

Ropivacaine With or Without Clonidine Improves Pediatric Tonsillectomy Pain

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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 \pm 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.

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MORE THAN 280 000 children undergo tonsillectomy annually in the United States.¹ 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.²⁻⁵ For example, Jeebles et al^{6,7} 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.^{8,9} 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-

SUBJECTS, MATERIALS, AND METHODS

To determine the possible benefit of preemptive analgesia for children undergoing tonsillectomy, a prospective, randomized, triple-blinded study of 64 children, aged 3 to 15 years, was performed. The study received University of Florida institutional review board approval. One hundred consecutive patients of a single attending surgeon (C.G.) scheduled for tonsillectomy were offered enrollment in the study. Parents gave written consent to enroll their children in the study. Children were randomized to 1 of 3 study arms described subsequently by use of a random number generator (Excel; Microsoft Corp, Redmond, Wash). The study drug was supplied as syringes of a liquid, identical in color and volume but designated by a letter to 1 of the study groups. All physicians, nurses, patients, parents, and others were blinded to the assignment of the children to the study arms until the conclusion of the study. Four patients were enrolled but did not complete the evaluation period and were excluded from statistical analysis.

Children received a premedication combination of oral ibuprofen (15 mg/kg) and midazolam hydrochloride (0.5 mg/kg; maximum dose, 20 mg) followed by a standard general inhalational anesthetic. Children also received 1 µg/kg of fentanyl citrate and 0.25 mg/kg of metaclopramide intravenously. All children had peritonsillar injection of the assigned study drug after induction of anesthesia and prior to excision of the tonsils. Those in the isotonic sodium chloride-treated group (hereafter referred to as the saline-treated group) received tonsillar injections of isotonic sodium chloride (0.16 mL/kg), those in the ropivacaine hydrochloride-treated group received tonsillar injections of a combination of 1% ropivacaine hydrochloride (0.15 mL/kg) and isotonic sodium chloride (0.01 mL/kg), and

those in the ropivacaine plus clonidine hydrochloride-treated group received tonsillar injections of a combination of ropivacaine hydrochloride (0.15 mL/kg) and clonidine (1 µg/kg [0.01 mL/kg]). The maximal total injectate volume was 4 mL per tonsil. A minimum duration of 5 minutes was allowed for the onset of action of the study drug. The procedures were performed by otolaryngology residents who had a similar level of experience under the direct supervision of one of us (C.G.). The same electrocautery dissection technique for tonsillectomy was used in all cases.

Postoperative care, including control of pain and nausea, was based on a study protocol and was identical for all patients. All children received acetaminophen with codeine (24 mg of acetaminophen; 2.4 mg of codeine per milliliter) (every 4 hours as needed) for postoperative pain control. Pain was measured at rest and when drinking and scored on a visual analogue scale (VAS). On postoperative days 0, 1, 2, 3, 5, and 10, VAS pain scores and activity level were recorded for all participants. Cumulative analgesic medication use was recorded on days 3, 5 and 10. Weight and urine specific gravity on days 0 and 5 were recorded as an indirect measure of hydration status. All adverse effects including bleeding and hospital admissions were recorded.

Tests of statistical significance for interval data were performed using a paired *t* test, a 1-way analysis of variance (ANOVA), or a 2-way repeated measured ANOVA followed by Bonferroni correction for multiple comparisons (SPSS Version 10.0; SPSS Inc, Chicago, Ill) when appropriate. Nominal data were analyzed using the χ^2 test or Fisher exact test when appropriate. All data are expressed as mean \pm SD. A value of $P < .05$ was considered statistically significant. The study was powered around the VAS pain score. Calculations were performed using a change in (VAS) means of 2.0 with an SD of 2.0. The study power was estimated to be 0.89% with a sample size of 20 subjects per group.

tions (eg, arrhythmogenicity, cardiac depression). Its duration of action is 6 to 8 hours in peripheral block. The addition of vasoconstrictors and certain other agents to local anesthetic injectate improves the onset, intensity, and duration of anesthesia and preemptive analgesia. Clonidine is a centrally acting sympathologic agent that has intrinsic analgesic properties and has been shown to prolong the effect of regional anesthesia with amide anesthetics. Because of its analgesic and sedating activity, clonidine has been used previously as an oral premedication in patients undergoing tonsillectomy,¹⁰ but its use, as an injectable supplement to a local anesthetic has not been evaluated. Therefore, we undertook this study to examine the effects of preemptive ropivacaine with or without clonidine on pain and recovery in children undergoing tonsillectomy.

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.

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 ($P = .049$). 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.

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

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

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

Table 2. Pain Medication Use

Variable	Saline-Treated Group*	Ropivacaine Hydrochloride-Treated Group	Ropivacaine + Clonidine Hydrochloride-Treated Group	P Value
Recovery room (day 0)				
No. of intravenous narcotic doses				
0	3†	12	11	<.05 Saline-treated group vs both ropivacaine-treated groups
1	16	8	9	
2	2	1	2	
No. of oral codeine doses				
0	10	10	14	
1	11	11	8	
Home (day 0-5)				
Total doses of codeine, mean ± SD				
At day 3	6.2 ± 5.5‡	7.8 ± 5.6	5.4 ± 4.1	<.05 Saline-treated group vs both ropivacaine-treated groups
At day 5	11.4 ± 7.1	12.2 ± 8.9	8.5 ± 7.6	

*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.

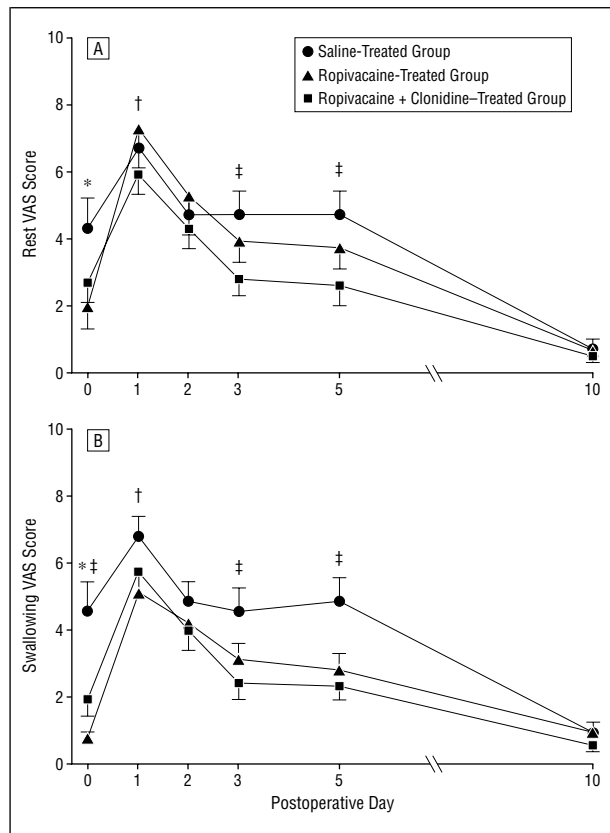
Cumulative codeine use was similar between the groups for the first 3 postoperative days but was significantly lower for the ropivacaine plus clonidine-treated group on postoperative day 5 (Table 2). Data for cumulative codeine use at day 10 could not be analyzed owing to the high percentage (42%, 27 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.

Parental assessment of activity on a 4-point scale was recorded on days 0, 1, 2, 3, and 5. No statistical difference was seen between the 3 groups. Injection of anesthetic with or without clonidine significantly accelerated the time to complete recovery as defined by the time to return to a completely normal level of activity. Injection of ropivacaine alone tended to improve recovery to



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 \pm SEM. $P < .05$: each group at postoperative days 1, 2, 3, 5, or 10 compared with itself at postoperative day 0 (\dagger); saline placebo compared with ropivacaine ($*$) or ropivacaine plus clonidine (\ddagger). 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 \pm 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 shortened from 8.1 \pm 1.6 days to 5.8 \pm 2.9 days in the placebo and ropivacaine plus clonidine-treated groups, respectively ($P = .03$).

COMMENT

Recent advances in the study of pain delineate clear differences 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 general anesthesia, a vicious cycle commences.¹¹ Continued injury of tissue causes long-lasting changes in sensitivity. 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 sensations creating central hypersensitivity.¹¹ Hypersensitivity, 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. Secondary hyperalgesia spreads hypersensitivity to noninvolved 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 anesthetics to relieve posttonsillectomy pain.¹³ Jeebeles et al,⁶ in 1991, renewed interest in preemptive analgesia for tonsillectomy 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.^{8,16-18} An overview of past studies suggested that higher patient numbers per study group, higher doses of local anesthetic, and addition of epinephrine to local anesthetics were potentially associated with positive preemptive effects.

In this study preemptive injection of a combination of ropivacaine plus clonidine significantly improved pain and recovery after tonsillectomy in several measured areas. One measure of pediatric pain assessment 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 drinking, on days 3 and 5 were statistically significantly lower in children receiving the combination injection compared with those receiving injections of either saline or ropivacaine alone. In adult patients VAS scores are generally 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 codeine use. The groups used similar amounts of pain medication through day 3, but by day 5 the study's ropivacaine 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 recovery, 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 supports the hypothesis that preemptive analgesia may act by decreasing central sensitization. The failure of the VAS pain scores and other variables to achieve significant differences in the ropivacaine-treated group compared with the control group is consistent with the finding of previous studies with few patients in the study groups. Because of the many pathways involved in surgical pain, one can hypothesize that local anesthetic alone cannot

Table 3. Subjective Symptoms*

Symptom	Saline-Treated Group	Ropivacaine Hydrochloride-Treated Group	Ropivacaine + Clonidine Hydrochloride-Treated Group	P Value
Nausea and/or vomiting	60†	30	41	.16
Headache	40	32	25	.63
Ear pain or otalgia	89	63	61	<.001

*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*

Complication	Saline-Treated Group	Ropivacaine Hydrochloride-Treated Group	Ropivacaine + Clonidine Hydrochloride-Treated Group
Surgical blood loss, mean ± SD, mL	58 ± 38	71 ± 79	45 ± 37
Emergency department visit (for those who were not admitted)	1 (2)	0	1 (4)
Hospital admission (day)	1 (5)	0	1 (1)
Weight loss, mean ± SD, % of baseline weight	1.7 ± 3.2	1.9 ± 3.2	1.0 ± 6.1
Posttonsillectomy hemorrhage	0	0	0

*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 $P > .05$.

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.

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.

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