Effectiveness of Peripheral Nerve Blocks for the Treatment of Primary Headache Disorders: A Systematic Review and Meta-Analysis

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Study objective: Primary headache disorders are prevalent and account for 2% of all emergency department visits. Current treatment options are effective; however, time to pain relief is suboptimal. Alternatives such as peripheral nerve blocks have shown promising results. The objective of this systematic review is to examine the effectiveness of peripheral nerve blocks for timely pain relief.

Methods: We searched Ovid MEDLINE, EMBASE, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials and included randomized controlled trials comparing peripheral nerve blocks to placebo or active therapy. The primary outcome was pain within 120 minutes. Secondary outcomes were pain after 120 minutes, adverse events, need for rescue medications, and relapse of headache. Two reviewers screened and extracted data independently; mean differences (MDs) were calculated, and results were pooled using a random-effects model.

Results: Eleven studies met our eligibility criteria (n=860), of which 9 were included in the meta-analysis. Pain scores were significantly lower in patients treated with peripheral nerve blocks than with placebo at 15 minutes (MD: −1.17; 95% confidence interval: −1.82 to −0.51) and 30 minutes (MD: −0.99; 95% confidence interval: −1.66 to −0.32), and no serious adverse events were reported. Pain scores for peripheral nerve blocks versus active therapy and secondary outcomes were not pooled due to clinical heterogeneity.

Conclusion: Our review shows peripheral nerve blocks are effective as a rapid treatment option when compared to placebo; however, we were unable to assess effectiveness against standard treatment. Emergency physicians should consider peripheral nerve blocks as an adjunct therapy for patients with primary headache disorders. [Ann Emerg Med. 2022;79:251-261.]

Please see page 252 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Headache disorders are one of the most common disorders of the nervous system and affect a majority of the population at some point in their lifetimes.[1,2] Headaches cause significant disability, which negatively impacts quality of life due to burden of pain and on a societal level in terms of loss in productivity.[3,4] According to the International Classification of Headache Disorders Third Edition (ICHD-3), headaches are divided into primary and secondary classifications, with primary being nontraumatic and benign in nature and secondary headaches being attributed to a secondary cause and potentially life-threatening.[5] The most common types of primary headache disorders include migraine, tension headache, and cluster headaches.

Importance

The main clinical problem for primary headache disorders in the emergency department (ED) is the relatively slow onset of current treatment options. First-line treatment options include nonsteroidal anti-inflammatory drugs, dopamine antagonists, and triptans, among others.[6,7] While recommended, these first-line agents may take time to be effective, cause side effects, or fail to control the headache.[8] Side effects for dopamine antagonists include extrapyramidal symptoms, such as acute dystonia, akathisia, and anticholinergic effects.[9,10] Recent interest has grown regarding the use of peripheral nerve blocks, such as

Editor's Capsule Summary

What is already known on this topic

Headaches are common in the emergency department. Peripheral nerves blocks have been fast and effective in small studies.

What question this study addressed

How fast do peripheral nerve blocks provide pain relief in headache?

What this study adds to our knowledge

Across several studies, the blocks reduced a 10-point numerical pain score for headache about 1 point in 15 minutes.

How this is relevant to clinical practice

The spenopalatine ganglion block involves dripping lidocaine into the nose. This is quick, easy to perform, cheap, and has minimal risk.

the greater occipital nerve block, sphenopalatine ganglion block, and trigger point injections (ie, as faster and more effective management of primary headaches).[6] Greater occipital nerve blocks are achieved by injecting an anesthetic with a needle toward the greater occipital nerve, which originates in the dorsal ramus of the C_2 and C_3 segments of the spinal cord.[11] The sphenopalatine ganglion block is achieved by blocking the extracranial parasympathetic sphenopalatine ganglion with an anesthetic through a device or simply using techniques such as the method of Barré, where a patient lies in a supine position with their head extended 45 degrees and rotated 30 degrees ispilaterally in preparation for intranasal droplets of lidocaine.[12-16] Trigger point injections involve injection of a local anesthetic into various trigger points located in the head, neck, and shoulder.[17] The exact mechanism for how peripheral nerve blocks work is unclear; however, there is evidence to suggest that local anesthetics break the pain cycle and thereby correlate with physiologic factors important to the production of chronic pain.[16] Previous systematic reviews have focused on the effects of individual peripheral nerve blocks for specific headache subtypes. However, the time to effective pain relief at clinically important time points remains unclear.[18-22] There is uncertainty as to whether patients may be quickly and safely discharged home within 120 minutes after receiving a peripheral nerve block. Time to relief of pain is important when the goal in emergency medicine is to treat acute and nonserious conditions, such as primary headache disorders, as quickly and effectively as possible while reducing intravenous medication and opioid use. If peripheral nerve blocks can be proven as effective alternatives for pain management, these procedures could be performed as first-line alternatives rather than adjunct therapy for rapid pain relief.

Goals of This Investigation

The primary objective of this systematic review is to evaluate the effectiveness of peripheral nerve blocks, including the greater occipital nerve block, the sphenopalatine ganglion block, and trigger point injections, for the treatment of primary headache disorders in the ED or clinic setting for pain intensity within 120 minutes when compared to placebo or other treatments. Secondary objectives are to assess pain intensity between 2 and 72 hours, adverse events, and relapse of headache resulting in readmission to the ED or clinic within 72 hours.

MATERIALS AND METHODS

Study Design and Selection of Participants

This study was registered and approved by PROSPERO (ID: CRD42020212187). The review protocol was not published but is available on request. This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Appendix E1, available at http://www.annemergmed.com) and with guidance from the Cochrane Handbook for Systematic Review of Interventions.[23,24]

We searched Ovid MEDLINE, EMBASE, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials from inception until November 24, 2020. We scanned the reference lists of included studies and relevant reviews identified through the search. Our search strategy was developed with a health sciences librarian and was subsequently peer reviewed by a second research librarian as per Peer Review of Electronic Search Strategies guidelines.[25] Search items related to primary headache and type of peripheral nerve block were included using Medical Subject Headings and indexed terms. The full search strategy can be found in Appendix E2 (available at http://www.annemergmed.com).

We included English-language studies reporting results from randomized controlled trials in humans. We included studies randomizing patients of any age presenting with primary headache disorders or benign headaches not yet diagnosed. Primary headache disorders were defined according to the ICHD-3 including acute or chronic migraine and tension and cluster headaches, which account for 90% of benign headaches.[26] Headaches must have been based on the ICHD-3 criteria or equivalent, as proposed by

the International Headache Society. If no criteria were specified, the diagnosis of headache must have been based on important characteristics of primary headache disorders. We excluded nonrandomized trials, review articles, and studies that assessed patients with secondary headache disorders.

The results of the search strategy were uploaded to Covidence (Veritas Health Innovation).[27] Duplicates were removed both electronically and manually during screening. DP and KY independently screened all titles and abstracts and subsequent full texts. Any remaining discrepancies and conflicts were resolved with a third reviewer (JJP or MT).

We extracted prespecified information from included randomized controlled trials using a standardized data extraction form (Appendix E3, available at http://www.annemergmed.com) created on Google Sheets. The data extraction form was piloted, and we made modifications as necessary to handle the variety of data. All data were abstracted from full texts independently by 2 authors (DP and KY), and conflicts were resolved by a third reviewer (JJP or MT). We converted medians and interquartile ranges to means and standard deviations by assuming median as the mean when distribution of the data was approximately normal and dividing interquartile range by 1.35 to obtain the standard deviation.[24] Trials reporting pain using the visual analog scale (VAS) on 0-to-100-mm scales were converted to 0 to 10 cm to ensure comparability with trials using the numeric rating scale (NRS; 0-to-10-point scale). We attempted to contact corresponding authors of studies if more information was required to meet our inclusion criteria.

Interventions

Patients must have been given a peripheral nerve block, defined as a form of regional anesthesia near a nerve bundle, with the intent to alleviate symptoms of headache. The types of peripheral nerve block included in this study were the greater occipital nerve block, the sphenopalatine ganglion block (ie, intranasal administration of a local anesthetic), and trigger point injections. We included trials comparing the intervention to either a placebo control or standard headache therapy.

Outcomes

Our primary outcome was pain intensity within 120 minutes. Pain intensity must have been assessed according to a self-reported scale, such as the VAS, NRS, or other permutations (eg, ordinal scales or rating scales) within a composite measure of pain. Outcomes were collected as either continuous pain scores or as dichotomous variables, defined as meeting a specified cut-off for improvement. Secondary outcomes included pain scores between 2 and 72 hours posttreatment, adverse events, the need for rescue medications, and any readmission to the ED or clinic for headache within 72 hours.

Primary Data Analysis

We conducted meta-analyses using a random-effects model on quantitative data when at least 2 studies were considered sufficiently homogenous and clinically appropriate, such as reporting the same outcome at a common time point using a common comparator. We separately pooled trials comparing peripheral nerve block versus placebo and those comparing peripheral nerve block versus standard headache therapy.

For continuous outcomes, we summarized the treatment effect using mean differences (MDs) measured on a scale from 0 to 10 cm. The VAS, measured on a scale from 0 to 100 mm, was converted to 0 to 10 cm to be comparable with the NRS. The VAS and NRS show strong statistical correlation and can be used interchangeably as long as scores on the 0-to-100-mm VAS are converted to the closest integer (0 to 10).[28] We assessed statistical heterogeneity using the I^2 statistic, where heterogeneity was considered low when I^2 was less than 50%, moderate when I^2 was 50% to 75%, and high when I^2 was more than 75%. If the I^2 statistic was considered high, we planned to explore possible sources of heterogeneity by sensitivity and subgroup analyses.

Statistical significance was assessed at the 5% level. Review Manager Version 5.4.1 was used for all statistical analyses.[29]

Risk of bias was assessed using the Cochrane Risk of Bias 2 tool.[30] This tool is structured in 5 domains for which bias in randomized controlled trials may arise. DP and KY independently ranked each domain as low-risk, some concerns, or high-risk to determine the overall risk of bias for each study, and any discrepancies were resolved by JJP or MT. Results were presented in a risk-of-bias summary figure using Risk-Of-Bias VISualization.[31] We planned to perform a sensitivity analysis for studies included in the meta-analysis at high risk of bias.

We rated the certainty of evidence for outcomes based on the sum of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation process.[32] The strength and certainty of evidence was assessed only for studies included in the meta-analysis.

RESULTS

Figure 1 demonstrates the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram for the

selection process and detailed identification of included studies. A total of 1,830 references were identified from our search strategy. After electronic deletion of 599 duplicates, 1,231 studies were imported for screening based on the updated search strategy of databases. We excluded 1,167 after reviewing titles and abstracts. Sixty-four full texts were assessed for eligibility, and we included 11 studies in our final review.[12,15,33-41] The main reasons for exclusion were irrelevant outcomes reported and wrong type of headache studied.

Characteristics of Study Subjects

Baseline characteristics of the 11 included randomized controlled trials are summarized in the Table.[33,35-40,42] All trials were double-blind except 1, which was single-blind, and were published between 1996 and 2020 in the United States, Turkey, or Iran.[36] Eight trials were conducted in an ED and 3 trials in a clinic setting.[33,35-40,42] Five trials included patients with episodic migraine alone, 1 trial included patients with chronic migraine alone, and the remaining 5 included patients with combinations of acute, chronic, or episodic migraine and/or cluster, tension, or benign headaches.

The Table summarizes patient characteristics of the 11 included studies. The total sample size was 860 (approximately 67% women) and ranged from 28 to 162 patients. Based on visual inspection of extracted data (Appendix E4, available at http://www.annemergmed.com), we concluded that baseline pain scores were not substantially different between the peripheral nerve block group and the control group.

Tables E1 and E2 in Appendix E4 display the journal, number of sites, diagnositic criteria, pain scale used, baseline pain scores, and the types of medications and modes of administration for both the peripheral nerve block and control groups. For the peripheral nerve block group, 7 trials studied the sphenopalatine ganglion block and 4 trials studied the greater occipital nerve block.[12,15,33-41] The sphenopalatine ganglion blocks were administered as intranasal droplets in 5 trials and with the Tx360 device in 2 trials.[12,15,33,38-41] No trials studying trigger point injections met our eligibility criteria. The peripheral nerve blocks were administered by emergency physicians, residents, physician assistants, or nurse practitioners. Five studies used lidocaine (10 to 80 mg) and 6 studies used bupivacaine (3 to 80 mg) as the choice of anesthetic when performing the peripheral nerve block.

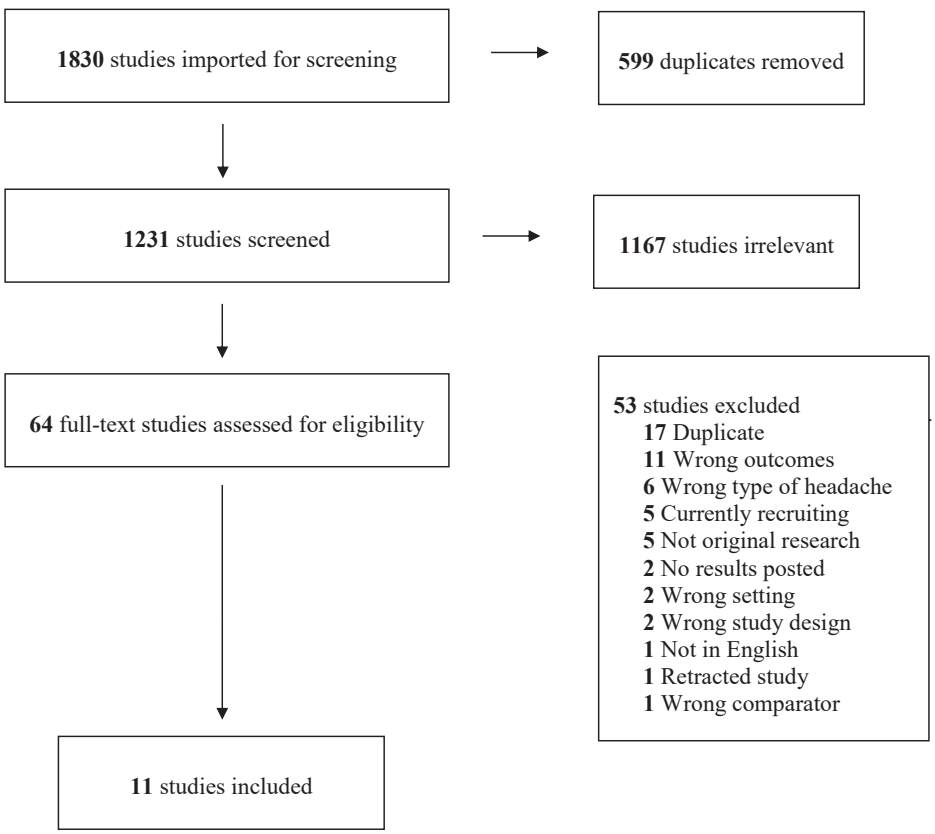

Figure 1. Flow diagram of selection process for the included studies.

Table. Baseline characteristics of included studies.

First Author Year	Country	Study Setting	Type of Primary Headache	Sample Size (N)	(% Female)	Mean Age (Years)	Type of Intervention	Type of Control
Maizels 1996[38]	United States	Clinic	Episodic migraine	81	67 (82.7%)	42 (36.3)	SPG Block	Placebo (saline solution)
Blanda 2001[12]	United States	ED	Episodic migraine	49	42 (85.7%)	Not reported	SPG Block and dopamine antagonist	Placebo (saline solution) and dopamine antagonist
Cady 2015[42]	United States	Clinic	Chronic migraine	41	31 (75.6%)	41.3 (12.6)	SPG Block	Placebo (saline solution)
Mohammadkarimi 2014[40]	Iran	ED	Migraine, tension	90	Not reported†	Not reported†	SPG Block	Placebo (saline solution)
Dilli 2015[34]	United States	Clinic	Episodic and chronic migraine	63	55 (87.3%)	43 (14)	GON Block and 0.5 mL of 20 mg methylprednisolone	Placebo (normal saline solution + 1% lidocaine without epinephrine)
Schaffer 2015[39]	United States	ED	Benign headache	87	64 (73.6%)	37.2 (15.95)	SPG Block	Placebo (saline solution)
Avcu 2017[15]	Turkey	ED	Episodic Migraine	162	125 (77.2%)	35.5 (11.3)	SPG Block and 10 mg in 100 mL of intravenous dopamine antagonist	Placebo (saline solution spray) and 10 mg in 100 mL of intravenous dopamine antagonist
Barzegari 2017[33]	Iran	ED	Multiple (migraine, cluster, or tension)	100	54 (54%)	31.3 (8.6)	SPG Block and 7.5 mg intravenous dopamine antagonist	Placebo (saline solution 0.9% and 7.5-mg intravenous dopamine antagonist)
Friedman 2018[36],*	United States	ED	Episodic migraine	28	24 (85.7%)	37.7 (11.4)	GON Block	Sham—0.5 mL of 0.5% bupivacaine intradermally into posterior scalp overlying the greater occipital nerve—1 mL total
Korucu 2018[37]	Turkey	ED	Episodic migraine	60	36 (60%)	38.3 (9.2)	GON Block and 1 mL normal saline solution	A. Placebo (saline solution) B. Intravenous dexketoprofen trometamol and 10-mg dopamine antagonist in 100-mL saline solution
Friedman 2020[35]	United States	ED	Episodic and chronic migraine	99	78 (78.8%)	38.5 (11)	GON Block and intravenous saline solution	Sham GON—6-mL saline solution and intravenous dopamine antagonist

SPG, sphenopalatine ganglion; *GON*, greater occipital nerve.

*Single-blind study design. All other studies were double-blinded.

†Age and number of female participants were not reported by migraine and tension headache subtypes. The total mean age of participants was 35.3 years (SD not reported). The mean age of patients in the intervention arm was 33.5 (13.3) years, and in the control arm, 37.2 (14.6) years. There were 54 (60%) women in the intervention arm and 50 (55.6%) women in the control arm. The reported age and number of women include secondary headaches.

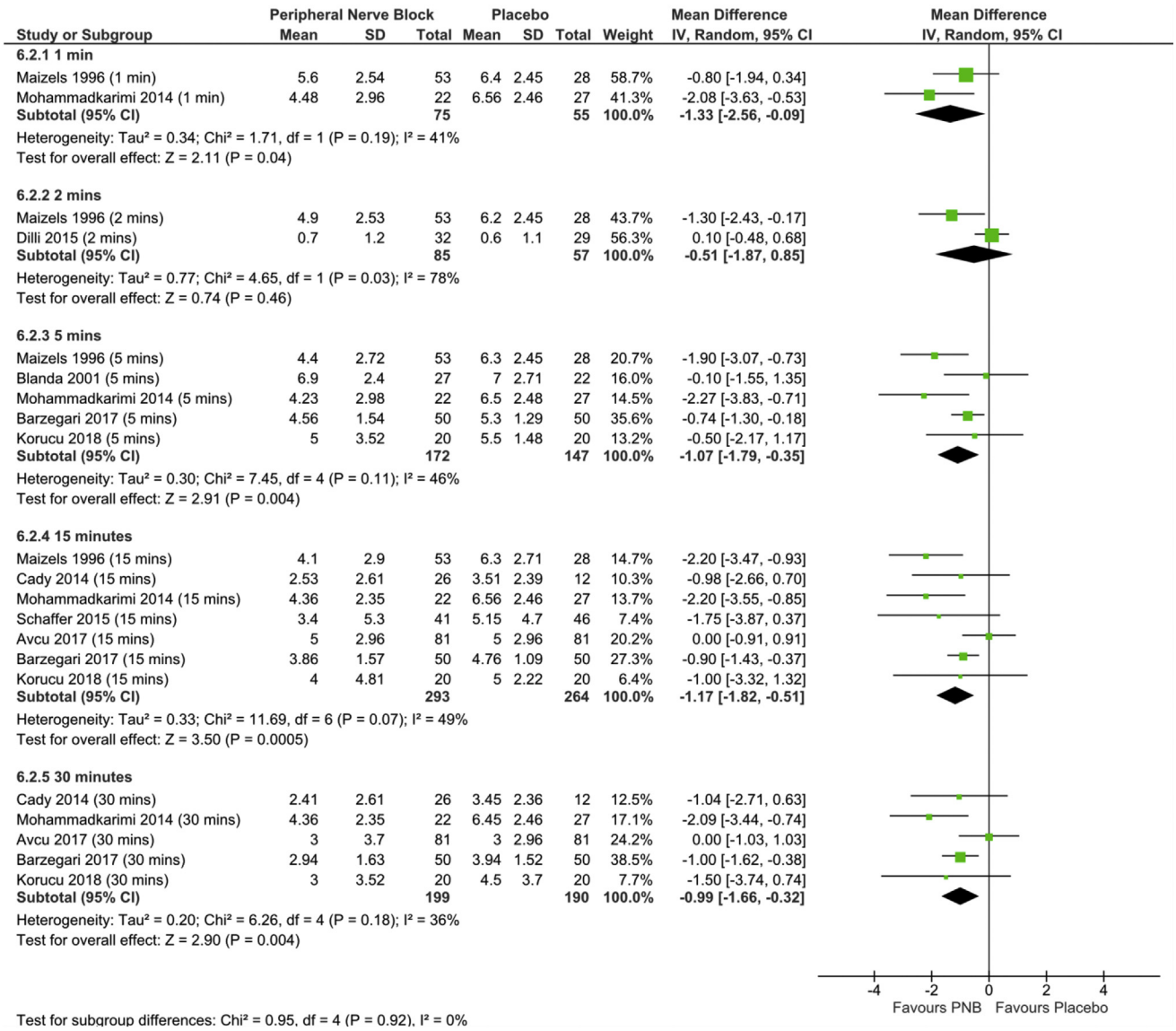

Figure 2. Forest plot of peripheral nerve block versus placebo: pain at 1, 2, 5, 15, and 30 minutes. Means (SDs) were estimated from medians (interquartile ranges) for Schaffer 2015,[39] Avcu 2017,[15] and Korucu 2018.[37]

We classified 10 trials as placebo-controlled, where normal saline solution was used in place of local anesthetic.[12,15,33,34,36,38-41] Two trials used standard headache treatment (eg, dopamine antagonist) in the control arm.[35,37] Korucu et al[37] was included in both placebo and standard treatment comparisons, as it had 2 distinct control arms.

Main Results

All studies reporting pain scores used a continuous measure according to the NRS or VAS. For the comparison of peripheral nerve block versus placebo, 9 studies were included in the meta-analysis. We pooled results separately at each time point (Figure 2). Our meta-analysis found that compared to placebo, pain scores were significantly lower in patients treated with peripheral nerve blocks at 1 minute, 5 minutes, 15 minutes, and 30 minutes. There was low-to-moderate statistical heterogeneity between studies. Based on an unpublished survey of a convenience sample of 10 emergency physicians at 2 large academic EDs, the majority of respondents selected 15 and 30 minutes as the time points of most clinical importance. At 15 minutes, the pooled point estimate suggests that pain scores were significantly lower in patients treated with peripheral nerve blocks than placebo (MD: −1.17; 95% confidence interval (CI): −1.82 to −0.51; *P*=.0005), with low statistical

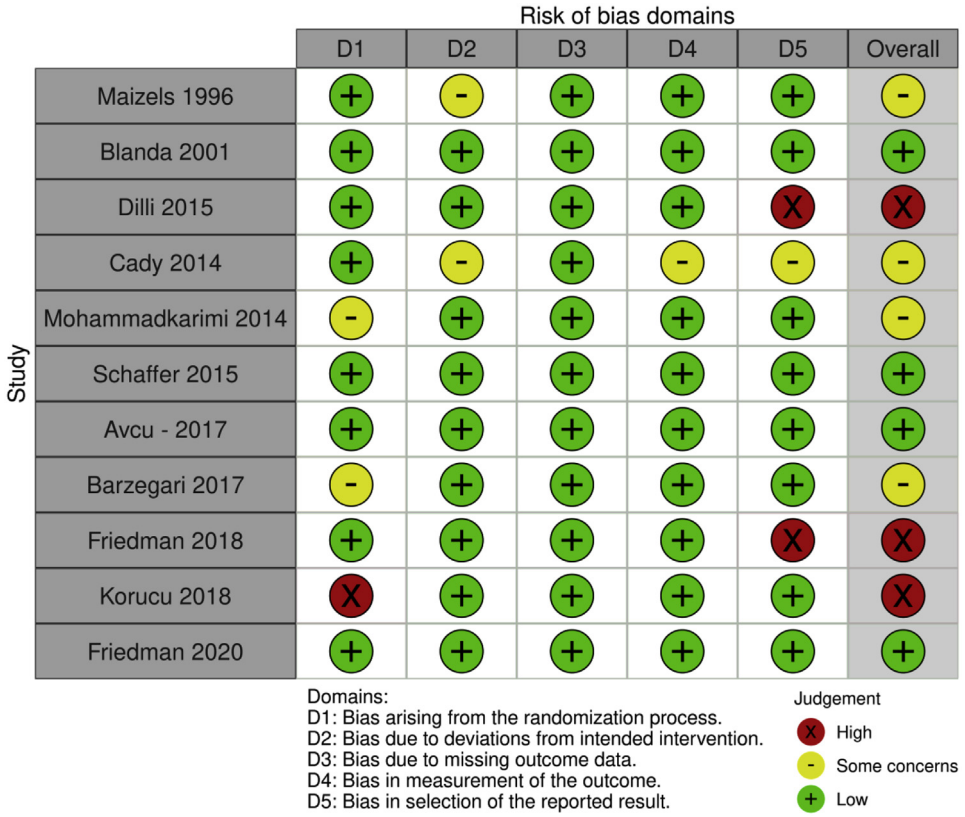

Figure 3. Risk of bias summary: review authors' judgments about each risk-of-bias item for each included study.

heterogeneity between studies (I^2=49%; heterogeneity *P*=.07). A similar result was seen at 30 minutes (MD: −0.99; 95% CI: −1.66 to −0.32; *P*=.004), with low statistical heterogeneity between studies (I^2=36%; heterogeneity *P*=.18). Based on Grading of Recommendations Assessment, Development, and Evaluation, the certainty of this evidence is moderate (due to some concerns with risk of bias).

A risk-of-bias summary for each included study is presented in Figure 3 using the Cochrane Risk of Bias 2 tool 2.0.[30] We rated 4 studies as low risk of bias overall.[12,15,35,39] Four studies were rated to have some concerns with bias arising from either the randomization process, deviations from the intended intervention, from the measurement of the outcome or from the selection of the reported result.[33,38,40,41] Three studies were rated as high risk of bias.[34,36,37]

We performed a sensitivity analysis for the primary outcome and excluded studies rated high risk of bias. After excluding these studies, the pooled estimates did not significantly change at 15 and 30 minutes (Figure E1, Appendix E4). We also performed a sensitivity analysis for the primary outcome based on study setting and excluded studies in outpatient clinic settings to determine if our results can be generalized to ED patients. After excluding these studies, the pooled estimates did not significantly change at 15 and 30 minutes (Figure E2, Appendix E4).

For peripheral nerve block versus active treatment, a meta-analysis was not possible due to an insufficient number of studies reporting outcomes at the same time points. We summarize the pain scores at the full range of observed time points within 120 minutes in Figures E3 and E4 of Appendix E4 (5, 15, 30, 45, and 60 minutes).

Six studies reported adverse events.[12,15,34-36,39] Adverse events were higher in the peripheral nerve block group, which was expected due to the burning sensation caused by anesthesia. All adverse events were minor, and there were no serious adverse events attributable to peripheral nerve blocks. The most common adverse events in the intervention arm were a burning or numbing sensation, dizziness, and injection site pain. A full list of reported adverse events can be found in Table E3 of Appendix E4.

Five studies reported the need for rescue medications.[12,15,35,38,39] The proportion of patients requiring rescue medications in the intervention and control arms are reported in Table E3 of Appendix E4. Two studies reported the type of rescue medications as

either a dopamine antagonist or intravenous fentanyl. The results were not consistent for this outcome.

Two studies reported any repeat visit to the ED or clinic within 72 hours due to relapse of headache (Table E3 of Appendix E4). Avcu et al[15] reported 9/66 (13.6%) repeat visits to the ED in the sphenopalatine ganglion block arm and 4/66 (6.1%) in the control arm.[12,15] Blanda et al[12] found that no patients in the sphenopalatine ganglion block arm or active therapy arm made a return visit to the ED for headache within 24 hours.

LIMITATIONS

Our systematic review has some limitations. First, there was significant heterogeneity for our primary outcome in terms of the time points for which pain was assessed. Multiple time points, ranging from 1 to 60 minutes, were used by studies. Based on a survey of local clinicians to determine the optimal time frame that would be considered clinically important to reassess pain, we included studies reporting pain scores within 120 minutes. There was further heterogeneity in the dosages of anesthetic and modes of administration of the peripheral nerve blocks, which may have affected treatment success. The type of anesthetic used was either lidocaine or bupivacaine and ranged from 1.5 to 80 mg. Lidocaine is typically a faster-acting anesthetic, whereas bupivacaine has a slower onset of action. Second, we pooled studies comparing the sphenopalatine ganglion block and greater occipital nerve block together. Although these are both types of peripheral nerve blocks, their mechanism of action is different in terms of having different target locations to block nerves responsible for pain, and this may contribute to heterogeneity. Despite the aforementioned heterogeneity, such as the mode of administration of peripheral nerve blocks in terms of differing target location, varying dosages of anesthetic, and headache subtypes, we believe a meta-analysis was appropriate and allows our review to make conclusions of how ED patients with primary headaches in general may benefit from a variety of peripheral nerve blocks. Third, we cannot comment on the utility of trigger point injections—from the literature, physicians have had success with trigger point injections for headaches; however, double-blind randomized controlled trials are rare. Fourth, 3 of our included studies were rated as high risk of bias overall, and 4 studies were rated as some concerns or unclear risk of bias. We addressed this issue by performing a sensitivity analysis and excluding studies included in the meta-analysis with high risk of bias and found no difference (Figure E3, Appendix E4). Fifth, 8 studies were conducted in the ED setting, whereas 3 were conducted in outpatient clinic settings. To determine if our findings could be generalized for ED patients, we conducted a sensitivity analysis (Figure E3, Appendix E4) for our primary outcome and found the point estimates did not significantly change after excluding studies conducted in the clinic. Therefore, our results can be generalized for all ED patients. Blinding is a challenging issue with trials in this area, since anesthesia causes a burning sensation and the associated numbness will likely unblind patients to their allocated treatment. Lastly, establishing a clinically significant reduction in pain is important but difficult to determine. Current evidence suggests the median minimum clinically important difference in acute pain scores for ED patients with a variety of acute pain presentations to be 1.5 (interquartile range 1.1 to 2.1), with a range of 0.8 to 2.4.[43] Although our pooled point estimates at 1, 2, 5, 15, and 30 minutes were less than 1.5, the confidence intervals overlapped with this value, and the possibility of a clinically significant improvement could not be ruled out. Thus, we have presented some evidence to support a reduction of pain when using peripheral nerve blocks compared to placebo for primary headaches in the ED based on limited available data; further, the speed of onset and ease of use make peripheral nerve blocks more appealing than current recommended treatment options. More evidence is needed to determine if a clinically significant reduction in pain can be achieved.

DISCUSSION

In our review, we found peripheral nerve blocks significantly improved pain at 1, 5, 15, and 30 minutes compared to placebo. When comparing peripheral nerve blocks against active therapy, there appeared to be a favored effect at earlier time points; however, we were unable to meta-analyze these studies due to limited data at similar time points. This systematic review also found peripheral nerve blocks are associated with minor adverse events, and there is inconclusive evidence about the need for rescue medications due to limited reporting. Duration of action is an important outcome to consider when choosing peripheral nerve blocks as a treatment option; however, the majority of studies examined shorter time frames for pain. We identified only 2 studies that reported repeat visits to the ED or clinic within 72 hours due to relapse of headache after treatment.[12,15] Although one of these studies demonstrated a higher proportion of return ED visits in the peripheral nerve block group (Appendix E4), there is insufficient evidence to comment on the influence of peripheral nerve blocks with respect to duration of effect.[15]

Headache presentations to the ED are complex and require thoughtful consideration by emergency physicians. Current recommendations for first-line medications, such as dopamine antagonists and other oral medications, have several disadvantages, such as slow onset to pain relief, unpleasant side effects, and a less-favorable route of administration. Alternatives such as peripheral nerve blocks have several advantages, such as their relatively noninvasive route of administration, and have shown promising results with their rapid time to relief. Nausea and vomiting are common symptoms with migraine and other headache presentations; therefore, providing oral medications is not ideal.[44] Peripheral nerve blocks bypass the gastrointestinal route and directly block the nerve bundle responsible for causing pain. This route of administration is preferred but comes with some challenges. Greater occipital nerve blocks and trigger point injections require a needle to administer a small amount of anesthetic, which causes pain and anxiety for patients and carries the risk of needle stick injuries for health care professionals. The sphenopalatine ganglion block is the least invasive and safest of the 3 peripheral nerve blocks, especially with intranasal drops. Furthermore, the nasal mucosa is relatively small and supplied with blood vessels, allowing for rapid absorption of drugs.[45] Currently, intranasal lidocaine is listed as a weak recommendation with low-quality evidence by the Canadian Headache Society and as a level C (possibly effective or ineffective for acute migraine) by the American Headache Society.[46,47] Our review adds evidence to support the use of sphenopalatine ganglion blocks for reducing pain within 120 minutes.

Previous systematic reviews and meta-analyses have concluded various peripheral nerve blocks to be effective for subtypes of headache. Chi et al[19] conducted a meta-analysis studying intranasal lidocaine and found this procedure to lower pain intensity at 5 minutes (standardized mean difference: −0.61; 95% CI: −1.04 to −0.19) and 15 minutes (standardized mean difference: −0.72; 95% CI: −1.14 to −0.19). In our review, we included a broader category of the intervention and analyzed pain within 120 minutes as our primary outcome. Dagenais and Zed[48] conducted a systematic review on the safety and efficacy of intranasal lidocaine for primary headaches and found this procedure to be effective from 1 minute to 30 minutes compared to placebo. They, however, did not meta-analyze their data. Zhang[21] conducted a systematic review and meta-analysis on the efficacy of the greater occipital nerve block for migraine and found this procedure could significantly reduce pain intensity (MD: −1.24; 95% CI: −1.98 to −0.49; P=.001); however, it was not clear at what time this reduction occurred. Our systematic review includes more trials than previous studies since our inclusion criteria were broad and we prespecified clinically important and meaningful outcomes. Furthermore, our review provides a summary of pain within clinically important time frames and trends that occur over time. Time to effective pain relief is an important outcome, and emergency physicians require more evidence to support the use of peripheral nerve blocks as a first-line treatment option.

One strength of our study is that we used a rigorous search strategy in a broad number of relevant databases, and it was peer reviewed by a second research librarian. Second, our review makes conclusions about pain in 60 minutes or less, which is a clinically important time frame for emergency physicians and patients. Determining the optimal time point to reassess pain is critical for emergency physicians and depends on the source of anesthetic and other variables, such as coadministration of antiemetics and other drugs. Despite the observed heterogeneity among studies with respect to the types of blocks, anesthetics, and doses, the effect of peripheral nerve blocks on pain scores for ED patients presenting with primary headache disorders has not been summarized before. Our findings are useful for emergency physicians who may be considering the use of peripheral nerve blocks to treat ED patients with headache as either an adjunct or alternative to routine treatment options.

Results from our systematic review and meta-analysis have several clinical and research implications. Our findings suggest the greater occipital nerve block and the sphenopalatine ganglion block are effective for pain relief at 1, 5, 15, and 30 minutes in the ED or clinic setting compared to placebo. This finding is useful for emergency physicians when considering peripheral nerve blocks as a first-line treatment option for primary headaches. Given more evidence, this assessment may result in faster relief of pain that is clinically significant and may have the potential to reduce intravenous medication and opioid use, which have known side effects. This is beneficial to both patients and the health care system. The sphenopalatine ganglion block is the simplest and least invasive method.

We found a relatively small number of relevant trials that measured clinically useful outcomes and significant heterogeneity across available studies; thus, further research is warranted to allow for more robust conclusions about whether peripheral nerve blocks can truly be considered as a first-line alternative to other approaches. Future trials of effectiveness of peripheral nerve blocks should measure pain at clinically important time points and use standard headache therapies as the comparator. Future trials should be sufficiently powered and well designed to protect against

various source of biases. More evidence is needed to compare peripheral nerve blocks against standard headache therapies for pain reduction within 120 minutes to determine if this procedure can be used as a first-line treatment option in the ED and potentially reduce the use of intravenous medications and opioids.

In conclusion, our review shows peripheral nerve blocks are effective as a rapid treatment option when compared to placebo; however, we were unable to assess effectiveness against standard therapy. Emergency physicians should consider peripheral nerve blocks as an adjunct therapy for patients with primary headache disorders.

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Author contributions: DP, KY, and JJP conceptualized the study. RS generated our electronic search strategy. DP and KY curated the data, and DP carried out the investigation, visualization, and formal analysis. DP and MT conducted the statistical analysis. JJP and MT supervised the manuscript. KY validated the data. The original draft was written by DP. The writing, reviewing, and editing of this manuscript was conducted by DP, KY, MT, RS, and JJP. DP takes responsibility for the article 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 in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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