Combined Versus Sequential Injection of Mepivacaine and Ropivacaine for Supraclavicular Nerve Blocks

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Background: An ideal local anesthetic with rapid onset and prolonged duration has yet to be developed. Clinicians use mixtures of local anesthetics in an attempt to combine their advantages. We tested the hypothesis that sequential supraclavicular injection of 1.5% mepivacaine followed 90 secs later by 0.5% ropivacaine speeds onset of sensory block and prolongs duration of analgesia compared with simultaneous injection of the same 2 local anesthetics.

Methods: We enrolled 103 patients undergoing surgery suitable for supraclavicular anesthesia. The primary outcome was time to 4-nerve sensory block onset in each of the 4 major nerve distributions: median, ulnar, radial, and musculocutaneous. Secondary outcomes included time to onset of first sensory block, time to complete motor block, duration of analgesia, pain scores at rest and with movement, and total opioid consumption. Outcomes were compared using the Kaplan-Meier analysis with the log-rank test or the analysis of variance, as appropriate.

Results: Times to 4-nerve sensory block onset were not different between sequential and combined anesthetic administration. The time to complete motor block onset was faster in the combined group as compared with the sequential. There were not significant differences between the 2 randomized groups in other secondary outcomes, such as the time to onset of first sensory block, the duration of analgesia, the pain scores at rest or with movement, or the total opioid consumption.

Conclusions: Sequential injection of 1.5% mepivacaine followed 90 secs later by 0.5% ropivacaine provides no advantage compared with simultaneous injection of the same doses.

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The choice of anesthetic technique combined with a suitable plan for postoperative analgesia can facilitate early discharge, improve patient comfort, and increase overall satisfaction. Patients having painful procedures under general anesthesia have a 2- to 5-fold greater risk of unplanned overnight admissions compared with those having regional anesthesia.[1] Regional anesthetic techniques and peripheral nerve blocks are especially favored for surgeries on the extremities.[1–4] For example, supraclavicular brachial plexus blocks are commonly performed for upper-extremity surgeries.

Both rapid onset of the block and prolonged postoperative analgesia are desired characteristics of regional anesthesia. The choice of local anesthetics or combinations thereof can greatly influence the effectiveness of the block, onset time, duration of postoperative analgesia, need for opioid use, and patient satisfaction.[2] Mepivacaine and ropivacaine are commonly used in peripheral nerve blocks, their drawbacks being a short duration with 1.5% mepivacaine[5–7] and a delayed onset with 0.5% ropivacaine.[8] A higher concentration of a local anesthetic such as ropivacaine 0.75% has a quicker onset, but at the cost of a greater potential toxicity.[9]

An ideal local anesthetic with high potency, low toxicity, rapid onset, and prolonged duration does not exist yet. Investigators have therefore tried mixtures of local anesthetics in an attempt to combine their advantages—with conflicting results.[10–12] When combinations of anesthetics are used, the drugs are usually mixed and injected simultaneously. For example, Moore et al[13] showed that mixing local anesthetics is safe in humans and that the combination can have desirable properties of both medications without producing toxicity.

A potential problem is that mixing drugs dilutes the effects of each. Thus, a mixture of a rapid-onset drug such as mepivacaine with a long-acting one such as ropivacaine may well result in slower onset than mepivacaine alone and shorter duration of action than ropivacaine alone. In contrast, sequential administration of the same amounts of the same drugs may preserve the desirable features of each. We therefore tested the hypothesis that sequential supraclavicular injection of 1.5% mepivacaine followed 90 secs later by 0.5% ropivacaine provides a quicker onset and a longer duration of analgesia than an equidose combination of the 2 local anesthetics.

MATERIALS AND METHODS

The study was approved by the institutional review board of the Cleveland Clinic with the plan to enroll 116 patients, aged 18 to 70 years, who were scheduled to undergo an upper-extremity procedure suitable for supraclavicular anesthesia. These procedures were expected to be associated with considerable postoperative pain. Patients were excluded from the study if they had a history of coagulopathy, infection at the needle insertion site, severe chronic obstructive pulmonary disease, neuropathy, pneumothorax, contralateral diaphragmatic paralysis, routine opioid use, or inability to obtain adequate ultrasound images of the supraclavicular area or were pregnant at the time.

Protocol

Randomization was generated by the plan procedure in SAS statistical software (SAS Institute, Inc, Cary, NC), within

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randomly sized blocks and was administered via sealed sequentially numbered opaque envelopes. Envelopes were opened just before blocks were performed by an attending anesthesiologist. Patients were assigned to either (1) combined group-ropivacaine and mepivacaine mixture: 1:1 volume mixture of 1.5% mepivacaine and 0.5% ropivacaine in 2 syringes (labeled 1 and 2) with 15 mL in each (total, 30 mL) injected in immediate sequence; or (2) sequential group—mepivacaine followed by ropivacaine: syringe 1 containing 15 mL of 1.5% mepivacaine, syringe 2 containing 15 mL of 0.5% ropivacaine (total, 30 mL); syringe 2 was injected with a 90-sec delay after injection of syringe 1.

We used a previously described ultrasound-guided supraclavicular approach.[14] All blocks were performed under the supervision of attending anesthesiologists proficient in ultrasound-guided regional anesthesia. The patient was positioned supine, with the head turned 45 degrees to the contralateral side after the standard sterile prep and drape. An ultrasound probe was placed in the coronal oblique plane in the supraclavicular fossa. The subclavian artery was identified, with the brachial plexus located immediately superficial and lateral to it, and the hyperechoic rib and pleura immediately deep to the artery.

A 5-cm-long, 22-gauge insulated needle (Stimuplex; B Braun Medical, Bethlehem, Pa) with nerve stimulation was advanced with the "in-plane" technique toward the junction of the first rib and the subclavian artery. Distal motor response in the surgical limb at a current of less than 0.5 mA at 0.1-millisecond duration was used as a confirmation of adequate needle position. Adequate spread of local anesthetic solution around the plexus was confirmed with ultrasound imaging. If necessary, the needle was repositioned to achieve adequate spread. In the sequential group, after injecting 15 mL of 1.5% mepivacaine (contents labeled syringe 1), we waited 90 secs and then injected the contents of syringe 2 (0.5% ropivacaine). In the combined group, with similar contents in the 2 syringes, the injection was performed without a 90-sec delay.

During surgery, patients received sedation at the discretion of the attending anesthesiologist. Patients with a failed block (defined as pain with surgical incision or manipulation) were administered general anesthesia and analyzed on an intention-to-treat basis.

Measurements

The primary outcome was time to 4-nerve sensory block onset, which was defined as time from the completion of anesthetic injection until development of sensory block to sharp pain in each of the 4 major nerve distributions: median, ulnar, radial, and musculocutaneous. Secondary outcomes were time to onset of first sensory block, time to complete motor block, duration of analgesia, 11-point verbal response pain scores at rest and with movement, and total opioid consumption.

Demographic variables (age, sex), morphometric measurements (weight, height), and the specific type of procedure were recorded. The specific intraoperative management strategies (ie, general anesthesia vs sedation) were recorded, along with total doses of fentanyl, midazolam, morphine, and propofol.

After performance of the block, patients were evaluated by a trained observer who was blinded to group assignment. The initial assessments of sensation to pinprick were at 30-sec intervals until it was determined that the block had started taking effect in the median, ulnar, radial, or musculocutaneous nerve distribution, as compared with the contralateral side. The time to onset of first sensory block was considered to be the time from complete injection of local anesthetic to the development of sensory block in any of the 4 nerve distributions. After the onset time was determined, the assessment frequency was at 1-min intervals until the development of 4-nerve sensory block in each of the 4 distributions mentioned above. Motor block was assessed by evaluation of motor strength in the muscle groups supplied by the above nerves, on a scale used by Marhofer et al,[15] where 1 = motor paralysis, 2 = decreased motor function, and 3 = normal motor function.

The severity of postoperative pain was assessed by an observer blinded to treatment using a 0- to 10-point verbal response score (VRS) at 10-min intervals for 30 mins in the postanesthesia care unit (PACU). Patients reporting pain scores greater than 2 were administered intravenous morphine (1–2 mg) every 5 mins until they were comfortable. After discharge from the PACU, supplemental analgesia for inpatients consisted of acetaminophen 325 mg with oxycodone 5 mg orally every 4 hrs as needed for pain for VRS greater than 4, administered by the nurse caring for the patient. Pain unrelieved by oral medication (VRS persistently >4) was treated with intravenous morphine. Outpatients received a prescription for oral acetaminophen with oxycodone. Patients were instructed to delay administration of analgesics until they experienced pain rather than taking oral analgesics prophylactically. The duration of analgesia was measured as the time from the onset of 4-nerve sensory block until the first request for an analgesic. This included the intraoperative and the PACU period. Information on total analgesic consumption was obtained during a 3-day follow-up after surgery and converted to morphine equivalents.

A blinded observer interviewed patients each day for 3 postoperative days, either in the hospital or by telephone. Data collection included analgesic duration, maximum VRS with rest and movement, and total opioid consumption. The time for first analgesic was obtained either from patients after discharge or from the medical record in those remaining hospitalized. The times and VRS scores for secondary outcomes were based on patient reporting of the corresponding events at the daily interview.

Statistical Analysis

Standard descriptive statistics were used to compare the randomized groups on baseline variables. Any covariables with a standardized difference greater than 0.3 in absolute value were adjusted for in the analysis. Analysis was intent-to-treat.

Primary Outcome

The average effect of the sequential injection of mepivacaine followed by ropivacaine compared with combination of mepivacaine and ropivacaine on time to 4-nerve sensory block onset was assessed by the Kaplan-Meier analysis with the log-rank test stratifying on imbalanced categorical baseline variables. In addition, a multivariable Cox regression model adjusting for any imbalanced baseline variables was used to estimate a hazard ratio with 95% confidence interval (CI) for the difference between groups on time reaching onset of 4-nerve sensory block. Patients who had failed block were marked as failure and were censored at the observed worst outcome of any patient.

In addition, we performed a sensitivity analysis using the start of anesthetic injection as the start point for the time to 4-nerve sensory block onset. We compared the 2 groups with use of the log-rank test with stratifying on imbalanced categorical baseline variables. The corresponding hazard ratio and 95% CI were estimated.

The proportional hazards assumption was assessed by visualizing whether the log hazard over time was parallel for levels of categorical variable and by Kolmogorov-type supremum test for continuous covariable(s).

TABLE 1. Patients Characteristics and Anesthetic Drugs

Variables	Sequential Group (n = 51)	Combined Group (n = 52)	Standardized Difference*
Male sex, n (%)	27 (53)	19 (37)	0.33
Age, mean (SD), y	46 (14)	49 (13)	−0.22
Body mass index, mean (SD), kg/m^2	29 (6)	30 (6)	−0.15
Fentanyl, median (Q1, Q3), μg	0 (0, 19)	0 (0, 31)	−0.12
Alfentanil, median (Q1, Q3), mg	0 (0, 1)	0 (0, 0)	0.22
Midazolam, mean (SD), mg	3 (1)	2 (2)	0.07

*Standardized effect sizes (*D*) are defined as the difference (sequential group − combined group) in means (symmetric continuous covariables), difference of mean ranks (skewed continuous covariables), or difference in proportions (binary covariables) divided by the average SD. We deemed covariables with a standardized difference greater than 0.3 in absolute value as indication of imbalance.

This clinical trial had a group sequential design,[16] allowing for early stopping if the interim analysis data revealed enough evidence for either efficacy or futility. Interim analyses at the first 58 patients and at 103 patients (logistically necessitated final analysis) were conducted to assess efficacy and futility using the γ spending function (γ = −4 for efficacy and −2 for futility). The *P* value (corresponding *Z* statistic) boundaries for efficacy and futility at the interim analysis with 103 patients were $P \leq 0.031$ ($Z \geq 2.157$) and $P > 0.09$ ($Z < 1.695$), respectively. Confidence intervals were adjusted for the interim analysis by using the group sequential critical value ($z = 2.157$ at n = 103) for significance instead of the traditional *Z* statistic of 1.96 in the 95% CI formula. East 5 statistical software (Cytel Inc, Cambridge, Mass) was used to design the trial and conduct the interim monitoring.

Secondary Outcomes

Outcomes of time to complete motor block, time to onset of first sensory block, and duration of analgesia were analyzed using the Kaplan-Meier analysis with the log-rank test. Cox proportional hazards regression was used to summarize the hazard ratio (95% CI), unless the assumption of proportional hazards appeared violated. Patients who had a failed block were marked as failure and were censored at the observed worst outcome of any patient. Also, for duration of analgesia, patients who did not take any analgesic medication were censored at 48 hrs.

We compared the 2 groups on the maximum verbal pain scores both at rest and with movement and total opioid consumption (after logarithm transformation) by analysis of covariance with adjustment for imbalanced covariables. The estimated difference between groups, 95% CI for difference, and *P* value were reported.

SAS statistical software version 9.2 for Windows (SAS Institute, Inc) was used for all analyses and R statistical software version 2.8.1 for Windows (the R Foundation for Statistical Computing, Vienna, Austria) was used for all graphics.

Sample Size Considerations

Sample size was based on being able to detect a true difference of 4 mins or more between the sequential and combined groups on the primary outcome of 4-nerve sensory block onset. Chan et al[14] reported that the mean sensory perception time was observed as 167 (SD, 5.5) mins in n = 46 supraclavicular brachial plexus block patients. We conservatively estimated the SD of the outcome to be approximately 6.5 mins for our study. We would thus need 116 total patients to have 90% power at the 0.05 significance level to detect a difference of 4 mins (effect size of 0.60 SD) or more between groups. We were clinically interested in differences in this moderate range and larger. Calculations included an interim analysis for efficacy and futility when the primary outcome was available on the first 50% of the randomized patients (n = 58 total).

RESULTS

Three investigators—including the principal investigator—left the institution after 103 of the planned 116 patients were enrolled. The Executive Committee, without access to interim results, decided to stop enrollment at that point on a feasibility basis. However, the group sequential design was maintained by appropriate adjustment in the analysis. Two patients in the sequential group had a failed block, required general anesthesia, and were analyzed on an intention-to-treat basis. Apart from the 2 failed blocks, all patients had adequate surgical anesthesia and were successfully operated on under regional anesthesia.

Most covariables were visually balanced between the randomized groups on most variables (Table 1). However, patients in the sequential group were more likely to be male, with a standardized difference greater than 0.3 in absolute value (combined group: 37% and sequential group: 53%). We thus adjusted for sex in our analyses.

Primary Outcome

With n = 103 patients, no difference between the sequential and combined injection of the 2 local anesthetics on time to 4-nerve sensory block onset was found, and the log-rank $P = 0.14$ crossed the futility boundary of $P > 0.09$. However, the combined group was superior using the Wilcoxon test ($P = 0.02$ crossing the efficacy boundary of $P \leq 0.031$), which is more sensitive to earlier points in time. Both analyses are informative, but the log-rank test should be considered primary because it best summarizes the overall time-to-event curves. The Kaplan-Meier–estimated median time to onset of all 4 nerve sensory blocks was 10 mins with the sequential injection versus 7.5 mins with the combined injection. Figure 1 shows the Kaplan-Meier

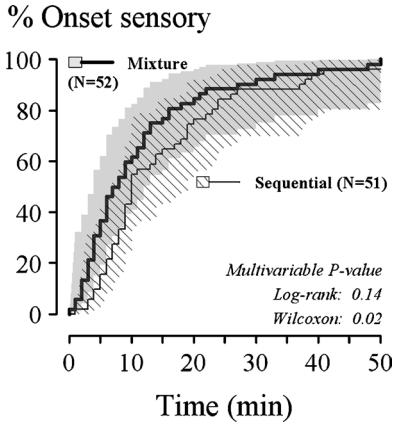

FIGURE 1. Plot of the Kaplan-Meier density function estimates and equal-precision 95% CIs of time to 4-nerve sensory block onset for the sequential group (n = 51) and the combined group (n = 52) separately. $P = 0.14$ (log-rank test, main result), and $P = 0.02$ (Wilcoxon test), stratifying on sex.

TABLE 2. Relationships Between Treatment (Sequential vs Combined) and Outcomes

	Sequential Group (n = 51)	Combined Group (n = 52)	Hazard Ratio* (95% Interim Adjusted CI)†	P‡
	Median (Q1, Q3)			
Primary outcomes				
Time to 4-nerve sensory block onset,§ min	10 (7, 20)	7.5 (4, 14)	0.71 (0.46–1.09)	0.14
Secondary outcomes				
Time to complete motor block,‖ min	19 (8, 29)	10 (5, 18)	0.71 (0.46–1.11)	0.02
Onset of first sensory block, min	0 (0, 1)	0 (0, 0)	N/A¶	0.66
Duration of analgesia,# hr	11 (7, 20)	9 (6, 22)	N/A¶	0.15
			Difference Means** (95% Interim Adjusted CI)†	
Max verbal pain score (at rest)	4 (1, 6)	4 (2, 7)	−0.3 (−1.6 to 1.0)	0.60††
Max verbal pain score (with movement)	5 (2, 7)	5.5 (3.5, 8)	−0.6 (−1.9 to 0.7)	0.34††
Total opioid consumption,‡‡ mg	30 (8, 83)	38 (11, 90)	0.9 (0.2 to 4.1)§§	0.88††

*Instantaneous risk ratio within the same sex (sequential vs combined).

†Using Z of 2.157 for rejecting the null hypothesis at the interim analysis (n = 103).

‡Adjusting for sex by log-rank test, unless specified.

§From the completion of injection to complete onset of sensory block (see Materials and Methods).

‖Time from the completion of injection until decreased motor function (see Materials and Methods).

¶Assumption of proportional hazards appeared violated.

#Time from the complete onset of sensory block until first request for an analgesic.

**Difference in means (sequential − combined), after adjusting for sex.

††Analysis of covariance.

‡‡In morphine equivalent dose.

§§Ratio of geometric means (sequential vs combined), after adjusting for sex.

estimates of time to 4-nerve sensory block onset for the sequential and the combined groups with equal-precision 95% confidence bands.

The 4-nerve sensory block onset was an estimated 29% less likely (95% CI of [52% less likely, 5% more likely]) at any given time point when using the sequential injection relative to using the combined injection, after stratifying on sex (Table 2).

Sensitivity Analysis

No difference was found between the 2 groups in the time to 4-nerve sensory block onset, where the time was counted from the start of anesthetic injection ($P = 0.30$, log-rank test stratifying on sex, and also crossing the futility boundary of $P > 0.09$).

Secondary Outcomes

The time to complete motor block onset was faster in the combined group as compared with the sequential group ($P = 0.02$, log-rank test stratifying on sex; Fig. 2). Furthermore, there was no significant differences in either the time to onset of first sensory block ($P = 0.66$; Fig. 3) or duration of analgesia ($P = 0.15$; Fig. 4) by log-rank test after adjusting for sex.

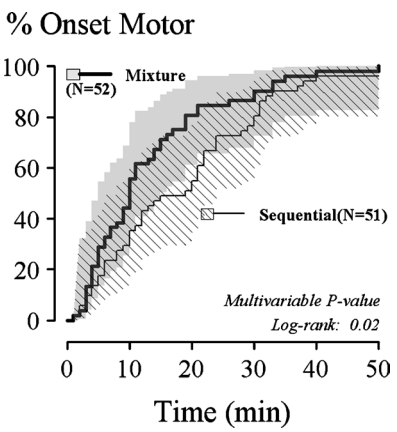

FIGURE 2. Plot of the Kaplan-Meier density function estimates and equal-precision 95% CIs of time to onset of complete motor block for the sequential group (n = 51) and the combined group (n = 52) separately. $P = 0.02$ (log-rank test, stratifying on sex).

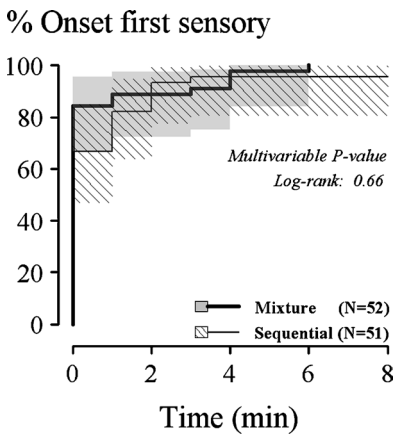

FIGURE 3. Plot of the Kaplan-Meier density function estimates and equal-precision 95% CIs of time to onset of first sensory block for the sequential group (n = 51) and the combined group (n = 52) separately. $P = 0.66$ (log-rank test, stratifying on sex).

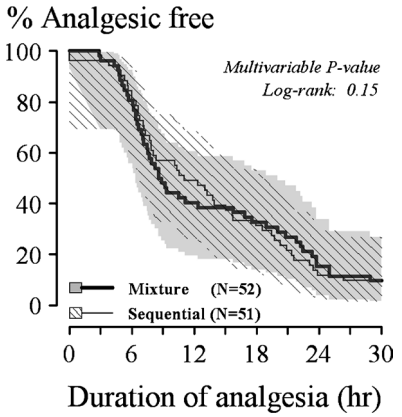

FIGURE 4. Plot of the Kaplan-Meier density function estimates and equal-precision 95% CIs of duration of analgesic free for the sequential group (n = 51) and the combined group (n = 52) separately. $P = 0.15$ (log-rank test, stratifying on sex).

No difference was found in the maximum verbal pain scores either at rest or with movement ($P = 0.60$ and $P = 0.34$, respectively), with estimated mean differences (sequential group − combined group, 95% interim-adjusted CI) of −0.3 (−1.6 to 1.0) and −0.6 (−1.9 to 0.7) for the VRS at rest and with movement, respectively.

There was no difference in the total opioid consumption between the sequential group and the combined group ($P = 0.88$, after adjusting for sex), with estimated ratio of the geometric means (95% interim-adjusted CI) of 0.90 (0.20 to 4.1) for sequential versus combined groups.

DISCUSSION

Simultaneous administration of short- and long-acting local anesthetics is a routine practice and has been evaluated several times.[17] For example, a recent study by Lee et al[18] showed that 1% lidocaine mixed with 0.5% bupivacaine does not prolong onset time, but shortens the duration of intrathecal blocks as compared with 0.5% bupivacaine alone. A study by Cuvillon et al[19] concluded that mixtures of long-acting local anesthetics with lidocaine induced faster-onset peripheral nerve blocks of decreased duration. However, we believe our study to be the first that compares onset time and block duration between simultaneous and sequential administration of local anesthetics.

One local anesthetic we tested was mepivacaine 1.5%, chosen for its rapid onset to minimize the time required between supraclavicular block and surgical incision. The other drug, ropivacaine 0.5%, was chosen because of its prolonged duration of action, which provides excellent postoperative pain relief. We did not identify any advantage of sequential administration of local anesthetics when compared with combined administration. Specifically, there were no statistically significant or clinically important differences in the onset times for sensory or motor blocks, or in the duration of analgesia.

It was not possible to blind the anesthesiologist performing the supraclavicular blocks because delayed injection was required in only 1 group. We considered including a delay between injections in both the groups, which would have allowed double-blinding. However, we elected to inject the total dose without a delay in the control group to mimic routine clinical practice. Moreover, all outcomes were evaluated by investigators blinded to treatment and therefore were unbiased. The purpose of our study was to determine whether sequential injection of fast-onset and long-acting anesthetics would optimize the desirable properties of each. There appears to have been little if any study of what duration of delay between injection of the rapid-acting and long-lasting anesthetics might be optimal. We thus chose 90 secs because longer delays would be clinically difficult in single-shot blocks. It remains possible that sequential injection would prove superior with a longer delay, perhaps in patients with indwelling catheters. It is also possible that the outcomes may have been different had we done the study for a lower-extremity nerve (such as sciatic) because the onset times are longer in larger nerves. Therefore, our results should be extrapolated with caution to other types of nerve blocks.

In our study, we found the onset times for 4-nerve sensory block onset as 7.5 mins for the combined group and 10.0 mins for the sequential group. These are shorter than the times reported for achievement of complete sensory block in previous studies. For instance, Fredrickson et al[20] and Chan et al[14] reported mean onset times for complete pinprick sensory block of 22 and 17 mins, respectively, with ultrasound-guided supraclavicular blocks. Faster onset times have been reported with the concomitant use of neurostimulation, ensuring local anesthetic injection in close proximity to the nerves.[21] We measured time to 4-nerve sensory block onset, defined as time to reduction in pinprick perception in all 4 nerves (median, musculocutaneous, ulnar, and radial nerves) after the completion of injection. For purposes of comparison in our study, we used the same measure for the 2 groups. Moreover, the same masked observer performed these assessments throughout the study.

We did not find a statistically significant difference in the duration of analgesia between our 2 groups, although there seemed to be a slight advantage in the sequential group of approximately 2 hrs. It is possible that this difference may be more pronounced with the use of different local anesthetic combinations as previously discussed. We used ultrasound guidance along with nerve stimulation to ensure that the needle tip remained appropriately positioned for the second injection. It is thus unlikely that our negative results were a consequence of needle dislodgement and injection of ropivacaine away from the nerve.

In summary, sequential injection of 1.5% mepivacaine followed 90 secs later by 0.5% ropivacaine for ultrasound-guided supraclavicular block did not speed onset of sensory or motor block or significantly prolong the duration of analgesia as compared with an injection of a mixture of the same drugs.

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