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

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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 (Cmax) 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.


PAIN CONTROL CONTINUES TO be a challenge for adenotonsillectomy patients. Warnock and Lander 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 noted a 1% readmission rate for patients undergoing tonsillectomy because of odynophagia and dehydration. The pathophysiologic mechanism is believed to be mediated by noxious stimulation of C-fiber afferents located in the peritonsillar space. 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. 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. Nonclinical pharmacology studies comparing the 2 anesthetics in animals found fewer cardiac toxic effects with ropivacaine. The objectives of this study were to determine whether the perioperative ad-
ministration of ropivacaine hydrochloride decreases post-operative 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 0.3 to 0.7 mg/kg of midazolam mixed with 3 to 5 mL of acetaminophen (160 mg/5mL) 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 was given as part of the envelope and instructions how to mix the epinephrine and ropivacaine. The operating surgeon was blinded to the study drug contents.

Three milliliters of the study medication was injected peritonsillar immediately after tonsillectomy. In addition, we sought to determine absorption of ropivacaine from the peritonsillar space to ascertain blood concentrations following injection.

Plasma ropivacaine levels were obtained before, and at 30, 60, and 90 minutes after tonsillar fossa infiltration. Levels were obtained in the isotonic saline arm to validate the assay. Levels were anticipated start of surgery. Anesthesia was induced and main- tained 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 otolaryngologist. The 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 otolaryngologist. The 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 otolaryngologist.

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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 Cmax (0.71±0.33 µg/mL) occurred at 30 minutes in 48 of the 53 patients. In the remaining 5 patients, the Cmax 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).
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 \((P=0.04)\) 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 \((P=0.006, \text{Table 4})\). 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.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Placebo Group</th>
<th>Ropivacaine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway obstruction</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Dehydration</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Neck spasms</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Croup</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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. 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 0.05. This assumption appeared reasonable because a pilot non-randomized 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-

### Table 3. Indirect Measures of Postoperative Pain*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Ropivacaine</th>
<th>(P) Value (Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first oral intake, mean ± SD, min†</td>
<td>51 ± 30</td>
<td>55 ± 38</td>
<td>0.51 ((t))</td>
</tr>
<tr>
<td>Time until oral intake exceeded 100 mL, mean ± SD, min‡</td>
<td>105 ± 50</td>
<td>120 ± 49</td>
<td>0.10 ((t))</td>
</tr>
<tr>
<td>Frequency of fentanyl citrate for rescue pain medication§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>17</td>
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<td>2</td>
<td>16</td>
<td>23</td>
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<tr>
<td>3</td>
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<td>4</td>
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<tr>
<td>5</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.97 ± 1.4</td>
<td>2.02 ± 1.1</td>
<td>0.84 ((t))</td>
</tr>
<tr>
<td>Frequency of acetaminophen + codeine for rescue pain medication§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58</td>
<td>58</td>
<td></td>
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<tr>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.02 ± 0.28</td>
<td>0.99 ± 0.4</td>
<td>0.62 (Fisher exact)</td>
</tr>
<tr>
<td>Total doses of codeine on day 1, mean ± SD</td>
<td>4.79 ± 1.23</td>
<td>4.73 ± 1.05</td>
<td>0.74 ((t))</td>
</tr>
</tbody>
</table>

*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.
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 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 adenotonsillectomy. 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-Lijewski11 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 al12 described a child who developed pulmonary edema and intracranial hemorrhage following epinephrine infiltration for a tonsillectomy. Alsarraf and Sic13 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.8,14,15 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 0.3% 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.

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