Ropivacaine Intramuscular Paracervical Injections for Pediatric Headache: A Randomized Placebo-Controlled Trial

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Study objective: We seek to determine whether ropivacaine cervical paraspinal injections compared with normal saline solution injections provide headache relief to pediatric patients that is sufficient for emergency department (ED) discharge.

Methods: We enrolled children aged 7 to 17 years in a double-blinded, randomized, controlled trial of patients presenting to a pediatric ED with headache. Subjects were randomized into 1 of 3 groups: bilateral cervical paraspinal injections of either (1) 0.5% ropivacaine or (2) normal saline solution, or (3) a natural history group (not blinded) receiving no headache therapy for the first 30 minutes. Pain scores were assessed at enrollment and at 10-, 20-, and 30-minute intervals after the administration of the injections. After the intervention period of 30 minutes, additional therapy was provided as needed. Primary outcome was the proportion of children discharged with adequate pain relief at 30 minutes without additional therapy. Secondary outcomes included reduction in pain scores, reoccurrence of headache, and re-presentation to health care with headache.

Results: One hundred fifty-three children were enrolled. The proportion discharged with adequate pain relief 30 minutes after the injections did not differ between the 2 intervention groups (32% in the ropivacaine group versus 28% in the saline solution group; effect difference 4%; 95% confidence interval –14% to 21%). In contrast, only 4% percent of patients in the natural history group were discharged without additional therapy after the 30-minute assessment. Reduction of pain scores (2.0 and 2.2 in ropivacaine versus saline solution), headache reoccurrence, and return to care was similar between the 2 treatment groups.

Conclusion: Cervical paraspinal injections of either ropivacaine or saline solution were effective for approximately one third of patients. [Ann Emerg Med. 2017;70:323-330.]

Please see page 324 for the Editor’s Capsule Summary of this article.

INTRODUCTION

Headaches affect 10% to 51% of children in the United States and are a common presenting complaint to emergency departments (ED). Common treatment options include nonopioid analgesics, dopamine receptor antagonists, ergotamines, and intravenous fluids. Although these therapies are reasonably effective, they are time consuming. A less well-known approach, described by Mellick et al, is bilateral, lower-cervical, intramuscular injections of a long-acting local anesthetic. An advantage to this approach is the ease of administration and the rapidity of therapeutic response. Mellick et al described a case series of 417 adults with headache treated with bupivacaine: 65% of patients experienced complete relief and an additional 20% experienced partial relief. Mellick and Pleasant published similar results in a small series (13 patients) of pediatric patients. In each of these series, local anesthetic therapy had a rapid therapeutic effect; many patients reporting relief had improvement within 5 to 10 minutes and the remainder in less than 30 minutes. A limitation of these studies is that they were observational and without a control group. Thus, a selection bias could have preferentially selected patients more likely to respond to the therapy. Furthermore, the placebo effect in pediatric headache studies is high (38% to 53%) and the response rate from the therapy may be largely a placebo response. To address these limitations, we performed a prospective, placebo-controlled trial of ropivacaine paraspinal cervical injections for acute treatment of pediatric headache.
Intramuscular injections of the lower cervical paraspinal muscles were randomly assigned to 1 of 3 groups: bilateral injections of the lower cervical paraspinal muscles with 1.5 mL of 0.5% ropivacaine (intervention), bilateral intramuscular injections of the lower cervical paraspinal muscles with 1.5 mL of normal saline solution (placebo control), or no therapy for the 30-minute duration of the study (natural history control) (Figure 1).

A 4% lidocaine cream (L.M.X.4; Ferndale Laboratories, Ferndale, MI) was applied topically over a peripheral vein in the event that intravenous therapy was required at the conclusion of the study. Patients randomized to the natural history group were notified of the assignment, waited for the 30-minute duration of the study, and were then offered intravenous therapy at the site of the topical lidocaine application. The rationale for this arm was to control for the unlikely event that patients might spontaneously improve during the 30-minute duration of the study. For patients randomized to an injection, an ED bedside nurse filled 2 syringes with the assigned ropivacaine or normal saline solution, each a clear and colorless liquid. Patients, families, research staff, and investigators remained blinded to the contents of the injections. Research nurses or physician-investigators performed the intramuscular injections, using 25-gauge needles injected approximately 1 to 1.5 in into the paraspinal muscles and 2 to 3 cm lateral to the spinous process on each side of the sixth or seventh cervical vertebrae. First-time injections were supervised by one of the study principal investigators (K.C. or R.W.H.). There was also a picture demonstrating the landmarks within the study packet. The ease of this procedure is readily demonstrated on YouTube videos available on the Internet (see Larry Mellick: https://youtu.be/oy1lggyxV9Y). All injections were performed by 1 of 3 pediatric emergency physicians or by 1 of the department’s 5 research nurses (all nurses had extensive experience in intramuscular injections). However, none of the investigators or research nurses had previous experience in this particular injection.

Methods of Measurement

Verbal report of pain scores on a 0-to-10 scale were recorded at enrollment and at 10-minute increments for a total of 30 minutes after the cervical injections (or application of the topical lidocaine for the natural history group). At the end of a 30-minute monitoring period, patients requesting more therapy had an intravenous line placed at the site of the topical lidocaine application and received intravenous medications as ordered by the patient’s treating physician. Our local clinical effectiveness guideline includes intravenous ketorolac and diphenhydramine plus promethazine or metoclopramide. All additional care and disposition after the 30-minute duration of the study were determined by
the patient and treating physician. All patients were contacted by study personnel by telephone calls at 3 days and 1 month after enrollment to inquire about adverse events, including recurrence of headache.

**Outcome Measures**

The primary outcome was the rate of adequate symptom improvement at 30 minutes such that no further therapy was needed and the patient could be immediately discharged.

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Figure 1. Study design.
discharged to home. Secondary outcomes included the following: reduction in pain scores, re-presentation to medical care for headache within 72 hours of enrollment, headache recurrence at 72 hours, and adverse events. Study data were collected and managed with REDCap (Research Electronic Data Capture) electronic data capture tools (version 6.15.13; Vanderbilt University, Nashville, TN) hosted at the University of Pittsburgh.

Sample size was calculated assuming 80% power to detect a 30% difference in the rate of headache resolution between ropivacaine and placebo, given a 2-sided type I error probability of .05. When a previously published headache resolution rate of 65% after ropivacaine injections in adults and a 35% placebo effect was used, 48 subjects were needed to detect a difference between ropivacaine and placebo in each of the 2 injection groups. A balanced group of 50 patients (natural history) was enrolled to control for the unlikely event that patients would spontaneously improve without therapy during the 30-minute duration of the study.

Primary Data Analysis

Analyses were performed with IBM SPSS (version 23), using $\chi^2$ for nominal variables and one-way ANOVA for scale variables.

RESULTS

Characteristics of Study Subjects

One hundred seventy patients were approached by study personnel but refused participation. The mean age, sex, and race were similar to those of patients consenting to the study (Table 1). Unfortunately, 6 of 96 months of data on patients who refused were missing because of an administrative error. One hundred fifty-three patients were enrolled. Two patients withdrew from the study after randomization but before intervention. One patient was excluded after enrollment because she was aged 18 years. Of the 150 patients who remained, 50 were assigned to each treatment arm (Figure 2). The median age was 15.1 years (range 7.7 to 17.8 years). The majority of participants were white (78%) and 76% were female patients. Forty-one percent of the participants had more than 15 days of headache in the past month and 42% had a previous migraine diagnosis. No significant differences were found between the groups in terms of age, sex, migraine prevalence, pre-enrollment medications, headache duration, and severity (Table 1).

Main Results

Sixteen patients receiving ropivacaine, 14 receiving placebo, and 2 in the natural history group had sufficient relief of pain at 30 minutes to be discharged from the ED without additional therapy. The proportion of children discharged with adequate pain relief after the injections did not differ between groups (32% in the ropivacaine group versus 28% in the normal saline solution group; effect difference 4%; 95% confidence interval [CI] −14% to 21%) (Table 1). The rate of adequate pain relief (4%) in the natural history group was significantly lower than in the 2 injection groups (28% difference from the ropivacaine group, 95% CI 13% to 42%; and 24% difference from the normal saline solution group, 95% CI 10% to 38%).

We were unable to detect a difference in pain score 30 minutes after the ropivacaine and normal saline solution injections (Figure 3). Additionally, we were unable to detect a difference in the rate of return to care, headache recurrence, neck pain, and pain medications received at 72 hours after the intervention (Table 2).

All adverse events caused by the study intervention were expected and described in the consent form. In the ropivacaine and normal saline solution groups, 16 and 11 participants, respectively, had pain at the injection sites that was expected and described in the consent form. In the normal saline solution group, 95% CI 10% to 38%.

LIMITATIONS

Any convenience sample is at risk for selection bias. But our poor therapeutic response rate makes it unlikely that

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Ropivacaine (n=50)</th>
<th>Normal Saline Solution (n=50)</th>
<th>Natural History (n=50)</th>
<th>Declined Participation (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>14.7 (2.0)</td>
<td>14.4 (2.3)</td>
<td>14.8 (1.9)</td>
<td>14.4 (2.1)</td>
</tr>
<tr>
<td>Sex, No. (%), female</td>
<td>38 (76)</td>
<td>38 (76)</td>
<td>38 (76)</td>
<td>132 (74)</td>
</tr>
<tr>
<td>Race, No. (%), white</td>
<td>37 (74)</td>
<td>37 (75)</td>
<td>42 (84)</td>
<td>135 (76)</td>
</tr>
<tr>
<td>Migraine diagnosis, No. (%)</td>
<td>19 (38)</td>
<td>19 (38)</td>
<td>25 (50)</td>
<td></td>
</tr>
<tr>
<td>Headache days in past week, days</td>
<td>4.5</td>
<td>4.5</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>More than 15 headache days, No. (%)</td>
<td>22 (43)</td>
<td>19 (39)</td>
<td>21 (42)</td>
<td></td>
</tr>
<tr>
<td>Doses of medication in past 24 h</td>
<td>2.5</td>
<td>2.4</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Pain score at enrollment (0–10 scale)</td>
<td>7.7</td>
<td>7.4</td>
<td>7.5</td>
<td></td>
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</tbody>
</table>
our study was biased in favor of enrolling patients we believed were more likely to respond to therapy. The majority of patients approached for the study declined, most expressing reluctance to have 2 injections of medicine into the neck region; thus, the time to complete this study was prolonged.

An unavoidable limitation of a randomized study is that patients who consent for the study may, in some way, differ from those who declined. We found no difference in age and sex in patients who consented versus those who refused. However, other important and unmeasured factors, including fear of needles, experience with therapy, etc, might have influenced consent rates and generalizability.

Although this study design is inherently at risk for patient-related selection bias, it is less at risk for the provider-related selection bias of a case series design.

Approximately 40% of the patients in our sample had greater than 15 headache days in the past month, suggesting that many patients met the diagnosis of chronic headache. Additionally, 20% or more of patients in all treatment arms required admission, which is greater than the reported admission rate of up to 15% for pediatric headache but is consistent with our local experience (unpublished data). Furthermore, the paraspinal technique has been promoted regardless of headache cause or chronicity.

Because of the differences in study design, and possible differences in the cause of adult versus pediatric headache, we cannot determine whether children respond differently to paraspinal muscle injections than adults do.

**DISCUSSION**

To our knowledge, this is the first randomized placebo-controlled trial of paraspinal cervical injections of a local anesthetic for headache. We chose to use ropivacaine instead of bupivacaine because of the theoretic concern for cardiotoxicity with bupivacaine expressed by our institutional review board. However, we believe that this decision is unlikely to explain the difference between this study and case series with bupivacaine. We were unable to detect a 30% difference in our primary outcome.
(no additional therapy) comparing injection of normal saline solution versus ropivacaine.

What is the mechanism by which approximately 30% of patients responded to paraspinal injection regardless of the vehicle? One mechanism, proposed by Mellick et al.,\textsuperscript{5} is through the trigeminocephalic complex of neurons implicated in the neurovascular cause of some headache syndromes.\textsuperscript{10} However, the peripheral component of this complex is limited to the upper cervical dorsal roots of C2 and C3 synapsing with the central trigeminal neurons; the paraspinal injections in this study were more caudal. Another potential mechanism is by injection of “trigger points,”\textsuperscript{11} which are “hyperirritable” areas of skeletal muscle associated with a palpable nodule or taut band, or local areas where palpation elicits pain typical of the patient’s headache syndrome. Treatment typically involves calming the hyperirritable locus with local anesthetics.\textsuperscript{12} However, there is conflicting evidence that normal saline solution, or even dry needling, may be effective, putatively by disrupting bands of tense muscles and local depolarization of neurons. This study, and the case series of paraspinal injections, targeted a specific anatomic location without reference to palpable triggers. Furthermore, the heterogeneity of headache syndromes that have been reported to respond to paraspinal injections makes this mechanism less attractive. The last mechanism is through a placebo response. The placebo response to pain is a powerful mechanism that recruits synaptic activation of pain-reducing circuits within the central nervous system in patients administered inactive

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**Figure 3.** Boxplot of pain score at enrollment and at each 10-minute assessment.
Table 2. Outcomes and adverse events.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Ropivacaine (n = 50)</th>
<th>Normal Saline Solution (n = 50)</th>
<th>Natural History (n = 50)</th>
<th>Effect Difference, % 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
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<tr>
<td>Adequate headache relief for discharge at 30 min, No. (%)</td>
<td>16 (32)</td>
<td>14 (28)</td>
<td>2 (4)</td>
<td>4 –14 to 21</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in pain score at 10 min (95% CI)</td>
<td>1.1 (0.59 to 1.54)</td>
<td>0.8 (0.38 to 1.26)</td>
<td>0.02 (–0.10 to 0.14)</td>
<td></td>
</tr>
<tr>
<td>Decrease in pain score at 20 min (95% CI)</td>
<td>1.7 (1.12 to 2.30)</td>
<td>1.5 (0.96 to 2.02)</td>
<td>0.22 (0.03 to 0.41)</td>
<td></td>
</tr>
<tr>
<td>Decrease in pain score at 30 min (95% CI)</td>
<td>2.2 (1.51 to 3.04)</td>
<td>2.0 (1.32 to 2.69)</td>
<td>0.30 (0.05 to 0.55)</td>
<td></td>
</tr>
<tr>
<td>Admission, No. (%)</td>
<td>10 (20)</td>
<td>10 (20)</td>
<td>12 (24)</td>
<td></td>
</tr>
<tr>
<td>Return to care within 3 days, No. (%)</td>
<td>7 (14)</td>
<td>7 (14)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>Headache reoccurrence within 3 days, No. (%)</td>
<td>30 (60)</td>
<td>34 (68)</td>
<td>31 (62)</td>
<td></td>
</tr>
<tr>
<td>Pain medications received at 3 days, No. (%)</td>
<td>33 (66)</td>
<td>35 (70)</td>
<td>30 (60)</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at injection site, No. (%)</td>
<td>16 (32)</td>
<td>11 (22)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Neck pain at 3-day follow-up, No. (%)</td>
<td>13 (27.1)</td>
<td>10 (20)</td>
<td>9 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Neck pain at 1-month follow-up, No. (%)</td>
<td>12 (25.5)</td>
<td>5 (10.2)</td>
<td>12 (25)</td>
<td></td>
</tr>
</tbody>
</table>

NA, Not applicable.

medication. A systematic review of the placebo response in studies of children with migraine (13 trials with 1,324 patients) found that a pooled placebo response for partial or complete resolution of pain was 46% and 21%, respectively, at 2 hours. Our results are squarely within this range, leaving little room for the other mechanisms described above. Last, the placebo response is augmented by the patients’ and providers’ belief that the therapy will work. Thus, patients enrolled in a placebo-controlled study presented in the context of therapeutic equipoise are less likely to develop a placebo response compared with similar patients treated outside of a study by a physician projecting confidence in the therapeutic benefit of the treatment. This phenomenon could explain the discrepancy between our modest results and the more robust results of the published case series. Taking into account all of the above considerations, we favor the mechanism of placebo to explain all, or most, of our results.

We recognize that implementing the results of this study into clinical practice is problematic. On one hand, a clinician could conclude that the effect of paraspinal injections is solely the result of a placebo effect, and it is unethical to administer without disclosing the placebo effect. On the other hand, a clinician could conclude that “it works” for a significant proportion of patients, is quick and effective, and is ethical to administer. Adjudicating this decision is beyond the scope of this article.

In summary, we failed to find a 30% difference in our primary outcome between ropivacaine versus normal saline solution injections for treatment of pediatric headache in a tertiary care pediatric ED. Both saline solution and ropivacaine were effective for approximately one third of patients.

The authors acknowledge the patients and their parents for participating in the study; and the research coordinators who made the study possible: Karli Carpenter, BSN, MSN, MBA, Amy Russell, RN, Kathleen Calabro, RN, BSN, Anthony Sciulli, BS, Rose Azrak, RN, BSN, Maria Nolan, RN, BSN, and Nicole Machi, RN, BSN.

Supervising editor: Jocelyn Gravel, MD

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Author contributions: KC, KAC, and RWH conceived the study and designed the trial. KC obtained research funding. SKY, KC, and RWH supervised the conduct of the trial and data collection. RWH chaired the data oversight committee. SKY, MCP, KC, and RWH undertook recruitment of participants and managed the data, including quality control. SKY, MCP, and RWH analyzed the data. SKY drafted the article and all authors contributed to its revision. RWH takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work.
the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Funding and support:** By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see [www.icmje.org](http://www.icmje.org)). The authors have stated that no such relationships exist. This project was supported in part by a grant from the National Headache Foundation. Additionally, statistical support was provided by the University of Pittsburgh’s Clinical and Translational Science Institute, which is funded in part by the National Institutes of Health through grant UL1-TR-000005.

**Publication dates:** Received for publication June 25, 2016. Revisions received November 28, 2016, and February 24, 2017. Accepted for publication March 3, 2017.

**Trial registration number:** NCT00680823

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**REFERENCES**


