Effect of adding tetracaine to bupivacaine on duration of analgesia in supraclavicular brachial plexus nerve blocks for ambulatory shoulder surgery

Linda T. Pearson, MD, Benjamin P. Lowry, MD, William C. Culp Jr., MD, Olen E. Kitchings, MD, Tricia A. Meyer, PharmD, Russell K. McAllister, MD, Charles R. Roberson, MD, and Christopher J. Burnett, MD

The objective of this study was to determine if the addition of 1% tetracaine to 0.25% bupivacaine prolonged the duration of postoperative analgesia of supraclavicular brachial plexus nerve blockade for patients undergoing ambulatory shoulder surgery. We conducted a prospective, double-blinded, randomized controlled clinical study at an ambulatory surgery center utilizing ultrasound- and nerve stimulation-guided supraclavicular nerve blockade for postoperative analgesia. The control group received 30 mL of 0.25% bupivacaine plus 4 mL preservative-free saline. The study group received 30 mL of 0.25% bupivacaine plus 4 mL of 1% tetracaine. Patients documented their visual analog scale scores and intake of pain medications for 3 days. Primary outcomes included time of first postoperative pain, time of first postoperative pain pill, and time of return of motor and sensory function. Secondary outcomes included pain score and pain medication intake trends and adverse events secondary to the nerve block. A total of 84 patients completed the study, 42 patients in each group. The study group was statistically significantly older than the control group (mean age, 54 vs 48 years; $P = 0.04$). The mean duration of analgesia was 16.6 ± 8.3 h for the control group and 17.1 ± 7.3 h for the study group ($P = 0.69$). No outcomes were statistically different. In conclusion, there was no significant difference in duration of postoperative analgesia with the addition of 1% tetracaine to 0.25% bupivacaine in supraclavicular brachial plexus nerve blockade. No differences were identified in postoperative pain medications, pain scores, or complications.

Brachial plexus blockade for upper-extremity surgery has been shown to be an effective form of postoperative analgesia, resulting in reduced opioid requirements, length of stay in the postanesthetic care unit, and time to discharge in the ambulatory surgery setting (1–3). Numerous studies have described the addition of adjunctive agents to a primary local anesthetic for peripheral nerve blockade resulting in longer duration of analgesia and decreased opioid requirements (4–10). Adjunctive agents include rapid-onset local anesthetics, sedative hypnotics, opioids, tramadol, and dexamethasone. A few studies have evaluated the addition of the long-acting amino-ester local anesthetic tetracaine to peripheral nerve blockade to prolong duration of anesthesia and analgesia (6, 11, 12). Tetracaine hydrochloride has a duration of action similar to that of the amino amide local anesthetic bupivacaine, both averaging 3 to 10 hours (13). Pflug et al and Van Gessel et al reported a similar duration of action between tetracaine and bupivacaine for spinal anesthesia (14, 15). Several studies have utilized tetracaine as the primary local anesthetic for trigeminal neuralgia and peripheral nerve blockade (5, 16–18). Moore reported a duration of analgesia of 4 to 10 hours utilizing tetracaine as a sole anesthetic in peripheral nerve blocks (16, 17). Moore et al compared sensory anesthesia between bupivacaine, mepivacaine, lidocaine, and tetracaine in peripheral nerve blocks and found that sensory anesthesia with bupivacaine was 20% to 30% longer than that of tetracaine (19). Sensory anesthesia with tetracaine was approximately twice as long as that of lidocaine or mepivacaine. At our institution, it is routine practice to combine tetracaine with other local anesthetics for peripheral nerve blocks in an effort to prolong anesthesia and analgesia. This practice is based on many years of anecdotal evidence from patient reports of prolonged analgesia (often >24 hours) and no reports of adverse events. Therefore, we hypothesized that the addition of 1% tetracaine to 0.25% bupivacaine for supraclavicular nerve blockade would significantly prolong the duration of postoperative analgesia after shoulder surgery in the ambulatory setting.

METHODS

After obtaining approval from the local institutional review board, informed consent was obtained from 100 patients. Selection criteria included patients 1) who were 18 years and older; 2) who had an American Society of Anesthesiologists (ASA) physical status of I, II, or III; 3) who were undergoing shoulder surgery at the ambulatory surgery center; and 4) who preferred regional anesthesia for postoperative pain control. Patients provided informed consent for general anesthesia for the surgical procedure, as well as regional anesthesia for postoperative pain control. Patients were randomly allocated to one of two groups. The control group received a supraclavicular nerve block containing 30 mL of 0.25% bupivacaine plus 4 mL preservative-free

From the Department of Anesthesiology, Baylor Scott and White Health, and the Texas A&M University System Health Science Center College of Medicine, Temple, Texas.

Corresponding author: Christopher J. Burnett, MD, Scott and White Pain Clinic Pavilion, 2401 South 31st Street, MS 32-P2032, Temple, TX 76508 (e-mail: cburnett@sw.org).

saline (34 mL total). The study group received a supraclavicular nerve block containing 30 mL of 0.25% bupivacaine plus 4 mL of 1% tetracaine (34 mL total). The dose and amount of medications assigned were based on the routine practice at the institution's ambulatory surgery center.

A pharmacist filled empty vials with either 4 mL of 1% tetracaine or 4 mL of preservative-free saline and labeled the vials with a study identification number according to a randomization log. The pharmacist had no direct patient interaction or access to the collected data. To minimize the technique variability, only five attending physician anesthesiologists and two anesthesiology pain fellows performed the supraclavicular nerve blocks using a protocoled approach.

Following placement of a peripheral intravenous line, each patient received 2 mg of midazolam intravenously prior to the performance of the supraclavicular nerve block. All nerve blocks were conducted utilizing a nerve-stimulating needle (Braun Stimuplex® A; Bethlehem, PA) and under direct sonographic guidance (Sonosite M-Turbo™ Ultrasound System; Bothell, WA) with a 10 to 13 MHz linear array transducer. The minimum amplitude when motor stimulation could no longer be identified ranged from 0.3 to 0.8 mA. After negative aspiration for blood, incremental doses of the local anesthetic solution were injected around nerve trunks consisting of the radial, ulnar, median, and musculocutaneous nerves. All images using the ultrasound machine were documented in the patient's medical record. After completion of the regional anesthetic in the preoperative area, all patients received a general anesthetic for the surgical procedure. No limitations were placed on the intraoperative use of opioids and/or adjuncts that could be utilized. All intraoperative medications were documented and utilized in the analysis.

Postoperatively, patient pain scores were assessed and managed according to routine practice with intravenous or oral medications in the postanesthesia care unit. No limitations were placed on the use of opioids and/or adjuncts in the postanesthesia care unit. All postanesthesia care unit medications were documented and utilized in the analysis. As per local standard practice, patients reporting pain in the shoulder in the postanesthesia care unit were evaluated by a physician and could receive a supplemental superficial cervical plexus nerve block if appropriate. The supplemental superficial cervical plexus nerve block was performed in a subset of patients (n = 23) who experienced significant postoperative pain along the superior and anterior aspect of the shoulder. These patients received a solution of 8 mL of 0.25% bupivacaine distributed along the superficial cervical plexus using a 25-gauge needle.

At the time of discharge, patients received a pain diary to document their pain scores using an 11-point visual analog scale. Pain scores were documented every 2 hours while awake from the time of discharge to the end of postoperative day 2. Patients were instructed not to take pain medications until they started to feel pain in the operated shoulder. They were also instructed to document when and how many pain pills they consumed during this period. Patients were issued a questionnaire to rate their satisfaction with the regional anesthetic for their postoperative pain control. Study personnel contacted patients via telephone on postoperative days 1 and 2 to verify their continued participation and to answer any questions. Subjects were required to return their completed pain diaries and questionnaires for inclusion in the final analysis of the study.

It was determined that 74 subjects (37 in each group) would be required using a two-tailed sample *t* test to achieve 80% power to detect a 4-hour difference in duration of analgesia between the two groups. The estimation assumed a group standard deviation of 6 hours with an alpha of 0.05. One hundred subjects were enrolled to account for an expected 25% attrition rate. To compare the duration of analgesia, the Wilcoxon rank-sum test was chosen. Linear regression analysis was used to compare duration of analgesia when there were significant differences between the groups in other variables. Significant variables were adjusted as covariates in the regression models. To assess all the variables related to quality of analgesia, need for additional pain medications, side effects, and/or complications between the two groups, the two-tailed sample *t* test and Wilcoxon rank-sum test were used for mean comparisons and the chi-square test or Fisher's exact test for proportion comparisons. A P value of <0.05 indicated statistical significance. SAS 9.2 (SAS Institute Inc.; Cary, NC) was used for data analysis.

RESULTS

Of the 100 patients initially enrolled, 84 completed and returned the pain diary and questionnaire. Two patients from the experimental group reported a failed block, as they had no analgesia or anesthesia immediately postoperatively. All results were similar when excluding the two patients who had a failed nerve block.

Analysis of the demographic data revealed that the study group was significantly older than the control group (mean age, 54 vs 49 years; $P = 0.04$). No significant differences were detected with regard to gender, body mass index, or ASA classification scores *(Table 1)*. There was no statistically significant difference between the groups with regard to preexisting diabetes mellitus or resultant neuropathy of the operative extremity. Preoperative pain score was reported on an 11-point visual analog scale with an average score of 3 out of 10 for both groups. No significant difference was noted in the preoperative consumption of opioids, neuropathic medications, or daily nonsteroidal antiinflammatory use between the two groups. The surgical approach (arthroscopic vs open) and the different types of surgical repairs and/or procedures were not significantly different between the two groups *(Table 2)*. Total opioid and adjunctive pain medications administered during the intraoperative and postoperative period were similar in both groups, with no significant differences *(Tables 2 and 3)*. Supplemental superficial cervical plexus blocks were provided for 27% of all patients: 29% in the control group and 26% in the study group ($P = 0.80$) *(Table 3)*. Visual analog pain scores at the time of discharge were similarly low (1 out of 10) for both groups. There were no significant

Table 1. Demographics and preoperative data

Variable	Saline (N = 42)	Tetracaine (N = 42)	Total (N = 84)	*P* value
Patient age (years), mean ± SD	48.7 ± 13.8	54.1 ± 15.4	51.4 ± 14.8	0.04†
Gender: Female	16 (38%)	19 (45%)	35 (42%)	0.51‡
Body mass index (kg/m^2), mean ± SD	30.2 ± 5.7	30.6 ± 5.7	30.4 ± 5.7	0.74†
ASA class				0.89*
I	4 (10%)	4 (10%)	8 (10%)	
II	26 (62%)	23 (55%)	49 (58%)	
III	12 (29%)	15 (36%)	27 (32%)	
Preexisting neuropathy	6 (14%)	9 (21%)	15 (18%)	0.39‡
Preexisting diabetes mellitus	8 (19%)	10 (24%)	18 (21%)	0.59‡
Prenerve block pain score, mean ± SD	3.2 ± 2.9	3.0 ± 2.9	3.1 ± 2.9	0.76†
Premedication with midazolam	42 (100%)	42 (100%)	84 (100%)	NA
Preop opioids: pills daily, mean ± SD	3.5 ± 2.5	4.5 ± 3.2	4.1 ± 3.0	0.50†
Preop neuropathics: pills daily, mean ± SD	2.3 ± 3.2	2.8 ± 1.6	2.7 ± 1.9	0.49†
Preop NSAIDS: pills daily, mean ± SD	2.2 ± 1.9	2.0 ± 1.4	2.1 ± 1.7	0.98†

* Fisher's exact test was used.
† Wilcoxon rank-sum test was used.
‡ Chi-square test was used.
ASA indicates American Society of Anesthesiologists; NSAIDs, nonsteroidal antiinflammatory agents.

Table 2. Surgical and intraoperative data

Variable	Saline (N = 42)	Tetracaine (N = 42)	Total (N = 84)	*P* value
Surgical approach				0.61‡
Arthroscopic	31 (74%)	33 (79%)	64 (76%)	
Open	11 (26%)	9 (21%)	20 (24%)	
Major surgical repair type				0.67*
Labral reconstructions	13 (31%)	8 (19%)	21 (25%)	
Rotator cuff repair	23 (55%)	26 (62%)	49 (58%)	
Both	2 (5%)	3 (7%)	5 (6%)	
Other	4 (10%)	5 (12%)	9 (11%)	
Additional procedures: shoulder				0.37‡
Acromioplasty	11 (26%)	5 (12%)	16 (19%)	
Coracoplasty	1 (2%)	4 (10%)	5 (6%)	
Debridement	11 (26%)	13 (31%)	24 (29%)	
Subacromial decompression	7 (17%)	7 (17%)	14 (17%)	
None	12 (29%)	13 (31%)	25 (30%)	
Additional procedures: clavicle				1.00‡
Distal clavicle excision	11 (26%)	11 (26%)	22 (26%)	
None	31 (74%)	31 (74%)	62 (74%)	
Additional procedures: biceps				1.00*
Biceps tenodesis	2 (5%)	3 (7%)	5 (6%)	
Biceps tenotomy	4 (10%)	4 (10%)	8 (10%)	
None	36 (86%)	35 (83%)	71 (85%)	
Total narcotic dose and adjuncts during surgery				
Intraop fentanyl (mcg), mean ± SD	103 ± 52	99 ± 48	101 ± 50	0.62†
Intraop ketorolac (mg), mean ± SD	12 ± 16	12 ± 15	12 ± 15	1.00†

* Fisher's exact test was used.
† Wilcoxon rank-sum test was used.
‡ Chi-square test was used.

differences in the average surgery time or in the average time to discharge home *(Table 3)*.

Patient satisfaction with the nerve block was favorable, with 90% of all patients stating they would undergo the same nerve block for any subsequent surgeries and would recommend the nerve block to a family member. There were no patient reports of permanent paresthesia from the nerve block. One patient from the study group reported dissatisfaction with temporary paresthesia from a dense nerve block on postoperative day 1. This sensation resolved with the return of motor function after about 24 hours. One patient from the control group reported flushing and mild itching on postoperative day 2, which resolved with oral diphenhydramine. Among patients in the control group, 53% reported being awakened from sleep by pain on the first night home, while 37% from the study group reported the same ($P = 0.33$). Similarly, 55% of the control group and 70% of the study group reported pain that awakened them from sleep on the second night home ($P = 1.00$).

Average pain scores during the study time period were similar between both groups, with no significant difference identified *(Figure 1a)*. The mean duration of analgesia was 16.6 hours for the control group and 17.1 hours for the study group ($P = 0.69$). The time to return of motor function was 21 hours in both groups ($P = 0.88$). The time to first pain pill was 11.6 hours in the control group and 10.5 hours in the study group ($P = 0.76$); *Figure 1b* shows the total number of pills taken in each group.

DISCUSSION

There is an ongoing search to identify adjunct medications to add to local anesthetics in order to prolong the anesthetic and analgesic effect to improve postoperative pain experiences. Reviews of additives to local anesthetics for peripheral nerve blocks provide insight on the efficacy of these additives along with their potential safety risks and neurotoxic effects (20, 21). Few studies have added the long-acting amino ester tetracaine to a long-acting amino amide such as bupivacaine to prolong anesthesia and analgesia. The purpose of this study was to identify differences in duration of analgesia of supraclavicular nerve blocks with the addition of tetracaine. No significant difference was identified in the duration of postoperative analgesia with the addition of 1% tetracaine to 0.25% bupivacaine in supraclavicular nerve blocks. There were no significant

Table 3. Postoperative data

Variable	Saline (N = 42)	Tetracaine (N = 42)	Total (N = 84)	*P* value
Total narcotic dose and adjuncts postoperatively				
Hydromorphone (mg), mean ± SD	0.7 ± 0.6	0.6 ± 0.7	0.6 ± 0.6	0.49†
Acetaminophen (mg), mean ± SD	386 ± 296	356 ± 307	369 ± 298	0.80†
Supplemental superficial cervical plexus block				0.81‡
No	30 (71%)	31 (74%)	61 (73%)	
Yes	12 (29%)	11 (26%)	23 (27%)	
Pain score at discharge, mean ± SD	1.1 ± 1.6	1.3 ± 1.9	1.2 ± 1.7	0.62†
Average surgery time (hours), mean ± SD	1.2 ± 0.9	1.4 ± 0.9	1.3 ± 0.9	0.33
Average time in PACU (hours), mean ± SD	1.5 ± 0.6	1.5 ± 0.5	1.5 ± 0.5	0.73

*Fisher's exact test was used.
†Wilcoxon rank-sum test was used.
‡Chi-square test was used.
PACU indicates postanesthesia care unit.

differences in postoperative pain medication intake, pain scores, or complications between the two groups either.

The safety of utilizing tetracaine in peripheral nerve blockade was a theoretical concern based on prior literature. Previous animal studies have shown neurotoxicity from the intrathecal administration of tetracaine (22, 23). However, there was minimal toxicity when ≤1% tetracaine was administered (23). Subsequent animal studies have shown similar neurotoxicity with intrathecal administration of lidocaine, bupivacaine, and ropivacaine (24). Kitawaga et al reported that the mechanism of action is hypothesized to be secondary to the detergent-like properties of the local anesthetics (25). These were all animal studies focused on intrathecal administration of the local anesthetics. No studies have shown any clinically relevant neurological sequelae from intrathecal or peripherally administered tetracaine in humans. Leonard et al reported that intrathecal administration of tetracaine produced a longer and denser motor blockade (40–50 minutes) than intrathecal bupivacaine (26). In this study, no persistent paresthesias, prolonged block, or other neurological sequelae were observed or reported.

Limitations of this study include a relatively small sample size in conjunction with the inability to directly observe patients following discharge home. Neurologic exams were not performed on these patients at the time of discharge. Return of motor function was determined by the patient reporting the ability to make a full fist. Furthermore, the study was limited by the subjective nature of patients' self-reporting their pain scores. An additional confounding variable was the timing of the first onset of postoperative pain. The average time of first pain was reported between 16 and 17 hours after placement of the nerve block, and most of these outpatient cases were performed between 7:30 AM and 4:00 PM. Consequently, many patients would have experienced first pain during the late night or early morning hours, making it difficult to ascertain the exact time of the onset of this pain. Additionally, patients were instructed to take pain medication only at the time of first pain; however, some patients likely took pain medication as a preemptive measure.

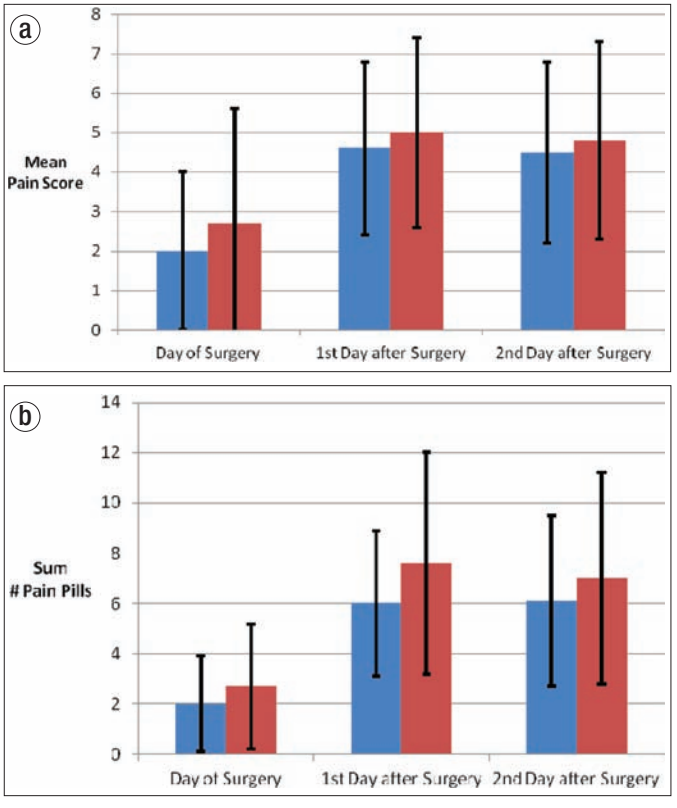

Figure 1. (a) Mean pain scores and **(b)** total number of pain pills over 3 days. Blue = control group (saline; 42 patients); Red = experimental group (tetracaine; 42 patients).

Acknowledgments

The investigators would like to thank Jared E. Anderson, MD, Rodney Lange, MD, Andrew L. Barker, MD, Adam M. Savage, MD, Juhee Song, PhD, and Ying Fang, MS, MPH, for their contributions to this study. This study was supported by funding from the Scott and White Office of Academic Research Development and the Department of Anesthesiology.

1. Brown AR, Weiss R, Greenberg C, Flatow EL, Bigliani LU. Interscalene block for shoulder arthroscopy: comparison with general anesthesia. *Arthroscopy* 1993;9(3):295–300.
2. D'Alessio JG, Rosenblum M, Shea KP, Freitas DG. A retrospective comparison of interscalene block and general anesthesia for ambulatory surgery shoulder arthroscopy. *Reg Anesth* 1995;20(1):62–68.
3. Mariano ER, Chu LF, Peinado CR, Mazzei WJ. Anesthesia-controlled time and turnover time for ambulatory upper extremity surgery performed with regional versus general anesthesia. *J Clin Anesth* 2009;21(4):253–257.
4. Bourke DL, Furman WR. Improved postoperative analgesia with morphine added to axillary block solution. *J Clin Anesth* 1993;5(2):114–117.

5. Candido KD, Franco CD, Khan MA, Winnie AP, Raja DS. Buprenorphine added to the local anesthetic for brachial plexus block to provide postoperative analgesia in outpatients. *Reg Anesth Pain Med* 2001;26(4):352–356.
6. Gadsden J, Hadzic A, Gandhi K, Shariat A, Xu D, Maliakal T, Patel V. 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. *Anesth Analg* 2011;112(2):471–476.
7. Jarbo K, Batra YK, Panda NB. Brachial plexus block with midazolam and bupivacaine improves analgesia. *Can J Anaesth* 2005;52(8):822–826.
8. Shrestha BR, Maharjan SK, Shrestha S, Gautam B, Thapa C, Thapa PB, Joshi MR. Comparative study between tramadol and dexamethasone as an admixture to bupivacaine in supraclavicular brachial plexus block. *JNMA J Nepal Med Assoc* 2007;46(168):158–164.
9. Tandoc MN, Fan L, Kolesnikov S, Kruglov A, Nader ND. Adjuvant dexamethasone with bupivacaine prolongs the duration of interscalene block: a prospective randomized trial. *J Anesth* 2011;25(5):704–709.
10. Vieira PA, Pulai I, Tsao GC, Manikantan P, Keller B, Connelly NR. Dexamethasone with bupivacaine increases duration of analgesia in ultrasound-guided interscalene brachial plexus blockade. *Eur J Anaesthesiol* 2010;27(3):285–288.
11. Berry JS, Heindel L. Evaluation of lidocaine and tetracaine mixture in axillary brachial plexus block. *AANA J* 1999;67(4):329–334.
12. Goto F, Ishizaki K, Yoshikawa D, Obata H, Arii H, Terada M. The long lasting effects of peripheral nerve blocks for trigeminal neuralgia using high concentration of tetracaine dissolved in bupivacaine. *Pain* 1999;79(1):101–103.
13. Covino BG. Physiology and pharmacology of local anesthetic agents. *Anesth Prog* 1981;28(4):98–104.
14. Pflug EA, Aasheim GM, Beck HA. Spinal anesthesia: bupivacaine versus tetracaine. *Anesth Analg* 1976;55(4):489–492.
15. Van Gessel EF, Miege B, Forster A, Salvaj G, Fathi M, Gamulin Z. Comparison of hyperbaric solutions of bupivacaine and tetracaine during continuous spinal anaesthesia. *Can J Anaesth* 1992;39(4):323–329.
16. Moore DC. Pontocaine hydrochloride for brachial block analgesia; 150 cases. *Anesthesiology* 1948;9(3):281–284.
17. Moore DC. The use of pontocaine hydrochloride for nerve block and infiltration analgesia, therapeutic, and diagnostic blocks; 1004 cases. *Anesthesiology* 1950;11(1):65–75.
18. Radwan IA, Saito S, Goto F. High-concentration tetracaine for the management of trigeminal neuralgia: quantitative assessment of sensory function after peripheral nerve block. *Clin J Pain* 2001;17(4):323–326.
19. Moore DC, Bridenbaugh LD, Bridenbaugh PO, Tucker GT. Bupivacaine for peripheral nerve block: A comparison with mepivacaine, lidocaine, and tetracaine. *Anesthesiology* 1970;32(5):460–463.
20. Bailard NS, Ortiz J, Flores RA. Additives to local anesthetics for peripheral nerve blocks: Evidence, limitations, and recommendations. *Am J Health Syst Pharm* 2014;71(5):373–385.
21. Brummett CM, Hong EK, Janda AM, Amodeo FS, Lydic R. Perineural dexmedetomidine added to ropivacaine for sciatic nerve block in rats prolongs the duration of analgesia by blocking the hyperpolarization-activated cation current. *Anesthesiology* 2011;115(4):836–843.
22. Saito S, Radwan I, Obata H, Takahashi K, Goto F. Direct neurotoxicity of tetracaine on growth cones and neurites of growing neurons in vitro. *Anesthesiology* 2001;95(3):726–733.
23. Takenami T, Yagishita S, Asato F, Hoka S. Neurotoxicity of intrathecally administered tetracaine commences at the posterior roots near entry into the spinal cord. *Reg Anesth Pain Med* 2000;25(4):372–379.
24. Yamashita A, Matsumoto M, Matsumoto S, Itoh M, Kawai K, Sakabe T. A comparison of the neurotoxic effects on the spinal cord of tetracaine, lidocaine, bupivacaine, and ropivacaine administered intrathecally in rabbits. *Anesth Analg* 2003;97(2):512–519.
25. Kitagawa N, Oda M, Totoki T. Possible mechanism of irreversible nerve injury caused by local anesthetics: detergent properties of local anesthetics and membrane disruption. *Anesthesiology* 2004;100(4):962–967.
26. Leonard M, Moore L, Algozzine R, Gregorino J, Giles B. Recovery times from subarachnoid blocks using bupivacaine hydrochloride and tetracaine hydrochloride with and without epinephrine. *AANA J* 1997;65(3):260–264.