

# The Effect of Mixing 1.5% Mepivacaine and 0.5% Bupivacaine on Duration of Analgesia and Latency of Block Onset in Ultrasound-Guided Interscalene Block

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**BACKGROUND:** Short- and long-acting local anesthetics are commonly mixed to achieve nerve blocks with short onset and long duration. However, there is a paucity of data on advantages of such mixtures. We hypothesized that a mixture of mepivacaine and bupivacaine results in a faster onset than does bupivacaine and in a longer duration of blockade than does mepivacaine.

**METHODS:** Sixty-four patients undergoing arthroscopic shoulder surgery (ages 18 to 65 years; ASA physical status I–II) with ultrasound-guided interscalene brachial plexus block as the sole anesthetic were studied. The subjects were randomized to receive 1 of 3 study solutions: 30 mL of mepivacaine 1.5%, 30 mL of bupivacaine 0.5%, or a mixture of 15 mL each of bupivacaine 0.5% and mepivacaine 1.5%. The block onset time and duration of motor and sensory block were assessed.

**RESULTS:** Onset of sensory block in the axillary nerve distribution (superior trunk) was similar among the 3 groups ( $8.7 \pm 4.3$  minutes for mepivacaine,  $10.0 \pm 5.1$  minutes for bupivacaine, and  $11.3 \pm 5.3$  minutes for the combination group;  $P = 0.21$  between all groups). The duration of motor block for the combination group ( $11.5 \pm 4.7$  hours) was between that of the bupivacaine ( $16.4 \pm 9.4$  hours) and mepivacaine ( $6.0 \pm 4.2$  hours) groups ( $P = 0.03$  between bupivacaine and combination groups;  $P = 0.01$  between mepivacaine and combination groups). Duration of analgesia was the shortest with mepivacaine ( $4.9 \pm 2.4$  hours), longest with bupivacaine ( $14.0 \pm 6.2$  hours), and intermediate with the combination group ( $10.3 \pm 4.9$  hours) ( $P < 0.001$  for mepivacaine vs. combination group;  $P = 0.01$  for bupivacaine vs. combination group).

**CONCLUSIONS:** For ultrasound-guided interscalene block, a combination of mepivacaine 1.5% and bupivacaine 0.5% results in a block onset similar to either local anesthetic alone. The mean duration of blockade with a mepivacaine–bupivacaine mixture was significantly longer than block with mepivacaine 1.5% alone but significantly shorter than the block with bupivacaine 0.5% alone. (Anesth Analg 2011;112:471–6)

Local anesthetics (LAs) that are typically used in clinical practice for peripheral nerve blockade are characterized by either fast onset and immediate duration (e.g., mepivacaine, lidocaine), or slower onset and longer duration (e.g., ropivacaine, bupivacaine).<sup>1,2</sup> A common practice is to mix LAs to achieve faster onset and longer duration of blockade; however, few studies have examined the clinical effects of various LA mixtures.<sup>3,4</sup> The few reports available in the literature lacked ultrasound monitoring of the LA disposition during injection, possibly contributing to inconsistent results due to variable patterns of LA spread.<sup>5–7</sup> This randomized, double-blind study determined the effect of mixing intermediate (1.5% mepivacaine) with long-acting LAs (0.5% bupivacaine) on latency of onset and duration of analgesia in an ultrasound-guided interscalene brachial (ISB) plexus block model. Our hypothesis was that a mixture of mepivacaine and bupivacaine provides a faster

onset than does bupivacaine alone, and provides a longer duration than does mepivacaine alone. The primary outcome of the study was the duration of nerve blockade.

## METHODS

### Study Subjects

The study protocol was approved by the St. Luke's—Roosevelt Hospital Center IRB, (New York, NY) and open to ASA physical status I and II patients, 18 to 65 years old, scheduled for elective, outpatient arthroscopic shoulder surgery. Exclusion criteria were severe chronic obstructive pulmonary disease, prior neck irradiation, coagulopathy, body mass index  $>35$  kg/m<sup>2</sup>, or inability to obtain clear ultrasound images of the brachial plexus at the interscalene level. After written informed consent, patients were randomized using a method of sealed envelopes to receive an ISB using 1 of 3 LA solutions: (a) 30 mL of 1.5% mepivacaine (*mepivacaine* group); (b) 30 mL of 0.5% bupivacaine (*bupivacaine* group); or (c) a freshly prepared mixture of 15 mL of 1.5% mepivacaine and 15 mL 0.5% bupivacaine (*combination* group). No adjuvants were added to the study solutions.

### Block Procedure

All blocks were performed preoperatively. Supplemental oxygen and standard ASA monitoring were used throughout the study period. Intravenous sedation (midazolam 0.05 to 0.08  $\mu$ g/kg) and analgesia (alfentanil 250 to 500  $\mu$ g) were administered for patient comfort while maintaining meaningful verbal contact (score of  $\leq 4$  on

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the Sedation–Agitation Scale).<sup>8</sup> A 38-mm linear ultrasound transducer was placed over the skin of the neck (LOGIQ e, GE Healthcare, Milwaukee, WI) approximately 3 cm superior to the clavicle to visualize the brachial plexus at the level at which all 3 trunks of the brachial plexus were clearly seen. After skin infiltration with 3 mL of 2% lidocaine, a 50-mm-long, 22-gauge stimulating needle (Stimuplex<sup>®</sup>; B. Braun Medical Inc., Bethlehem, PA) was inserted through the skin at the lateral aspect of the transducer. The needle was advanced in-plane in a lateral-to-medial direction under direct vision until the tip of the needle was in close proximity to the superior trunk of the brachial plexus. A nerve stimulator (Tracer II<sup>®</sup>; LifeTech Inc., Stafford, TX) initially set to deliver 0.7 mA (0.1 ms; 2 Hz) was used to elicit a motor response of the deltoid or upper-limb muscles, thereby confirming ultrasound-guided localization of the plexus. After the needle was determined to be in the correct position using ultrasound guidance, the lowest current threshold of motor response was sought; if the motor response was present at <0.2 mA, the needle was withdrawn 1 mm at a time until the motor threshold was >0.2 mA. After negative aspiration of blood, an initial injection of 1 mL of LA was administered to confirm proper needle placement, followed by deposition of 5-mL aliquots at the superior trunk with intermittent aspiration between each injection. The injection pressure was kept at ≤15 psi using an in-line injection pressure monitor to standardize the injection technique and prevent variations in the spread of the LA caused by variation in injection force applied during injection (Bsmart<sup>®</sup>; Concert Medical LLC, Norwell MA).

During the surgical procedure, sedation was maintained throughout the procedure using a propofol infusion (25 to 50  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). Intravenous fentanyl was administered in increments of 25  $\mu\text{g}$  at the discretion of the anesthesiologist if deemed necessary for patient comfort. Blocks were considered successful if surgery could be completed without the use of general anesthesia, defined as a propofol requirement of 50  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  or more, or any use of nitrous oxide or volatile drugs. After surgery, the propofol infusion was discontinued and the patients were transferred to the postanesthesia care unit (PACU).

### Block Assessment

The *block onset time* was determined by an observer blinded to the LA group starting from injection of the LA (time = 0 minutes) and every 5 minutes thereafter until 20 minutes after injection. Motor strength was evaluated in axillary, musculocutaneous, radial, median, and ulnar nerves by testing deltoid, biceps, triceps, flexor, and extensor digitorum using a 3-point scale: 0 = no visible or palpable contraction, 1 = weak movement, 2 = able to move against resistance. Successful motor block was defined as an inability to abduct the arm from a neutral position against minimal resistance (blockade of superior trunk). Sensory block was assessed with a pinprick test (using a paper clip) by asking patients to rate sensation as “normal” (score 2), “dull” (score 1), or “no sensation” (score 0). Successful sensory block was defined as an absence of sensation in the axillary territory. The sensory evaluation included territories of the axillary, musculocutaneous, radial, median,

ulnar, and medial antebrachial cutaneous nerves. Sensory evaluation was repeated upon arrival to the PACU and at 1 and 2 hours after completion of surgery. Pain scores from a verbal rating scale (numerical rating scale [NRS-11]: 0 = no pain, 10 = worst pain imaginable) were recorded by PACU nurses blinded to the study goals. Nurses were instructed to administer IV fentanyl 25  $\mu\text{g}$  every 5 minutes as needed for a NRS score higher than 3.

The *duration of the block* was determined by phone interview conducted by blinded research staff during follow-up calls to the patients at 24 and 48 hours after the block. Patients were instructed to record on a preprinted card the time at which they could first flex their elbows; this was defined as the end point for duration of the block. Arm flexion at the elbow was chosen as an unambiguous test to evaluate motor function during the phone interview, and patients were instructed to attempt to flex their arms every 30 minutes after discharge from the hospital. Likewise, the first occurrence of pain as perceived by the patient (“When did you first start feeling the pain?”) was used as a surrogate for return of the sensory function. Occurrences of any adverse events as reported by patients were also collected during the phone interviews.

### Statistical Analysis

A review of the literature revealed that published durations of postoperative analgesia for bupivacaine 0.5% and mepivacaine 2% are  $880 \pm 312$  minutes and  $251 \pm 47$  minutes, respectively<sup>9</sup>; no data on the duration of a bupivacaine/mepivacaine combination were available. Our principal research question was whether there was any difference in duration of action between the bupivacaine and combination groups. Assuming the duration of a 1:1 mixture would be the average of both individual durations, a calculation of sample size indicated that the required number of subjects was 20 per group, with a significance level  $\alpha$  of 0.05 and type II error  $\beta$  of 0.2. Given a predicted dropout rate of 10%, we chose to enroll 23 patients per group. Using the method of sealed envelopes, we randomly assigned patients to bupivacaine, mepivacaine, and the combination groups.

Continuous data are presented as mean  $\pm$  SD, and discrete data as  $n$  (%). Tests for differences among groups included analysis of variance (ANOVA) (continuous variables) and the Kruskal–Wallis test (discrete variables). Kaplan Meier life table analysis was performed for motor and sensory block duration. All tests were 2 sided, and  $P$  values <0.05 were considered statistically significant. Statistical analyses were performed with SAS version 9.1.3 (SAS Corporate Statistics, Cary, NC).

### RESULTS

Sixty-nine patients were enrolled in the study. One patient in the mepivacaine group was operated on before completion of the evaluation and therefore was not included in the analysis. In addition, 2 patients in the bupivacaine and 2 in combination groups could not be contacted the following day. Thus, data were analyzed for 22 patients in the mepivacaine group, 21 patients in the bupivacaine group, and 21 patients in the combination group who completed

**Table 1. Patients' Baseline Information**

	<b>Bupivacaine 0.5%</b> ( <i>n</i> = 21)	<b>Combination</b> ( <i>n</i> = 21)	<b>Mepivacaine 1.5%</b> ( <i>n</i> = 22)
Age (years)	54.3 ± 10.2	55.8 ± 15.3	57.3 ± 12.2
Gender (female/male)	15/8	15/8	16/8
Body mass index	30.0 ± 6.8	27.6 ± 5.5	28.8 ± 7.1
Stimulating current (mA)	0.62 ± 0.26	0.48 ± 0.17	0.54 ± 0.14
Duration of nerve block (minutes)	6.2 ± 3.7	6.4 ± 2.0	7.9 ± 3.8
Duration of shoulder surgery (minutes)	74.3 ± 39.8	82.2 ± 49.3	77.6 ± 23.5
Midazolam (mg)	4.0 ± 2.0	4.1 ± 2.2	4.0 ± 2.0
Propofol (mg)	188 ± 111	225 ± 207	239 ± 198
Fentanyl dose (μg)	119 ± 69	80 ± 60	109 ± 69

There were no significant differences among groups (*P* value calculated using Kruskal–Wallis Test with 2 tails).

**Table 2. Postblock Evaluation**

	<b>Bupivacaine 0.5%</b> ( <i>n</i> = 21)	<b>Combination</b> ( <i>n</i> = 21)	<b>Mepivacaine 1.5%</b> ( <i>n</i> = 22)	<b><i>P</i> value</b>
Onset time of superior trunk (minutes) (indicated by sensory assessment of axillary nerve)	10.0 ± 5.1	11.3 ± 5.3	8.7 ± 4.3	0.21*
Onset time of superior trunk (minutes) (indicated by inability to abduct arm against resistance)	7.3 ± 4.0	9.3 ± 4.9	7.0 ± 3.6	0.14*
Sensory block of inferior trunk @ postblock 20 minutes (Indicated by sensory assessment of ulnar nerve)	2/23 (8.7%)	2/23 (8.7%)	8/24† (33.3%)	0.03*
Sensory block of inferior trunk @ postsurgical 1 hour (Indicated by sensory assessment of ulnar nerve)	3/23 (13.0%)	6/23 (26.1%)	10/24† (41.7%)	0.03*
Motor function recovery time (hours) (Indicated by elbow flexion)	16.4 ± 9.4‡	11.5 ± 4.7§	6.0 ± 4.2	<0.001* 0.01§ 0.03‡
Duration of analgesia (hours)	14.0 ± 6.2‡	10.3 ± 4.9§	4.9 ± 2.4	<0.001* <0.001§ 0.01‡
Pain intensity (NRS-11) at postsurgical 24 hours	6.8 ± 2.1	7.7 ± 2.5	7.3 ± 1.9	0.40*

NRS = numerical rating scale.

\*Overall significance among the 3 groups.

†Mepivacaine vs. bupivacaine and combination groups.

‡Bupivacaine vs. combination group.

§Mepivacaine vs. combination group.

the study protocol. Demographic data and dose of premedication were similar among the groups (Table 1). All blocks resulted in successful surgical anesthesia; none of the patients required conversion to general anesthesia.

Duration of motor block for the combination group (11.5 ± 4.7 hours) was between that for the bupivacaine group (16.4 ± 9.4 hours) and the mepivacaine group (6.0 ± 4.2 hours), both of which were statistically significant differences (Table 2, Fig. 1). The onset of sensory and motor blocks of the axillary nerve (superior trunk) was similar among the groups; all patients had complete block of the axillary nerve at 20 minutes after injection (Table 2). In contrast, frequency of complete blockade of the ulnar nerve (inferior trunk) was higher in the mepivacaine group than in the other 2 groups. In the mepivacaine group, 33% had block of the inferior trunk at 20 minutes in comparison with 8.7% in the bupivacaine group and in the combination group (*P* = 0.03). At 1 hour after surgery, 42% of the mepivacaine group demonstrated an ulnar nerve sensory block in comparison with 26% of the combination group (*P* = 0.03) and only 13% of the bupivacaine group (*P* = 0.03). Duration of sensory block analgesia was also significantly different among the groups (Table 2, Fig. 2).

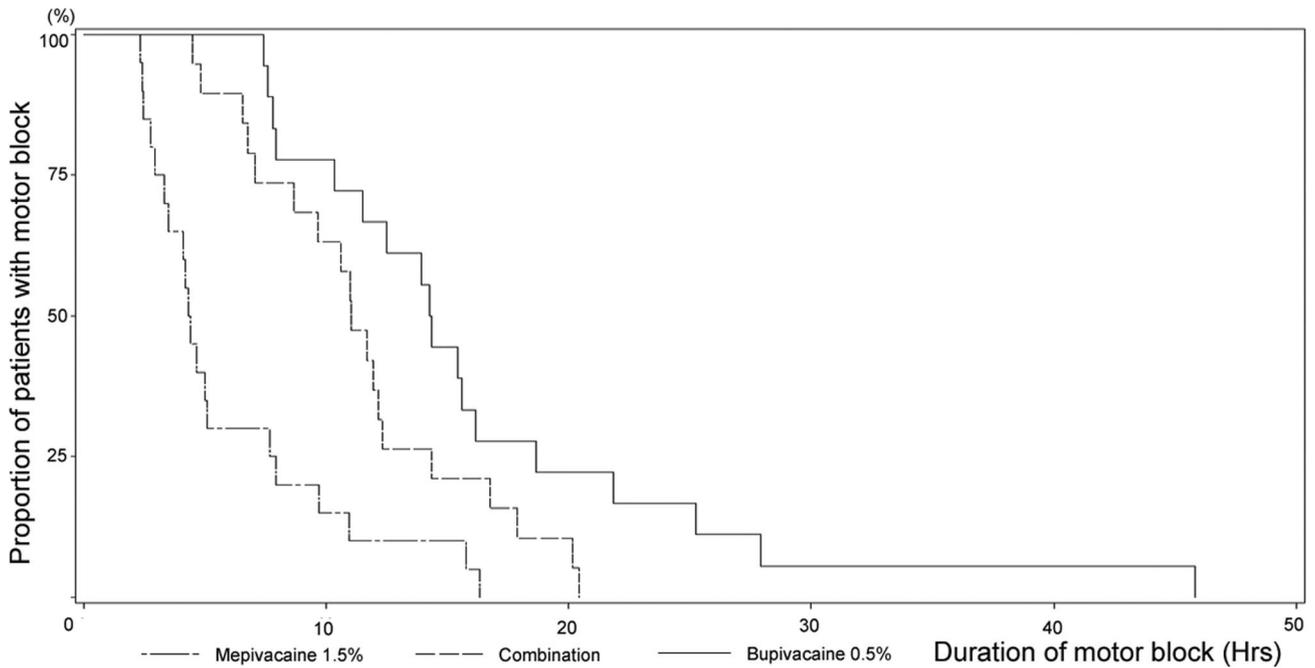
In the PACU, all patients reported verbal rating scores in the range of 0 to 3, and no patient required IV pain

medication. At 24 hours postoperatively when all blocks had resolved, verbal rating scores were similar among groups (Table 2). No adverse events were reported.

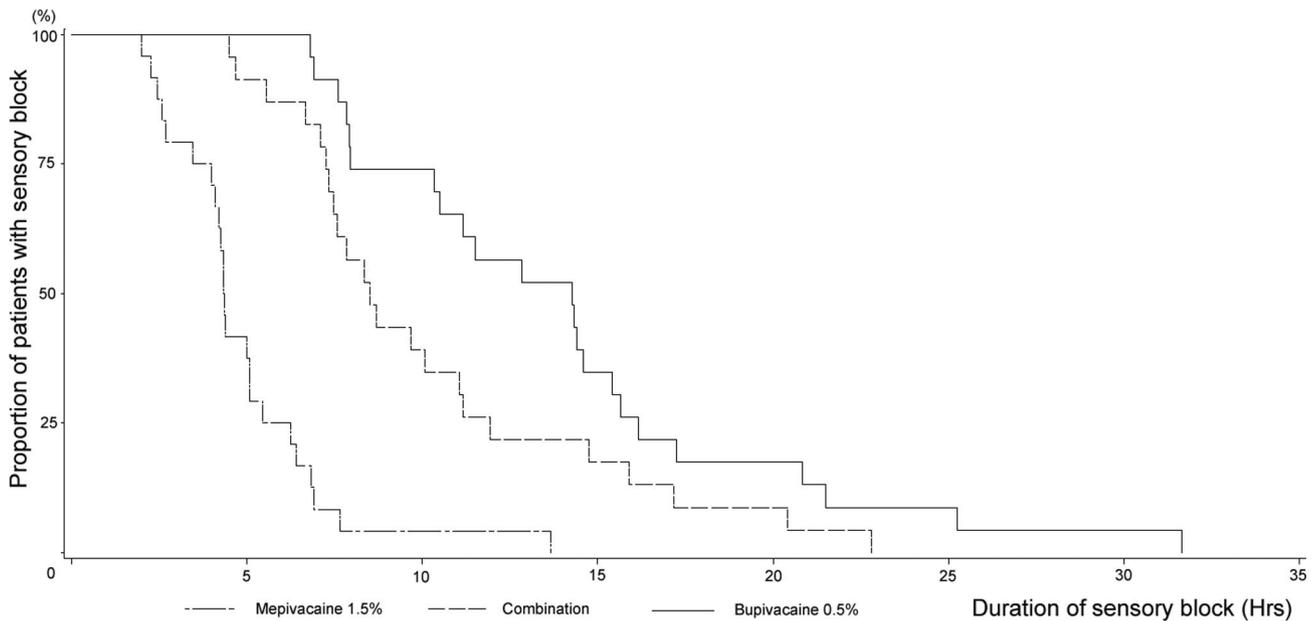
## DISCUSSION

Our data indicate that a combination of mepivacaine 1.5% and bupivacaine 0.5% results in a similar block onset to either LA alone. Blockade with the mepivacaine–bupivacaine mixture lasted significantly longer than did block with mepivacaine 1.5% alone and significantly shorter than did the block with bupivacaine 0.5% alone.

Combining LAs for regional anesthesia has been reported as early as 1952 and remains common in current clinical practice.<sup>10,11</sup> In 1972, Moore et al. described the safety and efficacy of combining tetracaine (a long-acting LA) with several intermediate-acting LAs, such as lidocaine and mepivacaine in >10,000 regional anesthetic procedures.<sup>12</sup> In their publication that included a heterogeneous series of nerve blocks, the authors suggested that the mixtures of LA compensated for the drawbacks of each drug; however, no randomized studies were conducted to document the claimed benefits. Bromage and Gertel later studied a mixture of carbonated lidocaine 1% and bupivacaine 0.25% for supraclavicular block and found that the combined solution demonstrated a more rapid onset, but



**Figure 1.** Survival analysis for motor block regression.



**Figure 2.** Survival analysis for sensory block regression.

shorter duration, than did bupivacaine 0.25% alone.<sup>7</sup> Unfortunately, the use of a very large volume of injectate (60 mL) in the mixture group, in comparison with 25 to 50 mL in the 6 other LA groups, both limited the interpretation of their data and made the findings less relevant in the setting of modern clinical practice.

The lack of consistency in the findings of previous studies may be due to differences in methodology, such as methods of evaluation, site of administration, type of LAs studied, additives (e.g., epinephrine), and concentration of each individual drug used.<sup>13</sup> Importantly, monitoring of the LA disposition via ultrasound guidance was not

available until recently, and prior investigators relied on more subjective methods of nerve location. As such, their conflicting findings may have resulted from variability in LA spread. Thus, our study is the first to compare the combination of short- and long-acting LAs with each drug itself during ISB under ultrasound monitoring of LA distribution. However, Cuvillon et al. compared ropivacaine and bupivacaine alone with ropivacaine-lidocaine and bupivacaine-lidocaine solutions for (nonultrasound guided) femoral and sciatic blockades.<sup>14</sup> These authors reported more rapid onset and shorter duration with the combined solutions, results that differ from ours. Because

these investigators did not include an “intermediate-acting only” group, it is unknown how onset with lidocaine alone might compare with the combined solution.

An unexpected finding was the higher frequency of sensory blockade of the inferior trunk with mepivacaine 1.5% alone despite our strict standardization of needle insertion and injection pressure (force) applied. Because we primarily ensured the spread of the LA in the vicinity of the upper trunk, it is possible that mepivacaine may have a greater intrinsic ability to spread because of its greater hydrophilicity, in comparison with the more lipophilic bupivacaine. Lipophilicity is related to the degree of tissue binding and sequestration, and therefore a lipophilic drug may be less likely to travel by bulk flow than would a hydrophilic drug.<sup>15</sup>

The mean duration of motor block in all 3 groups was longer than that of sensory block, a finding that although somewhat counterintuitive, was also reported by Winnie et al.<sup>16</sup> The authors opined that this was caused by the somatotropic organization of nerve fibers within the fascicles at the level of the trunks (i.e., outermost motor fibers and innermost sensory fibers).

The apparent lack of pharmacodynamic benefits when using combined solutions in our study has important clinical implications. Drug errors may increase when using LA mixtures, because LA must be drawn from separate ampules or vials to be mixed.<sup>17</sup> Although some authors assert that severe systemic toxicity may decrease when using LA mixtures,<sup>18</sup> LA toxicity appears to be additive.<sup>19,20</sup> The report of a case of sudden cardiovascular collapse with a “safe” mixture of ropivacaine (1.5 mg/kg) and lidocaine (3.7 mg/kg) underscores this point.<sup>21</sup> No patients in our study showed adverse effects; thus we were unable to examine the safety of our bupivacaine–mepivacaine combination in comparison with either drug alone. Moreover, the current trend with the ultrasound-guided brachial plexus block is to use much smaller mass and volumes of LA.<sup>22</sup> If such trends continue, any potential benefits of the mixtures with regards to their lower risk of systemic toxicity will diminish even further.

Our study has several limitations. First, the volume of LA used (30 mL) may have offset any difference that may have been observed with a smaller volume (e.g., <20 mL). Second, durations of both the sensory and motor block involved subjective patient interpretation of symptoms, a common strategy with studies in outpatients. We used surrogate outcomes of first arm flexion and time to first pain, both of which are somewhat subjective. Arm flexion could be influenced by pain, sleep, and inattention to return of function. Likewise, patient variability in pain perception and tolerance could have confounded the results for sensory duration.

In summary, for ultrasound-guided ISB, a combination of mepivacaine 1.5% and bupivacaine 0.5% results in a similar block onset to either mepivacaine 1.5% or bupivacaine 0.5% alone. The blockade with the mepivacaine–bupivacaine mixture lasted significantly longer than did block with mepivacaine 1.5% alone and significantly shorter than did the block with bupivacaine 0.5% alone. Consequently, the desired duration of blockade may be a

more important criterion for selecting LA mixture for ISB rather than the speed of onset. ■■

#### DISCLOSURES

**Name:** Jeff Gadsden, MD, FRCPC, FANZCA.

**Contribution:** This author helped design the study, conduct the study, analyze the data, and write the manuscript.

**Attestation:** Jeff Gadsden has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

**Conflict of Interest:** Jeff Gadsden reported no conflicts of interest.

**Name:** Admir Hadzic, MD, PhD.

**Contribution:** This author helped design the study, conduct the study, analyze the data, and write the manuscript.

**Attestation:** Admir Hadzic has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**Conflict of Interest:** Admir Hadzic has equity interest in Macosta Medical USA. Macosta Medical are the manufacturers of the BSmart pressure transducer device.

**Name:** Kishor Gandhi, MD, MPH.

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**Attestation:** Kishor Gandhi has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**Conflict of Interest:** Kishor Gandhi reported no conflict of interest.

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**Attestation:** Ali Shariat has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**Conflict of Interest:** Ali Shariat reported no conflicts of interest.

**Name:** Daquan Xu, MB, MPH.

**Contribution:** This author helped design the study, conduct the study, analyze the data, and write the manuscript.

**Attestation:** Daquan Xu has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**Conflict of Interest:** Daquan Xu reported no conflicts of interest.

**Name:** Thomas Maliakal, MD.

**Contribution:** This author helped conduct the study.

**Attestation:** Thomas Maliakal has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**Conflict of Interest:** Thomas Maliakal reported no conflict of interest.

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**Contribution:** This author helped conduct the study.

**Attestation:** Vijay Patel has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**Conflict of Interest:** Vijay Patel reported no conflict of interest.

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