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A randomized, double-dummy, emergency department-based study of greater occipital nerve block with bupivacaine versus intravenous metoclopramide for treatment of migraine

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Abstract

Background.—Greater occipital nerve blocks (GONB) are used increasingly to treat acute migraine.

Objective.—We conducted a randomized controlled trial to determine whether GONB was as effective as intravenous metoclopramide for migraine.

Methods.—This was a double-dummy, double blind, parallel-arm, non-inferiority study conducted in two emergency departments. Patients with migraine of moderate or severe intensity were randomized to receive bilateral GONB with each side administered bupivacaine 0.5%, 3mL, or metoclopramide 10mg IV, the putative standard of care. The primary outcome was improvement in pain on a 0-10 scale between time 0 and one hour later. To reject the null hypothesis that metoclopramide would be more efficacious in relieving pain, we required that the lower limit of the 95% CI for the difference in pain improvement between those randomized to GONB versus those randomized to metoclopramide be > -1.3 , a validated minimum clinically important difference. Secondary outcomes included sustained headache relief, defined as achieving and maintaining for 48 hours a headache level of mild or none without the use of additional analgesic medication, and use of rescue medication in the ED.

Results.—Over a 2.5 year study period, 1358 patients were screened for participation and 99 were randomized, 51 to GONB and 48 to metoclopramide. All of these patients were included in the primary analysis. Patients who received the GONB reported mean improvement of 5.0 (95% CI: 4.1, 5.8) while those who received metoclopramide reported a larger mean improvement

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Conflict of Interest:

The authors report no relevant conflict of interest

of 6.1 (95% CI: 5.2, 6.9). The 95% CI for the between group difference of -1.1 was $-2.3, 0.1$. Sustained headache relief was reported by 11/51 (22%) GONB and 18/47 (38%) metoclopramide patients (95% CI for rounded difference of 17%: $-1, 35\%$). Of the 51 GONB patients, 17 (33%) required rescue medication in the ED versus 8/48 (17%) metoclopramide patients (95% CI for rounded difference of 17%: $0, 33\%$). An adverse event was reported by 16/51 (31%) GONB patients and 18/48 (38%) metoclopramide patients (95% CI for (rounded) difference of 6%: $-13, 25\%$).

Conclusion.—GONB with bupivacaine was not as efficacious as IV metoclopramide for the first-line treatment of migraine in the ED.

Keywords

migraine; greater occipital nerve block; emergency department; metoclopramide; bupivacaine

Introduction

More than one million patients present to US emergency departments (ED) annually seeking relief from acute migraine.(1) Multiple different classes of medication are used to treat these patients, yet the goal of sustained headache relief remains elusive.(1, 2) Fewer than 25% of ED migraine patients achieve headache relief and remain headache free for 48 hours, regardless of which medication they receive.(2)

Greater occipital nerve blocks (GONB) are being used with increasing frequency to treat acute migraine in the ED.(3, 4) Some data suggest that these blocks may provide rapid and sustained relief with only minimal side effects.(5) This procedure is hypothesized to work by decreasing transmission through the trigeminocervical complex (TCC), an important way-station in migraine pathogenesis. Within the TCC, nociceptive input arriving from the trigeminal nerve is relayed to second order nerves that terminate in the thalamus. Upper cervical nerves, including the greater occipital nerve, also terminate in the TCC. It is believed that nerve fibers originating from the upper cervical nerves converge on the same second order nerves as the trigeminal nerve fibers. Decreasing transmission of sensory input through the TCC by blocking the greater occipital nerve can relieve the pain of acute migraine. Clinical evidence supporting this mechanism for acute treatment is limited.(5)

Our hypothesis was that among patients who present to an ED with migraine, bilateral GONB with bupivacaine would alleviate pain as well as or better than intravenous metoclopramide, a guideline-endorsed treatment of acute migraine, (6) as measured by improvement on a 0-10 scale between baseline and one hour.

Methods

Study Overview:

This was a randomized, double-dummy, clinical trial comparing GONB with intravenous metoclopramide. We initially intended to perform a standard superiority trial in which we compared the frequency of sustained headache relief between two arms. However, enrollment remained sluggish throughout the 2.5 year enrollment period. Therefore, at the

recommendation of our data monitoring committee and with the approval of our IRB, prior to unblinding, we changed the study to a non-inferiority design to lessen sample size requirements (ie, stop the study early). The Albert Einstein College of Medicine IRB approved the study. The trial was registered at <http://www.clinicaltrials.gov> (NCT03269435). All patients provided written informed consent.

Setting:

This study was performed in two EDs of Montefiore Medical Center in the Bronx, NY. These are academic, high volume EDs with a combined census of nearly 180,000 visitors. Salaried, trained, bilingual (English and Spanish) technician-level research associates, staff these emergency departments 24 hours per day/ seven days per week and enrolled all patients in this study.

Selection of Participants:

Eligible patients were adults age 18 years who presented to the ED with an acute headache of moderate or severe intensity that met International Classification of Headache Disorders, 3rd edition migraine criteria (1.1, migraine without aura).(7) Patients who met criteria for probable migraine without aura (1.5.1) were also included, provided they had had at least one similar attack previously. Status migrainosus, prolonged duration of headache (>72 hours), early attack presentation (<4 hours), or an additional diagnosis of migraine with typical aura (1.2.1) or probable migraine with typical aura (1.5.2) did not preclude participation. Patients were excluded if informed consent could not be obtained, if there was concern for a secondary cause of headache, for contra-indications to GONB (skull defect, suspected infection overlying injection site, known bleeding disorder, ongoing use of anti-platelet agents or anti-coagulants), prior treatment with GONB at any time previously, or allergy or contra-indication to the investigational medications. Pregnant and lactating patients were also excluded. Patients were identified by the attending emergency physician and referred to research personnel.

Intervention:

The randomization ratio was 1:1. Randomization assignments were generated without restriction by the research pharmacist. Patients randomized to the nerve block arm received a total of 6ml bupivacaine 0.5%, injected adjacent to the greater occipital nerve bilaterally (3ml each side) in addition to an intravenous drip containing normal saline placebo, administered over 15 minutes.

Patients randomized to the metoclopramide arm received a sham GONB consisting of 6ml normal saline, injected adjacent to the greater occipital nerve bilaterally (3ml each side) in addition to an intravenous drip containing 10mg metoclopramide, administered over 15 minutes.

A clinical nurse retrieved two vials from the pharmacy. The first vial contained either 2ml of metoclopramide 10mg or 2 ml normal saline. The second contained either 6ml of bupivacaine or 6 ml normal saline. The vials containing the active drug or saline placebo appeared identical, thus ensuring that patients and all study personnel were blinded to

assignment. The nurse inserted the contents of the first vial into a 100ml bag of normal saline and administered it as an intravenous drip over 15 minutes. The nurse gave the second vial to a healthcare provider to perform the GONB. All injectors were emergency medicine personnel including attending physicians, residents, nurse practitioners and physician assistants and thus were skilled at performing peripheral nerve blocks. Injectors received one-on-one training from the investigators during which we discussed and demonstrated techniques and landmarks for the GONB. The GONB or saline placebo injection was administered as shown in Figure 1.

Study participants, clinicians, and research associates who assessed outcomes were blinded. A randomization list was generated using an online generator at <http://www.randomization.com>. Based on the randomization schema, the pharmacist placed either 2ml of metoclopramide or normal saline into vial 1 (for intravenous administration) and either 6ml bupivacaine or normal saline into vial 2 (for subcutaneous injection). The research packets provided by the pharmacy were used in sequential order.

Methods of Measurement:

As a primary measure of headache intensity, we assessed pain using an 11-point pain scale. On this scale, patients assign their pain a number between zero and 10, with zero representing no pain and 10 representing the worst pain imaginable. We also utilized a descriptive headache intensity scale, in which subjects describe their headache as “severe”, “moderate”, “mild”, or “none”. Both of these measures are recommended for use in migraine research.⁽⁸⁾ We ascertained overall subject satisfaction with the experimental treatment by asking them, 48 hours later, if they would want to receive the same treatment the next time they came to the ED with a migraine headache. Adverse events were elicited using the simple dichotomous question, “Did you have any side effects that were caused by the study medications?”, followed by an open-ended question “Please tell us about the side effects you experienced”. Akathisia, a common side effect of metoclopramide, was assessed specifically by asking participants to rate their restlessness and anxiety on a zero to ten scale 30 minutes after medication administration. Research associates contacted participants by telephone 48 hours after ED discharge to ascertain headache status, satisfaction with treatment, and presence of additional adverse events.

Outcomes:

The primary outcome was improvement in 0 – 10 pain scale between baseline and one hour post-baseline. Secondary outcomes were: 1) Frequency of sustained headache relief, defined as obtaining a headache level of mild or none in the ED within two hours of medication administration, not requiring additional analgesic medication in the ED or at home, and not relapsing to a headache level worse than mild during the 48 hours after medication administration; 2) sustained headache freedom, defined as achieving a pain level of none within two hours of medication administration and maintaining a level of none without the use of additional analgesic medication for 48 hours; and 3) satisfaction with treatment, as evidenced by an affirmative response to the question: “Do you want to receive the same treatment the next time you come to the ER with migraine?” We also reported the frequency

of adverse events, requirement of rescue medication in the ED, and ED treatment time, defined as elapsed time between medication administration and ED discharge.

Sample size calculation:

We initially intended to enroll 170 patients in this study. However, enrollment remained slow throughout a 2.5 year recruitment period. Therefore, with the approval of our IRB, we changed the null hypothesis from a typical superiority design (no difference between the groups) to one appropriate for a non-inferiority design: metoclopramide would be more efficacious than GONB with regard to pain improvement between baseline and one hour later, as measured by a change in 0-10 pain score (improvement = baseline score- one hour score). The minimum clinically important difference on the 0-10 pain score has been shown to be 1.3.(9) Therefore, the noninferiority margin for the primary outcome (improvement in GONB minus improvement in metoclopramide) was -1.3. Using a standard deviation of 3.1, we calculated the need for 97 patients.

Analysis:

We used IBM SPSS Statistics V.25 (IBM, Armonk, NY, USA) to conduct all analyses. We report baseline statistics as mean (standard deviation), median (interquartile range), or frequency (percent). We compared improvement in pain score (baseline score minus one hour score) between the two groups. If the lower bound of the 95% CI of the between-group difference was > -1.3 , we would conclude GONB was non-inferior. All dichotomous secondary outcomes are reported as frequencies. Between group differences are reported with 95%CI. If the 95%CI does not cross 0, it was considered a statistically significant difference. We also report the percent improvement over one hour. This was calculated as: (baseline 0-10 score - one hour 0-10 score)/ (baseline 0-10 score). For akathisia, we compared zero versus non-zero scores on the 0-10 anxiety and restless scales between the two groups using logistic regression models and report odds ratio (OR) with 95%CI. We also performed an exploratory analysis in which we determined whether number of previously performed GONBs was associated with outcomes among patients randomized to GONB and display these results using a scatter plot. As part of this exploratory analysis, we compare outcomes between those patients who had a GONB performed by a provider who had performed at least seven GONBs previously and those who had a GONB performed by a provider who had performed six or fewer GONBs previously. P values were calculated using two-tailed tests. $P < 0.05$ was considered statistically significant.

Results

Enrollment commenced in November 2017 and ended in March 2020. 1358 patients were screened for eligibility and 99 were randomized (Figure 2). The sample consisted largely of young women (Table 1). Providers who performed the GONB or sham procedure reported performing a median of 2 [IQR 0,6] previous GONBs.

With regard to the primary outcome, patients who received the GONB reported mean improvement of 5.0 (95%CI: 4.1, 5.8) while those who received metoclopramide reported

mean improvement of 6.1 (95%CI: 5.2, 6.9). The 95%CI for the between group difference of -1.1 was -2.3, 0.1. We report secondary outcomes in Table 2.

Adverse events were reported by 16/51 (31%) GONB patients and 18/48 (38%) metoclopramide patients (95%CI for (rounded) difference of 6%: -13, 25%). This includes dizziness, reported by 4 GONB patients and 3 metoclopramide patients; drowsiness, reported by 3 metoclopramide patients; worsening or changed headache, reported by 3 GONB patients and 2 metoclopramide patients; head numbness for 48 hours, reported by 4 GONB patients; injection site reaction, reported by 2 GONB patients and 1 metoclopramide patient; and GI symptoms, reported by 2 GONB patients. No other adverse effects were reported by more than one patient. With regard to symptoms of akathisia, which was assessed 30 minutes after medication administration, receiving GONB rather than metoclopramide was protective against anxiety (OR 0.35, 95%CI 0.15, 0.85) but not restlessness (OR 0.64, 95%CI 0.29, 1.42).

We determined whether experience performing the GONB had an impact on outcomes. Among 15 patients who received a GONB from a provider who had performed the procedure at least seven times before, mean improvement in 0-10 pain scores was 6.9 (SD 2.6). Among 36 patients who had a provider who had performed the procedure fewer than seven times previously, the mean improvement was 4.1 (SD 2.9). The 95%CI for this difference of 2.8 is 1.1, 4.5. Other outcomes comparing experienced and unexperienced providers are presented in Table 3 and Figure 3. We compared the improvement in 0-10 pain scores between 15 GONBs performed by experienced providers and the 48 patients randomized to IV metoclopramide. The 95%CI for the difference of 0.9 (rounded) was -0.8, 2.6).

Discussion

In this randomized double dummy study, we did not find greater occipital nerve block with bupivacaine to be as effective as intravenous metoclopramide, the putative standard of care, for migraine. In fact, intravenous metoclopramide outperformed GONB on a number of outcomes including pain improvement between baseline and one hour, requirement of rescue medication in the ED, sustained headache relief, and patients' desire to receive the same treatment during a subsequent ED visit. These data indicate that a general strategy of first-line GONB with bupivacaine for ED patients with migraine will result in inferior short-term and sustained outcomes compared to a metoclopramide first strategy.

While GONB was not as efficacious as intravenous metoclopramide, an exploratory analysis suggested that in experienced hands, GONB and intravenous metoclopramide may have comparable efficacy. There was wide variability in the providers' experience performing GONBs. Poor one hour pain outcomes were common when the provider had previously performed fewer than seven GONBs. When performed by providers who had blocked the greater occipital nerve at least seven times previously, patients almost uniformly reported >50% relief of pain. Similarly, use of rescue medication and patient satisfaction with the procedure was much better when the provider was experienced. This has obvious

ramifications for the clinical care of patients, training of healthcare providers, and conduct of future ED based studies.

There is a relative paucity of high-quality literature examining the efficacy of GONB for acute migraine. In an ED based study, 60 patients with acute migraine were randomized to GONB with bupivacaine, metoclopramide + dextketoprofen IV, or a sham GONB using just normal saline. In this study, median improvement at 45 minutes in all three groups was substantial, though the active groups did outperform the sham block. Percent improvement in median pain scores at 45 minutes was: GONB 78%, IV medications 88%, sham GONB 63% (In our study, the metoclopramide group improved by 66% at one hour and the GONB group improved by 54%).(4) In a randomized, ED-based, sham controlled study of GONB as second line therapy for acute migraine (after failure of IV metoclopramide), GONB did indeed benefit some patients, with a number needed to treat of 3 for both immediate and sustained outcomes.(10) In this study too, there was an association between provider experience and outcomes. Randomized studies focused on longer-term migraine outcomes suggest that GONB with a local anesthetic is more efficacious than sham blocks.(11-13)

Metoclopramide is a guideline-supported, evidence-based treatment of acute migraine.(6) However, a specific mechanism of action for anti-dopaminergic medication efficacy in migraine has yet to be described.(14) The frequency of adverse events was relatively evenly distributed between the groups. Patients in the metoclopramide group were more likely to experience anxiety and drowsiness, which are known and expected side effects of this medication. Four patients in the GONB arm reported head numbness for 48 hours, which is longer than one would anticipate based on the known pharmacodynamics of bupivacaine. One metoclopramide patient experienced an injection site reaction, an adverse event that is no doubt a reflection of the study design and not directly related to metoclopramide.

There are several limitations of this study. The first and most important is the association we identified between healthcare provider experience and outcomes. If we had required healthcare providers to have substantial experience performing this procedure, the primary outcome may have been different. Another limitation is that the optimal peripheral nerve block technique for acute migraine is unclear. It is unknown what dose of topical anesthetic should be used, and whether the block should be performed bilaterally. Nor is it known whether targeting the lesser occipital nerve or trigeminal nerve branches in addition to the greater occipital nerve, which is commonly performed in outpatient practice,(15) would result in better outcomes. Third, a large number of patients who were screened for participation ultimately did not meet inclusion criteria or refused participation. Therefore, the generalizability of these data to a broad sample of ED headache patients is uncertain. Fourth, it is possible that in addition to blocking the greater occipital nerve, some providers may have blocked the lesser occipital nerve as well. Finally, we were unable to achieve our initial planned sample size and were forced to change our analysis plan. However, this was done without unblinding the data and so we do not believe it biased our results.

Conclusion

In conclusion, we did not find that GONB with bupivacaine was as efficacious as IV metoclopramide for the first-line treatment of acute migraine in an ED, but there is evidence that in experienced hands, the GONB may indeed be as efficacious.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. GONB technique

The injector identified the appropriate location using landmarks on the patient's head. The medial landmark was the occipital protuberance. The lateral landmark was the mastoid process. Using these landmarks to form a straight line, the injector identified the correct location, which was $1/3^{\text{rd}}$ of the distance from the occipital protuberance along this line ($2/3^{\text{rd}}$ of the distance away from the mastoid process). The injector felt for pulsation of the occipital artery and attempted to elicit pain or paresthesia in the distribution of the greater occipital nerve by pressing slightly. The injector then used a fanning technique, placing 1mL of anesthetic at the identified location, 1mL slightly medial of the identified location, and 1 mL slightly lateral to the identified location. The procedure was then repeated on the opposite side.

Figure 2.
CONSORT flow diagram

Figure 3. Improvement in pain score versus number of GONBs performed previously

This figure depicts only participants randomized to true GONB. When performed by providers who had done <7 GONBs previously, < 50% improvement in pain was quite common. However, when injected by a provider who had performed ≥ 7 GONBs previously, almost every patient experienced >50% reduction in pain.

Table 1.

Baseline characteristics

Variable	Greater occipital nerve block (n=51)	Metoclopramide (n=48)
Age, years, mean (SD)	39 (11)	38 (11)
Sex		
Women	44 (86%)	34 (71%)
Men	7 (14%)	14 (29%)
Headache duration, hours, mean (SD)	100 (137)	99 (159)
Aura symptoms		
No	25 (49%)	21 (44%)
Yes	26 (51%)	27 (56%)
Took medication for headache prior to ED visit		
No	19 (37%)	12 (25%)
Yes	32 (63%)	36 (75%)
Baseline pain intensity		
Moderate	13 (25%)	13 (27%)
Severe	38 (75%)	35 (73%)
Number of functionally impairing days with headache in the last 3 months	5 (2, 12)	5 (2, 14)
Healthcare provider experience. Number of GONBs performed previously		
<7	36 (71%)	40 (83%)
7	15 (30%)	8 (17%)

Table 2.

Efficacy outcomes

Outcome	Greater occipital nerve block (n=51)	Metoclopramide (n=48)	Between group difference (95%CI)
Sustained headache relief			
Yes	11 (22%)	18 (38%)	17% (-1, 35%) [*]
No	40 (78%)	29 (62%)	
Missing	0	1	
Sustained headache freedom			
Yes	3 (6%)	7 (15%)	9% (-3, 21%)
No	48 (94%)	41 (85%)	
Required rescue medication in ED			
Yes	17 (33%)	8 (17%)	17% (0, 33%) [*]
No	34 (67%)	40 (83%)	
ED dwell time, minutes, median, IQR	121 (87, 194)	127 (84, 196)	6 (-48, 61)
Would want same treatment again			
Yes	27 (53%)	35 (76%)	23% (5, 42%) ^{**}
No	12 (24%)	8 (17%)	
Not sure	12 (24%)	3 (7%)	
Missing	0	2	
Percent improvement in 0-10 pain score, mean (SD)	54% (30%)	66% (31%)	12% (0, 25%) ^{***}

^{*} rounded

^{**} Yes versus no/ not sure

^{***} mean difference (95%CI)

Table 3.

Efficacy outcomes by experience of provider with GONB

Outcome	7 previous GONBs (n=15)	<7 previous GONBs (n=36)	Between group difference (95%CI)
Sustained headache relief			
Yes	4 (27%)	7 (19%)	7% (-19, 33%) *
No	11 (73%)	29 (81%)	
Sustained headache freedom			
Yes	2 (13%)	1 (3%)	11% (-7, 29%) *
No	13 (87%)	35 (97%)	
Required rescue medication in ED			
Yes	1 (7%)	16 (44%)	38% (17, 58%) *
No	14 (93%)	20 (56%)	
Same treatment again *			
Yes	11 (73%)	16 (44%)	29% (1, 57%) **
No	0 (0%)	12 (33%)	
Not sure	4 (27%)	8 (22%)	

*
Rounded**
Yes versus no/ not sure