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Efficacy of interventional treatment strategies for managing patients with cervicogenic headache: a systematic review

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Review Article

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Cervicogenic headache (CeH) is caused by the disorder of the cervical spine and its anatomical structures. Patients who fail to respond to conservative therapies can undergo interventional treatment. The purpose of this review is to describe the various interventions and compare their relative efficacies. Although a few reviews have been published focusing on individual interventions, reviewing studies on other available treatments and establishing the most efficacious approach is still necessary. We performed a systematic review of studies available on the various interventions for CeH. The PubMed, Embase, and Cochrane databases were searched for literature published between January 2001 and March 2021. Based on the inclusion criteria, 23 articles were included. Two reviewers independently extracted the data from the studies and summarized them in a table. Eleven of twenty-three studies evaluated the effect of radiofrequency ablation (RFA), 5 evaluated occipital nerve blocks, 2 each for facet joint injections and deep cervical plexus blocks, and 1 study each evaluated atlantoaxial (AA) joint injections, cervical epidural injection, and cryoneurolysis. Most of the studies reported pain reduction except 2 studies on RFA. In conclusion, based on the available literature, occipital nerve blocks, cervical facet joint injection, AA joint injection, deep cervical plexus block, cervical epidural injection may be reasonable options in refractory cases of CeH. RFA was found to have favorable long-term outcomes, while better safety has been reported with pulsed therapy. However, our review revealed only limited evidence, and more randomized controlled trials are needed to provide more conclusive evidence.

Keywords: Injections; Nerve block; Pain management; Radiofrequency ablation; Secondary headache disorders; Systematic review; Zygapophyseal joint.

Introduction

Cervicogenic headache (CeH) is a secondary headache characterized by unilateral pain that is caused by a disorder of the cervical spine and its anatomical structures, mainly innervated by the C1, C2, and C3 spinal nerves [1]. It was first described in 1983 by Sjaastad et al. [2]. Due to its significant overlap with migraine and a lack of easily applicable tests and diagnostic criteria, CeH is difficult to diagnose and treat [3]. The diagnostic criteria for CeH have been revised and modified in the third edition (beta version) of the International Classification of Headache Disorders (11.2. Headache attributed to neck disorders: 11.2.1 CeH) [4]. The prevalence of CeH ranges from 1% to 4.1% in the general population, with no clear male or female predominance [5].

The pathogenesis of CeH is due to the convergence of nociceptive afferents from the

upper three cervical nerves and trigeminal nerves onto the second-order neurons in the trigeminocervical nucleus in the upper cervical spinal cord (C1–C3). Therefore, every cervical structure innervated by the trigeminocervical caudalis nucleus (joint, muscles, nerves, ligaments, and dura) is implicated in the genesis of CeH [6]. The patient's history and physical examination are the most useful tools for diagnosing CeH. Additionally, diagnostic zygapophyseal joint injections and cervical nerve and medial branch blocks can be used to confirm the diagnosis and predict treatment efficacy [7]. Owing to its complex etiology, a multidisciplinary treatment approach must be utilized. Currently, there is limited literature available regarding the effectiveness of pharmacological drugs and physical therapy, such as muscle stretching and manual cervical traction [8]. When conservative treatment fails, interventional pain management strategies can be used. This includes greater occipital nerve (GON) and lesser occipital nerve (LON) blocks, cervical spinal rami blocks (C1–C3), medial branch of C3, C4 dorsal rami blocks, intraarticular zygapophyseal joint (C2–C3, C3–C4) injections, atlantoaxial (AA) joint injections, cervical epidural steroid injections, radiofrequency ablations (RFAs), and occipital nerve stimulation [8,9]. Surgical interventions are also an option; however, these are often considered a last resort because of their ineffectiveness and high associated risk of complications [7]. In contrast to other secondary headaches, CeH does not improve over time [10]; therefore, finding an effective treatment is highly clinically important. Previously published reviews have mainly focused on individual interventions rather than summarizing all available interventions for managing CeH [11–13]. Therefore, an analysis and interpretation of the other available treatment modalities is warranted. The purpose of this review was to determine the various therapeutic interventions available and to make a comparative evaluation to establish the most efficacious approach for the management of CeH.

Materials and Methods

Study design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). A prior protocol for this review was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO, no. CRD 42021246403).

Literature search strategy

An electronic search of the PubMed, Embase, and Cochrane databases for studies published between January 2001 and March 2021 was performed. The search terms "cervicogenic headache," "secondary headache," "interventions," "nerve blocks," "occipital nerve block," "zygapophyseal joint injection," "median branch block," "pulsed radiofrequency," and "radiofrequency neurotomy" were combined in different ways to search the databases. Two independent researchers searched the available literature and collected all the relevant articles. All the selected abstracts were reviewed by another researcher. A well-drafted PICOS framework was used to conduct the study (Table 1).

After the electronic databases were searched and the duplicates were removed, 6,484 articles were retrieved. Articles in languages other than English, animal studies, and abstract-only articles were not included. We also excluded literature reviews, systematic reviews, editorials, case reports, case series, non-scientific commentaries, reports, and news articles from this analysis. The full text of the article was obtained if the title or abstract discussed interventions for CeH management. If there were other pathologies, such as cranial masses, head injury, or any intracranial surgeries, the article was excluded. A total of 130 full-text articles were reviewed for eligibility. The references of the selected articles were also searched for additional studies matching the inclusion criteria. A total of 23 articles were included in the final analysis (Fig. 1).

Table 1. PICOS Framework

Population	Age: adults > 18 years
	Diagnosis: patients with CeH unresponsive to conservative therapy
Interventions	Various interventional approaches for CeH management:
	• GON and LON block
	• Facet joint intraarticular injection
	• Lateral atlantoaxial intraarticular injection
	• Deep cervical plexus block
	• Cervical epidural steroid injection
	• Radiofrequency ablation
	• Cryoneurolysis
Controls	Varies from study to study, compared to control groups and/or placebo group
Outcomes	Primary objective
	• Reduction of pain scores (NRS or VAS)
	Secondary objective
	• Duration of pain relief
	• Effect on quality of life
	• Adverse effects
Study design	Prospective randomized and non-randomized controlled trials, cohort studies, retrospective studies

PICOS: Population, Interventions, Controls, Outcomes, Study design, CeH: cervicogenic headache, GON: greater occipital nerve, LON: lesser occipital nerve, NRS: numerical rating scale, VAS: visual analog scale.

Assessment of risk of bias in individual studies

The methodological quality of the included studies was assessed using the "risk of bias" of the Review Manager Software version 5.4 (The Cochrane 14 Collaboration, UK). Two authors independently assessed the quality of each study, and disagreements were resolved through discussion. Seven categories, which included random sequence generation and allocation concealment to detect selection bias, blinding of the participants for performance bias, blinding of the outcome assessor for detection bias, incomplete outcome data for attrition bias, selective reporting for reporting bias, and other bias, were rated as "high," "low," or "unclear" to assess the internal validity of each study (Figs. 2 and 3).

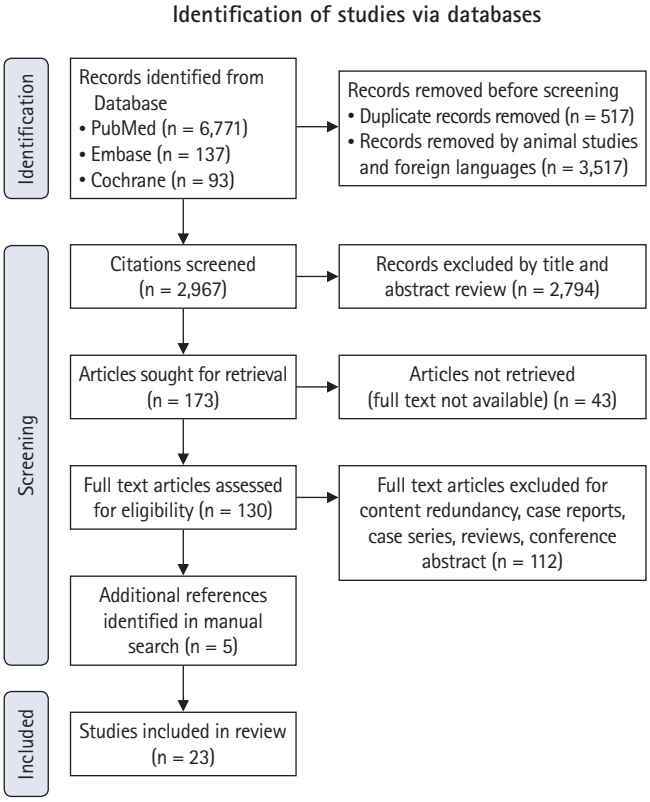

Fig. 1. PRISMA flow diagram.

Data extraction

The 23 included articles were fully reviewed by two reviewers who independently extracted and summarized the data in a table under the following headings: 1) author name, 2) year of publication, 3) type of study, 4) population, 5) intervention(s), 6) results, and 7) conclusion. Due to the lack of homogenous data and high-quality randomized controlled trials, only a systematic review could be performed.

Results

Therapeutic interventions for the treatment of CeH that were included in this systematic review included occipital nerve blocks (GON and LON blocks), facet joint intraarticular injections, lateral AA joint intraarticular injections, deep cervical plexus blocks, cervical epidural steroid injections, RFAs, and cryoneurolysis. Of the twenty-three included studies, eleven evaluated the effect of RFA on CeH, five evaluated the role of occipital nerve blocks (GON, LON), two evaluated facet joint injections, two evaluated deep cervical plexus blocks, and one study each evaluated AA joint injections, continuous cervical epidural injections, and cryoneurolysis (Fig. 4). Data from the included studies are summarized in Table 2.

The efficacy of occipital nerve blocks (GON, LON) in CeH treatment was evaluated by randomized controlled trials by Inan

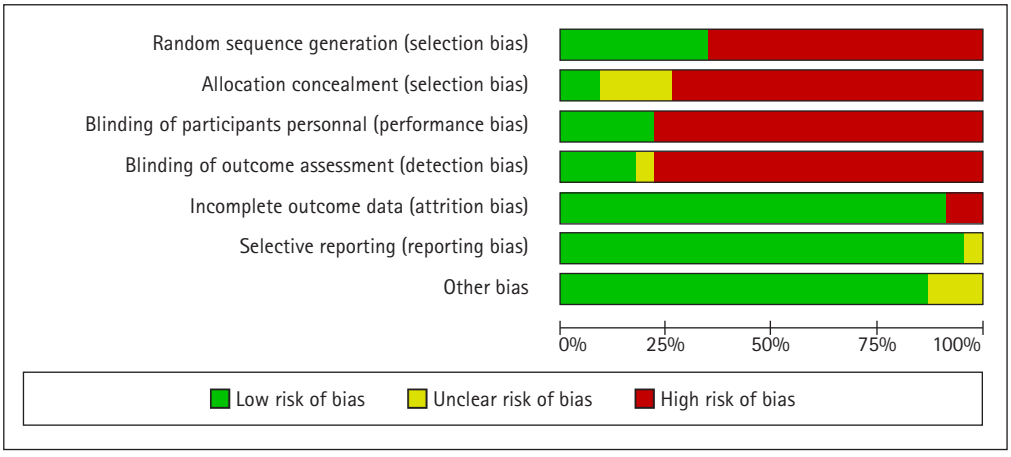

Fig. 2. Risk of bias graph. Review authors' judgements about each risk of bias item presented as percentages across all included studies.

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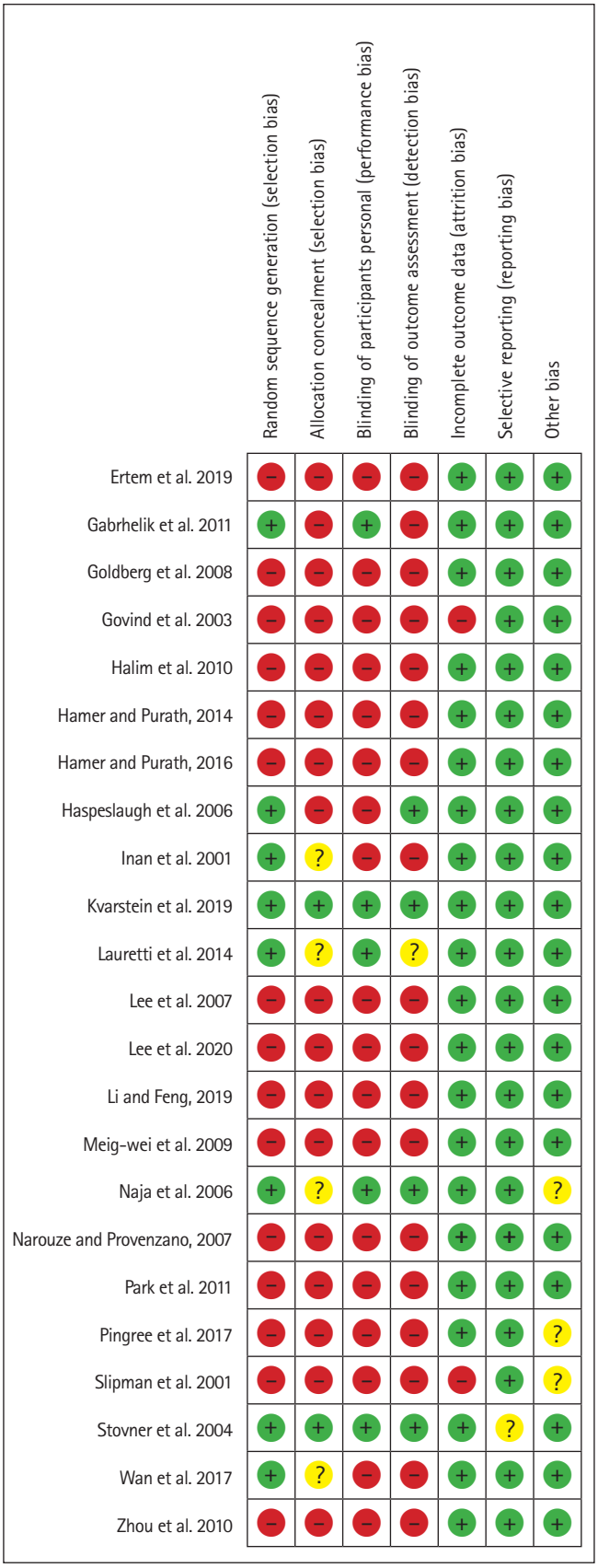

Fig. 3. Risk of bias summary. Review authors' judgements about each risk of bias item for each included study.

et al. [14], Naja et al. [9], Lauretti et al. [15] and found significant decrease in pain scores and rescue analgesics consumption in nerve block group. Another non-controlled prospective trial by Pingree et al. [16] reported significant pain reduction following GON block at C2 level and a retrospective review by Ertem and Yılmaz [17] described the successful role of repeated GON blocks in refractory cases of CeH.

Retrospective studies by Slipman et al. [18] and Zhou et al. [19] evaluated the role of facet joint injection in the treatment of CeH emanating from upper cervical facet joints. Zhou et al. demonstrated significant decrease in pain score after C1–C2, C2–C3 facet joint injection along with C2, C3 spinal rami block. Narouze and Provenzano [20] showed significant pain reduction following lateral AA joint injection in CeH patients showing AA joint involvement.

A randomized controlled study by Goldberg et al. [21] and non-randomized study by Wan et al. [22] demonstrated effective pain relief following deep cervical plexus block. A retrospective study by He et al. [23] showed significant pain reduction following continuous cervical epidural block for at least 6 months in CeH patients.

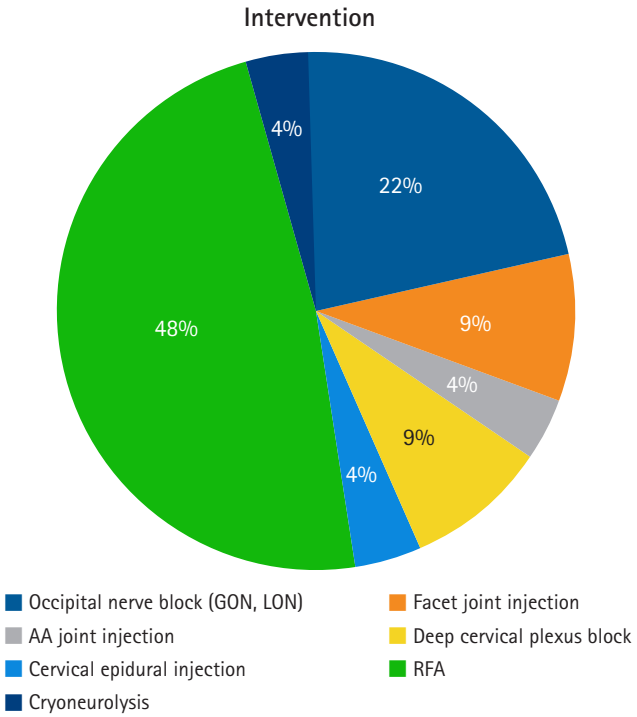

Fig. 4. Study interventions included in this review. Of the 23 included studies, 11 studies evaluated the effect of RFA, 5 evaluated the role of occipital nerve blocks, 2 studied facet joint injections, 2 studied deep cervical plexus blocks, and 1 each studied AA joint injections, cervical epidural steroid injections, and cryoneurolysis on CeH. GON: greater occipital nerve, LON: lesser occipital nerve, AA: atlantoaxial, RFA: radiofrequency ablation, CeH: cervicogenic headache.

Table 2. Summary of Studies Evaluating the Effects of Various Interventions

Article (yr)	Study type	Participants	Intervention	Results	Conclusion
Occipital nerve blocks (GON, LON)					
Inan et al. 2001 [14]	Randomized prospective comparative study	28 patients with CeH based on diagnostic criteria by Sjaastad et al.	GON block group and C2/C3 nerve block group (1% lidocaine diagnostic block followed by two weekly injections of 0.25% bupivacaine)	Decreased pain frequency/duration in both groups lasting at least 2 months, with no significant group differences except pain frequency in first week after first therapeutic block (significantly lower in C2/C3 group)	Both blocks are equally effective for diagnosis and treatment of CeH
Naja et al. 2006 [9]	Double blind, placebo controlled	50 (25 target, 25 control) patients with CeH	GON and LON blocks with or without facial nerve block (16/25); anesthetic block group compared with placebo group	Significant pain improvement, decreased analgesic use, and decreased duration/frequency of headache at 2 weeks	Nerve stimulator- guided occipital nerve block provides relief of pain and accompanying symptoms for up to 2 weeks
Lauretti et al. 2014 [15]	Randomized double-blinded	30 patients with unilateral cervical pain with most painful point located on ipsilateral GON	GON block performed using classic technique followed by sub-compartmental technique if VAS > 3; final volume of 5, 10, or 15 ml (10 mg dexamethasone + 40 mg lidocaine + nonionic iodine contrast + saline)	Significant decrease in VAS and rescue analgesic consumption in all subcompartmental groups lasting 24 weeks compared to only 2 weeks for classic technique	-Classic technique resulted in only 2 weeks of analgesia whereas sub-compartmental resulted in at least 24 weeks of analgesia; -5 ml volume sufficient for successful block
Pingree et al. 2017 [16]	Prospective open label	14 patients with occipital neuralgia or CeH	US-guided GON block at C2 level, 4 ml [1 ml of 2% lidocaine + 2.5 ml of 0.25% bupivacaine + 3 mg betamethasone] injected	-Successful block in 86% of patients. -Significant decrease in mean NRS from 4.71 (baseline) to 3.78 at 30 minutes, 2.64 at 2 weeks, and 2.21 at 4 weeks	-Successful blockade of GON at C2 using US-guided technique -Significant reduction in pain scores observed over 4-week period -No significant adverse effects reported
Ertem and Yılmaz, 2019 [17]	Retrospective cohort study	21 patients with CeH who underwent at least 3 GON blocks, attended at least 3 follow-up appointments, and were admitted to the headache clinic during a 6-month period	GON block at the scalp; injection mixture of 3–4 ml of 2% lidocaine + 1 ml methylprednisolone	-Significant decline in mean NRS by first month (second injection), second month (third injection), and third month (fourth injection) -8 patients reported no pain after the second injection and thus did not receive a fourth injection	-Repeat GON injections is an effective option in patients not responding to conservative therapy -No serious complication was noted

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Table 2. Continued

Cervical facet joint injections					
Slipman et al. 2001 [18]	Retrospective	-18 patients with unremitting daily headaches after flexion/extension injury of upper cervical spine with tender facet joint not responding to conservative therapy -Symptom duration ~34 months	-C2–C3 facet joint diagnostic block followed by therapeutic injection if decrease in VAS was > 80% -If symptom relief was < 90%, second therapeutic injection given after 2 weeks -Follow up at ~19 months	-Average decrease in VAS (from 8.2 to 5.5) -50% of patients experienced headache < 3 times/month, and 61% experienced < 3 episodes/week responsive to oral analgesics	Intraarticular facet joint injection is effective for treating headaches emanating from the C2–C3 joint after whiplash event
Zhou et al. 2010 [19]	Retrospective observational	31 patients who failed multiple pharmacological/ other treatments	C1/2, C2/3 facet joint block and C2 and C3 spinal rami blocks using 0.5 ml 0.25% bupivacaine + 3 mg betamethasone	> 50% headache relief in 90.3% (28) of patients immediately after procedure; however, 9.7% (3) of patients did not respond	C1/C2 and C2/C3 facet joint and spinal rami blocks provide significant prolonged pain relief in > 90% of patients
AA joint intraarticular injection					
Narouze and Provenzano, 2007 [20]	Retrospective	32 patients with clinical picture suggestive of AA joint pain, intractable headaches, and failed multiple drug treatment	Classic intraarticular posterior approach, lateral AA joint injection (1 ml bupivacaine 0.5% + 10 mg triamcinolone)	-Post-procedure pain score was 0 in 46.8% of patients (15); ≥ 50% decrease in pain score in 81.2% of patients (23) -Significant decrease in pain score at 1 and 3 months but not at 6 months	Lateral AA intraarticular steroid injections provide short-term analgesia
Deep cervical plexus block					
Goldberg et al. 2008 [21]	Prospective	39 patients with CeH	-Deep cervical plexus block @ C2/C3 using 10 ml 0.25% bupivacaine + 80 mg methylprednisolone -For unilateral headache, unilateral block given and repeated on contralateral side after 1 week for global headache -Pain assessed pre- and immediate post-injection and at 3 and 6 months	-Significant decrease in pain scores ($P < 0.001$) -33% of patients reported pain scores ≤ 4 after their last treatment -24% (10) had pain scores ≤ 4 at 3 months and 18% (7) had pain scores ≤ 4 at 6 months	-Significant decrease in pain after initial as well as last treatment -For some patients, effective pain relief was seen for 3 months but by 6 months, pain had returned to pre-treatment levels
Wan et al. 2017 [22]	RCT; single-blinded	56 patients with CeH randomly recruited to either US-guided or FL-guided injection group	Mixture of 2–4 ml 1% lidocaine + 7 mg betamethasone injected along C2 and/or C3 transverse process	-Significant decrease in NRS in both groups ($P < 0.05$) at 2, 12, and 24 weeks post-injection -No serious side effects reported	-DCP block provides significant pain relief (for up to 6 months) -US-guided approach showed similar satisfactory effect as FL-guided with advantage of no radiation exposure

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Table 2. Continued

Continuous cervical epidural block					
He et al. 2009 [23]	Retrospective observational	37 patients with CeH	Epidural catheter placed in C6–C7, C7–T1 or T1–T2 space; lidocaine (100–200 mg) + dexa. (1–2 mg) + saline (total 250 ml) infused @ 5 ml/hr for 3–4 weeks. In addition, 5 mg triamcinolone given once weekly for 3–4 weeks, then catheters removed	Days with mild/moderate pain, occurrence of severe pain, and daily NSAID dose (mg) significantly reduced 6 months after catheter placement compared to 3 months prior to procedure	-Effective for at least six months. -Further research is needed to elucidate mechanisms of action and to prolong this effect
Radiofrequency ablation (RFA)					
			RFA of facet joint and medial branches supplying the facet joint		
Stovner et al. 2004 [25]	Randomized, double-blind	12 patients with refractory CeH randomized into RFN of C2–C6 facet joints vs. sham treatment	RFA of medial branch of C2–C6 facet joints on the symptomatic side	Slight improvement was seen at 3 months in RFN group, but no significant difference was seen after 3 months	-No benefit with the procedure -Minor and short-term side-effects were seen
Haspeslagh et al. 2006 [26]	Randomized, controlled	30 patients with CeH randomized into two groups, the RFA group (n = 15) and the LA group (n = 15)	RFA of medial branches of dorsal rami of C3–C4 facet joint vs. LA with steroid injection at GON, followed by TENS when necessary	No statistically significant differences in pain scores	No evidence that RFN of cervical facet joints is a better treatment than infiltration of GON followed by TENS
Govind et al. 2003 [27]	Prospective, non-randomized	49 patients suffering from third occipital nerve headache	RFN of third occipital nerve (medial branch of C3 spinal nerve, supplying C2–C3 facet joint)	-88% achieved a successful outcome -Median duration of relief was around 297 days	Profound pain relief was seen and repeat ablation prolonged the duration of pain relief
Lee et al. 2007 [28]	Prospective observational	30 patients suffering from chronic CeH for > 6 months, with > 50% pain relief from two diagnostic C3–C4 cervical medial branch blocks	RFN of medial branch of C3–C4 facet joint	-Significantly reduced headache severity in 73% of patients at 12 months -75% pain relief seen in majority of patients -Reduced analgesic intake by 70% -Average headache episode decreased from 6.2 to 2.8 days/week	-Substantial pain relief was seen -No major complications reported
Park et al. 2011 [29]	Retrospective observational	11 patients with CeH	RFN of lower cervical medial branches (C4–C7)	-VAS score decreased by around 60% at 6 months -No serious complication was reported	Lower cervical disorders can also lead to headaches, which can be improved with RFN
			RFA of GON		
Gabrhelík et al. 2011 [30]	Randomized clinical pilot study	30 patients with refractory CeH randomized into two groups: the LA group (n = 15) and the PRF group (n = 15)	GON block with LA and steroid compared to PRF of GON	-Significant decrease in VAS seen in both groups at 3 months -at 9 months, greater pain relief in PRF group than LA group	-PRF provides greater long-term pain control -No complications reported

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Table 2. Continued

			RFA of lateral C1–C2 joint		
Halim et al. 2010 [31]	Retrospective study	86 patients with CeH	Lateral C1–C2 joint PRF using intra-articular anterolateral approach	Roughly 50% of patients had > 50% pain relief at 2 and 6 months and 1 year	PRF of lateral C1–C2 joints is feasible in refractory cases of CeH
			RFA of C2 DRG		
Hamer and Purath, 2014 [32]	Retrospective observational	40 patients with refractory CeH and/or occipital neuralgia	RFN of C2 DRG and/or third occipital nerve	-35% of patients reported complete pain relief -70% reported ≥ 80% pain relief	RFN of C2 DRG and/or third occipital nerve can provide > 50% pain relief
Hamer and Purath, 2016 [33]	Retrospective observational	23 patients with recurrent CeH or occipital neuralgia	Repeat RFA of C2 DRG and/or third occipital nerve	-86.5% of patients reported pain relief lasting for 25.4 weeks -Repeat RFA showed similar result to first RFA in 59% of patients -32% reported repeat RFA was more effective, while 9% reported first RFA was more effective	-Repeat RFA is a feasible option for recurrent cases -Effectiveness of repeat RFA is the same or better than the first RFA - High likelihood of side effects but well-tolerated
Li and Feng, 2019 [34]	Case control	139 patients with CeH, 87 in the PRF + ESI group and 52 in the ESI only group	PRF for C2 DRG and ESI	-Median pain relief was 4 months for the ESI group and 8 months for the PRF + ESI group -No serious adverse effects reported	Combination of PRF C2 DRG + ESI is relatively safe, provides sustained pain relief, and improves quality of life
Lee et al. 2020 [35]	Retrospective observational	Electronic medical records of 45 patients with CeH (initially 114 patients recruited, 45 of which underwent PRF of C2 DRG)	C2 DRG PRF after recurrence of CeH following initial relief 24 hrs after diagnostic C2 DRG block	-40% of patients (18/45, success group) ≥ 50% pain relief after 6 months -No post-procedure complications reported	C2 DRG PRF effective treatment for CeH, especially for those with positive C2 DRG diagnostic block
Cryoneurolysis					
Kvarstein et al. 2019 [36]	RCT, double-blind	52 patients with unilateral CeH not responding to conservative treatment	After positive diagnostic block, 52 patients were randomly allocated to two groups (3:2): the occipital cryoneurolysis (31) group and the injection group (21) [1 ml depo-medrol (40 mg/ml) + 1 ml bupivacaine (5 mg/ml)]	-Significant reduction in pain > 50% and number of people consuming opioids in both groups -No significant difference seen between groups -Various transient/ minor side effects reported but no significant group differences seen	Cryoneurolysis provides substantial but temporary pain relief, and the effect was not significantly different from the injection group

CeH: cervicogenic headache, GON: greater occipital nerve, AA: atlantoaxial, RFA: radiofrequency ablation, RFN: radiofrequency neurotomy, PRF: pulsed radiofrequency, ESI: epidural steroid injection, DRG: dorsal root ganglion, NRS: numerical rating scale, VAS: visual analog scale, LA: local anesthetic, US: ultrasound, FL: fluoroscopy, TENS: transcutaneous electrical nerve stimulation.

RFA is a promising approach that provides sustained pain relief. Pulsed radiofrequency (PRF) is considered a more satisfactory alternative to conventional RFA since it is associated with a better safety profile and fewer complications [24]. High-voltage radiofrequency pulses induce an inhibitory electric field around nociceptive fibers and disrupt pain transmission. Of the 11 included studies on the efficacy of RFA, three were RCTs, two were prospective, and six were retrospective. RFA targeting the medial branches supplying the cervical facet joints have been evaluated by Stovner et al. [25], Haspeslagh et al. [26] and demonstrated no benefit. Non-randomized studies by Govind et al. [27] and Lee et al. [28] showed significant headache relief after positive diagnostic block. Park et al. [29] demonstrated the role of lower cervical disorders in CeH genesis which could be improved by RFA of involved medial branches. PRF of GON was evaluated by Gabrhelik et al. [30] in a randomized study and reported long lasting significant pain relief in PRF group. PRF of lateral C1–C2 joint was evaluated by Halim et al. [31] and reported >50% pain relief in approximately 50% of the patients over 1 year follow-up period. Hamer and Purath [32] demonstrated >50% pain relief following RFA of C2 dorsal root ganglion (DRG) and in another study, also reported that efficacy of repeat RFA is usually same or better than first ablation in recurrent cases of CeH [33]. Efficacy of C2 DRG PRF combined with epidural steroid injection (ESI) was evaluated by Li and Feng [34] and reported significant pain relief with median relief of 8 months in PRF+ESI group. Another study by Lee et al. [35] also demonstrated significant pain relief following PRF of C2 DRG in patients who showed positive C2 DRG diagnostic block.

Cold temperature mediated ablation of sensory nerve fibers is relatively safe neuroablative technique. Cryoneurolysis of GON and LON was evaluated in refractory cases of CeH after positive diagnostic block in a randomized study by Kvarstein et al. [36] and found significant pain reduction in both the treatment groups with no significant group difference.

Discussion

CeH is a clinical syndrome with various presentations and multiple pain generators that involves cervical structures, mainly the upper cervical spinal nerves; C2–C3, C3–C4 facet joints; AA joints; C2–C3/C3–C4 intervertebral discs; atlantooccipital joints; GONs; and LONs [37]. Given the limited role of conservative management, this systematic review aimed to ascertain the efficacy of these different interventional approaches in the management of CeH.

Occipital nerve blocks (GON, LON)

Due to the convergence of the upper cervical and trigeminal sensory pathways, the bidirectional referral of nociceptive sensations between the neck and trigeminal receptive fields of the head and face leads to the referral of CeH pain from a cervical source to the forehead, temple, or orbit [6]. This forms the background for managing CeH through blocking the GON. Anesthetic blocks of the LON and facial nerve have also been found to be effective [9]. Inan et al. [14] compared the effect of GON blocks to C2/C3 spinal rami blocks in 28 patients with CeH and concluded that both blocks are equally effective. No significant difference was observed between the two groups in terms of pain frequency or degree of pain, except for pain frequency in the first week following the first therapeutic block, which was significantly reduced in the C2/C3 group. Another study by Naja et al. [9] evaluated 50 patients with CeH who received GON and LON blocks with or without facial nerve blocks. The anesthetic block group, which received a mixture of lidocaine, bupivacaine, epinephrine, fentanyl, and clonidine, was compared with the placebo group (normal saline) and a statistically significant improvement in pain intensity, frequency, and duration as well as a decrease in analgesic use were observed at 2 weeks in the block group compared to the placebo group. Lauretti et al. [15] evaluated 30 patients with unilateral CeH who underwent GON blocks using the classic technique (1 cm below the level of the superior nuchal line, just medial to the pulsation of the occipital artery). The visual analog scale (VAS), which is a tool used to evaluate pain using a 10 cm line with no marking that ranges from no pain (0) to worst possible pain (10), was used. Those with a score > 3 were randomly allocated into 3 groups (n = 10) who underwent GON blocks with 5, 10, or 15 ml of volume using the suboccipital compartmental technique. A significant decrease in the pain score and rescue analgesic consumption and an improved quality of life were seen in all subcompartmental groups for 24 weeks compared to only 2 weeks with the classic technique. Pingree et al. [16] evaluated 14 patients who underwent ultrasound-guided GON blocks at the C2 level and reported a successful block in 86% of patients 30 min post-injection. A significant decrease in the mean numerical rating scale (NRS) score, which is an 11-point scale ranging from 0 "no pain" to 10 "worst pain," was observed at 30 minutes, 2 weeks, and 4 weeks compared to baseline. Although the sample size was very small, a significant reduction in the pain score was observed. Ertem and Yılmaz [17] retrospectively evaluated 21 patients with CeH who underwent at least three GON blocks and attended at least three follow-up appointments. A significant reduction in pain scores was seen at 3 months post-treatment. Some other previous studies

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found an overall pain reduction of more than 50% [14–17] or nearly 50% [9] in the mean NRS or VAS score following occipital nerve blocks to treat CeH, with a short duration of pain relief usually lasting for a few weeks [9,14–16]. Repeat injections may be effective for sustained pain relief [17].

Facet joint injections

The beneficial effect of facet joint injections for the treatment of CeH has been reported in a few studies. Slipman et al. [18] reviewed 18 patients with unremitting headaches after flexion/extension injuries associated with tenderness over the upper cervical zygapophyseal joint who underwent a C2–C3 zygapophyseal joint injection. A second injection was administered after 2 weeks if pain relief was < 90%. Although the average decrease in the VAS score (from 8.2 pre-injection to 5.5 post-injection) was not significant, the headache frequency, response to analgesics, and employment status improved significantly. Another retrospective chart review of 31 patients with refractory CeH who underwent C1–C2 and C2–C3 facet joint injections and C2 and C3 spinal rami blocks was conducted by Zhou et al. [19]. In that study, 28 patients showed a > 50% reduction in pain for an average duration of 21.7 days. A significant decrease in the mean pain intensity was observed immediately after injection. The study outcomes suggested that C1–C2, C2–C3 facet joint dysfunction and subsequent irritation of the spinal rami at C2 or C3 may contribute to CeH development and that steroid injections reduce spinal nerve root irritation and thus improve CeH. Despite the small sample size in the above two studies, the suggested contribution of upper cervical arthropathy in the generation of CeH and the effectiveness of both cervical facet joint injections and C2–C3 spinal rami blocks for pain relief were notable. No treatment-related complications were observed.

AA joint intraarticular injection

Narouze and Provenzano [20] conducted a retrospective chart review of 32 patients with CeH suggestive of AA joint pain who underwent AA joint intraarticular injections. Complete pain relief was observed in 15 patients, and 23 patients experienced a ≥ 50% reduction in pain. The mean pain score decreased significantly from pre-procedure to immediate post-procedure and at 1 month and 3 months, but not at 6 months. Therefore, this study showed the short-term pain relief provided by intraarticular AA steroid injections. However, there was not sufficient data to determine its long-term effects.

Deep cervical plexus block

A deep cervical plexus block can be useful for refractory cases of CeH, as pain often occurs over the C2 or C3 spinal nerve root distribution. Goldberg et al. [21] demonstrated a significant reduction in pain scores immediately after receiving a deep cervical plexus block at the C2/C3 level in 39 patients with CeH. While some patients experienced effective pain relief for 3 months, pain scores had returned to baseline levels by 6 months. The injection effectiveness was rated at 42% effective for all first injections and 40% effective for the last injection. Wan et al. [22] evaluated 56 patients who underwent either an ultrasound-guided or fluoroscopic-guided deep cervical plexus block along the C2 and/or C3 transverse process and reported a significant decrease in pain intensity (NRS) in both groups at 2, 12, and 24 weeks post-injection, with no significant differences observed between the groups. However, the small sample size and lack of double-blinding limited the strength of these findings and a clear understanding of the role of this treatment for CeH management [21,22].

Continuous cervical epidural block

He et al. [23] evaluated 37 patients with CeH treated with continuous cervical epidural block using lidocaine, dexamethasone, and saline (5 ml/h) for 3–4 weeks and triamcinolone 5 mg once a week for 3–4 weeks, and found it to be effective for at least 6 months. However, further research is needed to elucidate the mechanism and validate this outcome.

Radiofrequency ablation

For CeH patients who fail the interventions mentioned above or for those with severe or refractory CeH, radiofrequency lesioning may be an option. The targeted pain generators are the facet joint and its nerve supply (medial branch of the spinal dorsal rami), the third occipital nerve (branch of the dorsal rami of the C3 spinal nerve, supplying the C2–C3 facet joint), the GON, lateral C1–C2 joint, and C2 DRG.

Stovner et al. [25] evaluated RFA of the medial branch of the C2–C6 facet joints ipsilateral to the pain in 12 patients and compared them to those receiving sham treatment. A slight improvement was noted at 3 months, but after this time and over a duration of 2 years, no statistically significant differences were observed. Haspeslagh et al. [26] evaluated 15 patients who received RFA of the C3–C6 facet joints and the DRG and compared them with a local anesthetic block of the GON. No statistically significant difference in pain scores was seen, suggesting that RFA of the

cervical facet joint was no better at reducing pain than local infiltration of the GON. Therefore, both of the above studies showed that RFA provided no significant benefit.

Govind et al. [27] described the effect of RFA of the third occipital nerve for the treatment of referred pain from C2–C3 facet joints in 49 patients and reported successful outcomes in 88% of the patients with pain-free intervals lasting for approximately 297 days. Fourteen patients underwent repeated procedures, 86% of which (12 patients) experienced pain relief for the next 217 days. The study concluded that third occipital nerve RFA was effective for pain relief and repeat ablations can prolong its efficacy. Lee et al. [28] evaluated 30 patients with CeH who underwent RF neurotomy of the cervical facet joints after positive diagnostic blocks and found substantial pain relief over a 12-month follow-up period. Another study by Park et al. [29] evaluated 11 patients with CeH who underwent RFA of the medial branches of the lower cervical nerves (C4–C7) and reported a significant decrease in VAS scores at 6 months (from 8.1 ± 1.1 to 2.7 ± 1.3). The study also concluded that lower cervical disorders may play a role in the genesis of CeH.

PRF of the GON was evaluated by Gabrhelik et al. [30] and compared with the GON block (using a local anesthetic and steroid). A significant decrease in VAS scores and analgesic consumption were observed in both groups at 3 months, with long-term pain control (at 9 months) in the PRF group. Halim et al. [31] evaluated 86 patients with CeH who underwent lateral C1–C2 joint PRF. The percentage of patients with pain relief ≥ 50% at 2 months, 6 months, and 1 year was 50% (43/86), 50% (43/86), and 44.2% (38/86), respectively. Long-term pain relief at 6 months and 1 year was predicted by ≥ 50 % pain relief at 2 months. The study concluded that PRF of the lateral C1–C2 joint was effective for pain relief in refractory CeH; however, outcome validation is limited by its retrospective nature and short follow-up period.

Hamer and Purath [32] evaluated 40 patients who received a bilateral RFA of the C2 DRG and were followed up for 6 months to one year. Pain relief was 100% in 35% of patients and ≥ 80% in 70% of patients. The mean duration of pain relief was 22.35 weeks. A total of 92.5% of patients reported satisfaction with the procedure and were willing to undergo the procedure again if the symptoms returned. The complication rate was 12–13%. Another study by Hamer and Purath [33] evaluated 23 patients with CeH who needed a repeat RFA of the C2 DRG and reported that the repeat RFA was effective. Compared to the first intervention, the repeat intervention showed either similar (in 59% of patients) or better (in 32% patients) effectiveness. Li and Feng [34] retrospectively evaluated 87 patients who underwent PRF of the C2 DRG and epidural steroid injection (ESI) and compared them with 52 patients who underwent only ESI. A significant reduction in the median pain score was observed in both groups at the 2-year follow-up. A significantly lower VAS score, pain attack frequency, analgesic use, total pain score, and improved quality of life were observed in the PRF + ESI group than in the ESI group. Median pain relief lasted 8 months in the PRF + ESI group and 4 months in the ESI group, suggesting that the combination of PRF of the C2 DRG and ESI may be an effective and safe option for CeH. Lee et al. [35] evaluated 45 patients who underwent C2 DRG PRF after CeH recurrence 24 h after receiving a diagnostic C2 DRG block. A ≥ 50% reduction in pain was observed in 40% of patients (success group). Significantly more patients in the success group than in the failure group showed a positive diagnostic block. The study concluded that C2 DRG PRF is an effective treatment, especially for patients with definite pain reduction after the diagnostic C2 DRG block.

Among the upper three cervical spinal nerves, the C2 spinal nerve is more susceptible to injury [38]. The ventral rami of C2 innervates the AA joint, and also gives rise to LON. The GON arises from the medial aspect of the dorsal rami of the C2 spinal nerve. The C2 DRG, therefore, may be an effective target for PRF; however, evidence is limited due to the lack of randomized trials.

Cryoneurolysis

To achieve a long-lasting analgesic effect, freezing destruction of nerve conduction has been attempted for refractory cases of CeH. Kvarstein et al. [36] evaluated the clinical efficacy of occipital cryoneurolysis and compared it with local anesthetic and steroid injections. Despite a significant reduction in pain scores, pain intensity gradually increased after 6–7 weeks but had not returned to baseline by 18 weeks in both groups. No or minimal improvement was seen in health-related quality of life and psychological distress in both groups. After 18 weeks, majority of patients (74%) reported much or moderately improved global status, 55% of patients reported much or moderately improved headache intensity and 29% reported improved neck movement in cryoneurolysis group. These results indicate that the role of occipital cryoneurolysis in treating CeH may be questionable; however, further studies with larger sample sizes are required.

In this review, various interventions targeting different pain generators for the management of CeH have been described. Occipital nerve blocks (GON, LON) showed only limited evidence, as most of the studies were non-controlled and yielded only transient benefits. Facet joint intraarticular injections, anesthetic blocks of the upper cervical spinal nerves, AA joint injections, deep cervical plexus blocks, and cervical epidural blocks may be

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effective treatments, they have generally only been shown to provide short-term relief, with limited or no long-term benefits. Further studies are needed to consolidate the role of freezing destruction of pain-generating fibers using cryoneurolysis. Radiofrequency lesioning may be preferable over other interventions because of its long duration of effect, better efficacy, and fewer side effects. Conventional RFA is neurodestructive and is associated with high complication rates, such as neuritis or deafferentation pain, which is not seen with PRF [32,33]. PRF, therefore, could be considered the preferred interventional approach for CeH management, given its better safety profile.

This systematic review had several limitations. First, most of the included studies were not RCTs. Second, the structure, inclusion/exclusion criteria, and outcomes assessed among the included studies were heterogenous. Third, most of the included studies had a small sample size and short follow-up period. Additionally, there were flaws and inconsistencies in the design of both randomized and nonrandomized trials. Although a few studies showed promising outcomes of a particular intervention for the management of CeH, carefully designed, high-quality, large, prospective, randomized trials are needed to investigate the long-term benefits of various interventions for effectively managing CeH.

In conclusion, based on the available literature, occipital nerve (GON, LON) blocks, cervical facet intraarticular injections, AA joint injections, deep cervical plexus blocks, and cervical epidural steroid injections may be reasonable options for CeH treatment. Radiofrequency lesioning was found to be better with long-term positive outcomes, and pulsed therapy had better safety. However, our review revealed only limited evidence, and more RCTs are needed to provide more concrete evidence and to establish the relative efficacy of the various available interventions discussed for the management of CeH.

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No potential conflict of interest relevant to this article was reported.

Author Contributions

Sonal Goyal (Conceptualization; Formal analysis; Methodology; Resources; Writing – original draft; Writing – review & editing)
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