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Outcomes of Greater Occipital Nerve Injections in Pediatric Patients with Chronic Primary Headache Disorders

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Abstract

Background—Chronic migraine is common in pediatrics and generally disabling. In adults, infiltration of the area around the greater occipital nerve can provide short to medium term benefit in some patients. This study reports the efficacy of greater occipital nerve infiltrations in pediatric patients with chronic primary headache disorders.

Methods—Retrospective chart review of patients <18 years with a chronic primary headache disorder undergoing a first-time injection. Infiltrations were unilateral and consisted of a mixture of methylprednisolone acetate, adjusted for weight, and lidocaine 2%.

Results—Forty-six patients were treated. Thirty-five (76%) had chronic migraine, nine (20%) New Daily Persistent Headache (NDPH), and two (4%) a chronic trigeminal autonomic cephalalgia. Medication overuse was present in 26%. Ages ranged from 7–17 years. Follow-up data were available for 40 (87%). Overall, 53% (21/40) benefitted, 52% (11/21) significantly. Benefit onset ranged from 0–14 days, mean 4.7(SD 4.3), with mean benefit duration of 5.4(SD 4.9) weeks. In chronic migraine, 62% (18/29) benefitted, 56% (10/18) significantly. In NDPH, 33% (3/9) benefitted; 33% (n=1) significantly. Neither child with a chronic trigeminal autonomic cephalalgia benefitted. In logistic regression modeling, medication overuse, age, sex, and sensory change in the distribution of the infiltrated nerve did not predict outcome. There were no serious side effects.

Conclusions—Greater occipital nerve injections benefitted 53% of pediatric patients with chronic primary headache disorders. Efficacy appeared higher in chronic migraine than NDPH. Given the benign side effect profile, a greater occipital nerve infiltration prior to more aggressive approaches seems appropriate.

Keywords

pediatric migraine; pediatric headache; NDPH; medication overuse headache

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Introduction

Chronic migraine is common in pediatric patients, affecting 0.8–1.75% of adolescents ages 12–17[1] and 0.6% of 5–12 year olds [2]. Children with chronic migraine have experienced headache at least 15 days per month for at least the last three months[3]. Pediatric migraine patients are often highly disabled by their headaches[1] and miss or perform poorly in school [2, 4]. Rarer primary headache disorders such as chronic trigeminal autonomic cephalalgias and the primary New Daily Persistent Headaches also affect children and can be highly disabling.

There are no FDA-approved therapies for chronic primary headache prophylaxis in pediatric patients, and treatment is often challenging. In adults, onabotulinum toxin type A injections are FDA approved for chronic migraine and topiramate has been studied for chronic migraine, however both often provide only partial relief even weeks to months into therapy [5–8]. Waiting this long for relief from pain in pediatric patients with chronic headache is challenging. Therapies with more rapid onset are urgently needed.

In adult patients with chronic primary headache disorders infiltration around the greater occipital nerve injection with methylprednisolone and lidocaine 2% has been shown to be beneficial in 53% of patients, with a mean latency of onset of benefit of two days [9]. The greater occipital nerve provides sensory innervation over most of the occipital region and derives its innervation predominantly from the C_2 spinal root [10]. At the level of second order neurons, C_2 spinal afferents overlap with trigeminal afferents in the trigeminocervical complex, an area of the brain important in headache disorders [11, 12].

This study reports the open-label efficacy and tolerability of greater occipital nerve infiltrations in pediatric patients with chronic primary headache disorders, and examines predictors of benefit.

Methods

The University of California San Francisco (UCSF) Committee for Human Research approved this retrospective chart review.

The study population consisted of patients under 18 years of age who were seen at the UCSF Headache Center between October 2008 and June 2012 and were treated with a first time greater occipital nerve infiltration for a chronic primary headache disorder: chronic migraine (CM), New Daily Persistent Headache (NDPH), or a chronic undifferentiated trigeminal autonomic cephalalgia (TAC). Given that tenderness to palpation over the greater occipital nerve predicts a beneficial response in adults[9], only those pediatric patients who had tenderness at the time of initial evaluation were offered a greater occipital nerve injection.

Headache disorder definitions

Chronic migraine, NDPH, and chronic undifferentiated TAC were defined using ICHD-III-beta criteria [3]. Medication overuse was determined to be present if the patient was currently using ≥4 days/month of barbiturate containing compounds, ≥10 days per month of opioids or triptans, or if they had been using NSAIDs or other non-specific analgesics for ≥15 days/month for the last three months. Patients with medication overuse were not withdrawn prior to the injection, as one of the treatment goals was that headache benefit from the injection would make it easier for the child to withdraw from the overused acute medication(s). Patients had generally failed at least one adequate trial of a headache prophylactic medication prior to the injection. In order to be clear whether a side effect is secondary to

the injection or a new medication, our clinic practice is to start a new prophylactic medication one week following the injection.

Administration of greater occipital nerve injections

The injections were performed by one of two headache neurologists (AAG and PJG). The clinician palpated over the greater occipital nerves and injected the side that was most tender. Children weighing ≥40 kg received a mixture of 80 mg Depo-medrol (Methylprednisolone acetate, Pharmacia & Upjohn Co, Division of Pfizer, NY, NY) and 40 mg 2% lidocaine (APP Pharaceuticals, Schaumburg, IL) and children <40 kg received 40 mg methylprednisolone acetate and 20 mg 2% lidocaine.

Definitions of outcomes

The definitions for "some benefit" and "significant benefit" were determined *a priori*. "Significant benefit" was defined as when the notes documented one or more of the following: 1) decrease in headache frequency by at least one third for at least one month, 2) decrease in headache intensity by at least one third for at least one month, 3) decrease in headache duration by at least one third for at least one month, or 4) notes document a "significant" or "substantial" improvement in headache for a period of at least one month. "Some benefit" was defined as when some degree of improvement was documented in the notes, but the criteria for "significant benefit" were not met. Ascertainment of treatment response was performed by one of the headache neurologists as part of routine clinical care prior to conceptualization of the study, and recorded in the medical record at the first clinic follow-up visit following the injection.

Side effects and adverse events

Side effects and adverse events noted in the medical records were collected and reported. Side effects are assessed for routinely at follow-up visits per clinic protocol.

Data collection

Data were collected from the medical records onto a standardized abstraction form and then entered into a secure web-based electronic REDCap (Research Electronic Data Capture)[13] database.

Data analysis

Data were analyzed using STATA v.12 (College Station, TX).

Descriptive statistics were calculated including demographics and clinical features, percent of total patients who benefitted, percent of patients with NDPH and CM who benefitted, and percent that benefitted significantly.

The primary predictor of interest in this study was headache diagnosis. As there were only two patients with a chronic TAC this was ultimately simplified to a binary predictor: chronic migraine vs. NDPH.

The primary outcome measure for this study was headache benefit. For most analyses this outcome was dichotomized such that having a benefit included both those patients who had some benefit and those who had significant benefit, as defined above.

First, the proportion of patients with chronic migraine and the proportion with NDPH who benefitted from the injections were calculated and a Fisher's exact test was performed to assess whether these proportions differed in a statistically significant way.

Recognizing that factors other than diagnosis may also influence response to treatment and therefore need to be controlled for to understand better the implication of diagnosis on treatment benefit, univariate and then multivariate logistic regression modeling were also performed. Medication overuse was included in the logistic regression model as a confounding variable given its influence on the development of chronic migraine[14] and response to treatment[6]. Age and sex were also included in the logistic regression model as potential confounders[15, 16]. Age was examined in two ways: 1) as a continuous variable, 2) as a binary variable: preadolescent (≤11 years) vs. adolescent (12–17 years). The continuous age variable was used in the multivariate logistic regression model. Lastly, sensory change (i.e. numbness and/or tingling) in the ipsilateral occipital region following the injection was included in the model as it was considered a possible mediator on the causal pathway and the goal of the analysis was to measure the direct effects of headache diagnosis on benefit. The presence of sensory change objectively indicates accurate targeting of the nerve and underlying diagnosis conceivably could influence how susceptible the nerve is to sensory change when injected. All variables were entered into the logistic regression model and then removed one by one to allow the detection of unmasked negative confounding.

Two other regression models were also generated to examine whether results differed from the logistic regression model 1) an ordinal logistic regression model (3 outcome categories: no benefit, some benefit, and significant benefit), and 2) an exact logistic regression model given the relatively small sample size in the study.

Results

Forty-six pediatric patients were treated with greater occipital nerve injections during the study period. Their diagnoses and demographics are shown in Table 1.

Follow-up information was available on 40 (87%). The six patients missing follow-up data did not return to the clinic for care. Overall, 53% (21/40) of children with a chronic primary headache disorder benefitted from the injection. Of those who benefitted, 52% (11/21) had significant benefit, for an overall significant benefit rate of 28% (11/40). Timing of benefit onset ranged from 0–14 days after the injection with a mean latency of onset of 4.7(SD 4.3) days. Duration of benefit ranged from <1 week to 16 weeks, with a mean of 5.4(4.9) weeks.

Of the 35 patients with chronic migraine, 29 had follow-up data available (83%). Of these 29, 62% (18/29) benefitted. Fifty-six percent (10/18) benefitted significantly, for a significant benefit rate in chronic migraine of 35% (10/29). Of the nine patients with NDPH, all had follow-up data available. Of these, 33% (3/9) benefitted; 33% (1/3) significantly (Table 2), for a significant benefit rate in NDPH of 11% (1/9). The difference in the benefit rate (62% vs. 33%, p=0.25, Fisher's Exact) and in the significant benefit rate (35% vs. 11%, p=0.23, Fisher's Exact) were not statistically significant. Neither of the two children with a chronic undifferentiated TAC benefitted.

Regression modeling

Those with chronic migraine had 3.4 times the odds of headache benefit from a first-time greater occipital nerve injection compared to those with NDPH in the fully adjusted logistic regression model (Table 2), though the 95% confidence interval crossed one (0.6–19.6). Presence of medication overuse, sex, age, and sensory change in the distribution of the infiltrated nerve all did not independently predict benefit (Table 3), though being an adolescent was associated with 2.5 times increased odds (95% CI 0.4–15.8) of benefitting compared to younger children, and each year increase in age was associated with 1.3 times increased odds of benefit (95% CI 0.98–1.7). Serially removing predictor variables did not unmask any negative confounding and furthermore did not meaningfully alter the results

(Table 3). In univariate logistic regression those with chronic migraine had 3.3 (95% CI 0.7–15.8) times the odds of benefit compared to those with NDPH. The results of univariate ordinal logistic modeling did not meaningfully differ (OR 3.4, 95% CI 0.8–15.8). Exact logistic modeling gave a similar point estimate but a somewhat wider confidence interval (OR 3.2, 95% CI 0.5–23.7).

Side effects

Twenty percent (8/40) noted <10 minutes of light-headedness immediately following the injection. Ten percent (4/40) had brief (<3 days) of local soreness at the site and one patient had prolonged soreness. There were no instances of local alopecia. Thirty-eight percent (15/40) of patients noted transient tingling/numbness in the distribution of the injected nerve immediately following the injection.

Discussion

Greater occipital nerve region infiltrations were beneficial in more than half of pediatric patients with chronic primary headache disorders. They appear to be more useful in those with chronic migraine (62% benefitted) than in those with NDPH (33% benefitted) though this difference was not statistically significant. The odds of benefit were 3.3 times higher (95% CI 0.7–15.8) in those with chronic migraine than for those with NDPH, and while the 95% confidence interval overlapped the null, the point estimate was resilient regardless of which type of regression modeling was used or how many variables were in the model. Given the small sample size in the study, the lack of statistical significance for the difference probably reflects underpowering.

The overall benefit rate from greater occipital nerve injections in children and adolescents is similar to what has been observed in adults. In a study of adults with chronic primary headache disorders, 53% of greater occipital nerve injections resulted in benefit[9]. The average delay in onset of benefit in that study was two days, whereas in this study it was a bit longer at 4.7 days. The mean duration of response was 45 days, which is similar to our mean of 5.4 weeks (approximately 38 days). The response rate among those with chronic migraine was actually lower in the adult study, with 46% responding (26/57), compared to 62% (18/29) in our study. This may reflect that the adult study was done before tenderness to palpation over the greater occipital nerve was known to predict response, so that study's patients were not selected for having this clinical feature whereas ours were. In contrast to our study and the previous work[9] a recently reported randomized parallel group, double-blind study in patients with chronic or episodic migraine reported a 30% fifty per cent or better response rate in the two groups examined. Interestingly a different local anesthetic (bupivacaine) and a lower dose of corticosteroid, methylprednisolone 20mg, were used, and the control group had a small dose of 1% lidocaine[17]. The differences will require exploration.

In earlier work 63% (10/16) of adult patients with NDPH had a benefit[9] compared to 33% (3/9) in our study. It is generally said that NDPH is more difficult to treat than chronic migraine[18] although there is a considerable issue of lumping unrelated clinical problems together[19]. Studies with careful phenotyping, consideration of age[20] and using appropriate controls are urgently required.

In our study, being an adolescent rather than a younger child was associated with 2.5 times the odds of benefitting, although the confidence interval did cross the null. It is possible that younger children move more at the time of the injection so that infiltration is more difficult. Further research is needed to see whether age generally predicts response to greater occipital nerve injections in pediatric patients.

As in our study of pediatric and adolescent patients, the presence of sensory change in the distribution of the injected greater occipital nerve did not predict clinical response in the adult study[9]. However, accurately targeting the region of the nerve still seems likely to be important as the greater occipital nerve derives its innervation predominantly from the C_2 spinal root[10] and at the level of second order neurons C_2 spinal afferents overlap with trigeminal afferents in the trigeminal cervical complex, an area of the brain important in migraine[11, 12]. Therefore it is possible that presence of sensory change in the nerve is not a sensitive enough indicator of accurate targeting of the nerve, or alternatively that this relatively small study was too small to show its effect in a statistically significant fashion. The latter explanation is supported by the finding that the observed odds of benefitting in this study were 45% higher in those who had the sensory change (OR 1.45; 95% CI 0.83–6.8), though the 95% confidence interval crossed one.

Notably, having a history of medication overuse did *not* decrease the odds of headache benefit in either our study or the adult study[9]. It is unlikely that this was due to simply underpowering as in fact the point estimate for odds of headache benefit in those with medication overuse was 1.1, with a relatively wide 95% CI of 0.3–4.5. This is useful clinically as medication overuse is present in many adolescent patients with chronic migraine[1, 21] and there is some evidence that other therapies may not work as well in the setting of medication overuse[6], hence greater occipital nerve injections may be a good treatment choice for these patients.

One small study of greater occipital nerve injection outcomes in pediatric patients has been reported previously[22]. Seventeen patients with chronic migraine underwent twenty-three injections. A partial response or complete resolution of headache at two weeks was seen in 78% (18/23 injections). However, four of the children received repeat injections. Presumably those who underwent the therapy multiple times were those who had a positive response to the first injection, perhaps explaining the somewhat higher efficacy rate in that study.

Chronic migraine and other chronic primary headache disorders are highly distressing for pediatric patients and their families. The majority of adolescents with chronic migraine are severely disabled, as measured by HIT-6 and PedMIDAS scores[1]. Patients and caregivers are eager for treatment that will begin to benefit the child or adolescent quickly. The benefit from chronic migraine treatments studied in adults is typically measured on the order of four [5, 6] to six [7, 8] months after starting treatment. Hospital admission for a five-day course of intravenous dihydroergotamine often yields benefit within four weeks in adults[23]. However, hospitalization has its own associated costs and risks that make rapid-onset outpatient therapies preferable for treating chronic migraine in children. With a mean latency of benefit onset of 4.7 days, greater occipital nerve injections potentially offer rapid onset of relief from chronic primary headache in children.

In isolation, greater occipital nerve injections are unlikely to be long-term solutions in the treatment of pediatric chronic migraine given the short to medium duration of benefit. Therefore the major clinical question is whether pairing a greater occipital nerve injection with a longer-term treatment strategy, such as a new migraine preventive medication, can “jump start” the child’s improvement and give them a reprieve from pain while waiting for a migraine preventive medication to take effect.

Placebo response to injection therapy for chronic migraine in adults can be substantial[7, 8]. It is likely at least some of the improvement seen in this study was due to the placebo effect. A randomized double-blind placebo-controlled trial of greater occipital nerve injections in pediatric and adolescent patients with chronic primary headache disorders is needed to see

whether such injections are indeed more effective than placebo, and whether such injections make a meaningful difference in children's level of disability and headache outcomes during the first few weeks following treatment.

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Table 1

Demographic Characteristics of 46 Pediatric Patients with Chronic Primary Headache Disorders

Diagnosis (*n*(%))	**Chronic migraine: 35 (76%)** **New Daily Persistent Headache: 9 (20%)** **Chronic undifferentiated trigeminal autonomic cephalalgia: 2(4%)**
Age, years (mean; SD); range	14.7 years (2.5); range 7–17 years
Female (*n*(%))	30 (65%)
Medication overuse present	12 (26%)

SD=standard deviation

Table 2

Effect of Diagnosis (Chronic Migraine vs. NDPH) on odds of benefit in logistic regression models

Predictor(s) in the model	**OR**	**95% CI**	***p*-value**
Diagnosis of chronic migraine (CM) alone	3.3	0.7–15.8	0.14
CM+ medication overuse	3.5	0.7–17.9	0.13
CM+medication overuse+age*	3.7	0.7–19.5	0.12
CM+medication overuse+age+sex	3.1	0.6–17.2	0.20
CM+medication overuse+age+sex+sensory change (Fully adjusted model)	3.4	0.6–19.6	0.17

CM=chronic migraine;

*age was a continuous variable in all of these models CI=confidence interval

Table 3

Univariate logistic regression models examining effects of secondary predictor variables on likelihood of benefit

Predictor variable	Odds Ratio	95% CI	*p*-value
Medication overuse	1.1	0.3–4.5	0.87
Female sex	1.6	0.4–6.0	0.46
Age (years)	1.3	0.98–1.7	0.08
Age dichotomized (12–17 vs. ≤11 years)	2.5	0.4–15.8	0.32
Sensory change in distribution of the infiltrated nerve	1.45	0.83–6.8	0.83

CI=confidence interval