ORIGINAL ARTICLE

Effect of Perioperative Administration of Ropivacaine With Epinephrine on Postoperative Pediatric Adenotonsillectomy Recovery

Albert H. Park, MD; Ana Lucia Pappas, MD; Elaine Fluder, MSN, RN; Steve Creech, MS; Ralph A. Lugo, PharmD; Andrew Hotaling, MD

Objectives: To determine whether perioperative administration of ropivacaine hydrochloride with epinephrine decreases postoperative pain following adenotonsillectomy and to determine the pharmacokinetics of ropivacaine following injection.

Design: Prospective, randomized, double-blind clinical trial.

Setting: University pediatric ambulatory center.

Participants: A total of 130 children, aged 2 to 12 years, undergoing adenotonsillectomy.

Intervention: Patients received injections, in the tonsillar fossae, of isotonic sodium chloride solution or 0.5% ropivacaine hydrochloride with epinephrine immediately following tonsillectomy.

Main Outcome Measures: Modified objective pain score, time to 100 mL of oral intake, serial plasma ropivacaine levels, use of analgesics, incidence of retching and emesis, and other symptoms.

Results: Fifty-three patients (80%) in the ropivacaine group had detectable plasma levels in at least 3 of the 4 measurement time periods. The mean±SD peak concentration (C_{max}) was 0.71±0.33 µg/mL and the half-life was 0.96 hours. The average modified objective pain scores over all time points favored the placebo group (P=.06 test of between-subjects effects). Similarly, the average behavior score over time favored the placebo group (P=.046 test of between-subjects effects). Neck pain was better in the placebo group when averaged over postoperative days 1, 3, 7, and 14 (P=.04). The percentage of patients who had retching in the recovery room was greater in the ropivacaine group (41% vs 19%, P=.006).

Conclusions: The injection of 0.5% ropivacaine with epinephrine immediately following adenotonsillectomy results in a measurable plasma level. Ropivacaine with epinephrine injection does not reduce pain postoperatively and adversely affects behavior scores, neck pain scores, and retching frequency compared with placebo. Ropivacaine with epinephrine injection for postoperative analgesia is not recommended for this patient population.

Arch Otolaryngol Head Neck Surg. 2004;130:459-464

From the Departments of Surgery (Dr Park), Pediatrics (Drs Park and Lugo), and Pharmacy Practice (Dr Lugo), University of Utah, Salt Lake City; Departments of Anesthesiology (Dr Pappas and Ms Fluder) and Otolaryngology (Dr Hotaling), and Oncology Institute (Mr Creech), Loyola University Medical Center, Maywood, Ill. *The authors have no relevant financial interest in this article.*

PAIN CONTROL CONTINUES TO be a challenge for adenotonsillectomy patients. Warnock and Lander[1] reviewed the outcomes of 129 children after tonsillectomy and noted considerable pain that lasted for more than 7 days. Pain was intense for the first 3 days followed by a gradual decline over the subsequent 4 days. Colclasure and Graham[2] noted a 1% readmission rate for patients undergoing tonsillectomy because of odynophagia and dehydration. The pathophysiological mechanism is believed to be mediated by noxious stimulation of C-fiber afferents located in the peritonsillar space.[3]

A local anesthetic administered to the peritonsillar space that provides analgesia and minimal adverse effects is an attractive solution to the problem of posttonsillectomy pain. Ropivacaine is a member of the amino amide class of local anesthetics that blocks the generation and conduction of nerve impulses similar to that of bupivacaine. It has been found to be effective in controlling postoperative pain following hernia surgery.[4] An attractive feature of ropivacaine is its low cardiac toxicity. Two clinical trials of human volunteers noted significantly fewer cardiac conductivity changes with intravenous ropivacaine compared with bupivacaine.[5] Nonclinical pharmacology studies comparing the 2 anesthetics in animals found fewer cardiac toxic effects with ropivacaine.[5] The objectives of this study were to determine whether the perioperative ad-

ministration of ropivacaine hydrochloride decreases postoperative pain and improves outcomes after adenotonsillectomy. In addition, we sought to determine absorption of ropivacaine from the peritonsillar space to ascertain blood concentrations following injection.

METHODS

After approval by the Loyola University Medical Center institutional review board for patient safety, a prospective, randomized, double-blind clinical trial of 130 children undergoing adenotonsillectomy was performed. Consent was obtained on the day of surgery for any patient scheduled for adenotonsillectomy who did not have any of the characteristics for exclusion. Exclusion criteria included a history of diabetes, cardiac conduction anomalies, electrolyte abnormalities, liver or kidney disease, hypersensitivity to ropivacaine, history of chronic pain, regular analgesic use within 1 week of surgery, peritonsillar abscess, pregnancy, and/or weight less than 15 kg. Families were notified of the study when first seen in clinic.

Children were randomized to receive injection of either isotonic sodium chloride solution or 0.5% ropivacaine hydrochloride with 1:200 000 epinephrine into the tonsillar fossa immediately after tonsillectomy while still under general anesthesia. Randomization was done by a computer-generated number table. A randomization sheet designated the contents of the envelope and instructions how to mix the epinephrine and ropivacaine. The operating surgeon was blinded to the study drug contents.

All children enrolled in this study received standardized premedication and anesthesia. All patients received oral administration of 0.5 to 0.7 mg/kg of midazolam mixed with 3 to 5 mL of acetaminophen (160 mg/tsp) 30 minutes before the anticipated start of surgery. Anesthesia was induced and maintained with sevoflurane. Intubation was facilitated by mivacurium chloride. Children also received an acetaminophen suppository (25-30 mg/kg); intravenous dexamethasone, 1 mg/kg (maximum dose, 25 mg); and fentanyl citrate (1 µg/kg). The tonsils were removed via monopolar electrocautery by an otolaryngology resident under the direct supervision of 1 of 2 surgeons (A.H.P., A.H.). The adenoids were removed using a curette. Packing and electrocautery were used for hemostasis. The technique for peritonsillar infiltration was the same for every patient. Three milliliters of the study medication was injected submucosally into the posteromedial tonsil pillar bilaterally. The dose for the ropivacaine arm of the study was 30 mg (maximal dose, 2 mg/kg). The epinephrine dose was 1:200 000 concentration.

Plasma ropivacaine levels were obtained before, and at 30, 60, and 90 minutes after tonsillar fossa infiltration. Levels were also obtained in the isotonic saline arm to validate the assay. Three milliliters of blood was drawn. Plasma samples were obtained from a dual-line T-connector connected to a previously inserted intravenous catheter. The samples were immediately centrifuged at 800*g*, and the plasma was separated and kept frozen at –70°C until analysis. The analysis was performed using high-performance liquid chromatography (HPLC) equipment, which consisted of a column 5 µm, 150 × 4.6 mm (Adsorbosphere XL C18-B; Alltech, Nicholasville, Ky); HPLC pump (Waters 515; Waters, Milford, Mass); an autosampler (Waters 717; Waters), and a UV detector (wavelength, 210 nm; Waters 486, Waters). Millennium chromatography manager (Waters) software was used to control and manage the instrument and data processing.

Mobile phase buffer for HPLC consisted of 0.05M sodium phosphate (Sigma-Aldrich Co, St Louis, Mo) with 30% HPLC-grade acetonitrile (Fisher, Pittsburgh, Pa). The pH was adjusted to 5.85 with sodium hydroxide from 10N to 2N. The standards of ropivacaine were prepared from the stock solutions (Astra USA, Westborough, Mass) by dilution with HPLC mobile phase to final concentrations of 0.153, 0.306, 0.6125, 1.25, 2.5, and 5 µg/mL, respectively.

For the extraction procedure, 0.5 mL of control plasma, 0.5 mL of standard ropivacaine solution, and 1.5 mL of distilled water, or 0.5 mL of sample plasma and 2.0 mL of distilled water were mixed in a Falcon tube (15-mL polypropylene conical). The mixture was preconditioned by adding 2 mL of acetonitrile, and then vortexed for 15 seconds. After centrifugation at 2200*g* for 20 minutes, the clear supernatant was transferred into a clean Falcon tube containing 0.5 mL of sodium hydroxide (0.2N) and 6 mL of hexane (Fisher). The mixture was shaken by using a 360° rotator (National Labnet Co, Woodbridge, NJ) for 20 minutes. Five milliliters of the organic phase was then separated by centrifugation at 2200*g* for 20 minutes and transferred to a clean glass tube. This organic phase was then evaporated by using Speed Vac Concentrator (SV0100II; Savant, Hicksville, NY) coupled with a Refrigerated Condensation Trap (RT-100, MC-1-60-SI; Savant) for 10 to 20 minutes for dryness. The residue was reconstituted in 200 µL of the mobile phase and 40 µL was injected into the HPLC. Millennium Chromatography Manager software (Waters) was used to identify and quantify the peak of ropivacaine in the chromatogram. The concentrations of ropivacaine in the plasma sample were calculated from the standard curve of ropivacaine.

Postoperative measurements, including the amount and incidence of rescue medication for retching, emesis, and pain were recorded. Ondansetron, 0.15 mg/kg intraveously, up to a maximal dose of 4 mg, was used for retching and/or emesis. Pain rescue medication was given for an objective pain score of 4 or higher or a behavior score (1 = calm child, 2 = crying child who could be consoled, 3 = crying child who cannot be consoled and 4 = agitated and thrashing child) of 3 or higher. Rescue medication included fentanyl citrate, 0.5 µg/kg in increments up to 2 µg/kg, and when patients tolerated fluids, acetaminophen and codeine. Pain was measured using a modified objective pain score while the children were observed in the postoperative recovery center for a minimum of 180 minutes. Time to first oral intake, time until oral intake exceeded 100 mL, emesis, retching episodes and frequency, average time for rescue medication, frequency and dose of rescue medications, and adverse events were recorded by a research nurse who was blinded to each patient's group status. The research nurse also contacted the families via phone on postoperative days 1, 3, 7, and 14 to record the type and quantity of oral intake, severity of throat, neck, or ear pain, presence and frequency of retching, emesis, and status of patient activity. The frequency and amount of pain medication were recorded for the first postoperative day.

Pharmacokinetic parameters were calculated by noncompartmental methods (WinNonlin version 3; Pharsight Inc, Cary, NC). After submucosal administration of the single dose of ropivacaine, the area under the plasma concentration-time curve (AUC) and the area under the moment curve (AUMC) from time 0 to infinity were calculated using the linear trapezoidal rule. The area from the last measured concentration (Cp_{final}) to infinity was extrapolated by dividing Cp_{final} by the slope of the terminal elimination phase (k). Ropivacaine clearance (CL) was calculated by dividing the dose by the AUC. Mean residence time (MRT) after intravenous administration was calculated by the equation [AUMC/AUC – (infusion time/2)]. Volume of distribution at steady state (Vdss) is equal to the product of CL and MRT. The peak concentration (C_{max}) and the time to reach C_{max} (t_{max}) were read directly from the concentration-time profile.

Tests of statistical significance for the data included 2-sample *t* test and repeated-measures analysis of variance. Nominal data were analyzed using the χ^2 and Fisher exact tests.

Table 1. Patient Demographics for Children Randomized to 2 Treatment Groups*

Variable	Placebo (n = 64)	Ropivacaine (n = 66)	*P* Value (Test)
Age, y	7 ± 3	7 ± 2	.64 (*t*)
Weight, kg	31 ± 13	29 ± 11	.25 (*t*)
Sex			
Male	34	31	.483 (χ^2)
Female	30	35	
Surgical indications			
Tonsillitis	11	12	.77 (χ^2)
Obstructive sleep apnea	50	49	
Both	3	5	
Duration of anesthesia, min	51 ± 16	50 ± 15	.65 (*t*)
Duration of surgery, min	31 ± 13	29 ± 12	.46 (*t*)
Estimated blood loss, mL	46 ± 35	42 ± 27	.46 (*t*)
Tonsil size†			
1	1	0	.60 (Fisher exact)
2	7	11	
3	32	31	
4	24	24	
Adenoid size†			
1	0	1	.75 (Fisher exact)
2	13	11	
3	32	34	
4	19	19	

*Data are mean ± SD or number of patients. Placebo was given as isotonic sodium chloride solution; ropivacaine as ropivacaine hydrochloride injection.
†Based on a scale of 1 to 4.

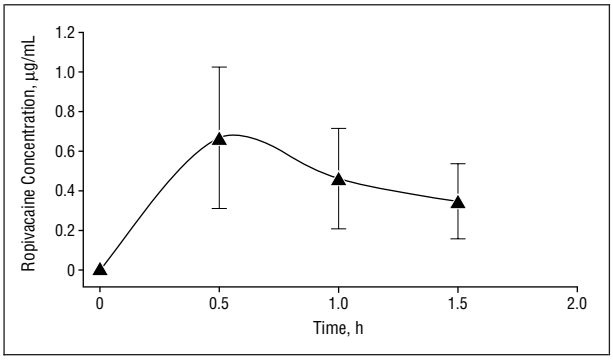

Figure 1. Plasma concentrations (mean±SD) vs time curves following submucosal injection of ropivacaine hydrochloride into the posteromedial tonsil pillar.

The study was powered based on the modified objective pain score. Calculations were performed to detect a standardized effect size of 0.60, power of 0.90, and 2-sided α of .05.

RESULTS

The patients were comparable between the 2 groups with respect to age, weight, sex, indications for surgery, duration of anesthesia, duration of surgery, estimated blood loss, and tonsil and adenoid size (**Table 1**). All patients underwent adenotonsillectomy. No other procedures, such as myringotomy and tube placement, were performed.

Fifty-three patients (80%) in the ropivacaine group had detectable plasma levels in at least 3 of the 4 time periods. Forty-eight patients had a complete set of blood samples suitable for pharmacokinetic analysis. There was significant interpatient variability in the plasma concentration-vs-time profile (**Figure 1**) and pharmacokinetic parameters (**Table 2**). The C_{max} (0.71±0.33 µg/mL) occurred at 30 minutes in 48 of the 53 patients. In the remaining 5 patients, the C_{max} was measured at 60 minutes after injection. The median half-life of ropivacaine was 0.96 hours (range, 0.22-5.96 hours).

Pain measurements based on a modified objective pain score for the first 120 minutes in postoperative recovery did not show any reduction in the ropivacaine-treated group. The average over all time points modified objective pain scores favored the placebo group over the ropivacaine group (*P*=.06 test of between-subjects effects; **Figure 2**). Similarly, the average over all time points behavior score favored the placebo group over the ropivacaine group (*P*=.046 test of between-subjects effects; **Figure 3**).

Table 2. Pharmacokinetic Parameters of Ropivacaine in 48 Children

Value	C_{max}, µg/mL	$t_{½}$, h	CL, mL/h per kg	Vdss, L/kg
Mean	0.71	1.29	1121	1.81
SD	0.33	1.03	1021	1.15
Median	0.67	0.96	870	1.51
Range	0.15-2.06	0.22-5.96	162-6083	0.36-6.56

Abbreviations: CL, ropivacaine clearance; C_{max}, peak concentration; $t_{½}$, half-life; Vdss, volume of distribution at steady state.

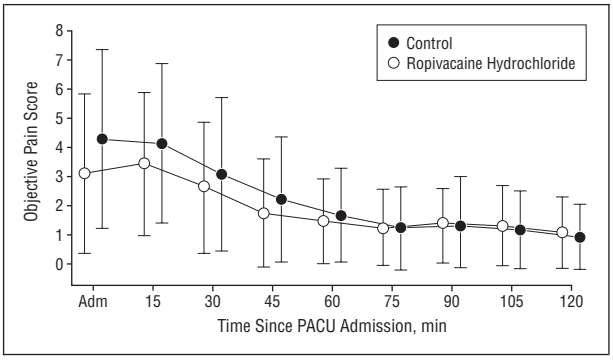

Figure 2. Change in objective pain score (mean±SD) over time by treatment group. Higher score represents greater pain. PACU indicates postanesthesia care unit; Adm, admission.

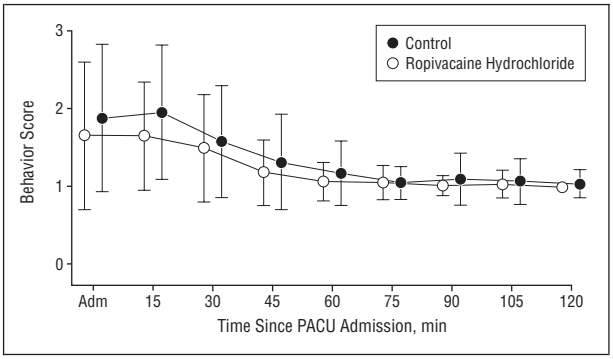

Figure 3. Change in behavior score (mean±SD) over time by treatment group. Higher score represents greater behavioral problem, ie, agitated and thrashing child. PACU indicates postanesthesia care unit; Adm, admission.

Table 3. Indirect Measures of Postoperative Pain*

Variable	Placebo	Ropivacaine	*P* Value (Test)
Time to first oral intake, mean ± SD, min†	51 ± 30	55 ± 38	.51 (*t*)
Time until oral intake exceeded 100 mL, mean ± SD, min‡	105 ± 50	120 ± 49	.10 (*t*)
Frequency of fentanyl citrate for rescue pain medication§			
0	12	5	
1	13	17	
2	16	23	
3	13	15	
4	6	5	
5	2	1	
6	1	0	
Mean ± SD	1.97 ± 1.4	2.02 ± 1.1	.84 (*t*)
Frequency of acetaminophen + codeine for rescue pain medication§			
0	2	5	
1	58	58	
2	3	2	
3	0	1	
Mean ± SD	1.02 ± 0.28	0.99 ± 0.4	.62 (Fisher exact)
Total doses of codeine on day 1, mean ± SD	4.79 ± 1.23	4.73 ± 1.05	.74 (*t*)

*Placebo was given as isotonic sodium chloride solution; ropivacaine as ropivacaine hydrochloride injection.
†Time interval from time of arrival to postanesthesia care unit to first oral intake.
‡Time interval from time of arrival to postanesthesia care unit to time exceeded 100 mL of oral intake.
§All values measured in recovery room only.

Indirect measures of postoperative pain such as time to first oral intake, time until oral intake exceeded 100 mL of fluids, and frequency of rescue pain medication use did not differ between the 2 groups (**Table 3**). Measures for throat and ear pain, proportion of patients taking solid or liquid foods, quantity of liquids taken, and proportion of patients resuming normal activity were not different between the 2 groups at postoperative days 1, 3, 7, and 14. Neck pain, however, showed a statistically significant difference ($P=.04$) when averaged over postoperative days 1, 3, 7, and 14 in the placebo group (**Figure 4**).

The frequency of emesis and use of rescue medication for retching or emesis were not different for the 2 groups (**Table 4**). The percentage of patients who had retching in the recovery room was greater, however, in the ropivacaine group ($P=.006$, Table 4). The proportion of patients with retching or vomiting was not found to be different at postoperative days 1, 3, 7, and 14.

Complications were similar between the 2 groups, as shown in the following tabulation.

Complication	Placebo Group	Ropivacaine Group
Airway obstruction	1	3
Dehydration	2	4
Hemorrhage	1	2
Neck spasms	0	1
Croup	1	0

There were 4 episodes of airway obstruction in the postanesthesia care unit. One patient in the placebo group was transferred to the pediatric intensive care unit for observation owing to a right-sided pneumonia. Two patients in the ropivacaine group developed airway obstruction in the immediate postoperative period. One child's obstruction resolved with oral suctioning of copious secretions and an albuterol treatment. The other child required a short period of positive airway pressure. An 11-year-old girl in the ropivacaine group complained of difficulty breathing. The patient received a racemic epinephrine treatment, which alleviated her breathing difficulties.

COMMENT

The hypothesis of this study was that 0.5% ropivacaine hydrochloride with epinephrine injection into the peritonsillar space would result in a markedly decreased pain intensity with minimal adverse effects. To our surprise, pain was not reduced in the ropivacaine-treated group based on the modified objective pain score. The average over all time points modified objective pain scores instead favored the placebo over the ropivacaine group. Similarly, the average over all time points behavior score favored the placebo over the ropivacaine group. The neck pain score showed a statistically significant difference that favored the placebo group when averaged over postoperative days 1, 3, 7, and 14. The percentage of patients who had retching in the recovery room was greater in the ropivacaine group.

The reason for these unexpected results is unclear. One possibility is that we did not use a large enough sample size to detect a more favorable result with the ropivacaine group. The sample size was calculated using a *t* test and assuming a 60% reduction in the ropivacaine group's objective pain score upon arrival to the recovery room, an SD of 2.7, power of 0.90, and *P* value of .05. This assumption appeared reasonable because a pilot nonrandomized study of 25 patients showed better objective pain scores in the ropivacaine group and a similar standard deviation. One conclusion from the data is that a favorable response of less than 60% from ropivacaine can exist. This conclusion is tempered by the observa-

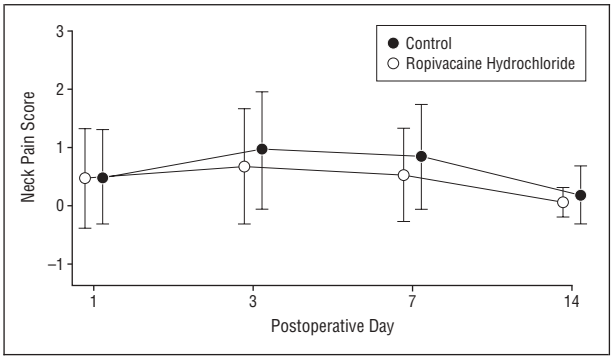

Figure 4. Change in neck pain score over time by treatment group. Higher score represents greater pain.

Table 4. Emesis and Retching Parameters in the Recovery Room for the 2 Treatment Groups*

Variable	Patients, %		*P* Value (χ^2 Test)
	Placebo	Ropivacaine	
Emesis	30	39	.24
Retching	19	41	.006
Rescue medication for retching or emesis	41	53	.21

*Placebo was given as isotonic sodium chloride solution; ropivacaine as ropivacaine hydrochloride injection.

tion that none of parameters measured in this study favored the ropivacaine group.

Another limitation of the study is the problem of peritonsillar dose. The peritonsillar space possesses a relatively small volume that can accommodate medication. A standard dose of 30 mg per patient was injected to maximize the volume of ropivacaine (6 mL) provided. Since there are no data on appropriate dosage of ropivacaine for pediatric adenotonsillectomy, we chose an arbitrary dose based on our pilot study of 25 nonrandomized patients. This small pilot study indicated a difference with respect to behavior and verbalization scores compared with placebo controls and no adverse effects. Perhaps, a higher dose may have provided a better outcome in this study.

One may speculate that the intraoperative administration of fentanyl may have masked the early postoperative pain scores of both treatment groups. The modified objective pain and behavior scores were quite low during the first 120 minutes in the postanesthesia care unit.

Another indicator of the relative comfort of the patients in the placebo group was the observation by the study nurses that almost every child slept during most of the 120-minute observation period. A number of studies have shown the beneficial effects of fentanyl for postoperative analgesia and emesis.[6,7] Since both groups received fentanyl, this effect would not have explained the better outcomes in the placebo group.

One may have questioned why the injection was performed after the tonsillectomy. Several articles have noted long-lasting efficacy of local anesthetic injection when performed before adenotonsillectomy.[3,8-10] Pharmacologic blockade of the sensory pathways is believed to prevent nociceptive impulses from reaching the spinal cord during surgery.[9] Giannoni et al[10] noted that preincisional injection of ropivacaine with clonidine prior to tonsillectomy provided decreased pain and opioid use and faster return to normal activity compared with a placebo group of pediatric patients. This technique was part of the original plan of this study but was abandoned several months prior to implementation when a child underwent preincisional injection of ropivacaine and developed transient bigeminy and pulmonary edema. This result occurred despite the principal investigator's careful aspiration of the medication with a control-top syringe, and slow, careful infiltration into the submucosal tissues. A subsequent pilot study and this study used a careful submucosal injection into the posteromedial aspect of the tonsillar pillar after adenontonsillectomy. The rationale for this approach was to maximally deliver medication away from important neurovascular structures.

Complications from local anesthetic injection into the peritonsillar space have been cited in the literature. Bean-Lijewski[11] terminated her study with bupivacaine local injection after 2 of 4 children developed upper airway obstruction and pulmonary edema. The technique for injection probably contributed to their high incidence of complications since the medication was placed deep into the parapharyngeal space in close proximity to several cranial nerves. Tajima et al[12] described a child who developed pulmonary edema and intracranial hemorrhage following epinephrine infiltration for a tonsillectomy. Alsarraf and Sie[13] presented a case of a 16-year-old girl who developed cardiac asystole and a central medullopontine infarct following bupivacaine and epinephrine injection into the tonsillar and adenoid bed.

Fortunately, we did not detect any central nervous system or cardiotoxic effects from infiltrating the medial aspect of the posterior tonsillar pillar. The plasma ropivacaine levels typically peaked 30 minutes following admission to the postanesthesia care unit then diminished over the ensuing 90 minutes. These peak levels were lower and had a more rapid decline over time than other adult studies of ropivacaine use following axillary or inguinal blocks.[4,14,15] The levels were much lower than reported in a patient who developed convulsions following intravascular injection of ropivacaine for axillary brachial plexus blockade.[16]

In summary, this study did not show any beneficial reduction in postadenotonsillectomy recovery from postprocedure injection of 0.5% ropivacaine and epinephrine over isotonic saline into the peritonsillar space. In addition, behavior score, retching frequency in the recovery room and neck pain over time favored the placebo over the ropivacaine-treated group in a statistically significant manner. The plasma concentrations of ropivacaine were low and relatively short-lived with peak levels decreasing 30 minutes following postanesthesia care unit admission. Thus, we cannot advocate the routine use of ropivacaine hydrochloride with epinephrine injection into the peritonsillar space after adenotonsillectomy. Additional studies using a higher ropivacaine concentration or longer-acting agent may show efficacy.

Submitted for publication July 11, 2003; final revision received September 16, 2003; accepted September 22, 2003.

We would like to acknowledge Xin Zhang, MD, Scott Jellish, MD, Gregory Matz, MD, Kristina Sawicki, RN, and Helen Kim, RN, for their invaluable assistance of this study and Astra-Zeneca for graciously providing the ropivacaine hydrochloride.

This study was presented at American Society of Pediatric Otolaryngology; May 5, 2003; Nashville, Tenn.

This study received the Medtronic Xomed Award for Excellence in Clinical Research.

Corresponding author and reprints: Albert H. Park, MD, Pediatric Otolaryngology, Primary Childrens Medical Center, 100 N Medical Dr, Suite 4500, Salt Lake City, UT 84113 (e-mail: pcapark@ihc.com).

REFERENCES

1. Warnock F, Lander J. Pain progression, intensity and outcomes following tonsillectomy. *Pain.* 1998;75:37-45.
2. Colclasure J, Graham S. Complications of tonsillectomy and adenoidectomy. In: Eisele D, ed. *Complications in Otolaryngology–Head and Neck Surgery.* St Louis, Mo: Mosby; 1993.
3. Jebeles J, Reilly JS, Gutierrez JF, Bradley EL Jr, Kissin I. The effect of preincisional infiltration of tonsils with bupivacaine on the pain following tonsillectomy under general anesthesia. *Pain.* 1991;47:305-308.
4. Mulroy M, Burgess F, Emanuelsson B. Ropivacaine 0.25% and 0.5% but not 0.125% provide effective wound infiltration analgesia after outpatient hernia repair but with sustained plasma drug levels. *Reg Anesth Pain Med.* 1999;24:136-141.
5. Naropin Injection (AstraZeneca LP). *Physicians' Desk Reference Electronic Library.* Montvale, NJ: Medical Economics Co; 2003.
6. Davis P, Finkel JC, Orr RJ, et al. A randomized, double-blinded study of remifentanil versus fentanyl for tonsillectomy and adenoidectomy surgery in pediatric ambulatory surgical patients. *Anesth Analg.* 2000;90:863-871.
7. Mukherjee K, Esuvaranathan V, Streets C, Johnson A, Carr AS. Adenotonsillectomy in children: a comparison of morphine and fentanyl for peri-operative analgesia [erratum published in *Anaesthesia.* 2002;57:208]. *Anaesthesia.* 2001;56:1193-1197.
8. Jebeles J, Reilly JS, Gutierrez JF, Bradley EL Jr, Kissin I. Tonsillectomy and adenoidectomy pain reduction by local bupivacaine infiltration in children. *Int J Pediatr Otorhinolaryngol.* 1993;25:149-154.
9. Goldsher M, Podoshin L, Fradis M, et al. Effects of peritonsillary infiltration on post-tonsillectomy pain: a double-blind study. *Ann Otol Rhinol Laryngol.* 1996;105:868-870.
10. Giannoni C, White S, Enneking FK, Morey T. Ropivacaine with or without clonidine improves pediatric tonsillectomy pain. *Arch Otolaryngol Head Neck Surg.* 2001;127:1265-1270.
11. Bean-Lijewski JM. Glossorpharyngeal nerve block for pain relief after pediatric tonsillectomy: retrospective analysis and two cases of life-threatening upper airway obstruction from an interrupted trial. *Anesth Analg.* 1997;84:1232-1238.
12. Tajima K, Sato S, Miyabe M. A case of acute pulmonary edema and bulbar paralysis after local epinephrine infiltration. *J Clin Anesth.* 1997;9:236-238.
13. Alsarraf R, Sie K. Brain stem stroke associated with bupivacaine injection for adenotonsillectomy. *Otolaryngol Head Neck Surg.* 2000;122:572-573.
14. Pettersson N, Emanuelsson BM, Reventlid H, Hahn RG. High-dose ropivacaine wound infiltration for pain relief after inguinal hernia repair. *Reg Anesth Pain Med.* 1998;23:189-196.
15. Pere P, Salonen M, Jokinen M, Rosenberg PH, Neuvonen PJ, Haasio J. Pharmacokinetics of ropivacaine in uremic and nonuremic patients after axillary brachial plexus block. *Anesth Analg.* 2003;96:563-569.
16. Muller M, Litz RJ, Huler M, Albrecht DM. Grand mal convulsion and plasma concentrations after intravascular injection of ropivacaine for axillary brachial plexus blockade. *Br J Anaesth.* 2001;87:784-787.