Review Article

Nerve blocks for occipital headaches: A systematic review and meta-analysis

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Abstract

Migraine surgeons have identified six "trigger sites" where cranial nerve compression may trigger a migraine. This study investigates the change in headache severity and frequency following nerve block of the occipital trigger site. This PRISMA-compliant systematic review of five databases searched from database inception through May 2020 is registered under the PROSPERO ID: CRD42020199369. Only randomized controlled trials utilizing injection treatments for headaches with pain or tenderness in the occipital scalp were included. Pain severity was scored from 0 to 10. Headache frequency was reported as days per week. Included were 12 RCTs treating 586 patients of mean ages ranging from 33.7 to 55.8 years. Meta-analyses of pain severity comparing nerve blocks to baseline showed statistically significant reductions of 2.88 points at 5 to 20 min, 3.74 points at 1 to 6 weeks, and 1.07 points at 12 to 24 weeks. Meta-analyses of pain severity of nerve blocks compared with treatment groups of neurolysis, pulsed radiofrequency, and botulinum toxin type A showed similar headache pain severity at 1 to 2 weeks, and inferior improvements compared with the treatment groups after 2 weeks. Meta-analyses of headache frequency showed statistically significant reductions at 1 to 6-week follow-ups as compared with baseline and at 1 to 6 weeks as compared with inactive control injections. The severity and frequency of occipital headaches are reduced following occipital nerve blocks. This improvement is used to predict the success of migraine surgery. Future research should investigate spinous process injections with longer follow-up.

Keywords: Cervicogenic headache, injection therapy, migraine, migraine surgery, occipital neuralgia

Introduction

Active headache disorders affect 47% of adults globally, and 3% of adults have chronic daily headaches, defined as 15 headache days per month for longer than 3 months.[1] The 3rd edition of The International Classification of Headache Disorders defined headaches as primary (i.e. migraine, tension-type headache, trigeminal autonomic cephalalgia, headaches associated with physical exertion, headaches attributed to physical stimuli, epicranial headaches, hypnic headache, and new daily persistent headache) or secondary headaches associated with a causative disorder.[1-4]

The occipital nerves have been a focus of much recent research.[5-34] Irritation or compression of the C2 and C3 axons causes occipital pain, which may be diagnosed as occipital neuralgia (ON) or cervicogenic headache (CEH) depending on whether the axonal compression occurs in the scalp or

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proximally around C2-C3 zygapophyseal or atlantoaxial joints. ON is defined as a paroxysmal, shooting, or stabbing pain in the occipital nerve dermatomes.[4] CEH arises from either bony or soft tissue disorders of the neck and often has neck pain, and palpation over the cervical vertebra (CV) 1-CV3 spinous processes may produce tenderness or provoke headache symptoms.[4] Alternatively, patients with occipital pain or tenderness may be diagnosed with migraine. Although the incidence of occipital neuralgia remains unknown,[35] cervicogenic headache is thought to be present in 8% to 32% of patients with severe headaches,[36] whereas migraine prevalence is reportedly between 2.6% and 21.7% of people and is the sixth most common cause of years lived with disability (YLDs).[37,38]

Six main trigger sites, corresponding to specific areas of the scalp or facial sensory nerve compression, have been proposed as triggers for migraine. From I to VI, these trigger sites are frontal, zygomaticotemporal, nasal, occipital, auriculotemporal, and lesser occipital.[21,30] In 2000, Guyuron reported an incidental resolution of migraines in his patients who underwent forehead rejuvenation surgery.[39] This finding has since been repeated, with early adapters reporting a 60% incidence of improvements.[40] A current hypothesis is that correct trigger point identification predicts which patients will improve following treatments targeted to that trigger site, where strict inclusion criteria may provide for a 100% incidence of treatment success.[41]

The present study provides the first systematic review and meta-analysis of occipital nerve injection treatment outcomes for people with occipital trigger site (Site IV) pain.

Material and Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[42] A detailed protocol was developed before initiating the systematic review and is registered under the PROSPERO ID: CRD42020199369.

Search strategy

Two reviewers (K.J. and M.S.) performed independent literature searches of all published articles up to June 11th, 2020 using the databases Cochrane Library, Ovid MEDLINE, Ovid EMBASE, Web of Science, and the clinical trials registry ClinicalTrials.org (http://clinicaltrials.gov/). The search was conducted in June 2020 using the Boolean operators "OR" and "AND" combined with search terms including "migraine," "headache," "cervicogenic headache," "occipital neuralgia," "occipital migraine," and "injection therapy," with word variations and medical subject heading (MeSH) terms. This search strategy was adapted as appropriate to each database [Appendix]. Bibliographies of included studies and relevant reviews were also searched. A primary screen was performed of titles and abstract, followed by a second screen by full-text for specific inclusion and exclusion criteria. If more than one study reported on the same cohort, then the study with the largest cohort was included. To capture the highest-quality evidence and effect sizes, only randomized controlled trials (RCTs) were included. Data extraction was performed by one reviewer (K.J.) with a second reviewer (A.E.) checking over 90% of the extracted data; additionally, experts in the field of plastic and reconstructive surgery and in the treatment of occipital pain were consulted and included in the study.

Inclusion and exclusion criteria

Included RCT studies were: 1) peer-reviewed, 2) published in English, 3) using injection therapies, 4) treating patients with occipital neuralgia, occipital headache, cervicogenic headache, occipital migraine, or migraine with tenderness or pain in the occipital scalp.

Excluded studies were: 1) studies with less than 10 total patients, 2) studies treating migraine headache without any mention of occipital pain or tenderness, 3) animal studies, abstracts, conference proceedings, case reports, retrospective reviews, noncontrolled studies, nonrandomized controlled trials, review articles, meta-analyses, and duplicates of cohorts, 4) nonpeer-reviewed "gray" literature.

Risk of bias

Risk of bias assessment was performed at a study and outcome level according to the Cochrane Handbook for Systematic Reviews of Interventions.[43]

Outcomes

Primary outcomes were the change in headache pain severity following injection as measured by visual analog scale (VAS)[8,44-49] or numeric rating scale (NRS)[33,50-52] from 0 to 10 and the change in the number of headaches days following injection as measured by days per week,[33,53] days per 2 weeks,[44] or days per 4 weeks.[48] Secondary outcomes included adverse effects.

Statistical analysis

All statistical analyses were performed using RevMan 5.4.1 (Cochrane Collaboration, London, UK). Only RCTs were included in the meta-analyses. To incorporate the heterogeneity between studies, the authors calculated I^2, which reports that the proportion of total variation is primarily due to the different trials rather than sampling error. I^2 values over 50% were considered highly heterogeneous and warranted investigation of study details that may contribute

to heterogeneity. A random-effects model was used for all meta-analyses. Continuous data were presented as mean differences and standard deviations on studies that provided data on objective and subjective measurements of headache pain severity and headache frequency. A P value < 0.05 was considered significant, *a priori*.

For studies reporting on multiple types of headaches, data were analyzed for the occipital pain pathology (i.e. occipital migraine, occipital headache, cervicogenic headache, occipital neuralgia) and data were excluded from other pathologies including tension-type headache, unspecified migraines, or general headache. For studies reporting on both patient-reported average pain and patient-reported worst pain, the data from worst pain were used. For studies reporting data by a subgroup of a mild headache, moderate headache, and severe headache, the moderate-to-severe headache severity data were analyzed. Data on headache pain were converted to a 0–10 scale in studies reporting pain on a 100-point scale. Data on headache frequency that were reported as headache days per 2 weeks or 4 weeks were converted to headache days per week for analysis by dividing by the number of weeks.

Results

Article selection

Applying the search strategy to databases produced 3552 records, and one additional study was identified through searching bibliographies of included studies. After deduplication, 2968 records were screened by title and abstract, leading to the exclusion of 2913 records. 55 articles were, therefore, assessed by full-text review, 43 of which were excluded for the following reasons: 25 were nonrandomized or uncontrolled clinical studies, nine did not treat patients with occipital pain or tenderness, four were abstracts only, one treated fewer than 10 patients with occipital pain or tenderness, one was a review article, one was a duplicate cohort, one was not in English, and one was off-topic. Therefore, 12 studies[8,33,44-53] were included in the qualitative synthesis and nine in quantitative synthesis.[44,33,46-51,53] The article selection process is shown in Figure 1.

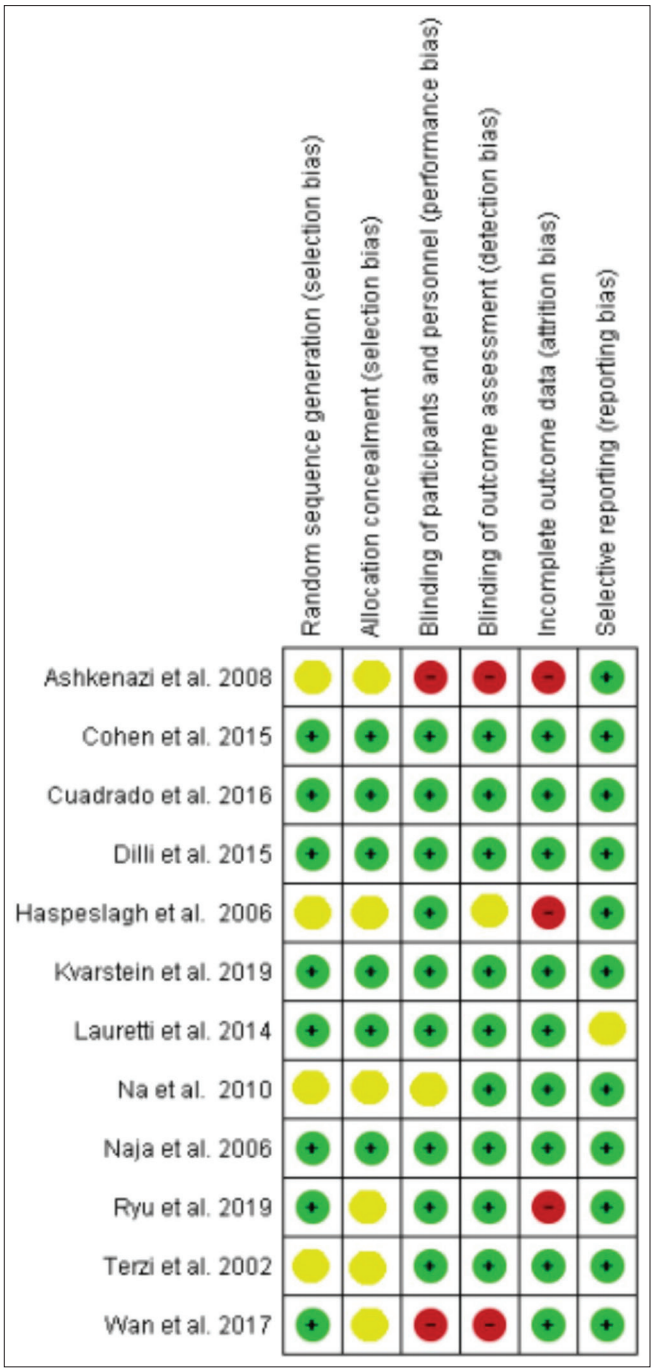

Figure 1: 3552 records were identified through a database search and one was identified through a search of study bibliographies, leading to 2968 unique records which were screened. A full-text screen was performed of 55 studies leading to the exclusion of 43 studies. Twelve studies met criteria for inclusion, nine of which had comparable data for meta-analysis

Study characteristics and treatment protocols

Study details and demographics are summarized in Table 1. All 12 studies included [8,33,44-53] were randomized controlled trials (RCTs) published between 2002 and 2019. Five studies treated cervicogenic headache,[8,44,45,50,51] three treated migraine with occipital tenderness,[46,48,53] one treated cervicogenic headache with occipital neuralgia,[52] one treated occipital neuralgia or migraine with occipital tenderness,[33] one treated cervicogenic headache or migraine without aura or tension-type headache,[47] and one treated primary occipital headaches including tension-type, migraine, cluster, or new daily persistent headache.[49] A total of 586 patients, including 178 males and 400 females, were included. The mean age of included patients for each study ranged from 33.7 to 55.8 years. Four studies were conducted in Asia,[47,49,51,52] three were in North America,[33,46,48] three were in Europe,[8,50,53] one was in South America,[45] and one was conducted in Africa.[44] In the seven studies reported on occipital pain laterality, 180 patients

Table 1: Study Demographics

Authors, Year Country	N, (F: M)	No of Treatment: Control	Age		Treatment	Control
			Treatment (group 1)	Control (group 2)		
Na *et al.*, 2010 South Korea	26 (12:14)	13:13	53.8±11.3	55.7±10.6	US-guided lidocaine (3 mL, 1%)	Lidocaine (3 mL, 1%) medial to occipital artery
Ryu *et al.*, 2019 South Korea	54 (39:15)	27:27	52.2±11.2	55.2±10.5	Botulinum toxin type A (1 mL, 50 units)	Bupivacaine (1 mL, 0.1%), levobupivacaine (1 mL, 0.1%), and dexamethasone (1 mg)
Wan *et al.*, 2017 China	60 (42:12)	30:30	49.2±10.3	47.6±9.7	US-guided blockade using 2-4 mL of 1% lidocaine with 7 mg betamethasone	FL-guided blockade using 2-4 mL of 1% lidocaine with 7 mg betamethasone
Kvarstein *et al.*, 2019 Norway	52 (25:27)	31:21	55.8±8.3	45.9±10.5	Greater occipital nerve cryoneurolysis	Nerve stimulator-guided methylprednisolone (1 mL, 40 mg/mL), bupivacaine (1 mL, 5 mg/mL)
Naja *et al.*, 2006 Egypt	50 (37:13)	25:25	46.44±9.63	47.36±10.25	Nerve stimulator-guided lidocaine (3 mL, 2%), lidocaine with epinephrine (3 mL, 2% and 1:200,000), bupivacaine (2.5 mL, 0.5%), fentanyl (0.5 mL, 50 µg/mL)	Saline (10 mL)
Dilli *et al.*, 2015 Canada	70 (59:11)	35:35	44±11	42±16	Bupivacaine (2.5 mL, 0.5%), methylprednisolone (0.5 mL, 20 mg)	Normal saline (2.75 mL), lidocaine (0.25 mL, 1%)
Terzi *et al.*, 2002 Turkey	60 (39:21)	30:30	CEH MH TTH	42.0±7.9 39.7±7.7 33.7±2.9 33.9±6.1 29.8±6.3 31.7±5.7	Prilocaine (1 mL, 2%)	Saline (1mL)
Cohen *et al.*, 2015 USA	81 (38:43)	42:39	41.67±10.72	41.08±13.61	PRF 4 min after bupivacaine (1 mL, 0.5%), lidocaine (1 mL, 2%), normal saline (0.75 mL) to each targeted nerve (up to 4) + PRF after 4 min	Placebo: sham cannula after nerve stimulator-guided bupivacaine (1 mL, 0.5%), lidocaine (1 mL, 2%), and methylprednisolone (0.75 mL, 40 mg/mL)
Lauretti *et al.*, 2014 Brazil	30 (20:8)	10:10:10	44±6	42±8 43±9	Subcompartmental technique: 5, 10, or 15 mL mixture of dexamethasone (10 mg), lidocaine (10 mg), and nonionic iodine contrast	Classic greater occipital nerve block: 5, 10, or 15 mL mixture of dexamethasone (10 mg) and lidocaine (10 mg)
Ashkenazi *et al.*, 2008 USA	37 (31:6)	18:19	41.9±11.3	40.3±8.9	Lidocaine (4.5 mL, 2%), bupivacaine (4.5 mL, 0.5%), triamcinolone (1 mL, 40 mg/mL)	Lidocaine (4.5 mL, 2%), bupivacaine (4.5 mL, 0.5%), and 1 mL saline
Cuadrado *et al.*, 2016 Spain	36 (36:0)	18:18	35.7±8.6	35.9±13.4	Bupivacaine (2 mL, 0.5%)	Saline (2 mL)
Haspeslagh *et al.*, 2006 The Netherlands	30 (22:8)	15:15	47.5±11	49.1±12.8	RF lesioning at CV3-CV6, after 8 weeks a diagnostic lidocaine (1mL, 2%) nerve block with absent response indicating TENS and present response indicating adjacent CV RF lesioning	Greater occipital nerve block: bupivacaine (2 mL, 0.5%), repeated at 8 weeks if no response to block, and TENS if no response to repeat block

Data are reported as means±standard deviation. N=number of patients), CEH=cervicogenic headache, MH=migraine headache, TTH=tension-type headache, PRF=pulsed radiofrequency, RF=radiofrequency, CV=cervical vertebra, US=ultrasound, FL=fluoroscopy, mL=milliliter, TENS=transcutaneous electrical nerve stimulation

had right-sided pain, 126 patients had left-sided pain, and 76 patients had bilateral pain. In the five studies recording whether pain was unilateral or bilateral, 130 patients had unilateral and 76 patients had bilateral pain. Treatments and outcomes of treatment are summarized in Table 2.

Risk of bias assessment

Cochrane Risk of bias analysis of the 12 RCTs is shown in Figure 2. Five studies had a low risk-of-bias, three studies had an unknown risk-of-bias, and four studies had a high risk-of-bias.

Meta-analysis of pain severity with anesthetic versus baseline

Two RCTs had comparable data for meta-analysis of 5–20 min postinjection effects on occipital headache pain severity in patients affected with acute headaches. Included injections were prilocaine,[47] bupivacaine with lidocaine,[46]

Table 2: Study Outcomes and Results

Authors, year	Follow-up	Outcomes	Results	Adverse events
Na *et al*., 2010	5-15 min	Pain (NRS 0-10*), Sensory loss (NRS of sensation), Distance from external occipital protuberance to injection site	Differences in pain score and difference in distance to injection site were not significantly different between the groups. Complete sensory loss was achieved in 76.90% of patients in the USD group compared with 30.80% in the control group ($P<0.05$)	Bleeding at injection site in one patient
Ryu *et al*., 2019	4 weeks to 6 months	Pain (VAS 0-10), Patient satisfaction (4-point Likert scale), distance from GON to midline	Improvement in average pain score was significantly better in the botulinum toxin type A group compared with the bupivacaine group at 8 weeks and 6 months ($P<0.05$). The 4 weeks patient satisfaction score was also significantly better in the botulinum toxin type A group compared with the bupivacaine group ($P<0.05$)	NR
Wan *et al*., 2017	2-24 weeks	Pain (NRS 0-10 with 10 being the worst pain)	$P<0.05$ compared with baseline in both groups. No significant difference between groups	Dizziness, Neck and shoulder discomfort
Kvarstein *et al*., 2019	1-18 weeks	Pain (NRS 0-100), patient impression (5-category Likert scale) of change in global status, headache intensity, and neck movement	No significant difference was found in the average pain score between the cryoneurolysis group and the injection group ($P=0.22$). The average pain score in the cryoneurolysis group improved significantly from baseline after 18 weeks ($P<0.001$)	Local pain, tenderness, dizziness, and sedation
Naja *et al*., 2006	2 weeks	Pain (VAS 0-10 with 10 being the worst pain), Frequency (headaches/2 weeks), TPI	Max pain score, TPI and headache frequency were significantly decreased in the injection group compared with the control ($P=0.0001$, 0.0001, and 0.026, respectively)	NR
Dilli *et al*., 2015	2 min to 4 weeks	Headache frequency (days/4 weeks), Migraine duration (h/4 weeks), 2-min pain (VAS 0-10)	No significant difference was found in any parameter (headache frequency and migraine duration at 4 weeks, pain at 2 min) between the treatment group and control group ($P=0.39$, 0.9, and 0.74, respectively)	Pseudotumor cerebri in one placebo patient
Terzi *et al*., 2002	5-30 min	Pain (VAS 0-10 with 10 being intense pain)	A significant decrease in pain was seen in the injection group at 30 min compared with the control group in the CH subgroup ($P<0.01$). Reduction in severity of pain at 30 mi in the injection group was not significantly different from the control group in either subgroup (MWOA and TTH)	NR
Cohen *et al*., 2015	2 weeks to 6 months	Pain (NRS 0-10)	The PRF group had better pain scores than the injection group at all follow-ups. These values were significant at 2 weeks through 6 months ($P<0.001$ and $P=0.017$). Overall headache pain was significantly better in the PRF group than the injection group at 2 weeks ($P=0.018$) but not at 6 months ($P=0.063$)	9 events, none serious, all resolved in 2 weeks. PRF: headache, rash, swelling. Control: dizziness, rash, swelling, headache, vomiting
Lauretti *et al*., 2014	2-24 weeks	Pain (VAS 0-10 with 10 being the worst pain), Analgesic use	Significant improvement in pain and use of rescue analgesics was identified in all suboccipital compartment groups at 24 weeks compared with the classical technique ($P<0.01$). The classical technique groups only had significant reduction in pain and analgesic use up to 2 weeks ($P<0.05$). Quality of life measures (night sleep, daily activities, and concentration) improved for 10 to 14 days after the classic GON technique and 24 weeks after the suboccipital compartment technique ($P<0.05$)	NR
Ashkenazi *et al*., 2008	20 min to 4 weeks	Mean headache severity (VAS 0-10), 4-week headache-free duration	The change in headache severity 20 min after treatment did not differ significantly between Groups A and B. 4-week headache-free duration was similar between both groups ($P=0.67$)	NR
Cuadrado *et al*., 2016	1-h to 1 week	Frequency (headache days/week), Pressure pain threshold, Acute medication consumption	There was a significant decrease in headache days per week in the treatment group compared with the placebo group ($P=0.04$). Threshold for pain was greater in treatment group than placebo group in supraorbital and infraorbital distributions following greater occipital nerve block at 1 h ($P=0.022$, $P=0.013$, respectively) and 1 week ($P=0.031$, $P=0.005$, respectively). Acute medication consumption did not differ between groups ($P=0.7$)	Presyncope immediately following injection in three patients, transient stinging sensation at puncture site
Haspeslagh *et al*., 2006	8 weeks to 1 year	Pain (VAS 0-100), headache days, intensity	Each study parameter showed nonstatistically significant improvement compared with baseline at each follow-up (8 weeks, 16 weeks, 32 weeks, and 1 year) and no statistical difference between study groups	NR

**This study assessed NRS from 0-10 where 10 was preoperative pain. VAS=visual analog scale, NRS=numerical rating scale, TPI=total pain index, MWOA=migraine without aura, TTH=tension-type headache, GON=greater occipital nerve, PRF=pulsed radiofrequency, min=minute, NR=not reported*

and bupivacaine with lidocaine and triamcinolone.[46] As shown in Figure 3, the injected anesthetic significantly reduced the severity of occipital headache pain in these patients as compared with baseline pain scores ($P < 0.00001$, $I^2 = 0\%$).

Investigating local anesthetic effect on headache pain severity, three studies had comparable data between 1 and 6 weeks,[33,50,51] and two studies had comparable data between 12 and 24 weeks after injection.[33,50] The ultrasound-guided,[49,51] fluoroscopy-guided,[51] and nerve stimulator-guided[50] anesthetic injections produced a statistically significant reduction in headache pain severity between 1 and 6 weeks compared with baseline ($P < 0.00001$, $I^2 = 55\%$), as shown in Figure 4. Combined corticosteroid and anesthetic injections produced a statistically significant reduction in headache pain severity at 12–24 weeks compared with baseline ($P = 0.003$, $I^2 = 0\%$), shown in Figure 5.

Meta-analysis of pain severity with treatment versus control

Three studies had comparable data for analysis of headache pain intensity at 1–2 weeks postinjection of treatment versus control. Treatments included cryoneurolysis,[50] pulsed radiofrequency with bupivacaine and lidocaine,[33] and botulinum toxin type A.[44] All controls included an injection of a corticosteroid combined with ultrasound-guided levobupivacaine,[49] nerve stimulator-guided lidocaine,[50] and a sham placebo cannula procedure with both nerve stimulator-guided bupivacaine and lidocaine.[33] At 1–2 weeks postinjection, there were no significant differences in pain between treatment and control groups ($P = 0.52$, $I^2 = 59\%$), as shown in Figure 6. At 2–6 weeks postinjection, the treatment groups provided a statistically significant improvement in headache pain over the controls ($P < 0.00001$, $I^2 = 0\%$), as shown in Figure 7. In addition, at 8–24 weeks, the treatment groups provided

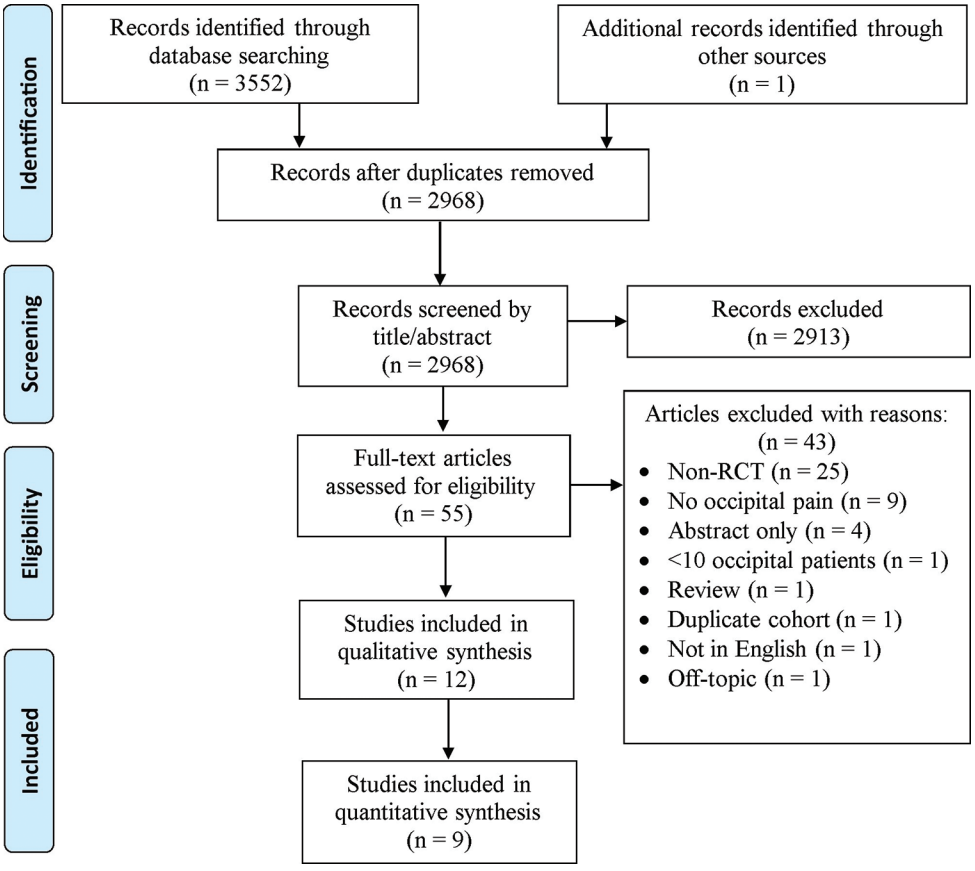

Figure 2: Risk of bias assessment of randomized controlled trials resulted in five studies with low risk-of-bias, three studies with unclear risk-of-bias, and four studies with high risk-of-bias. Red = high risk-of-bias, Yellow = unclear risk-of-bias, Green = low risk-of-bias

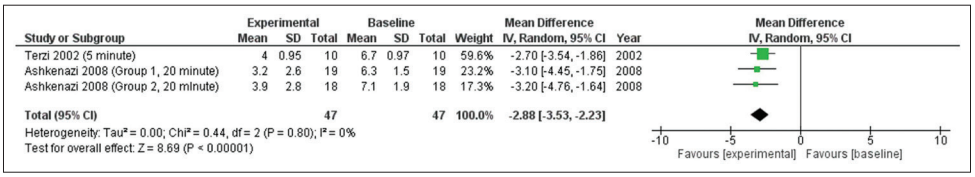

Figure 3: Compared with baseline, injected local anesthetics provided a statistically significant improvement in headache pain at 5 to 20 min after injection

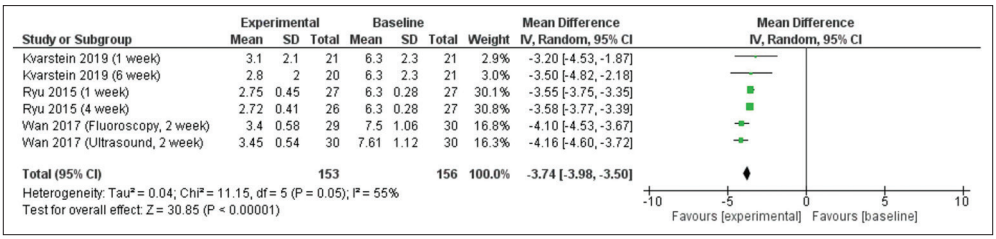

Figure 4: Compared with baseline, injected local anesthetic with corticosteroid provided a statistically significant improvement in headache pain at follow-ups between 1 and 6 weeks

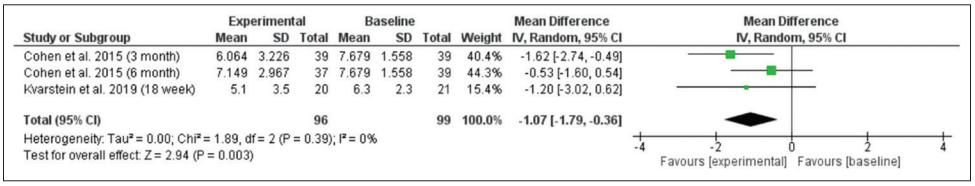

Figure 5: Compared with baseline, injected local anesthetic with corticosteroid provided a statistically significant improvement in headache pain at follow-ups between 12 and 24 weeks

a statistically significant improvement in headache pain over the controls ($P < 0.00001$, $I^2 = 0\%$), as shown in Figure 8.

Meta-analysis of headache frequency

Four RCTs had comparable data for meta-analysis of headache frequency of injection with bupivacaine,[53] bupivacaine with methylprednisolone,[48] nerve stimulator-guided injection of bupivacaine, lidocaine, dimethylprednisolone, and a sham cannula procedure,[33] or nerve stimulator-guided injection of bupivacaine with lidocaine, fentanyl, and clonidine[44] as compared with baseline. There was a statistically significant reduction in the number of headaches following injection treatment at follow-up times ranging from 1 to 6 weeks ($P < 0.00001$, $I^2 = 15\%$), as shown in Figure 9. Three of these studies had comparable data for meta-analysis comparing effect on headache frequency of anesthetic injections and controls of normal saline,[53] dilute (0.083%) lidocaine,[48] or nerve stimulator-guided injection of normal saline.[44] As compared with control, anesthetic injections provide a statistically significant superior reduction in the number of headache days per week at follow-ups ranging from 1 week to 4 weeks ($P < 0.02$, $I^2 = 3\%$), as shown in Figure 10.

Discussion

Local anesthetic injections have been previously shown to reduce symptoms of cervicogenic headache, migraine, cluster headache, and occipital neuralgia.[54-58] Although each is a distinct syndrome, the symptoms and diagnostic criteria often overlap between cervicogenic headache, occipital neuralgia, and migraine with occipital tenderness or occipital pain, and so the data from these pathologies were the focus of this study. Alternatively, the symptomatology of cluster headache is easily distinguished clinically[59] and was excluded from the present study.

Headache resolution following anesthetic nerve block is a proposed method of elucidating who will improve following surgeries, such as nerve decompression or neurolysis.[22,56] The optimal injection technique and quantification of pain reduction for nerve blockade for the occipital trigger site have yet to be elucidated. Our meta-analysis shows that in patients suffering from an acute headache, with pain scores of 6.3 to 7.1 on a 0–10 VAS pain scale, a nerve block will provide a pooled mean reduction of 2.88 points within 20 min, representing a 40%–45% reduction in pain. Therefore, when nerve blocks are used to select surgical candidates, this magnitude of pain reduction may be the appropriate response to consider. Interestingly, our meta-analysis shows that the pooled mean reduction in pain severity at 6 weeks postinjection was 3.74 points, a 51%–57% reduction, which is larger than the change at 20 min. The increased efficacy at 6 weeks may be attributed to a delayed central nervous system desensitization, a delayed effect of the adjunct corticosteroid injection or limitations of patient-reported questionnaires. Chronic central sensitization secondary to dorsal root ganglia compression has been shown in rat models to involve cGMP-PKG signaling, neuronal hyperexcitability, and behavioral hyperalgesia.[60] Further central nervous system modulation of occipital headache pain is thought to occur in the trigeminal nucleus caudalis where cross-talk between cranial nerve sensory and nociceptive afferents of additional dermatomes, particularly the trigeminal V3 dermatome is thought to contribute to the pain of migraines.[57,61-65]

Six main areas of greater occipital nerve compression have been identified: 1) between semispinalis capitis and obliques capitis inferior muscles, 2) upon entering the semispinalis capitis, 3) upon exiting semispinalis capitis, 4) upon entering the trapezius muscle, 5) upon exiting the trapezius fascia, and

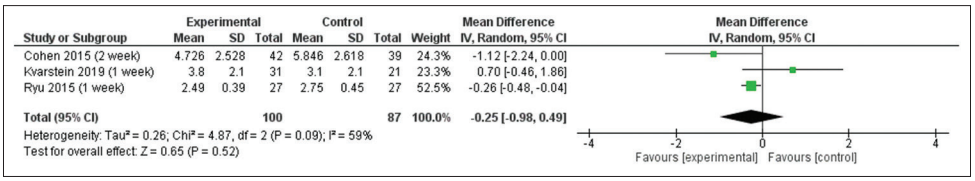

Figure 6: Comparing injected local anesthetic to treatment groups, no statistical difference in headache pain is present at follow-ups between 1 and 2 weeks

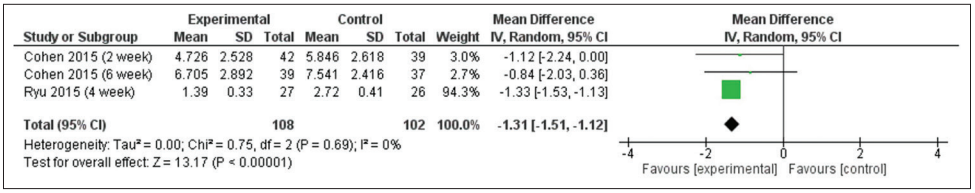

Figure 7: Comparing injected local anesthetic to treatment groups, the treatment groups provided a statistically significantly greater improvement than local anesthetic controls at follow-ups between 2 and 6 weeks

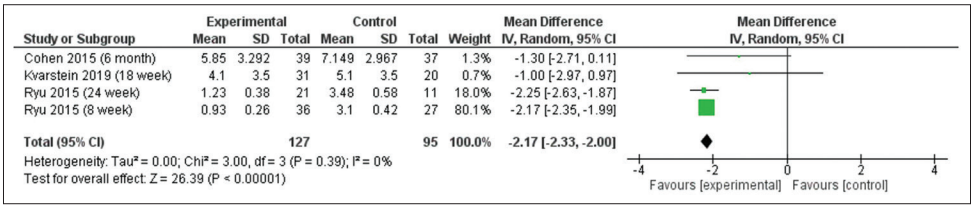

Figure 8: Comparing injected local anesthetic to treatment groups, the treatment groups provided a statistically significantly greater improvement than local anesthetic controls at follow-ups between 8 and 24 weeks

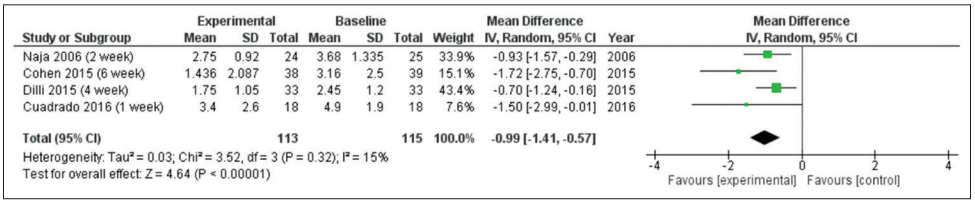

Figure 9: Compared with baseline, injected local anesthetics provide a statistically significant reduction in the frequency of headache occurrence at follow-ups between 1 and 6 weeks

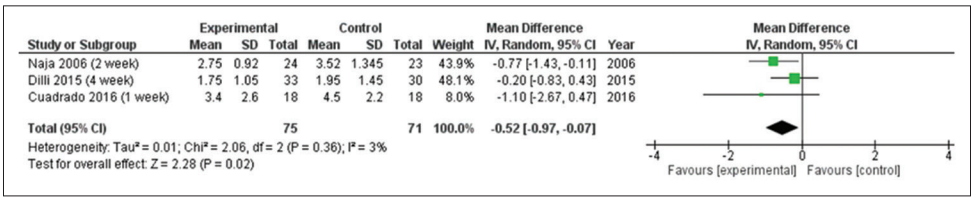

Figure 10: Compared with controls, injected local anesthetics provide a statistically significant superior reduction in the frequency of headache occurrence at follow-ups between 1 and 4 weeks

6) by the occipital artery.[13,16] In addition to causing pain in the dermatomal distribution of the nerve, chronic cranial sensory nerve compression has been shown in a rat model by Filipović *et al*.[66] to induce plasma protein extravasation in the dura, a marker of inflammation, which is associated with migraine.[67,68]

We show that headache pain severity improvements remain statistically significant up to 6 months after treatment, although the mean pooled reduction diminished to 1.07 points at which point management with botulinum toxin type A injection, pulsed radiofrequency, or cryoneurolysis provided statistically significant superiority to the injected anesthetic with corticosteroid. In addition to lesser occipital nerve blocks, most studies included in the meta-analyses utilized a "classical greater occipital nerve block," where the anesthetic is injected 1.5–3 cm lateral to the midline and 1–2 cm inferior to the occipital protuberance.[33,50] An alternate method, the "subcompartmental injection technique," appears promising in efficacy and duration of improvements,[45,49,51]

and should be included in future research on outcomes of injected anesthetics. For the subcompartmental injection technique, ultrasound or fluoroscopy are utilized to guide the injection inferior to the CV1 arch, 1–2 mm posterior to the C2 spinous process.[69] In a 2015 RCT of 30 participants, the subcompartmental injections of Lauretti *et al.*[45] provided 24 weeks of significant analgesia ($P < 0.001$), reduction in medication usage ($P < 0.05$), and improvement in quality of life ($P < 0.05$), whereas their control arm of lidocaine injections by the classic technique provided 2 weeks of quality of life improvement and rescue pain medication reduction. The improved outcomes of the subcompartmental technique are speculated to be attributed to improved central desensitization from anesthetic being injected near the dorsal root ganglia,[45] but the subcompartmental injection technique was also shown by Greher *et al.*[69] in a cadaver study to be 100% accurate at reaching the target greater occipital nerve compared with the 80% accuracy of the classic technique ($P = 0.002$). The decreased accuracy of the classic technique suggests that more than one diagnostic block attempt may be needed to elucidate which patients are good surgical candidates. Additional RCTs should investigate the long-term outcomes of the subcompartmental block as compared with nonsurgical controls such as botulinum toxin. For patients who are poor surgical candidates, these injection options may provide clinically significant improvements to their quality of life.

Our meta-analysis shows that anesthetic injections provide a statistically significant reduction in the frequency of headaches which persisted to at least until 6 weeks postinjection, and pain severity which persisted to at least 6 months postinjection. Future studies with longer-term follow-up are needed to investigate the reduction in headache frequency beyond 6 weeks.

This review is limited by a small number of RCTs with comparable data for meta-analysis. These studies included studies utilizing nonhomogenous criteria for patient inclusion, different injection techniques, and different injected medications. Furthermore, several studies utilized nerve stimulator-guided injections. Although the electrical stimulation is presumably subtherapeutic, the lowest duration of stimulation needed to upregulate neurotrophic factors and the unknown effect of these factors on sensory outcomes may make this a confounding factor.[70,71] In addition, multiple different headache diagnoses were included, however, a strength of this study is that all included studies described occipital pain.

Conclusion

Occipital pain is a common debilitating disorder that leads to profound decreases in quality of life. Before occipital nerve surgery, anesthetic injections are utilized to confirm occipital trigger site presence. These diagnostic injections should be repeated to confirm an absence of response to injection or performed under guidance technique using the subcompartmental injection technique. Patient headache pain severity is improved for at least 6 months after anesthetic and corticosteroid injection, and patient headache frequency is improved for at least 6 weeks after anesthetic and corticosteroid injection. Future research should investigate the subcompartmental injection technique's long-term outcomes, particularly for changes in headache frequency.

Clinical implications

- Injected local anesthetic with corticosteroid improves occipital headaches for 6 months
- A mean 40%–45% acute headache pain reduction is achieved with local anesthetic injections
- Peak improvement in pain from injected local anesthetics is seen after 6 weeks
- Injection local anesthetics improve both pain severity and headache frequency

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Conflicts of interest

There are no conflicts of interest.

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Appendix: Full-Search Strategy

Cochrane Library Search performed from inception to June 11th, 2020		
Search #	**Search Terms**	**Results**
1	MeSH descriptor: [Neuralgia] explode all trees	1609
2	MeSH descriptor: [Posttraumatic Headache] explode all trees	84
3	MeSH descriptor: [Migraine Disorders] explode all trees	2577
4	MeSH descriptor: [Tension-Type Headache] explode all trees	298
5	(neuralgia* OR "Arnold's neuralgia" OR "cranial neuralgia" OR "cranial neuralgias" OR "cervical neuralgia" OR "occipital neuralgia" OR "postoperative occipital neuralgia" OR "occipital pain" OR "nerve pain" OR "nerve pains" OR "neuropathic pain" OR "neuropathy" OR "neurodynia" OR "neurodynias" OR "neurotmesis" OR "axonotmesis" OR "neurapraxia" OR "nervous system trauma" OR "nervous system injury" OR "craniocervical injury" OR "craniocervical injuries" OR "nerve compression" OR "nerve entrapment" OR "entrapment neuropathy" OR "cranial nerve disease" OR "cranial nerve diseases" OR "occipital headache" OR "occipital headaches" OR "cervicogenic headache" OR "cervicogenic headaches" OR "migraine" OR "occipital migraine" OR "cephalgia" OR "cephalalgia") Word variations have been searched	22848
6	#1 or #2 or #3 or #4 or #5 Word variations have been searched	23340
7	("cervical plexus" or "greater occipital nerve" or "GON" or "lesser occipital nerve" or "third occipital nerve" or "occiput" or "occipital" or "C2 dorsal root" or "C2 nerve") Word variations have been searched	2241
8	MeSH descriptor: [Cervical Plexus] explode all trees	113
9	#7 or #8 Word variations have been searched	2295
10	MeSH descriptor: [Nerve Block] explode all trees	3932
11	MeSH descriptor: [Lidocaine] explode all trees	5853
12	MeSH descriptor: [Steroids] explode all trees	57825
13	MeSH descriptor: [Injections] explode all trees	22046
14	MeSH descriptor: [Bupivacaine] explode all trees	5630
15	MeSH descriptor: [Anesthesia] explode all trees	19025
16	MeSH descriptor: [Dexamethasone] explode all trees	4444
17	MeSH descriptor: [Triamcinolone Acetonide] explode all trees	1076
18	MeSH descriptor: [Botulinum Toxins, Type A] explode all trees	1603
19	("steroids" or "injections" or "injection" or "injection therapy" or "injected" or "nerve block" or "trigger point injections" or "pain management" or "corticosteroid" or "corticosteroid injection" or "lidocaine" or "triamcinolone" or "kenalog" or "marcaine" or "botulinum" or "dexamethasone" or "bupivacaine" or "anesthesia" or "anesthetic") Word variations have been searched	225470
20	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 Word variations have been searched	264098
21	#6 and #9 and #20 Word variations have been searched	149 (12 reviews, 137 trials)

Ovid EMBASE and Ovid MEDLINE Search performed from inception to June 11th, 2020		
23	remove duplicates from 22	1408
22	6 and 9 and 21	1779
21	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	4720926
20	(steroids or injections or injection or injection therapy or injected).ti, ab, kw.	1834607
19	(nerve block or trigger point injections or pain management or corticosteroid or corticosteroid injection or lidocaine or triamcinolone or kenalog or marcaine or botulinum or dexamethasone or bupivacaine or anesthesia or anesthetic).ti, ab, kw.	557528
18	exp Botulinum toxins, type A/	31204
17	exp Triamcinolone Acetonide/	20298
16	exp Dexamethasone/	199446
15	exp Anesthesia/	511082
14	exp Bupivacaine/	49150
13	exp Injections/	450137
12	exp Steroids/	2336719
11	exp Lidocaine/	95780
10	exp Nerve block/	61563
9	7 or 8	103628
8	exp Cervical plexus/	8586
7	(cervical plexus or greater occipital nerve or GON or lesser occipital nerve or third occipital nerve or occiput or occipital or C2 dorsal root or C2 nerve).ti, ab, kw.	95950
6	1 or 2 or 3 or 4 or 5	436315
5	(neuralgia* or cranial neuralgia or cranial neuralgias or cervical neuralgia or occipital neuralgia or postoperative occipital neuralgia or occipital pain or postoperative occipital neuralgia or nerve pain or nerve pains or neuropathic pain or neuropathy or neurodynia or neurodynias or neurotmesis or axonotmesis or neurapraxia or nervous system trauma or nervous system injury or craniocervical injury or craniocervical injuries or nerve compression or nerve entrapment or entrapment neuropathy or cranial nerve disease or cranial nerve diseases or occipital headache or occipital headaches or cervicogenic headache or cervicogenic headaches or migraine or occipital migraine or cephalgia or cephalalgia).ti, ab, kw.	344516
4	exp Tension-type headache/	9747
3	exp migraine disorders/	90084
2	exp Posttraumatic headache/	1077
1	exp neuralgia/	124126

Web of Science Search performed from inception to June 11th, 2020		
#17	#16 AND #12 AND #8 AND #4	359
#16	#15 OR #14 OR #13	1,074,052
#15	KP = (steroids or injections or injection or injection therapy or injected)	146,601
#14	AB = (steroids or injections or injection or injection therapy or injected)	841,827
#13	TI = (steroids or injections or injection or injection therapy or injected)	259,190
#12	#11 OR #10 OR #9	691,062
#11	KP = (nerve block or trigger point injections or pain management or corticosteroid or corticosteroid injection or lidocaine or triamcinolone or kenalog or marcaine or botulinum or dexamethasone or bupivacaine or anesthesia or anesthetic or lidocaine or steroids or triamcinolone acetonide or botulinum toxins, type A)	178,625
#10	AB = (nerve block or trigger point injections or pain management or corticosteroid or corticosteroid injection or lidocaine or triamcinolone or kenalog or marcaine or botulinum or dexamethasone or bupivacaine or anesthesia or anesthetic or lidocaine or steroids or triamcinolone acetonide or botulinum toxins, type A)	422,786
#9	TI = (nerve block or trigger point injections or pain management or corticosteroid or corticosteroid injection or lidocaine or triamcinolone or kenalog or marcaine or botulinum or dexamethasone or bupivacaine or anesthesia or anesthetic or lidocaine or steroids or triamcinolone acetonide or botulinum toxins, type A)	272,663
#8	#7 OR #6 OR #5	40,119
#7	KP = (cervical plexus or greater occipital nerve or GON or lesser occipital nerve or third occipital nerve or occiput or occipital or C2 dorsal root or C2 nerve)	3,467
#6	AB = (cervical plexus or greater occipital nerve or GON or lesser occipital nerve or third occipital nerve or occiput or occipital or C2 dorsal root or C2 nerve)	34,016
#5	TI = (cervical plexus or greater occipital nerve or GON or lesser occipital nerve or third occipital nerve or occiput or occipital or C2 dorsal root or C2 nerve)	7,013
#4	#3 OR #2 OR #1	236,413
#3	KP = (neuralgia* or cranial neuralgia or cranial neuralgias or cervical neuralgia or occipital neuralgia or postoperative occipital neuralgia or occipital pain or postoperative occipital neuralgia or nerve pain or nerve pains or neuropathic pain or neuropathy or neurodynia or neurodynias or neurotmesis or axonotmesis or neurapraxia or nervous system trauma or nervous system injury or craniocervical injury or craniocervical injuries or nerve compression or nerve entrapment or entrapment neuropathy or cranial nerve disease or cranial nerve diseases or occipital headache or occipital headaches or cervicogenic headache or cervicogenic headaches or migraine or occipital migraine or cephalgia or cephalalgia or tension-type headache or posttraumatic headache)	80,600
#2	AB = (neuralgia* or cranial neuralgia or cranial neuralgias or cervical neuralgia or occipital neuralgia or postoperative occipital neuralgia or occipital pain or postoperative occipital neuralgia or nerve pain or nerve pains or neuropathic pain or neuropathy or neurodynia or neurodynias or neurotmesis or axonotmesis or neurapraxia or nervous system trauma or nervous system injury or craniocervical injury or craniocervical injuries or nerve compression or nerve entrapment or entrapment neuropathy or cranial nerve disease or cranial nerve diseases or occipital headache or occipital headaches or cervicogenic headache or cervicogenic headaches or migraine or occipital migraine or cephalgia or cephalalgia or tension-type headache or posttraumatic headache)	142,414
#1	TI = (neuralgia* or cranial neuralgia or cranial neuralgias or cervical neuralgia or occipital neuralgia or postoperative occipital neuralgia or occipital pain or postoperative occipital neuralgia or nerve pain or nerve pains or neuropathic pain or neuropathy or neurodynia or neurodynias or neurotmesis or axonotmesis or neurapraxia or nervous system trauma or nervous system injury or craniocervical injury or craniocervical injuries or nerve compression or nerve entrapment or entrapment neuropathy or cranial nerve disease or cranial nerve diseases or occipital headache or occipital headaches or cervicogenic headache or cervicogenic headaches or migraine or occipital migraine or cephalgia or cephalalgia or tension-type headache or post traumatic headache) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years Edit	92,919

ClinicalTrials.gov

Searched All Study Types, All Study Results

Condition or Disease

Occipital neuralgia OR migraine headache OR cervicogenic headache OR greater occipital nerve OR lesser occipital nerve OR third occipital nerve OR GON OR LON OR TON OR C2 neuralgia OR Arnold's neuralgia OR occipital nerve entrapment

Other terms

Infiltration OR injection OR nerve block OR corticosteroid OR steroid OR lidocaine OR bupivacaine OR dexamethasone OR botulinum 176