Ropivacaine With or Without Clonidine Improves Pediatric Tonsillectomy Pain

Carla Giannoni, MD; Sno White, MD; F. Kayser Enneking, MD; Timothy Morey, MD

Objective: To determine if preemptive analgesia with ropivacaine hydrochloride with or without clonidine hydrochloride decreases pain and hastens recovery after tonsillectomy.

Design: Prospective, randomized, triple-blinded trial.

Setting: University referral center; pediatric ambulatory practice.

Participants: Sixty-four children, aged 3 to 15 years, undergoing tonsillectomy.

Interventions: Patients received injections in the tonsillar fossae of isotonic sodium chloride, ropivacaine, or ropivacaine plus clonidine prior to tonsil excision.

Main Outcome Measures: Visual analogue (pain) scale scores at rest and when drinking, opioid use, recovery time to normal activity, and incidence of symptoms such as otalgia.

Results: Pain was reduced on postoperative day 0 in the ropivacaine-treated and ropivacaine plus clonidine–treated groups as compared with the isotonic sodium chloride–treated group (P<.05). Pain was also decreased in the ropivacaine plus clonidine–treated group on postoperative days 3 and 5 (P<.05). Intravenous narcotic use was decreased on day 0 in the ropivacaine–treated and ropivacaine plus clonidine–treated groups (P<.05). Cumulative codeine use was similar at day 3 for all patients, but was decreased at day 5 in the ropivacaine plus clonidine–treated group (P<.05). The incidence of otalgia decreased from 89% (16/18) in the isotonic sodium chloride–treated group to 63% (12/19) in the ropivacaine–treated and 61% (11/18) in the ropivacaine plus clonidine–treated groups (P<.01). Recovery to normal activity was shortened from 8.1±1.6 days to 5.8±2.9 days (mean±SD) in the isotonic sodium chloride–treated and ropivacaine plus clonidine–treated groups, respectively (P=.03).

Conclusion: Preincisional injection of ropivacaine with clonidine prior to tonsillectomy has a preemptive analgesic effect that outlasts the local anesthetic and decreases pain, opioid use, and the time to return to normal activity.


More than 280,000 children undergo tonsillectomy annually in the United States. Although children receive analgesics for pain control, operative pain remains a significant problem that is often undertreated in the pediatric population for several reasons. Children often refuse analgesics because the medication is not palatable or causes adverse effects such as nausea, vomiting, or somnolence. In addition, parents may not always recognize that a child is suffering because the child does not complain, but rather withdraws or becomes depressed. Prevention of pain perception may be a key factor in the management of postoperative pain. Several studies have shown that the analgesic effects of local anesthetics applied prior to injury far outlast the effects of local anesthetics instilled following injury. For example, Jeelese et al. reported a 10-day amelioration of pain scores in children who received bupivacaine local anesthetic infiltration prior to tonsillectomy compared with placebo injection. Subsequent studies, however, have failed to reproduce these results. Furthermore, no studies have assessed the effects of ropivacaine or the value of clonidine supplementation to the injectate. Ropivacaine is a new, synthetic, long-acting, amide-type local anesthetic with intrinsic vasoconstrictive properties. Compared with racemic bupivacaine hydrochloride, ropivacaine has equivalent anesthetic properties but has less potential to cause serious cardiotoxic reac-
RESULTS

The study patients were comparable between groups for age, sex, and operation performed (Table 1). Fifty-seven patients had adenotonsillectomy and 7 had tonsillectomy only. Eight patients concurrently had placement of tympanostomy tubes, 1 had removal of a retained tympanostomy tube, and 1 had a frenulectomy.

The study patients were comparable between groups for age, sex, and operation performed (Table 1). Fifty-seven patients had adenotonsillectomy and 7 had tonsillectomy only. Eight patients concurrently had placement of tympanostomy tubes, 1 had removal of a retained tympanostomy tube, and 1 had a frenulectomy.

Pain medication use in the immediate postoperative period was significantly different between the groups (Table 2). Use of additional intravenous fentanyl was higher in the saline-treated group than the ropivacaine–treated or ropivacaine plus clonidine–treated groups (P = 0.049). Remarkably, all of the patients in the saline-treated group required additional intravenous or oral narcotic pain medications during the 3-hour recovery room stay, whereas 5 patients (24%) in the ropivacaine–treated group and 8 (36%) of the patients in the ropivacaine plus clonidine–treated group required no additional analgesics.

Children in the saline-treated group had significantly more pain both at rest and with swallowing in the recovery room than did children in either of the ropivacaine–treated groups (Figure). No difference between groups was seen at 24 and 48 hours postoperatively. The VAS pain scores taken at rest and with swallowing were greater for the saline-treated group compared with the ropivacaine plus clonidine–treated group on postoperative days 3 and 5 (P<.05). The VAS scores taken at rest were similar to those taken with swallowing although the scores with swallowing tended to be lower. All children had normal or near-normal VAS scores (VAS=0) by postoperative day 10.
Cumulative codeine use was similar between the groups for the first 3 postoperative days but was significantly lower for the ropivacaine plus clonidine–treated group on postoperative day 5 (Table 2). Data for cumulative codeine use at day 10 could not be analyzed owing to the high percentage (42%, 27 subjects) of subjects for whom that data could not be collected. The first 5 days of recovery are clearly the most significant for analysis: 26 (62%) of 37 parents who did report total codeine use at day 10 reported that 2 or fewer additional doses were used between days 5 and 10. Analyses of the doses of other analgesic medications, such as ibuprofen and plain acetaminophen, showed no differences between the 3 groups.

Subjective symptoms of headache, otalgia, and nausea were evaluated (Table 3). There was a significant decrease in the incidence of referred ear pain (otalgia) from 89% (16/18) in the control group to 63% (12/19) and 61% (11/18) in the 2 ropivacaine-treated groups. A trend of less nausea and vomiting was seen in those 2 groups.

Complications were similar among the 3 groups including estimated surgical blood loss, weight loss, hospital admission, and posttonsillectomy hemorrhage (Table 4). Bleeding was defined as the appearance of bright red blood by mouth or nose or the occurrence of hematemesis regardless of whether the bleeding required a physician’s evaluation. No patient in any group reported posttonsillectomy bleeding and no subject required a second surgical procedure. All surgical procedures were performed on an outpatient basis; no unexpected hospital admissions occurred in the first 24 hours after surgery. The 2 emergency center visits and 2 hospital admissions were due to pain, poor oral intake, and/or dehydration. Overall hydration status was assessed by weight loss between day 0 and day 5 and was found to be similar between all children. Children had both weight measurements taken on the same scale at the outpatient surgical center. The weight loss experienced by patients varied widely. The average weight loss was 1.5% of preoperative weight, whereas the maximal weight loss was 10% of preoperative weight. Specific gravity of morning urine was collected on day 5 but showed no differences between groups even when compared with immediate postoperative urine samples.

### Table 1. Patient Demographics for Children Randomized to the 3 Treatment Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Saline-Treated Group* (n = 21)</th>
<th>Ropivacaine Hydrochloride–Treated Group (n = 21)</th>
<th>Ropivacaine + Clonidine Hydrochloride–Treated Group (n = 22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. of children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>9</td>
<td>13</td>
<td>.52</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>12</td>
<td>9</td>
<td>.88</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>7.4 ± 3.7</td>
<td>7.0 ± 2.9</td>
<td>7.6 ± 3.5</td>
<td></td>
</tr>
<tr>
<td>Type of surgical procedure, No. of children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenotonsillectomy</td>
<td>20</td>
<td>20</td>
<td>17</td>
<td>.09</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*The saline-treated group indicates those given a dose of isotonic sodium chloride placebo.

### Table 2. Pain Medication Use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Saline-Treated Group*</th>
<th>Ropivacaine Hydrochloride–Treated Group</th>
<th>Ropivacaine + Clonidine Hydrochloride–Treated Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery room (day 0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of intravenous narcotic doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3†</td>
<td>12</td>
<td>11</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>No. of oral codeine doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>10</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Home (day 0-5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total doses of codeine, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 3</td>
<td>6.2 ± 5.5‡</td>
<td>7.8 ± 5.6</td>
<td>5.4 ± 4.1</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>At day 5</td>
<td>11.4 ± 7.1</td>
<td>12.2 ± 8.9</td>
<td>8.5 ± 7.6</td>
<td></td>
</tr>
</tbody>
</table>

*The saline-treated group indicates those given a dose of isotonic sodium chloride placebo.

†Number of patients requiring a given number of doses of narcotic in the recovery room.

‡Total doses of medication used since discharge from the recovery room.
Hypersensitivity lowers the intensity of stimuli re-
test to begin transmitting painful sen-
tivity, hyperalgesia, and secondary hyperalgesia occur.
Hypersensitivity lowers the intensity of stimuli re-
quired to trigger a reaction. Hyperalgesia magnifies
the response generated by the sensed stimulus. Second-
ary hyperalgesia spreads hypersensitivity to nonin-
olved tissue.

The idea of providing preemptive analgesia to block
the development of hypersensitivity and hyperalgesia and,
thus, decrease postsurgical pain is not new. As early as
1953, otolaryngologists were using local injection of an-
esthetics to relieve postsillectomy pain.12 Jebeles et al6
in 1991, renewed interest in preemptive analgesia for ton-
sillectomy when they demonstrated that the preemptive
effect of preincisional bupivacaine plus epinephrine on
pain lasted a full 10 days after surgery.6 Goldsher et al14
and Johansen et al15 also showed a decrease in pain after
tonsillectomy using preincisional bupivacaine for 2 and
10 days, respectively. Not all investigators, however, have
been able to reproduce these promising results.9,10-16 An
overview of past studies suggested that higher patient
numbers per study group, higher promising results for local,
and addition of epinephrine to local anesthetics were
potentially associated with positive preemptive
effects.

In this study preemptive injection of a combina-
tion of ropivacaine plus clonidine significantly im-
proved pain and recovery after tonsillectomy in several
measured areas. One measure of pediatric pain assess-
ment is the self-reported VAS. The main limitation of the
self-report assessment is the wide degree of interpatient
variability. The scale has been validated in children as
young as 3 years and provides reasonable trending for a
given patient. Pain scores, both at rest and with drink-
ing, on days 3 and 5 were statistically significantly lower
in children receiving the combination injection com-
pared with those receiving injections of either saline or
ropivacaine alone. In adult patients VAS scores are gen-
erally correlated as follows: 3 or less, minimal pain; 4 to
6, moderate pain; and 7 to 10, severe pain. Thus, these
VAS results are not only statistically but also clinically
significant because they show a decrease from moderate
pain to minimal pain. Further evidence of the subjects'
improved clinical recovery is seen in the analysis of co-
dine use. The groups used similar amounts of pain medica-
tion through day 3, but by day 5 the study's ropiva-
caine plus clonidine–treated group had used significantly
less pain medication. A final behavioral measure of pain
is the parental report of time to final recovery. The
children in the saline-treated group had the longest recov-
er, 8.1 days on average, compared with the ropivacaine-
treated group, 6.1 days, and the ropivacaine plus clonidine–treated group, 5.8 days (P < .05).

To our knowledge, associated quality-of-life issues
such as referred pain (otalgia) have not been evaluated
in other studies. Otolgia was significantly decreased for
both ropivacaine-treated groups. This observation sup-
ports the hypothesis that preemptive analgesia may act
by decreasing central sensitization. The failure of the VAS
pain scores and other variables to achieve significant dif-
fferences in the ropivacaine–treated group compared with
the control group is consistent with the finding of pre-
vious studies with few patients in the study groups. Be-
cause of the many pathways involved in surgical pain,
one can hypothesize that local anesthetic alone cannot

**COMMENT**

Recent advances in the study of pain delineate clear dif-
fferences between inflammatory pain, the type produced
by surgical trauma, and physiologic or functional pain.
Physiologic pain is a response to a specific stimulus, a
warning to the organism to withdraw from danger. When
the organism cannot retreat, as when immobilized by gen-
eral anesthesia, a vicious cycle commences.11 Contin-
ued injury of tissue causes long-lasting changes in sen-
sitivity. Two mechanisms help produce this state. First,
chemical mediators released by injury cause peripheral
hypersensitivity of primary sensory neurons.12 Second,
hyperexcitation of the spinal cord causes low threshold
A-B mechanoreceptors to begin transmitting painful sen-
sations creating central hypersensitivity.13 Hypersensi-
tivity, hyperalgesia, and secondary hyperalgesia occur.
Hypersensitivity lowers the intensity of stimuli re-

---

**Graph:**

Effect of tonsillar infiltration with isotonic sodium chloride (saline) placebo, ropivacaine hydrochloride alone, and ropivacaine plus clonidine hydrochloride on postoperative pain in children at rest (A) or following swallowing (B) as measured using the visual analogue scale (VAS). Data are given as mean ± SEM. P < .05: each group at postoperative days 1, 2, 3, 5, or 10 compared with itself at postoperative day 0 (*); saline placebo compared with ropivacaine (†) or ropivacaine plus clonidine (‡). P values for overall 1-way analysis of variance for VAS over time for pain at rest or following swallowing were .03 and less than .001, respectively.

6.5 ± 2.0 days (P = .17 compared with placebo) but did not
affect recovery time compared with the ropivacaine plus clonidine–treated group. The duration of recovery short-
ened from 8.1 ± 1.6 days to 5.8 ± 2.9 days in the placebo
and ropivacaine plus clonidine–treated groups, respec-
tively (P = .03).
consistently lessen the incidence or severity of postoperative pain. In our patients there were relatively high VAS scores in all groups initially but an abrupt decrease in the VAS in the ropivacaine plus clonidine–treated group compared with the control group at postoperative days 3 and 5. This was consistent within each group of patients as reflected by the low SDs within each group and was also correlated with the behavioral scores between each group reflected in the more rapid return to activity in the ropivacaine–treated and ropivacaine plus clonidine–treated groups. As discussed earlier, current theories for the mechanisms of surgical pain, as well as some chronic pain conditions, explain the seemingly unusual finding of lessened pain at postoperative days 3 and 5 but not postoperative days 1 and 2 in our study group. Preemptive analgesia has been investigated by numerous studies and is proposed to work by preventing “windup” or central sensitization. Preemptive analgesia using local anesthetics has its effect by decreasing the peripheral nociceptive stimulus that, in turn, decreases the development of peripheral hyperalgesia and peripheral hypersensitivity. The lessening of peripheral sensitization decreases the central spinal cord stimulation thereby preventing central hyperexcitation and central sensitization. Overall, this has the effect of maintaining a high nociceptive threshold and low state of central sensitization compared with the state where no peripheral analgesia is present before the traumatic stimulus is initiated. The study results suggest that the initial inflammatory pain due to tissue trauma is not lessened by preemptive analgesia. As the inflammatory pain subsides, the effect of preemptive analgesia is seen in the lessening of the physiologic component of surgical pain.

These data suggest that combining clonidine with local anesthetics has an additive effect on pain control. The VAS pain scores and recovery rate in the ropivacaine–treated group were in between the values of the control group and those of the ropivacaine plus clonidine–treated group. The addition of clonidine in the ropivacaine plus clonidine–treated group proved to be an important factor that significantly enhanced analgesia and recovery in these children. Clonidine seems to be responsible for the decrease in the need for supplemental analgesia in the later postoperative period (days 3–5). In our study, the addition of clonidine to ropivacaine significantly improved pain and recovery after tonsillectomy.

There are some limitations of this study. Although a computer-generated randomization was used to assign children to the study arms, a trend to assign more patients undergoing tonsillectomy only to the ropivacaine plus clonidine–treated group occurred. This might influence early pain but is probably not a notable factor in late pain and recovery where our most substantial findings occurred. Arguably, the number of subjects in this study is not adequate to fully assess the effect of ropivacaine or ropivacaine plus clonidine on postoperative complications such as posttonsillectomy bleeding or hospital admission. Finally, the evaluation of pain in children is difficult. Although validated for children as young as 3 years, the VAS pain scale can be confusing for children to use. Pain medication use is difficult to quantify since it requires precise dosing of a liquid preparation; accounting for loss due to spillage, vomiting, and spitting; and precise record keeping. Furthermore, the use of pain medication varies widely among children after identical surgical procedures. Despite these intrinsic limitations, because multiple measures of pain and recovery were used, the results reflect a clear effect of ropivacaine plus clonidine on tonsillectomy pain.

### Table 3. Subjective Symptoms*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Saline-Treated Group</th>
<th>Ropivacaine Hydrochloride–Treated Group</th>
<th>Ropivacaine + Clonidine Hydrochloride–Treated Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and/or vomiting</td>
<td>60†</td>
<td>30</td>
<td>41</td>
<td>.16</td>
</tr>
<tr>
<td>Headache</td>
<td>40</td>
<td>32</td>
<td>25</td>
<td>.63</td>
</tr>
<tr>
<td>Ear pain or otalgia</td>
<td>89</td>
<td>63</td>
<td>61</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data are given as percentages. The saline-treated group indicates those given a dose of isotonic sodium chloride placebo. †Percentage of subjects experiencing the symptom.

### Table 4. Complications of Tonsillectomy*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Saline-Treated Group</th>
<th>Ropivacaine Hydrochloride–Treated Group</th>
<th>Ropivacaine + Clonidine Hydrochloride–Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical blood loss, mean ± SD, mL</td>
<td>58 ± 38</td>
<td>71 ± 79</td>
<td>45 ± 37</td>
</tr>
<tr>
<td>Emergency department visit (for those who were not admitted)</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hospital admission (day)</td>
<td>1.7 ± 3.2</td>
<td>1.9 ± 3.2</td>
<td>1.0 ± 6.1</td>
</tr>
<tr>
<td>Weight loss, mean ± SD, % of baseline weight</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Posttonsillectomy hemorrhage</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are given as the number of patients who experienced an adverse event unless otherwise indicated. The saline-treated group indicates those given a dose of isotonic sodium chloride placebo. For all data P > .05.
CONCLUSIONS

This study shows that a significant reduction in late post-tonsillectomy pain and medication use can be achieved using a combination of ropivacaine plus clonidine. The injection of local anesthetic had a clear effect on immediate postoperative pain control in both ropivacaine-treated groups that disappeared by the next morning. After 2 days of significant discomfort, the ropivacaine plus clonidine–treated group began to do significantly better than their counterparts; this effect continued to complete recovery. Thus, we believe the value of preemptive analgesia is in the reduction of pain in the recovery room and in the latter half of the recovery period. Referred pain likely results from stimulation of a different pain pathway than local surgical pain. This may explain the remarkable decrease in otalgia in both ropivacaine-treated groups in the late postoperative period. The combined data of VAS pain scores, medication use, and return to normal activity demonstrate that there is a preemptive effect of the use of ropivacaine plus clonidine on recovery from tonsillectomy.

Accepted for publication May 17, 2001.

Presented at the 16th Annual Meeting of the American Society of Pediatric Otolaryngology, Scottsdale, Ariz, May 9-12, 2001.

We gratefully acknowledge the administrative efforts of Susan Degennaro, RN, who was essential in the organized implementation of this study.

Corresponding author and reprints: Carla Giannoni, MD, Pediatric Otolaryngology, 1102 Bates, Suite 340, Houston, TX 77030 (e-mail: cmsgianno@texaschildrenshospital.org).

REFERENCES