Randomized Study of the Effect of Local Anesthetic Volume and Concentration on the Duration of Peripheral Nerve Blockade

Michael J. Fredrickson, MD, FANZCA,† Amitha Abeysekera, FANZCA,† and Richard White, MA‡*

Background and Objectives: Ultrasound guidance reduces the required local anesthetic volume for successful peripheral nerve block, but it is unclear whether this influences block duration. We investigated the ropivacaine volume and concentration effect on interscalene block duration.

Methods: One hundred eighty-five patients were randomized to 5 ropivacaine volume/concentration combinations (0.75% 5, 10, and 20 mL; 0.375% 20 and 40 mL) administered preoperatively via an interscalene catheter before shoulder surgery under general anesthesia. An elastomeric ropivacaine infusion commenced at the onset of pain. Patients were questioned at 24 hours primarily for the primary outcome: time to first pain. Group 5 mL was excluded post hoc because of an unacceptably high block failure rate. Multivariate Cox regression was used to assess the effect of volume and concentration (each corrected for the other) on the primary outcome.

Results: Probability of pain as a function of time was associated with not only dose, but also volume corrected for concentration and concentration corrected for volume: hazard ratio (95% confidence interval) for dose = 0.992 (0.987–0.997) (P = 0.002), volume = 0.959 (0.937–0.982) (P = 0.001), concentration = 0.852 (0.743–0.976) (P = 0.021). Increasing the volume of ropivacaine 0.375% from 10 to 40 mL was estimated to increase median (quartiles) block duration from 10.0 (9.5–11.5) to 15.0 (10.75–21) hours. Similarly, increasing the concentration of 20 mL ropivacaine from 0.375% to 0.75% was estimated to increase median (quartiles) block duration from 10.75 (9.75–14.0) to 13.75 (10.5–21.0) hours.

Conclusions: Block duration is influenced by both local anesthetic volume and concentration, a finding of increasing relevance with the current trend to lower volumes for ultrasound-guided regional anesthesia.

(*Reg Anesth Pain Med* 2012;37: 495–501)

Although peripheral nerve blocks have been used for more than a century, no previous studies have evaluated the effect of local anesthetic volume and concentration primarily on block duration. Of previous modern studies that incorporated block duration as a study outcome,[1–9] 2 methodological issues limited their interpretation. Block duration was either a secondary outcome,[1,2,4–7,9] or volumes/concentrations were administered using different neurolocalization techniques.[3,8]

The importance of this knowledge deficit has gained new relevance because of the recent increase in popularity of ultrasound-guided regional anesthesia. Ultrasound guidance reduces the required local anesthetic volume for successful block, a factor resulting in a recent trend for administering lower local anesthetic volumes for regional anesthesia.[3,8,10–13] Block duration has clinical importance, as it is a well recognized key to the effectiveness of regional anesthesia for postoperative analgesia.

Compared with other blocks, in particular, those involving the lower extremity, interscalene block for shoulder surgery represents an ideal block-procedure combination to test the effect of local anesthetic volume/concentration on block duration: a block provided from a single injection can provide complete analgesia to the operative area.

We performed a prospective randomized trial to investigate the impact of local anesthetic volume (and concentration), primarily on the duration of interscalene block as assessed by the time to first pain after shoulder surgery. We hypothesized that block duration would be dependent on each variable. We also evaluated the effect of these variables on postoperative analgesia effectiveness and block-related adverse effects.

METHODS

The local institutional review board (Northern Y Regional Ethics Committee, Hamilton, New Zealand) approved the trial. Primary and secondary end points, including the specific timing of their measurement together with the intended sample size, were prespecified before trial commencement (ie, "a priori")[14] at the Australian and New Zealand Clinical Trials Registry (ACTRN12611000155998, February 2011). A statement regarding the background and rationale for the trial was also made at this time. The primary statistical method, which was regression analysis, was stated on record in the ethics committee application. We enrolled consenting consecutive adult patients, American Society of Anesthesiologists physical status 1 to 3, of all body mass indices, aged 16 to 80 years, scheduled for elective shoulder surgery in the investigators' practice at the Southern Cross Brightside (M.J.F.) and North Harbour (A.A.) Hospitals from February through December 2011. We excluded subjects who refused brachial plexus block, had known neuropathy involving the arm undergoing surgery, had known amide local anesthetic allergy, or received preoperative opioid therapy administered for more than 1 month before surgery. Written and oral informed consent was obtained from all patients, and the trial was in keeping with the Helsinki Declaration. A research assistant made the initial invitation for participation, but definitive recruitment was by the operating investigator. The design was a dual-center, prospective, randomized, observer-blinded trial.

From the *Department of Anaesthesiology, University of Auckland; †Auckland Southern Cross Hospital Group, Auckland, New Zealand; and ‡Harvard School of Public Health, Harvard University, Boston, MA.
Accepted for publication March 24, 2012.
Address correspondence to: Michael J. Fredrickson, MD, FANZCA, Anesthesia Institute, PO Box 109199, Newmarket, Auckland, New Zealand (e-mail: michaelfredrickson@yahoo.com).
This work was funded by a grant of US $8000 from the I-Flow Corporation, Lake Forest, CA.
This study has not been presented in any meeting.
Trial Registration: Australian and New Zealand Clinical Trials Registry: ACTRN12611000155998 (www.anzctr.org.au/registry/trial_review.aspx?ID=336501)
The authors declare no conflict of interest.

ISSN: 1098-7339
DOI: 10.1097/AAP.0b013e3182580fd0

Study Interventions and End Points

The randomly assigned groups were ropivacaine 0.75% 5, 10, and 20 mL and 0.375% 20 and 40 mL. The primary end point was time to first shoulder pain. The main secondary end points were numerically rated pain, tramadol consumption, numerically rated hand numbness/weakness, and adverse effects during the first 24 hours.

Randomization and Blinding

One hundred eighty-five patients were randomly assigned to the 5 combinations of ropivacaine volume and concentration. Randomization was not procedure or operator stratified. Using a computer-generated random number in blocks of 20 (www.random.org), random assignment to the 5 groups was implemented by a research assistant remote from the study procedures. Because of a higher-than-expected exclusion rate because of recovery room pain in groups 5 and 10 mL, from patient ID 130 onward, randomization was modified to increase the number of patients assigned to these groups. Randomization was to 7 groups as follows: 1 + 2 = 5 mL 0.75%, 3 + 4 = 10 mL 0.75%, 5 = 20 mL 0.375%, 6 = 20 mL 0.75%, and 7 = 40 mL 0.375%. Group concealment was by 185 preprepared, sealed opaque envelopes, opened immediately after catheter placement.

Anesthesia and Analgesia

A standardized technique was used.[15] Multimodal oral analgesia consisted of oral acetaminophen 1 g (started 1 h before surgery) and intraoperative intravenously administered parecoxib 0.5 mg/kg to a maximum of 40 mg. A hospital policy change in August 2011 mandated a change in acetaminophen administration from preoperative oral to intaoperative intravenously administered.

Intravenous sedation up to midazolam 2 mg and alfentanil 0.5 mg was administered immediately outside the operating room. Both investigators, who were experienced with this procedure, performed all blocks.

Perineural Catheter Placement

To facilitate catheter placement and ensure supraclavicular nerve(s) blockade, a "modified"[16] superficial cervical plexus block was first placed, using a 22-gauge, 2-in (5-cm) B-Plex needle (Plexufix; B|Braun, Bethlehem, Pennsylvania) bent by hand at its midpoint to 30 degrees to facilitate subcutaneous injection.[17] Subsequently, an ultrasound-guided (SonoSite HFL/M-Turbo; SonoSite, Bothell, Washington) anterolateral-approach interscalene catheter was placed, using a previously described technique (see www.ultrasoundblock.com).[15] A 10-mL, 5% dextrose -filled syringe connected to a nerve stimulator (Pajunk Vario, Tucker, Georgia) set at 0.8 mA (0.1 ms, 2 Hz) was inserted approximately 1 cm posterior to the sternomastoid muscle dorsal border approximately 3 cm cephalad of the sixth/seventh cervical vertebral level. Appropriate root/trunk visualization (fifth and sixth cervical roots/superior or middle trunks) was confirmed by brief elicitation of a deltoid, biceps, or triceps motor response, with final needle tip position confirmed by the injection of 10 mL 5% dextrose and observation of injectate spread directly lateral to the target roots/trunks. If motor responses persisted or reappeared after dextrose injection, sonography was abandoned (to free up a hand), and the current reduced from 0.8 mA until responses ceased. This needle end point was still labeled as an ultrasound end point because the end point was primarily based on dextrose visualization rather than deliberate elicitation of a sustained motor response. If a satisfactory brachial plexus ultrasound image could not be obtained, appropriate needle tip position was confirmed by elicitation of a sustained deltoid, biceps, or triceps motor response at less than 0.5 mA. This needle end point was designated a neurostimulation end point because it was based primarily on neurostimulation rather than ultrasound.

A nonstimulating catheter was blindly advanced several centimeters beyond needle tip, and then after needle withdrawal, the catheter was withdrawn until 3 cm of catheter remained past the original needle tip position.

Intraoperative Management

General anesthesia was also standardized using a laryngeal mask airway and spontaneous desflurane respirations (end-tidal minimum alveolar concentration, 0.8–1.0). After general anesthesia induction but before surgery, the studied ropivacaine bolus was injected using a 20-mL syringe at a rate of approximately 10 mL/min (5 mL = 30 s, 40 mL = 4 min; flow rate expected, >400 mL/h). No long-acting opioid was administered; however, alfentanil 0.25 mg was administered pro re nata for a respiratory rate greater than 25 breaths/min.

Postanesthesia Care Unit Protocol

In the postanesthesia care unit (PACU), patients reporting a numerical rating pain score (NRPS, 0–10) of greater than 2 were excluded from further data collection. These patients received a 20-mL bolus of local anesthetic and morphine 2 mg every 2 to 3 minutes to achieve an NRPS of 2 or less. If the NRPS remained greater than two 60 minutes after the local anesthetic bolus, the catheter was replaced.

Postoperative Management

An elastomeric pump preset to deliver ropivacaine 0.2% at 2 mL/h with patient-controlled 5-mL boluses of up to 1 bolus every hour (PainBuster; Surgical Synergies, Auckland, New Zealand) was connected to the catheter but was clamped off with a screw clamp on the tubing distal to the bolus device. At the onset of operative site pain, patients or nurses removed the clamp and delivered the first ropivacaine bolus. From the onset of shoulder pain until 48 hours postoperatively, patients depressed the ropivacaine bolus button "on the clock" every 6 hours irrespective of the NRPS.[18] Additional 5-mL boluses were administered in between mandatory 6 hourly boluses if the NRPS increased to more than 2. Multimodal analgesia was continued after surgery: acetaminophen (1 g every 6 h) and diclofenac slow release (75 mg every 12 h) if any postoperative pain occurred; tramadol slow release (100 mg every 12 h) if the NRPS increased to greater than 2 despite regular acetaminophen, diclofenac, and 2 consecutive ropivacaine boluses. Home discharge occurred on the day of surgery, day 1 (all open procedures), or, for total shoulder joint replacement, on day 2.

Data Collection

The operating investigator recorded the catheter placement needle end point (ultrasound or neurostimulation) and the specific motor response with current threshold. The principal investigator also recorded the number of alfentanil 0.25-mg boluses administered during surgery. The patient's primary PACU nurse recorded the emergence NRPS in the shoulder, arm, or elbow and details of PACU interventions (local anesthetic bolus, morphine rescue). After surgery, patients were instructed to note when they first experienced pain. A research assistant phoned all subjects at 24 postoperative hours and questioned for time to first pain, supplemental tramadol consumption, ropivacaine bolus demands, numerically rated pain (worst and "average"),

TABLE 1. Patient and Surgical Characteristics (n = 185)

	5 mL 0.75% (n = 40)	10 mL 0.75% (n = 41)	20 mL 0.375% (n = 35)	20 mL 0.75% (n = 33)	40 mL 0.375% (n = 36)
Male sex	24 (60)	30 (73)	22 (63)	24 (73)	29 (81)
Age, y	49 (12)	48 (15)	49 (16)	49 (14)	46 (18)
Weight, kg	83 (53–121)	85 (47–115)	83 (52–134)	88 (64–125)	87 (61–125)
Body mass index, kg/m^2	28 (19–45)	29 (19–41)	27 (18–47)	29 (21–38)	29 (20–39)
Surgery					
Open rotator cuff repair	6	12	6	11	9
Arthroscopic rotator cuff repair	12	9	2	8	6
Arthroscopic stabilization	5	8	9	8	11
Arthroscopic lateral clavicle resection	4	3	2	1	2
Arthroscopic acromioplasty	8	6	9	3	3
Arthroscopic capsular release	2	1	1	0	1
Total shoulder joint replacement	1	1	4	0	2
Other	2	1	2	2	2

Values are mean (SD), mean (range), or n.

hand numbness/weakness, and satisfaction during the previous 24 hours (0–10, 0 = no pain, numbness/weakness, very unsatisfied; 10 = worst imaginable pain, numbness/weakness, very satisfied). Patients were also questioned for breathlessness or difficulty taking a deep breath present at any time during the previous 24 hours.

Statistical Analysis

An independent statistician (R.W.) performed all calculations. After trial conclusion, we excluded all group 5 mL patients from post-PACU discharge data analysis because of an unacceptably high block failure rate and therefore a high probability that the remaining pain-free patients in this group would not represent the population (eg, more accurately placed catheters and/or patients with "higher pain thresholds").

Because the primary outcome was subject to 2 variables (volume and concentration), it was not appropriate to analyze this outcome by simply comparing the raw data from each group (eg, using the Mann-Whitney *U* test), as the relative influence of each variable would remain unknown. Instead, a multivariate regression method was used; it tests for the effect of the variable of interest (eg, volume) "controlled" for another variable (called a covariate; eg, concentration) on the outcome of interest (time to first pain). A significant proportion of patients had not reported pain by the 24-hour follow-up time point. Therefore, survival analysis was used: we used a Cox proportional hazards model, which is a multivariate regression method specific for survival data. The effect of the variable of interest is expressed as a hazard ratio, which is the probability of pain at a particular time for a 1-unit increase in the variable of interest relative to a specified value (called the baseline level). This hazard ratio assumes the subject has no pain up until that time. The Cox proportional hazards model also assumes that the effect of the variable of interest, relative to the baseline, is constant over time. Variables incorporated into the Cox proportional hazards model included dose, volume, and concentration. Because hazard ratios

TABLE 2. Catheter Placement and Intraoperative and PACU Interventions (n = 185)

	5 mL 0.75% (n = 40)	10 mL 0.75% (n = 41)	20 mL 0.375% (n = 35)	20 mL 0.75% (n = 33)	40 mL 0.375% (n = 36)	*P**
Ultrasound needle end point	38 (97)	40 (98)	32 (91)	32 (97)	34 (94)	0.77
Stimulated motor response: deltoid/biceps/triceps/none	11/9/4/16	11/10/2/18	3/8/6/18	8/6/3/16	11/5/2/18	0.30
Minimum stimulation threshold, mA	0.65 (0.5–0.80)	0.70 (0.50–0.80)	0.60 (0.3–0.7)	0.70 (0.50–0.80)	0.70 (0.39–0.80)	0.66
Intraoperative alfentanil bolus ≥1	3 (8)	4 (10)	1 (3)	0 (0)	4 (11)	0.26
Surgery duration	75 (60–90)	80 (60–90)	80 (60–105)	80 (75–90)	75 (60–91)	0.73
PACU						
Exclusions						
PACU local anesthetic bolus	12 (30)	5 (12)	1(3)	2 (6)	3 (8)	0.006†
PACU catheter failure/reinsertion	0	1	0	0	2	
Protocol violation	0	0	1	0	1	
Lost to follow-up	0	2	1	1	1	

Values are n (%), n, or median (interquartile range).

**P* values refer to a 5-group comparison.

†With group 5 mL excluded, $P = 0.50$.

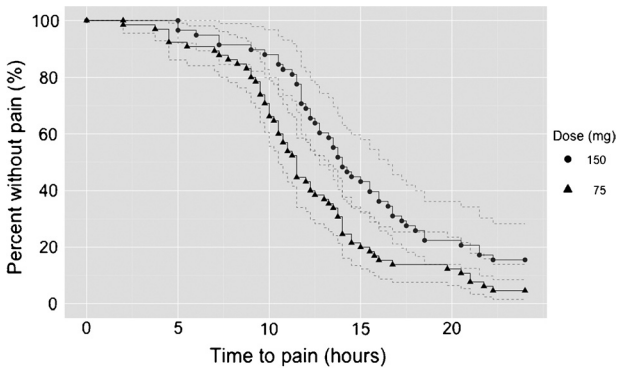

FIGURE 1. Time to first pain, according to ropivacaine dose. Broken lines are 95% CIs. Dose hazard ratio, 0.992 (95% CI, 0.987–0.997), $P = 0.002$.

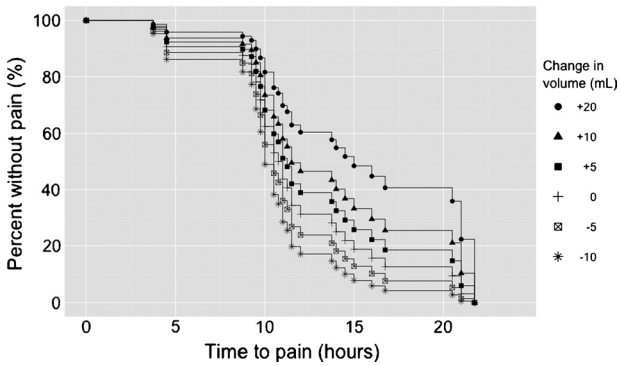

FIGURE 3. Time to first pain, according to volume changes relative to 20 mL 0.375% (adjusted for concentration). Estimated median for 10, 20, and 40 mL = 10.0 (interquartile range, 9.5–11.5), 10.75 (interquartile range, 9.75–14.0), and 15.0 (interquartile range, 10.75–21) hours.

have limited clinical applicability of their own, they were used to estimate changes in the overall survival curve from baseline (which was specified as 20 mL 0.375%)[19] for volume changes of −10, −5, +5, +10, and +20 mL and concentration changes of −0.4%, −0.1%, +0.1%, and +0.4%. From these estimated survival curves, 25th, 50th, and 75th percentiles for survival time were calculated. All reported hazard ratios (and associated *P* values) are without inclusion of the 0.75% 5 mL group.

Categorical outcomes were compared using the Fisher test (needle end point, stimulated muscle response, frequency of pain on emergence, adverse effects). Non–normally distributed continuous variables (minimum stimulation threshold, surgery duration) and ordinal outcomes (tramadol consumption, ropivacaine boluses, all numerical rating scores) were compared using the Kruskal-Wallis test. $P < 0.05$ was designated statistically significant. Two-sided tests were used for all study outcomes.

Other data were summarized using appropriate descriptive statistics (mean [SD] or mean [range] for normally distributed or symmetric variables; median [interquartile ranges] for skewed variables; number [proportion] for categorical variables). All statistical analyses were conducted using R 2.12.1 (R Foundation, Vienna, Austria).

Sample size estimates were based on Hsieh and Lavori's[19] method for calculating event numbers required for a Cox proportional hazards model with a nonbinary covariate. Dose was used as the explanatory variable of interest, with a variance of 2000 obtained by planned treatment allocation. To achieve an α of 5% and a power of 80%, for an expected hazard ratio of 0.995 per milligram dose, it was calculated that approximately 150 pain events were needed. To allow for dropouts, we planned to recruit 180 patients.

RESULTS

One hundred eighty-five patients presenting for elective shoulder surgery were enrolled: 40, 41, 35, 33, and 36 patients were randomized to the 5 mL 0.75%, 10 mL 0.75%, 20 mL 0.375%, 20 mL 0.75%, and 40 mL 0.375% groups, respectively. Patient and surgical characteristics were comparable across groups (Table 1). Needle end points, stimulated muscle groups, and the associated minimum stimulation thresholds were similar among groups; however, 12 patients (30%) in the 5 mL group had pain on emergence ($P = 0.006$) (Table 2). A total of 61 patients were excluded. Forty patients from group 5 mL were excluded, and another 21 patients were excluded in the other 4 groups: 11, because of pain on emergence (difference between groups not significant); 3, because of catheter failures requiring reinsertion; 2 patients activated the pump before experiencing pain; and 5 patients could not be contacted on day 1 (Table 2).

The proportion of patients experiencing pain as a function of time was associated with dose, volume corrected for concentration, and concentration corrected for volume: dose hazard ratio,

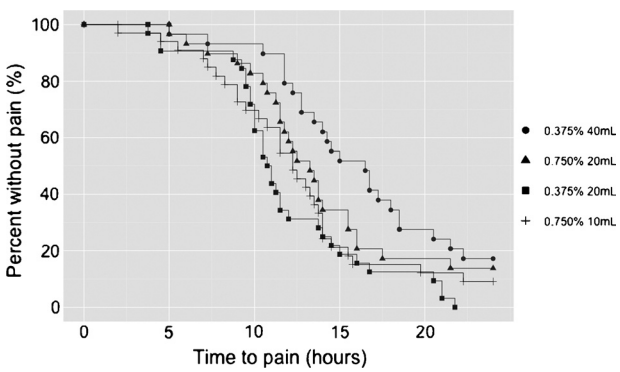

FIGURE 2. Time to first pain for ropivacaine 40 mL 0.375%, 20 mL 0.75%, 20 mL 0.375%, and 10 mL 0.75%. Volume hazard ratio adjusted for concentration, 0.959 (95% CI, 0.937–0.982), $P = 0.001$. Concentration hazard ratio adjusted for volume, 0.852 (95% CI, 0.743–0.976), $P = 0.021$.

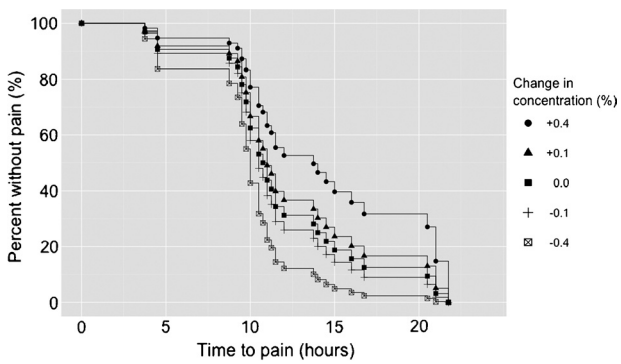

FIGURE 4. Time to first pain, according to concentration changes relative to 20 mL 0.375% (adjusted for volume). Estimated median for 0.375%, 0.5%, and 0.75% = 10.75 (interquartile range, 9.75–14.0), 11.5 (interquartile range, 10.0–16.75), and 13.75 (interquartile range, 10.5–21.0) hours.

TABLE 3. Postoperative Outcomes (n = 152)

	5 mL 0.75% (n = 28)	10 mL 0.75% (n = 33)	20 mL 0.375% (n = 32)	20 mL 0.75% (n = 30)	40 mL 0.375% (n = 29)	*P**
Tramadol consumption	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0.50
Ropivacaine boluses	3 (2–4)	3 (1–5)	3 (2–4)	3 (2–5)	2 (1–4)	0.62
Worst shoulder pain NRS	3 (2–6)	5 (3–6)	4 (3–6)	4 (3–6)	3 (3–5)	0.42
"Average" shoulder pain NRS	1 (0–3)	2 (0–3)	2 (1–3)	2 (1–3)	2 (1–3)	0.98
Hand numbness NRS	9 (6–10)	8 (5–10)	7 (5–8)	8 (6–10)	8 (7–10)	0.17
Hand weakness NRS	8 (5–10)	7 (3–9)	7 (5–9)	7 (5–10)	8 (5–10)	0.85
Adverse effects**	9 (32)	12 (36)	9 (28)	17 (56)	12 (41)	0.14
Satisfaction NRS	9 (8–10)	10 (8–10)	10 (8–10)	9 (7–10)	10 (9–10)	0.16

Values are n (%) or median (interquartile range).

**P* values refer to comparisons of the 4 groups excluding 5 mL 0.75%. Respective *P* values were similar with inclusion of the 5 mL group.

NRS indicates numerical rating score (0–10, 0 = 0 = no pain, hand numbness/weakness, very unsatisfied; 10 = worst imaginable pain, hand numbness/weakness, very satisfied).

**Adverse effects included "breathlessness" or "difficulty taking a deep breath."

0.992 (95% confidence interval [CI], 0.987–0.997; $P = 0.002$) (Fig. 1); volume hazard ratio 0.959 (95% CI, 0.937–0.982; $P = 0.001$); concentration hazard ratio, 0.852 (95% CI, 0.743–0.976; $P = 0.021$) (Fig. 2). (A volume hazard ratio of 0.959 means that, at a specific time, a patient given a 1-mL higher volume than another patient has a 4% lower risk [or "hazard"] of experiencing pain, assuming neither experienced pain.) Associations for all 3 variables were maintained with inclusion of the 5 mL group. Figures 3 and 4 depict estimates of the proportion of patients pain-free as a function of time for given changes in volume (Fig. 3) or concentration (Fig. 4) relative to a 20 mL 0.375% baseline. Corresponding estimates for the effect of volume and concentration on median time to first pain were 10.0 (interquartile range, 9.5–11.5), 10.75 (interquartile range, 9.75–14.0), and 15.0 (interquartile range, 10.75–21) hours for 10, 20, and 40 mL, respectively, and 10.75 (interquartile range, 9.75–14.0), 11.5 (interquartile range, 10.0–16.75), and 13.75 (interquartile range, 10.5–21.0) hours for 0.375%, 0.5%, and 0.75%, respectively.

Secondary outcomes associated with block effectiveness (tramadol consumption, ropivacaine boluses, numerically rated pain) and adverse effects (dyspnea) were similar across groups; however, the study did not have sufficient power to confidently conclude these secondary outcomes were equivalent (Table 3).

One patient required catheter reinsertion (before local anesthetic placement) because of likely intravascular placement. No patient demonstrated symptoms or signs of systemic local anesthetic toxicity. No patient reported significant dyspnea, requiring more than simple reassurance, before or after hospital discharge.

DISCUSSION

This study demonstrated a clear association between local anesthetic volume, concentration (and dose), and the duration of interscalene block. No differences were noted among groups during the first 24 hours for the effectiveness of analgesia (nor adverse effects); however, the study was not designed or adequately powered to detect between-group differences for these secondary outcomes.

Although peripheral nerve blocks have been used for more than a century, a clinical trial specifically evaluating the effect of local anesthetic volume and concentration on nerve block duration has not been conducted. The clinical relevance of the issue has recently attracted attention because of the increased popularity of ultrasound-guided regional anesthesia using low local anesthetic volumes: volumes as low as 0.11 mL/mm nerve cross-sectional area have been advocated.[20] Despite multiple studies showing that these "ultra-low" volumes can result in successful block,[10–13] no clinical studies have specifically evaluated the effect of volume (or concentration) on block duration.

A previous tightly controlled laboratory study in rat sciatic nerves demonstrated an association between lidocaine concentration and block duration.[21] However, the study method did not permit an assessment of the effect of volume corrected for concentration. Previous clinical studies evaluating the effect of volume (or concentration) on block duration have been limited in their interpretation for 3 possible reasons. In 2 studies, the studied variables were confounded by the use of different neurolocalization techniques.[3,8] In 1 of these studies, blocks also involved the blockade of multiple nerves: local anesthetic volume administered at each individual nerve, for each group, was not constant for each subject.[8] In other studies, block duration was a secondary outcome.[1,2,4–7,9] Drawing conclusions from secondary outcomes, particularly negative outcomes, can be problematic because the studies may not be powered to detect secondary outcome effects.[1,2,4,6,9] On the other hand, without correction for multiple comparisons, the probability of a type I error increases with the number of secondary outcomes studied.[14] Nevertheless, 2 tightly controlled, sequential, up-down dose-finding studies for sciatic and median/ulnar nerve blocks are notable in that they suggest a correlation between local anesthetic volume and the secondary outcome, block duration.[5,7]

Despite the present study's demonstration of a clear association between local anesthetic volume, concentration (and dose), and the primary outcome block duration, the clinical relevance of the shift demonstrated might be questioned: the estimated effect of a volume increase from 10 to 40 mL was a median 10 to 15 hours and a concentration increase from 0.375% to 0.75%, 10.75 to 13.75 hours. However, for interscalene block, volumes as low as 3 mL and as high as 60 mL have been used.[13,22–24] Based on the association currently demonstrated, this volume range might represent an even greater difference in block duration. That said, this speculation assumes the association remains at these volume extremes, which cannot be assumed from the present data.

Regardless of the treatment effect demonstrated, practitioners might argue that a theoretical reduction in the local anesthetic systemic toxicity risk from lower volumes and concentrations outweighs the downside of shorter block duration, even though published clinical evidence does not support this principle.[25,26] Similarly, the relatively modest effect of both volume and concentration could be interpreted to mean that the only way to significantly prolong block duration is through perineural catheter placement.

We decided after study completion to exclude the 5 mL group because of an unacceptably high block failure rate (30%): there existed the possibility that the remaining patients were not representative of the population. First, the excluded patients may have represented patients with "low pain thresholds" and would be expected to report pain earlier after block resolution compared with the population. Second, the excluded patients may have represented less accurately placed catheters—the less accurately placed catheters in the other groups were likely retained because of the higher administered volumes that likely masked these catheters. Both factors may have rendered the remaining pain-free patients in the 5 mL group unrepresentative of the studied population. Nevertheless, with inclusion of the 5 mL group, the demonstrated associations between volume, concentration, and block duration were maintained.

The technique used for local anesthetic deposition warrants comment. We injected local anesthetic at a single point immediately lateral to the appropriate roots/trunks. However, practitioners often inject local anesthetic at several locations based on the elicitation of more than 1 motor response, or sonographic assessment of inadequate local anesthetic spread. A single-point injection was used because it was thought to minimize data variability across groups (randomized controlled trial). We cannot automatically conclude that the study findings can be generalized to such a multipoint injection technique.

The raw post-PACU discharge outcome data for indices of catheter effectiveness and adverse effects (Table 3) should be interpreted with caution. First, each group was associated with changes to 2 independent variables (volume and concentration); thus, an effect from 1 variable may have been countered by an effect from the other variable. Second, the study was not powered to detect differences for secondary outcomes: "absence of evidence is not evidence of absence." Third, from the onset of pain, patients received a continuous ropivacaine infusion supplemented with patient-controlled boluses. It is therefore not surprising that pain scores were similarly low for all groups and lacked a between-group difference.

We performed the present study in the interscalene area because it represents an ideal block surgery combination to study the tested hypothesis: the operative area can be blocked by a single local anesthetic injection. The results may similarly apply to other peripheral nerve blocks; however, ideally, confirmatory studies should be conducted.

In summary, this study found a clear association between local anesthetic volume, concentration (and dose), and the duration of interscalene block, findings that have particular relevance for the current trend in ultrasound-guided regional anesthesia of administering low local anesthetic volumes.

REFERENCES

1. Klein SM, Greengrass RA, Steele SM, et al. A comparison of 0.5% bupivacaine, 0.5% ropivacaine, and 0.75% ropivacaine for interscalene brachial plexus block. *Anesth Analg*. 1998;87:1316–1319.
2. Krone SC, Chan VW, Regan J, et al. Analgesic effects of low-dose ropivacaine for interscalene brachial plexus block for outpatient shoulder surgery-a dose-finding study. *Reg Anesth Pain Med*. 2001;26:439–443.
3. Oberndorfer U, Marhofer P, Bosenberg A, et al. Ultrasonographic guidance for sciatic and femoral nerve blocks in children. *Br J Anaesth*. 2007;98:797–801.
4. Riazi S, Carmichael N, Awad I, Holtby RM, Mccartney CJ. Effect of local anaesthetic volume (20 vs 5 mL) on the efficacy and respiratory consequences of ultrasound-guided interscalene brachial plexus block. *Br J Anaesth*. 2008;101:549–556.
5. Latzke D, Marhofer P, Zeitlinger M, et al. Minimal local anaesthetic volumes for sciatic nerve block: evaluation of ED 99 in volunteers. *Br J Anaesth*. 2010;104:239–244.
6. Marhofer P, Eichenberger U, Stockli S, et al. Ultrasonographic guided axillary plexus blocks with low volumes of local anaesthetics: a crossover volunteer study. *Anaesthesia*. 2010;65:266–271.
7. Ponrouch M, Bouic N, Bringuier S, et al. Estimation and pharmacodynamic consequences of the minimum effective anesthetic volumes for median and ulnar nerve blocks: a randomized, double-blind, controlled comparison between ultrasound and nerve stimulation guidance. *Anesth Analg*. 2010;111:1059–1064.
8. Fredrickson MJ, White R, Danesh-Clough TK. Low-volume ultrasound-guided nerve block provides inferior postoperative analgesia compared to a higher-volume landmark technique. *Reg Anesth Pain Med*. 2011;36:393–398.
9. Sinha SK, Abrams JH, Al BE. Decreasing the local anesthetic volume from 20 to 10 mL for ultrasound guided interscalene block at the cricoid level does not reduce the incidence of hemidiaphragmatic paresis. *Reg Anesth Pain Med*. 2011;36:17–20.
10. O'donnell BD, Iohom G. An estimation of the minimum effective anesthetic volume of 2% lidocaine in ultrasound-guided axillary brachial plexus block. *Anesthesiology*. 2009;111:25–29.
11. Van Geffen GJ, Van Den Broek E, Braak GJ, Giele JL, Gielen MJ, Scheffer GJ. A prospective randomised controlled trial of ultrasound guided versus nerve stimulation guided distal sciatic nerve block at the popliteal fossa. *Anaesth Intensive Care*. 2009;37:32–37.
12. Danelli G, Ghisi D, Fanelli A, et al. The effects of ultrasound guidance and neurostimulation on the minimum effective anesthetic volume of mepivacaine 1.5% required to block the sciatic nerve using the subgluteal approach. *Anesth Analg*. 2009;109:1674–1678.
13. Mcnaught A, Shastri U, Carmichael N, et al. Ultrasound reduces the minimum effective local anaesthetic volume compared with peripheral nerve stimulation for interscalene block. *Br J Anaesth*. 2010;106:124–130.
14. Fredrickson MJ, Ilfeld BM. Prospective trial registration for clinical research: what is it, what is it good for, and why do I care? *Reg Anesth Pain Med*. 2011;36:619–624.
15. Fredrickson MJ, Ball CM, Dalgleish AJ. Catheter orifice configuration influences the effectiveness of continuous peripheral nerve blockade. *Reg Anesth Pain Med*. 2011;36:470–475.
16. Fredrickson MJ. Superficial cervical plexus neuropathy with chronic pain after superficial cervical plexus block and interscalene catheter placement. *Reg Anesth Pain Med*. 2011;36:206.
17. Fredrickson MJ, Ball CM, Dalgleish AJ. Posterior versus anterolateral approach interscalene catheter placement: a prospective randomized trial. *Reg Anesth Pain Med*. 2011;36:125–133.
18. Fredrickson MJ, Abeysekera A, Price DJ, Wong AC. Patient-initiated mandatory boluses for ambulatory continuous interscalene analgesia: an effective strategy for optimizing analgesia and minimizing side-effects. *Br J Anaesth*. 2010;106:239–245.
19. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. *Control Clin Trials*. 2000;21:552–560.

20. Eichenberger U, Stockli S, Marhofer P, et al. Minimal local anesthetic volume for peripheral nerve block: a new ultrasound-guided, nerve dimension-based method. *Reg Anesth Pain Med*. 2009;34:242–246.
21. Nakamura T, Popitz-Bergez F, Birknes J, Strichartz GR. The critical role of concentration for lidocaine block of peripheral nerve in vivo: studies of function and drug uptake in the rat. *Anesthesiology.* 2003;99:1189–1197.
22. Borgeat A, Dullenkopf A, Ekatodramis G, Nagy L. Evaluation of the lateral modified approach for continuous interscalene block after shoulder surgery. *Anesthesiology.* 2003;99:436–442.
23. Fredrickson MJ, Smith KR, Wong AC. Importance of volume and concentration for ropivacaine interscalene block in preventing recovery room pain and minimizing motor block after shoulder surgery. *Anesthesiology.* 2010;112:1374–1381.
24. Liu SS, Zayas VM, Gordon MA, et al. A prospective, randomized, controlled trial comparing ultrasound versus nerve stimulator guidance for interscalene block for ambulatory shoulder surgery for postoperative neurological symptoms. *Anesth Analg*. 2009;109:265–271.
25. Neal JM. Ultrasound-guided regional anesthesia and patient safety: an evidence-based analysis. *Reg Anesth Pain Med*. 2010;35:S59–S67.
26. Neal JM, Brull R, Chan VW, et al. The ASRA evidence-based medicine assessment of ultrasound-guided regional anesthesia and pain medicine: executive summary. *Reg Anesth Pain Med*. 2010;35:S1–S9.

