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Equal mixture of 2% lidocaine with adrenaline and 0.5% bupivacaine 20 mL provided faster onset of complete conduction blockade during ultrasound-guided supraclavicular brachial plexus block than 20 mL of 0.5% bupivacaine alone: a randomized double-blinded clinical trial

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ABSTRACT

Introduction Recent evidence has questioned the advantage of local anesthetic (LA) combinations. This study tested the hypothesis that mixing rapid-onset (lidocaine) and long-duration (bupivacaine) LA would provide faster onset of complete conduction blockade (CCB) compared with bupivacaine alone and longer duration of analgesia compared with lidocaine alone during low-volume (20 mL) ultrasound-guided (USG) supraclavicular brachial plexus block (SCBPB).
Methods Sixty-three patients receiving USG-SCBPB were randomly allocated into: group *L*: 20 mL 2% lidocaine with epinephrine 1:200 000; *group B:* 20 mL 0.5% bupivacaine; *group LB*: 20 mL of equi-volume mixture of both drugs. Sensory and motor blockade was recorded on a three point sensory and motor assessment scale at 10 min intervals for up to 40 min and the total composite score (TCS) at each time point was determined. The duration of analgesia was also noted.
Results The mean time to CCB of group LB (16±7 min) was comparable (p>0.05) with group L (14±6 min) and group B (21±8 min) in patients who were attained CCB. However, the proportion of patients attaining complete conduction block (TCS=16/16) was significantly lower (p=0.0001) in group B (48%) when compared with group L (95%) and group LB (95%) at the end of 40 min. The median (IQR) duration of postoperative analgesia was longest in group B; 12.2 (12–14.5) hours, followed by group LB 8.3 (7–11) hours and 4 (2.7–4.5) hours in group L.
Conclusion At 20 mL LA volume, equal mixture of lidocaine and bupivacaine provided significantly faster onset of CCB compared with bupivacaine alone and longer duration of postoperative analgesia compared with lidocaine alone but shorter than bupivacaine alone during low-volume USG-SCBPB.
Trial registration number CTRI/2020/11/029359.

INTRODUCTION

Mixing of two local anesthetics (LAs) to take advantage of the rapid onset of one agent and prolonged duration of action of another has been practiced since the 1960s.[1–4] However, the recent research yields conflicting findings about the clinical

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The clinical advantage of mixing two local anesthetics is not established.

WHAT THIS STUDY ADDS

⇒ At 20 mL local anesthetic (LA) volume, equal mixture of lidocaine and bupivacaine provided clinically significant faster onset of complete conduction blockade compared with bupivacaine alone and prolonged analgesia compared with lidocaine alone but shorter than bupivacaine alone during ultrasound-guided (USG) supraclavicular brachial plexus block.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The pharmacodynamics of LA mixtures during USG low-volume precision blocks might be different—need to be explored.

advantages of LA mixing. 40 mL equal mixture of Mepivacaine 1.5% (faster-onset, intermediate-duration) with bupivacaine 0.5% (slower-onset, longer-duration) was shown to hasten the onset of conduction blockade in infraclavicular brachial plexus block (BPB); however, 30 mL of the same mixture was found to provide no benefit over bupivacaine in the onset of conduction blockade during interscalene BPB (ISB).[3 5] In the recent years, an improved understanding of the sonoanatomy of BP elements and injection techniques has enabled us to decrease the LA volume from 30–40 mL to 10–20 mL to provide a successful BPB at the supraclavicular area.[6–9] In our experience, using bupivacaine alone in such low volume, substantially delayed the onset of complete conduction blockade (CCB). Hence, we designed this study to test the hypothesis that 20 mL equal mixture of 2% lidocaine with epinephrine 1:200 000 and 0.5% bupivacaine would provide faster onset of CCB compared with 20 mL bupivacaine alone and longer duration of analgesia compared with 20 mL lidocaine alone during low-volume (20 mL) ultrasound-guided (USG) supraclavicular BPB (SCBPB).

METHODS

The study protocol was approved by the institutional human ethics committee (MGMCRI/IRC/04/2020/35/IHEC/177). Patients aged 18–60 years belonging to American Society of Anesthesiologists (ASA) physical status I and II scheduled for upper extremity bone surgeries, at or below the elbow under SCBPB, were included in the study. Patients who refused to participate, gave a history of allergy to LA drugs, and had evidence of coagulopathy, neurological deficit, infection at supraclavicular fossa, respiratory compromise or difficult sonoanatomy were excluded. A consecutive sampling technique was employed. First patient was recruited on 1 December 2020. All participants submitted a written informed consent before enrollment into the study.

All the blocks were performed in the anesthetic procedure room, approximately 60 min before the planned surgery. 18-gage intravenous access and ASA standard monitoring were established before the BPB. Simple permuted block randomization (7 blocks of nine patients each) was used for group allocation. The randomization sequence was generated by a statistician and handed over in sealed opaque sequentially numbered envelopes. The envelope was opened by an anesthesia resident not involved in the study and prepared the LAs or LA mixtures as per the allocation card. A total of 20 mL of 2% lidocaine HCl with epinephrine 1:200 000 (5 µg/mL) was used in group L. 10 mL of each 2% lidocaine HCl with 1:200 000 epinephrine and 0.5% bupivacaine HCl was used for group LB. A total of 20 mL of 0.5% bupivacaine HCl was used for group B. The study drug was loaded in a 20 mL syringe, connected to a 100 cm pressure monitoring line and handed over to the performer. The performer was not aware of the content of study drug.

Two of the three investigators (SR and ST) who had extensive experience in multipoint subfascial injections performed all the BPBs and took no further part in the study. Patients were positioned with arms by the side and the head turned slightly to the contralateral side, for the block. All the blocks were performed under US guidance and strict aseptic precautions, using a high-frequency linear array transducer (HFL 50, 15–6 MHz) of X-Porte US system (FUJIFILM Sono Site, Bothell, USA). A 25-gage, short-beveled Quinke spinal needle was used to perform the BPB. The needle insertion was either in-plane or out-of-plane depending on the ergonomics achieved. The needle was well introduced into the outermost hyperechoic fascial layer and the tip was positioned within the hyperechoic connective matrix between the hypoechoic neural elements. A test bolus of 0.5 mL LA was administered to note the swelling of the neural cluster without any obvious swelling of the individual hypoechoic circles or paraesthesia. A random multiple site subfascial injections were made. No specific sequence of injections was followed. Maximum of 4–5 mL of LA solution was injected at a single site in order to ensure spread of the LA in and around all the elements of brachial plexus, including the corner pocket.[10] The routine performance time for LA injection was 3–5 min. The final needle removal time was noted as 'time 0'.

The sensory-motor assessment was performed by an independent anesthesiologist who was also blinded to group allocation. Sensory block was assessed on a 3-point qualitative scale (Grade 0, presence of cold and touch sensation; Grade 1, loss of cold but not touch sensation and Grade 2, loss of both cold and touch sensation) using ether-soaked cotton swabs. The distalmost territories of the musculocutaneous nerve (MCN)—lateral forearm, median nerve (MN)—the tip of the middle finger, the ulnar nerve (UN)—the tip little finger and radial nerve (RN)—anatomical snuff box, were tested. A score of 2 in all four nerve distribution areas (8/8) was taken as the time for the complete sensory block. Motor blockade of the four-terminal branches (MCN-elbow flexion, MN-thumb opposition, UN-thumb adduction, RN-thumb abduction) was assessed using a 3-point qualitative scale [0—normal motor function (Power 4/5, 5/5), 1—decreased motor function (Power 3/5, 2/5), 2—no motor power (Power 0/5, 1/5)]. A score of 2 in all 4 terminal nerve distribution areas (8/8) was taken as the *time for the complete motor block*. The time to achieve a sensory score of 2 and motor score of 2 in all four terminal nerve territories (total composite score; TCS=16/16) was taken as the *time for complete conduction block (CCB)*. Sensory and motor testing was done at 10 min intervals after time 0 until 40 min or till CCB whichever was earlier. The TCS was noted at each time point.

Inside the operating room, patients were sedated for comfort before the start of surgery using intravenous midazolam 1 mg and fentanyl 1 µgm/kg. Block was considered a failure if the patients complained of pain during any stage of surgery or required any form of rescue analgesic interventions. Postoperatively, patients were instructed to inform when they perceived pain at the surgical site and received injection acetaminophen 1 gm and ketorolac 30 mg intravenously and subsequently put on regular oral analgesics as per departmental acute pain service protocol. The time gap from time 0 to the first perception of pain by the patient was taken as the *duration of analgesia*. Twenty-four hours later, the patients were questioned for the presence of paresthesia, dysesthesia or motor weakness in the operated limb.

Statistical analysis
Sample size estimation
The 'Statistics and Sample Size' App (Thai Thanh Truc) was used to calculate the sample size. Time for CCB was the primary outcome variable. In a pilot study on ten patients, we observed that the onset of CCB with drug combination was 19±11 min (mean±SD), while with bupivacaine it was 30±12 min. With a power of 80% and a two-sided type 1 error rate of 0.05, the minimum sample size required to detect the difference between the two groups (LA mixture vs Bbupivacaine—one pair) was estimated to be 18 per group. Hence, the total sample size of the study was 54 (18×3). To facilitate block randomization and take into account the drop-outs, 63 (21×3) patients were recruited.

Data analysis
SPSS for Windows V.16.0 (SPSS, Chicago, Illinois) was used for statistical analysis. The χ^2 test was used to compare categorical variables. The normality of continuous variables was tested by the Kolmogorov–Smirov test. Normally distributed data are reported as mean±SD and analyzed using one-way analysis of variance (ANOVA). Kaplan-Meier survival plots were created for the proportion of patients attaining CCB, CCB of individual nerves in each group and duration of analgesia. CCB in the three groups and the onset of CCB of individual nerves in each group were individually analyzed using the log-rank test (Mantel-Cox test) when censoring was observed. Duration of analgesia is reported as median (IQR) and compared using the Kruskal-Wallis test. p<0.05 was taken as the threshold of statistical significance.

RESULTS
Seventy patients were evaluated for eligibility, 63 patients were randomly assigned to receive the intervention, and all 63 patients completed the analysis (figure 1). The three study groups were comparable with respect to demographic data, type of surgery performed, and other clinical variables (table 1).
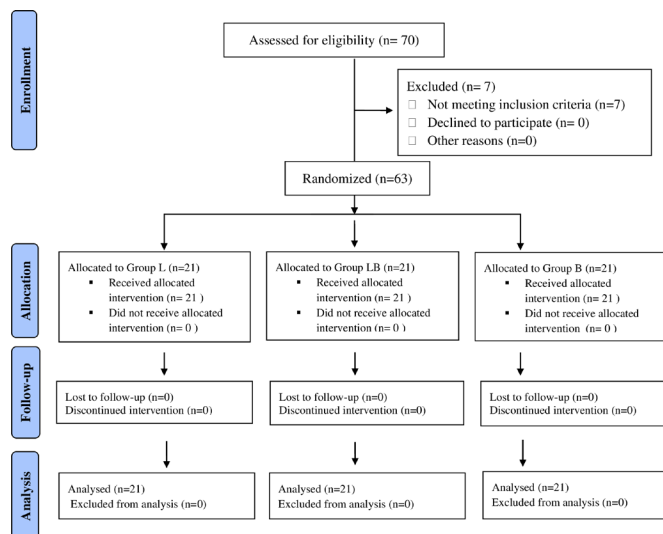
Figure 1 Consolidated Standards of Reporting Trials (CONSORT).

Table 1 Demographic characteristics and clinical characteristics of the study groups

Parameter	group L (n=21)	group LB (n=21)	group B (n=21)
Mean age (SD) in years	45 (14)	44 (13)	37 (13)
Sex, n (%)			
Male	16 (76)	14 (67)	14 (67)
Female	5 (24)	7 (33)	7 (33)
ASA classification, n (%)			
I	15 (71)	13 (62)	16 (76)
II	6 (29)	8 (38)	5 (24)
Mean BMI (SD) in kg/m^2	25 (3)	23 (5)	26 (4)
Surgery, n (%)			
Fracture radius	11 (52)	9 (42)	10 (48)
Fracture ulna	6 (29)	6 (29)	7 (33)
Both bone fracture	4 (19)	6 (29)	4 (19)
Mean time gap between the block performance (time 0) to skin incision* (SD) in minutes	21 (8)	26 (9)	64 (20)
Mean surgical duration (SD) in minutes	60 (12)	52 (18)	54 (20)

*One-way ANOVA is used to compare means between group L vs B and group LB vs B; p<0.001.
ANOVA, analysis of variance; ASA, American Society of Anesthesiologists; BMI, body mass index.

It took approximately 5 min to perform the block. In patients who had a CCB, the mean time to CCB was significantly different between group L and group B (14±6 vs 21±7 min; p=0.02), whereas the group LB (16±7 min) was comparable (p>0.05) with other two groups. However, the proportion of patients attaining CCB (TCS=16/16) was significantly lower (p=0.0001) in group B (14, 33, 48, 48%) when compared with group L (62, 86, 95, 95%) and group LB (43, 81, 90, 95%) at all four time point intervals. 52% (11/21) of the patients in group B did not attain CCB even at the end of the 40 min observation period (figure 2). TCS against time was used to compare the degree of conduction blockade between groups at different time points. This demonstrated that group LB achieved comparable (p>0.05) conduction blockade to group L in 20 min, whereas group B took 40 min to reach comparable conduction blockade with group L. However, high variation in TCS even at the end of 40 min suggests that the conduction blockade was more unpredictable in group B (figure 3). The MN and UN took relatively more time for CCB compared with MCN and RN in all three groups (figure 4). The median (IQR) duration of postoperative analgesia was longest in group B; 12.2 (12–14.5) hours, followed by group LB; 8.3 (7–11) hours and least in group L; 4 (2.7–4.5) hours; p=0.0001 (figure 5).

Thirteen patients (11 in group B, 1 in group LB and 1 in group L) did not attain CCB at the end of 40 min. Incomplete blockade of the MN and UN contributed to a lower TCS in all 13 patients. None of the patients in any group required >2 µg/kg of fentanyl or conversion to GA. There were no complications observed in any patient during or after the performance of the block. None of the patients reported persistent neurological symptoms at the end of 24 hours.

DISCUSSION

In this randomized, double blinded clinical trial we found, 20 mL of bupivacaine–lidocaine mixture significantly increased the proportion of patients who experienced CCB within the first 40 min of observation (95% vs 48%; p=0.0001) compared with bupivacaine alone, and extended the duration of postoperative analgesia (8.3 vs 4 hours; p=0.0001) compared with lidocaine alone during USG-SCBPB.

As the final needle tip position and injection techniques like subfascial/extra fascial, targeted intracluster and selective truncal

can significantly influence the block onset time, one of the two authors (RS or ST) experienced with the technique performed all the blocks.[9–11] Patients with difficult sonoanatomy were excluded because it is challenging to confirm adequate LA distribution across all components of the BP. To reduce the observer bias and increase the objectivity, a CCB of the core fibers assessed at the distal most innervation area of the terminal nerves was alone considered for a successful block. Only bone operations were included in our study cohort because the degree of tissue injury and the intraoperative nociceptive insult can affect the duration of postoperative analgesia.

The conflicting results from clinical studies evaluating the onset of peripheral nerve blockade with LA mixtures arise from three fundamental differences in the methodologies, namely, the type of nerves assessed (proximal nerves arising from mantle
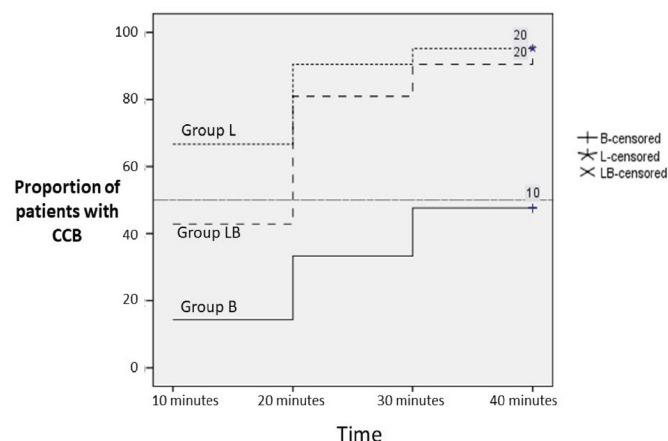

Figure 2 Kaplan-Meier plot of the proportion of patients who attained CCB by the time is shown. Group L vs LB; p=0.64. Group LB vs B; p<0.001. Numerical (10,20,20) indicates the number of patients who attained CCB. Patients not achieving CCB within the stipulated time are grouped as Censored. CCB, complete conduction blockade.
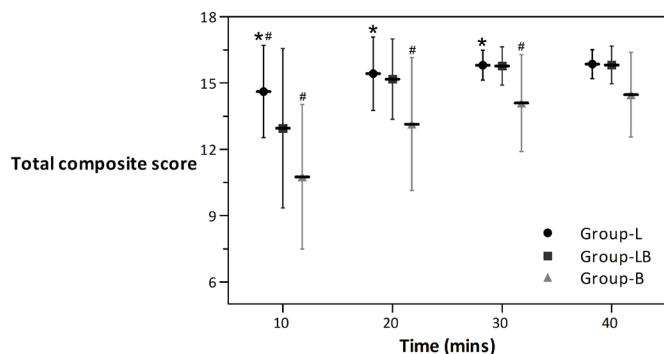
Figure 3 Total composite score at different time intervals is represented as mean±SD. *group L vs group B; p<0.05. #group LB vs group B and group L; p<0.05.

Figure 5 Kaplan-Meier plot of the proportion of patients reporting pain by the time shown. Group L vs LB; p<0.001, group LB vs B; p<0.001.

fibers/distal nerves arising from core fibers), the definition of a successful block (sensory onset/motor onset/time to readiness for surgery/CCB) and the volume/concentration of LA administered.

Gadsen *et al* compared the onset of sensory blockade in the AN territory (a proximal nerve) following ISB and concluded that there was no significant difference between the LA mixture and bupivacaine.[5] However, according to the same study, the sensory block in the UN region (a distal nerve) was substantially lower in bupivacaine group compared with the mixture (13 vs 26%; p=0.03) even an hour after the procedure. Even though the ulnar sparing is a well-known fact during ISB, since the performer and the injection techniques were same, the difference in the incidence of UN sparing between the two groups of ISB can only be attributed to the pharmacodynamic difference of LA mixture over bupivacaine. Even in our study, a higher percentage of patients had achieved CCB of the proximal nerves (MCN, RN) than the distal nerves (UN, MN) at the various time points in all three groups. The gap was very prominent in group B, where at the end of 40 min, 100% of the patients had achieved CCB of MCN and RN but only 48% had achieved the same for the UN and MN (figure 4). Various laboratory investigations have demonstrated that highly lipid-soluble drugs like bupivacaine enter the membrane faster with greater efficacy, however, this benefit is negated by their avid non-specific binding to adventitia, perineurium, and superficial fascicles (mantle fibers). This limits their diffusion across different tissue barriers. Lidocaine on the other hand is one-tenth as lipophilic as bupivacaine (by octanal-to-buffer partition coefficient), and 2.5 times more permeant through the perineural sheath.[12 13] Thus, the slow
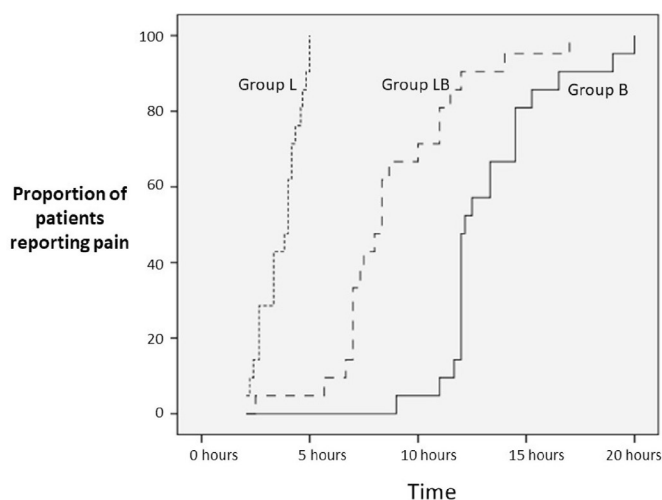
onset of bupivacaine became evident at distal nerves (core fibers) as opposed to proximal nerves (mantle fibers).

The spectrum of conduction blockade following PNB ranges from normal sensory and motor function on one end to the CCB (complete loss of sensation (anesthesia) and motor paralysis (power 0/5, 1/5)) at the other end. Between the two extremes, the onset of sensory block, the onset of motor block, time to readiness for surgery, and surgical anesthesia are various endpoints requiring progressively more soakage time. The soakage time is primarily required for the intraneural diffusion and blockade of all types of nerve fibers.[14] A portion of the injected drug may, however, be lost due to extraneural diffusion. The pharmacodynamic difference between lidocaine and bupivacaine becomes very evident when we compare the final point in the conduction blockade spectrum, especially in the larger-diameter nerves. Cuvillon *et al* demonstrated a faster onset of CCB with a mixture of lidocaine and bupivacaine compared with bupivacaine alone during both femoral and sciatic nerve blocks.[15] Similarly, in our study, when we compared the progress of conduction blockade through TCS, we can appreciate significant degree of conduction blockade even at the end of 10 min in the bupivacaine group. However, to reach the CCB in all patients, it took beyond 40 min. Furthermore, that the TCS variation was much higher at all-time intervals makes bupivacaine more unpredictable for
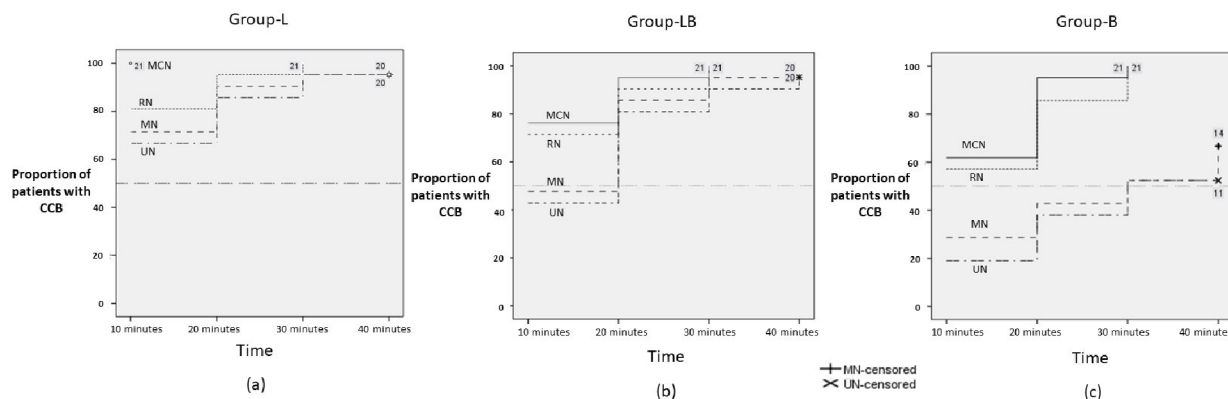

Figure 4 Kaplan-Meier plot of the proportion of patients with complete conduction block of the four terminal nerves by the time shown in all three groups. Group-L; p=0.36, group LB; p =0.06, group B; p<0.001. CCB, complete conduction blockade.

CCB compared with lidocaine and LA mixture group (figure 3). But blocks at the digits,[16] dermis[17] and epidural space,[18] may not exibit similar differences as connective tissue barriers between the injection point and the axons are very less at the epidural space and the nerve diameter is extreamly small at the digits and dermis.

The block onset time is also influenced by injecting an LA dose below the minimum effective concentration (MEC) or over the minimum effective local anesthetic volume (MELAV). Almasi *et al* in their study comparing LA mixture did not find a difference in the onset of sensory block between bupivacaine (17.21 min) and lidocaine–bupivacaine mixture (16.64 min) due to a very low concentration of lidocaine (0.5%) in the LA mixture, against the MEC of 1%.[19 20] Similarly, in a dose-finding study on infraclavicular BPB, Baskan *et al* demonstrated that reducing the volume of 0.5% bupivacaine from 30 mL to 14 mL (MELAV) increased the block onset time from 15 min to 40 min (r=−0.089).[21] Hence, increasing the bupivacaine volume to 30 mL or using concentration more than 0.5% in 20 mL volume might have changed the block onset time.

In our study, even though 52% of the patients in group B did not achieve CCB at the end of 40 min, all of them completed surgery without the need for rescue analgesia. This may give the notion that CCB is not mandatory for surgical anesthesia. But, the truth lies in the time gap between the block and the surgical incision time (table 1). The patients in the bupivacaine group were moved into the operating room following a 40 min observation period. Prewashing, surgical painting, and draping added another 15–20 min, resulting in a block-to-skin incision time of 64±20 min compared with 21±8 min in group L and 26±9 min in group LB. Fracture end manipulation would have taken an additional 10–15 min, depending on the speed of the surgical team. Since we could not assess the finger movements under the drapes, we were unable to measure how many patients achieved CCB before skin incision. However, if the incision had been made within 30 min, as in group L and group LB, the failure rate in the bupivacaine group would have been significantly higher. Hence, these pharmacodynamic differences will come into light only when just adequate LA dose (concentration close to MEC and volume close to MELAV) is used for the block and faster turn-around surgical units demand skin incision within 30 min and osteotome manipulation within 45 min. Laur *et al* found that the number of patients feeling surgical incision (7 out of 31), block failure rate (6 out of 31) and GA conversion rate (4 out of 31) were significantly higher with bupivacaine even after 64 (50–84) minutes of the needle out to incision time.[3] In the present-day practice of US-guided precise injection techniques, where the MELAV for the US-guided supraclavicular BPB is below 20 mL, worries about the additive effect on toxicity caused by mixing of LA are also of no clinical relevance.[8 9]

The limitation of our study is that we did not wait beyond 40 min to note the time for CCB in the bupivacaine group. The time for first perception of pain by the patient was considered to determine the duration of analgesia which is a subjective endpoint as described by many authors before.[3 5] However, our finding of the duration of analgesia following LA mixture as significantly more than lidocaine and less than bupivacaine is well reported by many authors.[3–5] We represented 20 mL as low volume for USG–SCBPB. This is based on our experience that 5–6 mL more than the MELAV-99 will provide satisfactory duration of surgical anesthesia and analgesia for the most common bony surgical procedures of the elbow and forearm.[10] However, this distinction remains an opinion until common consensus arrives.

CONCLUSION

Clinical research looking at the dynamics of LA mixtures has produced contradictory results, due to methodological differences. Clinically significant pharmacodynamic variations are discernible when LA dose close to MELAV and MEC is accurately deposited within the Brachial Plexus sheath, and CCB is determined. At 20 mL local anesthetic volume, the equal mixture of lidocaine and bupivacaine provided significantly faster onset of CCB compared with bupivacaine alone and longer duration of postoperative analgesia compared with lidocaine alone but shorter than bupivacaine alone during USG-SCBPB.

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