Statistical analysis was done using the R statistical software package, version 4.1.1 (R Core Team, Vienna, Austria; 2021, http://www. R-project.org).
RESULTS

The study included a total of 53 patients to achieve 45 successful blocks. The patients’ demographic characteristics are described in Table 1. Needling time and block characteristics are presented in Table 2. The sensory and motor blockade onset times were $1.84 \pm 0.77$ min and $3.85 \pm 1.1$ min, respectively [Table 2]. The duration of analgesia was $585 \pm 99.5$ min [Table 2]. The up and down sequence of the individual patient’s response is presented in Figure 3. The MELAV90 for 0.5% bupivacaine was estimated as $5.85$ ml (95% CI, 5.72-6.22). Eight patients needed supplemental LA volume or other forms of anaesthesia to complete the surgery. All the eight patients with failed blocks had an absent or incomplete motor block. The surgery proceeded with additional bolus of 0.5% bupivacaine and ketamine supplementation. There was no demonstrable intravascular or intraneural injection or parenthesis or pain site injection following the nerve blocks. No patients developed injection site haematoma or local site infection or persistent weakness or newer onset paraesthesia in the lower limb after the procedure.

DISCUSSION

In this prospective dose-finding study, the MELAV90 of 0.5% bupivacaine for ultrasound-guided subparaneural PSNB in patients with DPN was established as 5.85 ml. This finding of low LA volume is well corroborated in a study where 6 ml of 1% ropivacaine was given intraneural to achieve effective sensory-motor block in 90% of patients without any neuropathy.[13] In contrast, the calculated minimum volume required to produce an effective ultrasound-guided PSNB with 0.5% ropivacaine, injected perineural and estimated by isotonic regression in 95% of patients with no known neuropathy was 16 ml, and ED90 of 0.75% ropivacaine, estimated by probit analysis was 8.9 ml.[14,15] Similarly, in another dose-finding study of a mixture of 1% lidocaine and 0.25% bupivacaine with epinephrine 5 µg/ml for ultrasound-guided PSNB using subparaneural injection at the level of neural bifurcation, the ED90 dose estimated by isotonic regression method was 13.3 ml (95% CI, 10.2 -16.4 ml).[16]

The results of the current study, namely, the high success rate of using low local anaesthetic volume can be attributed to several factors. It includes the subparaneural deposition of the local anaesthetic drug, achievement of circumferential local anaesthetic spread around the nerves using ultrasound guidance and neural changes secondary to DPN.[6,17-19]

The block onset times of distal and proximal popliteal sciatic nerve blockade under ultrasound guidance with 30 ml of equal parts of 2% lignocaine with 1 in 200000 adrenaline and 0.5% bupivacaine were demonstrated as 24 and 34 minutes, respectively.[20] Similarly, the estimated block onset times for subepineural and target-specific injections of the tibial and common peroneal nerves were found as 10.7 and 16.4 ml.[21] In contrast to the above findings, a mean sensory and motor block onset time of $1.84 \pm 0.77$ and $3.85 \pm 1.1$ min, respectively, was obtained in the present study. The quicker onset of nerve blockade could be possibly due to the subparaneural injection of LA at the neural divergence causing the

| Table 1: Patient demographic data and duration of surgery |
| Parameter | Patients (n=45) |
| Age (years) | 59.4±9.3 |
| Gender (Male/female) | 29/16 |
| Height (cm) | 161.16±6.8 |
| Weight (kg) | 66.91±7.5 |
| BMI (kg/m²) | 25.79±2.7 |
| Surgery duration (minutes) | 54.84±18.4 |

Values are represented as mean (standard deviation) or number; BMI: Body mass index

| Table 2: Block characteristics and performance data |
| Parameter | Patients (n=45) |
| Needling time (min) | 2.04±0.45 |
| Sensory block onset time (min) | 1.84±0.77 |
| Motor block onset time (min) | 3.85±1.1 |
| Duration of analgesia (min) | 585±99.5 |

Values are represented as mean (standard deviation)
circumferential spread of LA and neural changes secondary to diabetic neuropathy.

Animal data from diabetic rats have demonstrated a mean increase in the block duration by 25-50% over healthy rats after perineural LA deposition. In DPN patients, the block characteristics evaluated by Baeriswyl et al. showed the median time to first analgesic demand following ultrasound-guided PSNB with 30 ml of an equal mixture of lignocaine 1% and bupivacaine 0.5% as 24 h. This cohort of patients experienced a longer median time to first analgesia, 157% longer than the control group. In a study by Cuvillon et al., the median sensory (21 versus 17 h) and motor block duration (16 versus 12 h) in diabetic patients were increased compared to non-diabetic patients. Our study demonstrated the time to first analgesia as 585 ± 99.5 min (10 h), similar to the finding obtained in patients without diabetic neuropathy. Although measuring the time to first analgesia and the sensory blockade duration is not the same, both measures can be considered as substitutes for a pain-free period that is clinically pertinent. Though there is fear of long-term neurological injury or exacerbation of existing neuropathy with peripheral nerve blockade, there is inadequate evidence demonstrating the association of preceding neuropathy and nerve injury after peripheral nerve block. Also, there is a paucity of data on the association between long-acting LA use and the nerve injury risk after peripheral nerve block. Nevertheless, bupivacaine induced myotoxicity in peripheral and interfascial plane blocks has already been reported. The current study supports the recommendation of utilising lower LA doses in cases of DPN to produce adequate surgical anaesthesia with enhanced block onset time without causing prolonged recovery. In addition, the above finding is worthy of consideration to prevent LA systemic toxicity in clinical contexts such as frail elderly or paediatric patients or when the same patient requires several peripheral nerve blocks.

This study has some limitations. First, the electrodiagnostic evaluation for assessment of neuropathy was not done in this study which is considered the gold standard. Secondly, although there were no signs of worsening neuropathy with the long-acting LA bupivacaine, the possibility of the “double crush phenomenon” in this high-risk population cannot be excluded entirely, and caution should be exercised to avoid needle trauma and pressure injury while performing peripheral nerve block. Therefore, further studies are required to determine MELAV at lower concentrations to reduce the risk of further nerve damage and worsening of neuropathy.

**CONCLUSION**

In conclusion, this prospective study demonstrates MELAV90 of 0.5% bupivacaine required for ultrasound-guided subparaneural PSNB to achieve surgical anaesthesia for ankle and foot surgery in patients with DPN. The MELAV90 obtained was 5.85 ml with a quicker block onset time and optimal recovery.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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