A Randomized, Sham-Controlled Trial of Bilateral Greater Occipital Nerve Blocks With Bupivacaine for Acute Migraine Patients Refractory to Standard Emergency Department Treatment With Metoclopramide

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Background.—Greater occipital nerve block (GONB) is thought to be an effective treatment for acute migraine, though no randomized efficacy data have been published for this indication. We hypothesized that bilateral GONB with bupivacaine would provide greater rates of headache freedom than a sham injection among a population of emergency department (ED) patients who reported persistence of moderate or severe headache despite standard treatment with intravenous metoclopramide.

Methods.—This was a randomized clinical trial conducted in 2 urban EDs. Patients with acute migraine who reported persistence of a moderate or severe headache for at least 1 hour or longer after treatment with 10 mg of intravenous metoclopramide were randomized to bilateral GONB with a total of 6 mL of 0.5% bupivacaine or bilateral intradermal scalp injection with a total of 1 mL of 0.5% bupivacaine. The primary outcome was complete headache freedom 30 minutes after the injection. An important secondary outcome was sustained headache relief, defined as achieving a headache level of mild or none in the ED and maintaining a level of mild or none without the use of any additional headache medication for 48 hours.

Results.—Over a 31 month period, 76 patients were screened for participation and 28 were enrolled, of whom 15 received sham injection and 13 received GONB. This study was stopped before achieving the a priori sample size due to slow enrollment. The primary outcome—headache freedom at 30 minutes—was achieved by 0/15 (0%) of patients in the sham arm and 4/13 (31%) of patients in the GONB arm (95% CI for difference of 31%: 6, 56%, P = .035). The secondary outcome, sustained headache relief for 48 hours, was reported by 0/15 sham patients (0%) and 3/13 (23%) GONB patients (95% CI for difference of 23%: 0, 46%, P = .087). Reported side effects did not differ substantially between the groups.

Conclusion.—GONB may be an effective treatment for ED patients with acute migraine who continue to suffer from moderate or severe headache after administration of intravenous metoclopramide; however, this study was stopped prior to achieving the a priori sample size.

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achieve freedom from their headache and remain headache free for 48 hours, regardless of which medications they receive. Medications commonly used to treat acute migraine are burdened by a host of minor side effects, including drowsiness, dizziness, and restlessness. There remains a need for an acute migraine intervention that can deliver rapid, complete, and sustained headache relief without causing side effects that prevent a patient from returning to work or usual activities. Greater occipital nerve blocks (GONB) are used and discussed increasingly in the headache, pain, and emergency medicine literature. We conducted a randomized, sham-controlled clinical trial of GONB to determine acute efficacy for migraine following failure of more traditional treatment. We hypothesized that among patients who presented to an ED with acute migraine and failed to improve after receiving intravenous metoclopramide, bilateral GONB with bupivacaine would provide greater rates of short-term and sustained headache relief than sham intradermal scalp injections of bupivacaine.

METHODS
This was a randomized clinical trial conducted in 2 academic EDs of Montefiore Medical Center. Salaried, trained, bilingual (English and Spanish) technician-level research associates collected all data for this study. Patient outcomes were determined in person for up to 2 hours in the ED and then by telephone 48 hours later. The Albert Einstein College of Medicine IRB reviewed and approved this study. All participants provided written informed consent. The trial was registered at https://www.clinicaltrials.gov (NCT02665273). The trial was conducted in accordance with the original protocol. The protocol can be requested from the corresponding author.

Eligible patients were adults presenting with an acute moderate or severe headache meeting migraine criteria, as defined by the International Classification of Headache Disorders-3 beta (1.1, migraine without aura). Patients who met criteria for probable migraine without aura (1.5.1) were also included, provided they had at least one similar acute headache previously. Status migrainosus, prolonged duration of headache (>72 hours), or early presentation (<4 hours) did not preclude participation. Patients were enrolled if they failed standard first line parenteral migraine therapy with metoclopramide and requested additional treatment for persistent moderate or severe headache. Patients were excluded if informed consent could not be obtained, if there was concern for a secondary cause of headache, if the patient had a skull defect, a suspected infection overlying the injection site, a known bleeding disorder, ongoing use of anti-platelet agents or anti-coagulants, prior treatment with GONB, pregnancy, or allergy, intolerance, or contra-indication to the study medication.

Study participants were randomly assigned to one of two interventions:

Active arm: 3 mL bupivacaine 0.5% injected adjacent to the greater occipital nerve bilaterally (6 mL total) using a fan technique, in which approximately 1 mL was injected immediately adjacent to each greater occipital nerve and the remaining 2 mL on each side were distributed laterally to the greater occipital nerves (Supplementary Fig. 1).

Sham arm: 0.5 mL bupivacaine 0.5% injected intradermally into the posterior scalp overlying the greater occipital nerve bilaterally (1 mL total). The injector located the injection site using the same technique as if he or she were performing a true GONB. However, instead of injecting the anesthetic deep into the scalp, he or she injected the anesthetic into the dermis layer of the skin of the scalp.

The study injectors were emergency medicine attending physicians, physician assistants, or senior residents. All healthcare providers performing this procedure had been previously trained in the technique by the study investigators and were experienced in the performance of peripheral nerve blocks. All injectors underwent a 30 minute training session that included a discussion of the techniques and the landmarks for the procedure. Injectors were also provided with a review of the landmarks immediately prior to injection.

Study participants and outcome assessors were blinded. Because the injection technique varied depending on assignment, the clinician performing the procedure could not be blinded. A randomization list was generated in blocks of 4 using an online generator at https://www.randomization.com. Participants were assigned to active or sham arm in a 1:1 ratio. Assignment was stratified on baseline pain intensity (moderate or severe). Assignment was placed in an opaque, sealed envelope with sequential study IDs written on the outside. Research personnel handed the next sequential
envelope to the injector who shredded the envelope and its contents after reading the assignment.

As a primary measure of headache intensity, this study utilized the ordinal headache intensity scale commonly used in headache research, on which patients describe their headache as “severe,” “moderate,” “mild,” or “none.” We also asked patients to describe their pain using a 0–10 scale, on which 0 represented no pain and 10 represented the worst pain imaginable. We ascertained participants’ overall satisfaction with the investigational treatment by asking them if they would want to receive the same treatment the next time they came to the ER with a migraine headache. Adverse events were assessed using a dichotomous question: “Did you have any side effects that were caused by the procedure?” followed by an open-ended question directed at affirmative responders (“Please tell us about any side effects that you experienced).

The primary outcome was complete headache freedom (headache level = none) 30 minutes following the procedure. We chose this outcome because we hoped to minimize the influence of placebo on the primary outcome by requiring headache freedom rather than just headache improvement, and because we felt it unlikely that a patient would progress from moderate or severe migraine to headache freedom within 30 minutes spontaneously and without intervention. Important secondary outcomes were the frequency of sustained headache relief (achieving a headache level of mild or none within 1 hour of the procedure and maintaining a level of mild or none without the use of additional medication for 48 hours) and subject satisfaction with the procedure measured 48 hours later. We also report the frequency of procedural side effects, pain scores 1 hour after the procedure, and absolute and percent improvement in 0–10 pain scores between baseline and 1 hour.

The success of blinding was evaluated by asking both research subjects and blinded outcome assessors whether they thought the research participant received active or sham treatment.

The primary outcome was the rate of headache freedom at 30 minutes. Absolute risk reduction is reported with 95% CI. All secondary outcomes are reported as frequencies with percent. The between-group differences are reported with 95% CI. We report chi-square $P$ values for all dichotomous outcomes with at least 5 responses per category. Otherwise, we used Fisher’s exact test. We report Student’s $t$ test $P$ values for continuous outcomes. Our criterion for statistical significance was .05 (2-tailed). SPSS v. 25 (IBM Corp., Armonk, NY, USA) was used for all analyses.

Prior to study initiation, we estimated a sham rate of headache freedom of 20% and an intervention rate of 50%. Using an alpha of 0.05 and a beta of 0.20, we calculated the need for 39 subjects in each arm. These estimates were based on our clinical expectations.

RESULTS
Enrollment commenced in August, 2015 and ended in January, 2018. During these 31 months, 76 patients were screened for participation and 28 patients were enrolled (CONSORT Diagram, Fig. 1). The rate of enrollment in the study remained slow throughout the entire study period, despite multiple interventions by the study investigators. Ultimately, the data monitoring committee recommended halting the study because the full sample size would not be achieved in a timely enough manner to be relevant. The enrolled population consisted of mostly young and middle-aged women, who reported generally low-levels of baseline functional impairment (Table 1).

The primary outcome, headache freedom at 30 minutes, was achieved by 0/15 (0%) of patients in the sham arm and 4/13 (31%) of patients in the GONB arm (95% CI for a difference of 31%: 6, 56%). Secondary outcomes are reported in Table 2. Scores on the 0–10 pain scale are reported in Table 3 and in Supplementary Fig. 2.

The injections were well tolerated. Two patients in the GONB arm developed injection site pain. One patient in each arm reported neck pain. One patient in the sham arm reported dizziness. One patient who received GONB subsequently developed shingles. The small sample size precludes a statistical evaluation of the association between number of procedures performed previously and outcome. The principal investigator, who had the most experience among all the injectors performing this procedure, injected 8 research subjects, of whom 3 received active treatment. Of these 3, all reported headache freedom at 30 minutes, though none reported sustained headache relief. Conversely, none of the remaining 5 patients who received sham injection from the same principal
investigator reported headache freedom at 30 minutes, nor did any report sustained headache relief. Our assessment of the adequacy of blinding is reported in Table 4.

**DISCUSSION**

In this small, ED-based, randomized, sham-controlled clinical trial of GONB with bupivacaine for acute migraine refractory to intravenous metoclopramide, the GONB resulted in greater rates of headache freedom 30 minutes post-procedure. These data also suggest that patients who received the GONB were more likely to experience sustained headache relief, though the trial was underpowered to convincingly make this claim. These data must be interpreted cautiously because the study was halted prior to achieving the required sample size, research subjects in the study may not have been blinded adequately, and the efficacy of the procedure may be operator-dependent.
Existing evidence supporting efficacy of GONB for acute migraine is limited.\textsuperscript{5,9} Randomized studies of GONB for migraine to date have assessed the role of steroids as adjunctive therapy\textsuperscript{10,11} or focused on short-term migraine prevention.\textsuperscript{12,16} In published case series, post-procedure outcomes have generally

### Table 2.—Study Outcomes

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Sham Injection (n = 15)</th>
<th>Greater Occipital Nerve Block (n = 13)</th>
<th>Difference (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache freedom 30 minutes after injection</td>
<td>0 (0%)</td>
<td>4 (31%)</td>
<td>31% (6, 56%)</td>
<td>.035</td>
</tr>
<tr>
<td>Sustained headache relief\textsuperscript{†}</td>
<td>0 (0%)</td>
<td>3 (23%)</td>
<td>23% (0, 46%)</td>
<td>.087</td>
</tr>
<tr>
<td>Would want the same injection again</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (20%)</td>
<td>5 (38%)</td>
<td>18% (−15, 52%)\textsuperscript{†}</td>
<td>.306</td>
</tr>
<tr>
<td>No</td>
<td>6 (40%)</td>
<td>6 (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not sure</td>
<td>6 (40%)</td>
<td>2 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache intensity at 60 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe/Moderate</td>
<td>10 (67%)</td>
<td>4 (31%)</td>
<td>36% (1, 71%)</td>
<td>.058</td>
</tr>
<tr>
<td>Mild/None</td>
<td>5 (33%)</td>
<td>9 (69%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{†}Achieved headache level of mild or none in the ED within 1 hour of the procedure and did not relapse to moderate or severe within 48 hours. Patients who required additional headache or pain medication in the ED or used headache or pain medication at home were considered outcome failures.

\textsuperscript{†}Yes vs No/Not sure.

### Table 3.—0–10 Pain Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham Injection (n = 15)</th>
<th>Greater Occipital Nerve Block (n = 13)</th>
<th>Difference (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.7 (1.6)</td>
<td>7.9 (1.9)</td>
<td>0.3 (−1.1, 1.6)</td>
<td>.703</td>
</tr>
<tr>
<td>60 minutes post-injection</td>
<td>5.5 (2.4)</td>
<td>3.3 (2.8)</td>
<td>2.2 (0.1, 4.2)</td>
<td>.039</td>
</tr>
<tr>
<td>Baseline – 60 minutes</td>
<td>2.2 (3.2)</td>
<td>4.6 (3.3)</td>
<td>2.4 (−0.1, 5.0)</td>
<td>.063</td>
</tr>
<tr>
<td>Percent improvement\textsuperscript{†}</td>
<td>24% (41%)</td>
<td>57% (39%)</td>
<td>33% (2%, 64%)</td>
<td>.038</td>
</tr>
</tbody>
</table>

\textsuperscript{†}(Baseline – 60 minutes)/Baseline.

### Table 4.—Adequacy of Blinding

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sham (n = 15)</th>
<th>Greater Occipital Nerve Block (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research subject’s opinion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I got sham</td>
<td>10 (67%)</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>I got the nerve block</td>
<td>5 (33%)</td>
<td>8 (62%)</td>
</tr>
<tr>
<td>Outcome assessor’s opinion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient got sham</td>
<td>6 (40%)</td>
<td>6 (46%)</td>
</tr>
<tr>
<td>Patient got nerve block</td>
<td>9 (60%)</td>
<td>7 (54%)</td>
</tr>
</tbody>
</table>
been substantially better than those reported here.\textsuperscript{17,18} Among a series of 18 patients with acute migraine with prolonged aura who received bilateral GONB, 55\% reported complete pain relief and 25\% partial pain relief.\textsuperscript{18} Among a series of 19 patients with episodic or transformed migraine and brush allodynia who received a GONB with trigger point injection, 89\% reported reduction in pain 20 minutes later.\textsuperscript{17} However, in a retrospective database review of 562 patients who received GONB for an acute migraine in a clinic setting, results were similar to those reported here: 82\% of patients had a ≥30\% response to GONB and 58\% reported ≥50\% response.\textsuperscript{19} This disparity in outcomes may be related to characteristics of the patient population, proficiency of the performing provider, technique, or placebo effect.

A number of limitations must be mentioned. The principal limitation of this randomized clinical trial is a failure to achieve our planned sample size. We were able to enroll only 28 patients out of a target N = 78 over a period of 32 months. The rate of enrollment in the study of less than one patient per month remained slow throughout the entire study period despite multiple interventions by the study investigators targeted at the referring providers. Ultimately, the data monitoring board for the study stopped the trial because the estimated additional 7–8 years that would be required to achieve our target sample size could not be justified. The data remained blinded during the decision to terminate the study so we do not believe overt bias affected these results, but we cannot know whether the magnitude of the effect size would have increased, decreased, or remained the same had we continued the study to its pre-determined endpoint. It is likely that recruitment would be easier in outpatient settings where, unlike the ED, GONB would be performed by clinicians managing patients longitudinally rather than seeing them episodically for migraine headache.

Another important limitation of this study is that it involves a procedure that is necessarily operator-dependent. The small sample size precludes a statistical evaluation of the association between individual provider, number of procedures performed previously, and patient outcome. However, all 3 patients who were randomized to GONB and were injected by the principal investigator, the injector who had the most experience performing this procedure, achieved the 30 minute pain free outcome. While all providers were emergency clinicians, and therefore proficient at peripheral nerve blocks in general, it is quite possible that inexperience with this type of block in particular biased the study toward the null hypothesis. Conversely, the relative inexperience of our injectors enhances the generalizability of these data.

A third limitation of this study was what may have been inadequate blinding of subjects. When designing this study, we sought a sham that we believed would adequately blind both the patients and the outcome assessors, and would have no known anti-migraine efficacy other than placebo effect. As shown in Table 4, when we queried both research associates and patients to confirm adequacy of blinding at the end of the study, although the research associates appear to have been adequately blinded, the research subjects may not have been. Because the blinding mechanism was probably insufficient, the magnitude of effect of the intervention may have been amplified. Until an adequate blinding mechanism is identified, this is a problem that will continue to affect randomized double-blind trials of GONB. It is not clear why our blinding mechanism did not work. It may be that patients who received the true GONB were more likely to feel better, and therefore, were more likely to believe they received the true intervention. Alternatively, patients who received the true intervention may have been more likely to be numb and thereby more likely to guess their true assignment. However, neither of these conjectures was born out in the actual data (see supplementary data). Other possibilities include less enthusiasm on the part of the sham injectors (who were necessarily unblinded), which may have been inadvertently conveyed to the patient. Alternatively, the complexity of the procedure, which incorporated a fan technique only for those who received the true GONB, may have provided subjects with an unintended cue.

Finally, it is possible that our sham was not a true sham because there are nerve branches all over the scalp; some of the local anesthetic from the intradermal injection may have had some analgesic effect via some of these branches. Alternatively, it is possible that some of the anesthetic we injected intradermally could have diffused through the scalp to the greater occipital nerve itself.

Clearly, more research on the efficacy of GONB for acute migraine is needed. However, technical
Headache questions still abound. It is not yet clear if the injection should be performed bilaterally or if the lesser occipital or trigeminal nerve branches should be targeted as well. It is also unclear whether medication is needed – GON injections with saline or dry needling alone may have neuromodulatory effects that improve acute migraine. Finally, it is not at all clear how best to blind research subjects. The technique we used appears to be inadequate because nearly two-thirds of subjects deduced their true assignment. Other techniques for sham GONB have been reported, including using saline rather than a local anesthetic or using very low doses of local anesthetic. However, the former technique is unlikely to generate scalp numbness and the latter may have true anti-migraine efficacy. In a study of paracervical injections for pediatric headache, the investigators used a 3-arm design, in which one-third of patients were randomized to local anesthetic, one-third to saline, and one-third to no intervention at all. This design, although not without potential intrinsic bias, may be useful for future trials of GONB, provided that a sufficiently large number of patients could be recruited.

In conclusion, though limited by the biases described above, these data suggest that GONB may be an effective treatment for ED patients with acute migraine who fail to improve after first-line treatment with intravenous metoclopramide.

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