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Systematic Review

Systematic Review of Radiofrequency Ablation and Pulsed Radiofrequency for Management of Cervicogenic Headache

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Background: Cervicogenic headache is a secondary headache that has a source in the upper cervical spine. There is a small but growing body of evidence to establish effectiveness of radiofrequency (RF) neurotomy, and the pulsed RF (PRF) procedure for management of cervicogenic headache.

Objective: To investigate the clinical utility of RF neurotomy, and PRF ablation for the management of cervicogenic headache.

Study Design: Systematic review.

Methods: The review included relevant literature identified through searches of PubMed, Cochrane, Clinical trials, U.S. National Guideline Clearinghouse and EMBASE from 1960 to January 2014.The quality assessment and clinical relevance criteria utilized were the Cochrane Musculoskeletal Review Group criteria for randomized control trials and the Newcastle-Ottawa Scale criteria for observational studies. The level of evidence was classified as good, fair, and poor based on the quality of evidence.

Outcomes Measured: The primary outcome measures were reduction in pain scores and improvement in quality of life.

Results: The primary outcome measures were headache relief and improved quality of life. Twenty five studies were identified for full text review of these, 9 studies met inclusion criteria. There were 5 non-randomized, among them 4/5 were of moderate quality, 3/5 showed RF ablation and 1/5 showed PRF as an effective intervention for cervicogenic headache. There were 4 randomized trials among them 2/4 were of high quality, 3/4 investigated RF ablation as an intervention for CHA, 1/4 investigated PRF ablation as an intervention for CHA and none of the randomized studies showed strong evidence for RF and PRF ablation as an effective intervention for CHA.

Limitations: In the selected studies there were inconsistencies between randomized trials, flaws in trial design, and gaps in the chain of evidence.

Conclusion: There is limited evidence to support RF ablation for management of CHA as there are no high quality RCTs and/ or multiple consistent non-RCTs without methodological flaws. There is poor evidence to support PRF for CHA as there are no high quality RCTs or Non-RCTs.

Key Words: Chronic pain, cervicogenic headache, radiofrequency (rf) neurotomy, pulsed radiofrequency (PRF) ablation, reduction in pain, improvement in quality of life, level of evidence

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Cervicogenic headache (CHA) was first described over 2 decades ago in 1983 (1). Despite acceptance of the clinical aspects of headache of cervical origin, good clinical diagnostic paradigms to guide clinicians in the interventional treatment of CHA are lacking. This is due to at least 2 reasons: 1) the overlap of symptomatology between migraine and CHA and 2) the lack of an easily applicable "gold standard diagnosis" for CHA (2). The Cervicogenic Headache International Study Group (CHISG) Diagnostic Criteria for CHA include (a) unilateral pain (although it is recognized that bilateral CHA may occur), (b) restriction of range of motion in the neck, (c) provocation of head pain by neck movement or sustained awkward neck positions, (d) provocation of head pain with external pressure over the upper cervical or occipital region on the symptomatic side, (e) usual vague ipsilateral nonradicular nature neck, shoulder, or arm pain, occasionally radicular, (f) confirmatory local anesthetic blocks in the cervical region, (g) patients should have had only a marginal response to ergotamines, triptans, or indomethacin, and (h) posterior onset of the headache pain seems to be an another important feature (2-4). The International Headache Society diagnostic criteria for CHA attributed to whiplash injury, another category of headache related to cervical spine structures, provide more flexibility (2).

1.0 Cervicogenic Headache

International Headache Society Diagnostic Criteria (5)

A. Pain referred from a source in the neck, but perceived in the head and/or face, fulfilling criteria C and D.
B. Clinical, laboratory, and/or imaging evidence of a disorder or lesion in the cervical region accepted as a valid cause of headache (Tumors, fractures, infections, and rheumatoid arthritis of the upper cervical spine are accepted; cervical spondylosis and myofascial tender points are not considered valid causes for these criteria).
C. Evidence that the neck problem is causing the pain, based upon
    1. Clinical signs that implicate a source of pain in the neck (No clinical signs are considered validated at present).

    And/or

    2. Abolition of headache by diagnostic (local anesthetic) blockade (There must be at least a 90% reduction in pain, and placebo or other adequate controls should be used).
D. Pain resolves within 3 months after successful treatment of the cervical lesion/disorder.

The CHA is a result of pain referred to the head from a source in the upper cervical spine and is seen in 4.1% of the population (4). There are many potentially painful structures in the neck with rich nociceptive innervation, such as the zygapophysial joints (z-joints), the intervertebral discs, the ligaments and muscles, and the skin (6). The C2-C3 z-joint is innervated by the third occipital nerve (TON) and is the most common cause, accounting for 70% of CHA, followed by the atlanto-axial (A-A) joint as the second common source for CHA (7). The other sources of CHA include the C2-C3 intervertebral disc, the atlanto-occipital (A-O) joint, and the C3-C4 z-joint (8). The several treatment options include medication, physical therapy, acupuncture, manipulation, injections, interventional procedures, and surgery (9). This systematic review will focus on radiofrequency (RF) neurotomy and pulsed RF procedure for the management of CHA.

1.1 Anatomy Review

The pars caudalis of the trigeminal nerve spinal nucleus is continuous longitudinally with the outer laminae (laminae I to V) of the dorsal horns of the upper 3 to 4 segments of the cervical spinal cord (10). Collectively, this column of gray matter constitutes the trigeminocervical nucleus (11). This nucleus is defined by its afferents and this column of gray matter, the trigeminal nucleus caudalis, receives second-order neuron afferents from the trigeminal nerve and any of the upper 3 cervical spinal nerves (12). Studies have described dural trigeminovascular nociception for migraine, including intravital microscopy and laser doppler flowmetry at the level of the vasculature, and electrophysiology and Fos techniques used to observe neuronal activation at the trigeminal nucleus caudalis (13). In monkeys it has been shown that the trigeminocervical nucleus extends caudally down to the C2-C3 level (14). This convergence leads to pain referral to the head from these cervical structures (Fig. 1) (10).

The anatomical convergence of pain fibers from the trigeminal nerve, including the ophthalmic division, and the upper cervical nerves is the basis for the referral of pain from the upper cervical region to the head including radiation to the frontal head regions (15). In both the trigeminal and cervical nerves (Fig. 1),

there is convergence of inputs of afferent nerve fibers from deeper structures and more superficial structures, allowing for the referral of pain to various parts of the head and neck from both the dura and deeper neck structures (16,17).

The pain referral patterns of the first 3 cervical spinal segments mainly include the head. Convergence between the spinal accessory nerve, trigeminal sensory descending tracts, and the upper cervical nerve roots can result in referred pain patterns between the neck and the trigeminal sensory receptive fields of the face and neck. The pain generators in the cervical spine are primarily the C2-C3 and C3-C4 z-joints (18,19), A-A joint, C2-C3 intervertebral disk (20), and the A-O joint (21).

1.1.1 C1

Through its dorsal ramus, C1 innervates the short muscles of the suboccipital triangle (22). Through C1 ventral ramus and the cervical plexus, it contributes to the innervation of the prevertebral muscles and to the sensory innervation of the sternocleidomastoid muscle and trapezius. Its ventral ramus passes behind and just below the A-O joint, to which it furnishes articular branches (Table 1) (20). The ventral ramus innervates the A-O joint, and its recurrent meningeal branch joins those from C2 and C3 to innervate the medial A-A joint and its ligaments and the dura mater of the upper cervical spinal cord. The C1, C2, and C3 sinuvertebral branches innervate the duramater over the clivus in the posterior cranial fossa (23).

1.1.2 C2

The ventral ramus of the C2 spinal nerve joins the cervical plexus, ultimately innervating the prevertebral muscles, the sternocleidomastoid muscle, and the trapezius, as well as the lateral A-A joint (7,22) (Fig. 2). The dorsal ramus innervates the splenius capitis and semispinalis capitis (24). The medial branch emerges from the semispinalis capitis to become the greater occipital nerve (GON), which supplies the skin over the occiput (Table 1) (20).

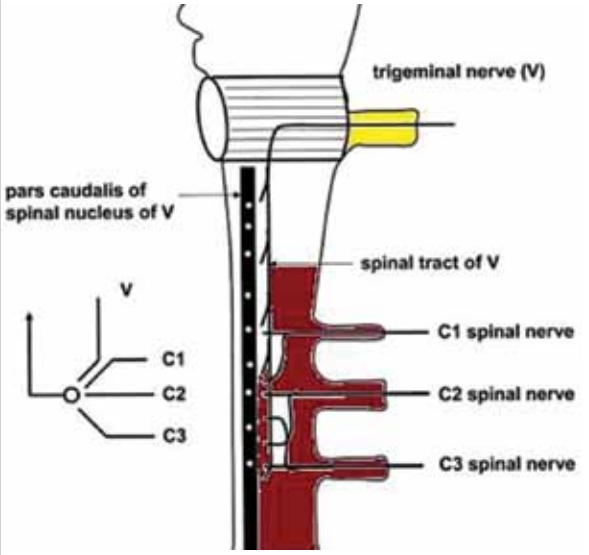

Fig. 1. A schematic representation of a longitudinal view of the brainstem and upper cervical spinal cord. Afferents of the trigeminal nerve descend through the spinal tract of the trigeminal nerve. Their collaterals terminate in the pars caudalis (10).

Table 1. *The possible sources of CHA, listed according to innervation and type of structures (20).*

	Innervation		
Structure	**C1**	**C2**	**C3**
Joints	Atlanto-occipital	Median Atlantoaxial	
		Lateral Atlantoaxial	C2-C3 zygapophyseal
			C2-C3 Disc
Muscles	Suboccipital	Prevertebral; sternocleidomastoid, trapezius	
		Semispinalis, splenius	
			Multifidus; semispinalis
Ligaments	Transverse atlantoaxial and alar; membrana tectoria		
Arteries	Vertebral; internal carotid		
Dura	Upper spinal cord; posterior cranial fossa		

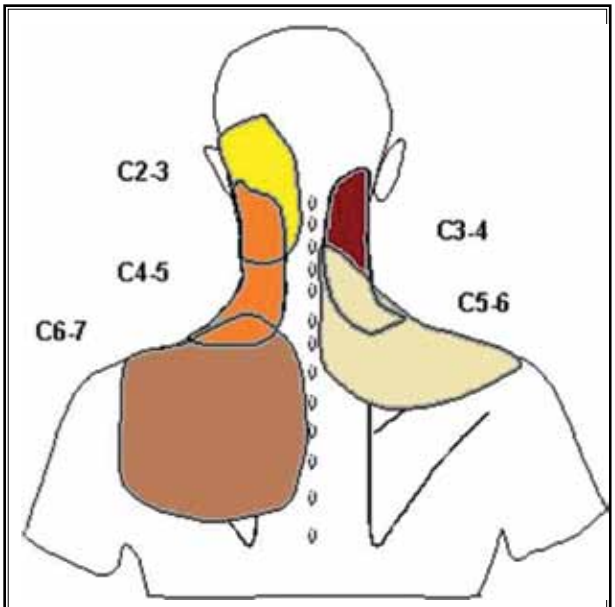

Fig. 2. *The patterns of referred pain from the cervical zygapophysial joints (7).*

1.1.3 C3

The ventral ramus of C3 joins the cervical plexus and innervates the prevertebral muscles. The dorsal ramus of C3 innervates various posterior neck muscles with the exact innervation having some variation (22). Its lateral branch is distributed to the splenius capitis and cervicis and to the longissimus capitis. Its deep medial branch supplies the semispinalis cervicis and multifidus. Its superficial medial branch, known as the TON, supplies the semispinalis capitis and becomes cutaneous over the suboccipital region (Fig. 2) (7). It innervates the C2-C3 z-joint with a sinuvertebral branch that innervates the C2-C3 intervertebral disk (Table 1) (20). The TON wraps around the lateral and posterior aspects of the C2-C3 z-joint, ending in the fascia around the joint capsule, and thus supplying innervation to the joint. The dorsal ramus of C3 is the lesser occipital nerve (23).

Investigators have injected the A-O and lateral A-A joints and reproduced pain in the occipital and suboccipital areas (21); pain from the lateral A-A joint can refer to the vertex, orbit, and ear (18). It has been shown that the C2-C3 z-joint can produce pain in the occipital area (Fig. 2) (7,24), while other studies have demonstrated that pain originating at C2-C3 z-joint can spread across the parietal area to the frontal area around the orbits (18). Additionally, noxious stimulation of the C2-C3 intervertebral disk can provoke pain that radiates to the occipital area (25,26).

1.2 Interventional Management

Patients who have not improved with conservative management such as activity modification, physical and manual therapies, and oral/transdermal medication trials are considered candidates for injection therapies. Interventional pain management procedures can be diagnostic and/or therapeutic. Anesthetic blocks to the medial branch of the dorsal ramus (diagnostic), intra-articular z-joint corticosteroid injections (diagnostic), the medial branch of the dorsal ramus area corticosteroid injections (therapeutic), RF ablation of the pain generator dorsal root medial branches (therapeutic), and pulsed RF (therapeutic) have been used. These cervical spine procedures require imaging guidance (such as real-time fluoroscopy and use of contrast media) to ensure correct placement of the injectate and/or probe at the target structure (27).

Interventional pain management procedures in general are associated with risks such as infection, radiation exposure, corticosteroid side effects, and structural damage from placement of the spinal needle. Z-joint injections are generally regarded as being relatively safe procedures because the needle is accessing elements of the spine outside of the spinal canal, even though there is the potential complication for the needle to pass through a joint and contact the traversing nerve root. Additional precaution is required for lateral A-A (C1-C2) joint injections, as there is a risk of injury to the vertebral artery and the C2 spinal nerve (27).

1.2.1 Radiofrequency Ablation

Percutaneous RF ablation (RFA) of the cervical medial branch and TON neurotomy is the most-researched interventional treatment for CHA (8,28). The purpose of RFA of the cervical medial branch nerve and TON is destruction of the afferent nerve supply that is considered as a pain generator for the CHA. To create a thermal lesion with monopolar RFA, the ground plate, with a large surface area is applied to the body. The procedure is performed by placing a needle probe directly at the target site (Fig. 3) (29). The electrode is insulated along its length; the terminal tip distance 2 – 10 mm is saved (12). An alternating current in the frequency range of 100 – 500 kHz is applied continuously to a target, with the aim of producing thermal injury at the target nerve by causing coagulation of the medial branch (29- 31).

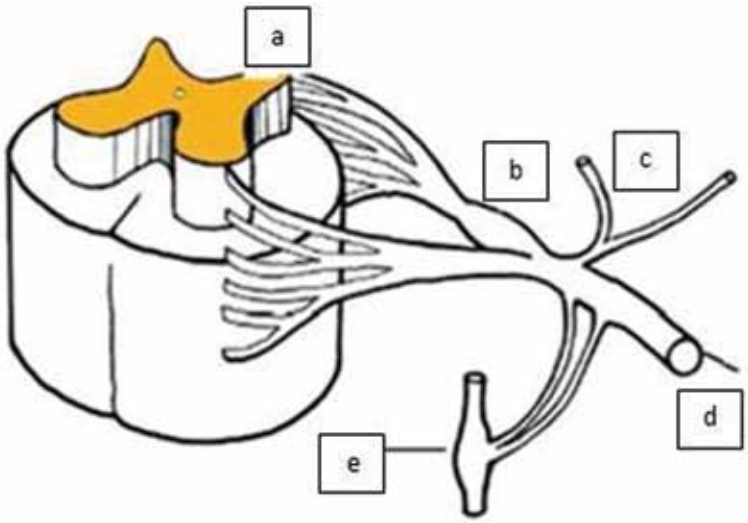

Fig. 3. *Target sites for RF therapies: (a) dorsal root entry zone, (b) dorsal root ganglion, (c) medial branch of dorsal ramus, (d) peripheral nerves, and (e) sympathetic ganglia (29).*

Lesion diameter depends on the size of the electrode in general; the lesion will spread 1 – 1.5 times the electrode diameter. Heating of the tissues sufficient to cause coagulation occurs when the electrode temperature reaches 60 – 65°C (29). If a higher temperature of 80 – 85°C is established at the surface of the electrode, tissues within a few millimeters of the electrode will be heated to 60 – 65°C or more (12).

The electrode is positioned tangential to the target nerve to produce the optimal lesion. Thermal equilibrium occurs as the needle tip reaches its target temperature and therefore optimal lesion size, occurs after 60 – 90 seconds (29,32,33). Anatomic variability in the course of a nerve (33) should be taken into consideration. Investigators have advocated needle placement parallel to the nerve with multiple lesions placed in series to adequately cover the common anatomic locations of the target neural structures (10,28). The size of the TON requires modification of the neurotomy procedure as described by Boduk et al in which multiple lesions at the C2-C3 joint line in sagittal plane are created resulting in adequate coagulation and ablation of the nerve (10,28). RFA has not been shown to be selective for any specific nerve type, but creates lesions of both motor and sensory nerves at the described temperatures; therefore, caution in using ablation must be exercised (32,34, 35).

1.2.2 Pulsed Radiofrequency

Pulsed RF similarly involves placement of a heat/RF probe at a targeted neural structure. RF energy is applied intermittently (in a pulsatile fashion). High-voltage RF current is generally applied in short bursts, thus allowing dissipation of heat in between application phases. Temperature control is maintained at a level at which neuronal destruction generally does not occur (36). Even though the exact mechanism is not entirely clear, the applied energy results in temporary neuromodulation of pain transmission and morphologic changes in the tissue under an electron microscopy have been identified (37,38).

The literature cited above indicates that CHA can be treated by various approaches based on the patient populations. Based on the available literature, the primary objective of this review is to measure the effectiveness of CHA relief and improved quality of life with RF and pulsed RFA. Some of the older systematic reviews have documented insufficient evidence for the use of RF facet denervation in the management of CHA (39); definite conclusions about the clinical efficacy of the treatment of CHA by means of RF procedures can only be drawn from randomized controlled trials (RCTs) (40). The most recent review has stated, RF neurotomy may provide the most sustained relief of CHA symptoms, although the relief typically is not permanent

(23). Consequently, the primary aim of this systematic review is to update and determine the effectiveness of RF and pulsed RFA for CHA. This review is unique because it is rare that systematic reviews have performed methodological quality assessment for CHA. This review will enrich our understanding of the role of RF and pulsed RFA for the CHA population, so that the CHA patients can be effectively managed by interventional procedures.

2.0 Methods

The methodology utilized in this systematic review followed the review process derived from evidence-based systematic reviews and meta-analysis of randomized trials and observational studies (41- 47), Cochrane guidelines (45,46,48), Standards for Reporting Observational Studies (STROBE) (49), and quality of reporting of analysis (41).

2.1 Criteria for Considering Studies for This Review

2.1.1 Types of Studies

RCTs and prospective non-randomized, case-control, cohort, and cross-sectional studies in English language were included. Case reports, case series, book chapter, and reviews were excluded.

2.1.2 Type of Participants

Adult (18+ years to 80 years) patients with cervicogenic pain

2.1.3 Types of Intervention

RFA, pulsed RFA

2.1.4 Types of Outcomes

The primary outcome measures were reduction in pain scores and improvement in quality of life.

2.2 Search Methods for Identification of Studies

A computerized search was conducted for English articles published between 1960 and March 2014 in the following databases.

1. PubMed from www.ncbi.nlm.nih.gov/pubmed
2. EMBASE from www.embase.com/
3. Cochrane Library www.thecochranelibrary.com/
4. U.S. National Guideline Clearinghouse (NGC) www.guideline.gov
5. Clinical Trials www.clinicaltrials.gov

2.3 Search Strategy

Key words and combinations of key words were used to search the electronic databases and were organized following the Population Intervention Control Outcome (PICO) model. Different combinations of the topics were made with the use of AND, OR, and NOT in order to achieve a specific selection of literature. Together with the databases, the reference lists in the articles were scanned separately for relevant publications. Independent selections in 3 categories (irrelevant, possibly relevant, and relevant) were made by 2 researchers after they read the full texts.

2.4 Data Collection and Analysis

The review focused on randomized trials and case-control, prospective, cohort, and cross-sectional studies. The population of interest was patients suffering from CHA and failed conservative management. The studies providing appropriate study design, statistical evaluations, and with outcome evaluations were reviewed. Reports without appropriate diagnosis, systematic reviews, book chapters, case series, and case reports were excluded from review.

2.4.1 Selection of Studies

In an unblinded standardized manner, 2 review authors screened the abstracts of all identified studies against the inclusion criteria. Any disagreements between reviewers were resolved by a third author (AA) for consensus. All articles with possible relevance were then retrieved in full text for a comprehensive assessment of internal validity, quality, and adherence to inclusion criteria. Later only the relevant articles were selected for qualitative and quantitative analysis.

2.4.2 Inclusion and Exclusion Criteria

Inclusion Criteria

Studies with patients with CHA; English language studies; randomized control studies; and prospective non-randomized, case-control, cohort, and cross-sectional studies that provided appropriate outcome evaluations and appropriate statistical analysis were included.

Exclusion Criteria

Headaches types such as migraine, tension, and cluster were excluded. Animal studies or studies on children or non-English language studies, case series and case reports, reviews, and book chapters were excluded.

2.4.3 Clinical Relevance

The clinical relevance of the included studies was evaluated according to 5 questions recommended by the Cochrane Back Review Group (45). Each question was scored as positive (+) if the clinical relevance item was met, negative (–) if the item was not met, and unclear (?) if data were not available to answer the question. Thirteen studies were assessed for clinical relevance.

2.4.4 Validity Assessment

The quality of each individual article used in this analysis was assessed by Cochrane review criteria (Table 2) (45) for randomized trials. Studies achieving Cochrane scores of 9 or higher would be considered as high quality, scores of 6 to 8 considered as moderate quality, and studies scoring less than 6 as low quality (45). The Based on the Newcastle-Ottawa Scale for case control and cohort studies (Table 3) (49), studies achieving scores of 67% or higher were considered high quality, 50% or higher were considered as moderate quality, and studies scoring less than 50% were considered low quality (50,51).

2.5 Analysis of Evidence

The analysis of the evidence was performed based on United States Preventive Services Task Force (USPSTF) criteria which have been utilized by multiple authors (47,51). The analysis was conducted using 3 levels of evidence: good, fair, and limited or poor (Table 4). At least 2 of the review authors independently, in an unblinded standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus.

2.6 Outcome of the Studies

In the randomized trials, a study was judged to be positive if the interventions provided headache

Table 2. *Assessing the sources of risk of bias in randomized control trial studies (n = 4). P – Positive; N – Negative, and U – Unclear; Scoring adapted from Furlan AD et al., 2009 (45). Methodological quality assessment of the RCTs meeting inclusion criteria was carried out. Studies achieving Cochrane scores of 9 or higher were considered as high quality, scores of 6 to 8 were considered as moderate quality, and studies scoring less than 6 were excluded.*

	PRFA	**RFA**		
	Gabrhelík et al, 2011 (52)	Stovner et al, 2004 (53) (*)	Haspeslagh et al, 2006 (54)	Lord et al, 1996 (55) (*)
A) 1. Was the method of randomization adequate?	+	+	+	+
B) 2. Was the treatment allocation concealed?		+		+
C) Was knowledge of the allocated interventions adequately prevented during the study?				
3. Was the patient blinded to the intervention?	+	+		+
4. Was the care provider blinded to the intervention?		+	+	+
5. Was the outcome assessor blinded to the intervention?				
D) Were incomplete outcome data adequately addressed?				
6. Was the drop-out rate described and acceptable?	+	+	+	+
7. Were all randomized participants analyzed in the group to which they were allocated?	+	+	+	+
E) 8. Are reports of the study free of suggestion of selective outcome reporting?	+		+	+
F) Other sources of potential bias:				
9. Were the groups similar at baseline regarding the most important prognostic indicators?	+		+	+
10. Were co-interventions avoided or similar?		+	+	+
11. Was the compliance acceptable in all groups?	+		+	+
12. Was the timing of the outcome assessment similar in all groups?	+	+	+	+
Total	8	8	9	11

(*) = Due to low CHA population in study has been considered as poor evidence for CHA. RFA- radio-frequency ablation; PRFA – Pulsed radio-frequency ablation

Table 3. *Methodological quality assessment for cohort studies (n = 5) utilizing Newcastle-Ottawa quality assessment scale. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of 2 stars can be given for comparability.*

	RFA				PRFA
	Govind et al, 2003	**van Suijlekom et al, 1998**	**Hamer and Purath, 2014**	**Lee et al, 2007**	**Halim et al, 2010**
Selection					
1) Representativeness of the exposed cohort					
a) truly representative of the average (describe) in the community*					
b) somewhat representative of the average pain patients in the community *	*	*	*	*	*
c) selected group of users (e.g. nurses, volunteers)					
d) no description of the derivation of the cohort					
2) Selection of the non-exposed cohort					
a) drawn from the same community as the exposed cohort *					
b) drawn from a different source					
c) no description of the derivation of the non-exposed cohort					
3) Ascertainment of exposure					
a) secure record (e.g. surgical records) *	*	*	*	*	*
b) structured interview *	*	*		*	*
c) written self-report					
d) no description					
4) Demonstration that outcome of interest was not present at start of study					
a) yes *	*	*	*	*	*
b) no					
5) Comparability of cohorts on the basis of the design or analysis					
a) study controls for (select the most important factor) *					
b) Study controls for any additional factor * (Criteria could be modified to indicate specific control for a second important factor.)					
Outcome (Exposure)					
1) Assessment of outcome					
a) independent blind assessment *					
b) record linkage *	*	*	*	*	*
c) self-report					
d) no description					
2) Was follow-up long enough for outcomes to occur					
a) yes (select an adequate follow-up period for outcome of interest) *	*	*	*	*	*
b) no					
3) Adequacy of follow up of cohorts					
a) complete follow-up - all subjects accounted for *		*	*	*	*
b) subjects lost to follow-up unlikely to introduce bias - small number lost - > 25% (select an adequate %) follow-up, or description provided of those lost) *	*				
c) follow-up rate < % (select an adequate %) and no description of those lost					
d) no statement					
SCORE	**7/13**	**7/13**	**6/13**	**7/13**	**7/13**

RFA – radio-frequency ablation; PRFA – Pulsed radio-frequency ablation {Halim only has 6 stars.}

Table 4. *Method for grading overall strength of systematic review*

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least 2 consistent, higher-quality RCTs or studies of diagnostic test accuracy).
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least one higher-quality trial or study of diagnostic test accuracy of sufficient sample size; 2 or more higher-quality trials or studies of diagnostic test accuracy with some inconsistency; at least 2 consistent, lower-quality trials or studies of diagnostic test accuracy, or multiple consistent observational studies with no significant methodological flaws).
Limited or poor	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Based on USP-STF criteria (47,51)

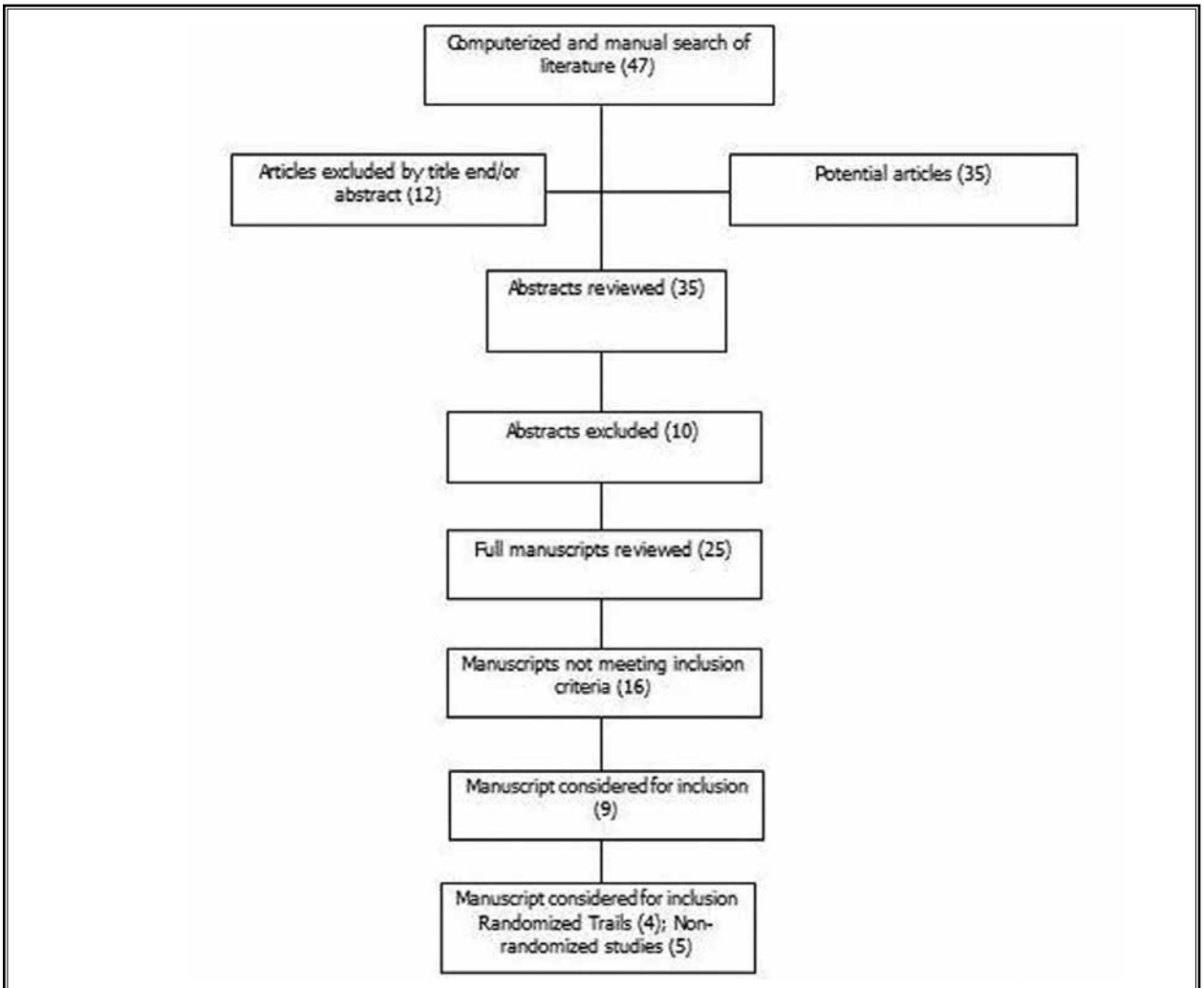

Fig. 4. *The flow chart based on study selection recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Search strategy. After discussion, there was a 100% final consensus among the 3 researchers.*

relief and improved quality of life. For observational studies, a study was judged to be positive if the interventions provided headache relief and improved quality of life.

3.0 Results

3.1 Methodological Quality Assessment

The flowchart (Fig. 4) gives an overview of the literature search protocol and is based on study selection recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (43). Twenty-five studies were identified for full text review, of these, 9 studies met inclusion criteria. There were 4 RCTs (52-55) among them 2 were of high quality (54, 55); 3 investigated RFA as an intervention for CHA (53-55); and 1 investigated pulsed RFA as an intervention for CHA (52) (Tables 2-3). Among the 2 high quality studies one study (54) found that there is no evidence that radiofrequency neurotomy (RFN) of cervical facet joints and upper dorsal root ganglion (DRG) is a better treatment than the infiltration of the GON, followed by transcutaneous electrical nerve stimulation (TENS). Whereas another high quality study (55) had a low number of CHA patients. There were 5 non-randomized (28,56-59), among them 4 were of moderate quality (28,56,58,59), 3 showed RFA (28,56,58), and 1 showed pulsed RF (59) as an effective intervention for CHA (Tables 3, 5). The RF and pulsed RF treatment were considered as independent variable and headache and quality of life improvement were considered as dependent variables.

Methodological quality assessments of RCTs and observational studies meeting inclusion criteria have been illustrated in Tables 2 and 3.

Table 5. Detailed description of all the 4 randomized trials.

Study	Participants	Demography	Intervention	Control group	Follow-up	Outcome measured	Result(s)	Conclusion(s)
RF ABLATION								
RANDOMIZED								
Lord et al, 1996 (55) (*) Randomized, double-blind trial	24 patients (9 men and 15 women; mean age, 43 years) who had one or more CZJP after an automobile accident (median duration of pain, 34 months)	Treatment Gp Age yr: (44 ± 12) Gender: 5/7 Employed: 4 Involved in litigation: 4 mts of pain: 44 (23-94) VAS score: 40 ± 15; McGill Questionnaire Pain rating: 37 ± 19; Total word count: 14 ± 5; Control Gp Age yr: (43 ± 12) Gender: 4/8 Employed: 7 Involved in litgation: 10 mts of pain: 34 (25-92) VAS score: 47 ± 18 McGill Questionnaire Pain rating: 32 ± 16 Total word count: 12 ± 5	RFN of multiple lesions were made and the temperature of the electrode making the lesions was raised to 80°C with a control treatment using an identical procedure except that the radio-frequency current was not turned on.	Yes	Yes, patients followed by telephone interviews and clinic visits until they reported that their pain had returned to 50 percent of the pre-RFN level.	100 mm VAS, McGill Pain Questionnaire, 4 ADLs affected by pain, SCL-90-R	The median time that elapsed before the pain returned to at least 50 percent of the preoperative level was 263 days in the active-treatment group and 8 days in the control group (P = 0.04). At 27 weeks, 7 patients in the active-treatment group and one patient in the control group were free of pain. Five patients in the active-treatment group had numbness in the territory of the treated nerves, but none considered it troubling.	In patients with chronic CZJP confirmed with double-blind, placebo-controlled local anesthesia, percutaneous RFN with multiple lesions of target nerves can provide lasting relief.

Years – yrs; Weeks –Wk; Months – mts; RF – radio-frequency; PRF – Pulsed radio-frequency; RFN –radiofrequency neurotomy; CHA – cervicogenic headache; CZJP – cervical zygapophysial joint pain; CZJ – cervical zygapophysial joint; VRS – Verbal Rating Scale, PT – Physical Therapy; TENS – Transcutaneous electrical nerve stimulation; VAS- visual analogue scale; MQS – Medication Quantification Scale; BMI – Body Mass Index; DRG – dorsal root ganglion; GON – greater occipital nerve. (*) = Due to low CHA population in study has been considered as poor evidence for CHA

Table 5 (cont.). Detailed description of all the 4 randomized trials.

Study	Participants	Demography	Intervention	Control group	Follow-up	Outcome measured	Result(s)	Conclusion(s)
Stovner et al, 2004 (53) (*) Randomized, double-blind study	Twelve patients with a disabling, long-standing and treatment resistant strictly unilateral CHA. The diagnosis was based on purely clinical criteria. Six were randomized to receive RFN of facet joints C2-C6 ipsilateral to the pain, and 6 were randomized to sham treatment Gender: 6 males, 6 females	RF Men/women: 3/3 Median age yr: 44.5 (34–52) Involved in litigation: 3 Yrs from diagnosis to inclusion: 5.0 (2–10) Days with significant headache per 2 wks prior to treatment: 14 (7–14) Sham Men/women: 3/3 Median age yr: 52.5 (41–64) Involved in litigation: 1 Yrs from diagnosis to inclusion: 6.0 (2–50) Days with significant headache per 2 wks prior to treatment 12 (5–14)	Blockades of the GON on symptomatic side were performed before inclusion. Cervical RFN of medial branch were performed on facet joints C2-6 on the symptomatic side.	Yes	Yes, followed for 2 yrs with diary registration of pain for 14-day periods after 1, 3, 6, 12, 18, and 24 mts, and also followed with algometry and neck mobility measurements at 3, 12, and 24 mts	Days of intense headache Hours with pain Days with headache Neck pain days Shoulder/arm pain days Headache intensity Neck pain intensity Shoulder/arm pain intensity Analgesics intake Neck flexion/extension Neck lateral flexion Neck rotation Algometry	Side effects were minor and short .lasting, and those patients who were treated with RFN were somewhat improved at 3 mts, but later there were no marked differences between the groups.	The procedure is probably not beneficial in CHA
Haspeslagh et al, 2006 (54) Randomized controlled study	30 patients with CHA according to the Sjaastad diagnostic criteria were randomized to Group I: RFN lesion of the medial branches of the posterior primary rami of the facet joints C3–C4, C4–C5, and C5–C6. Group II: injection with local anesthetic of the GON on the affected side.	RFN Mean age (SD) [min/max] (yr) 47,5 (11,0) [22/62] Men/women (n) 4/11 Duration of pain (yr) 9,7 Control Mean age (SD) [min/max] (yr) 49,1 (12,8) [28/64] Men/women (n) 4/11 Duration of pain (yr) 6,6	Fifteen patients received a sequence of RFN (cervical facet joint denervation, followed by cervical DRG lesions when necessary), and another 15 patients underwent local injections with steroid and anesthetic at GON, followed by TENS when necessary.	Yes	Yes	VAS for pain, global perceived effects scores, quality of life scores were assessed at T0, T1 (8 wks), T2 (16 wks), T3 (6 mts), and T6 (12 mts). Patients also kept a headache diary. Primary outcome measure (pain and global perceived effect at 8 weeks) and also in the secondary outcome parameters, at any given time point in the study	There were no statistically significant differences between the 2 treatment groups at any time point in the trial.	No evidence that RFN of cervical facet joints and upper DRG is a better treatment than the infiltration of the GON, followed by TENS for patients fulfilling the clinical criteria of CHA.

Years – yrs; Weeks –Wk; Months – mts; RF – radio-frequency; PRF – Pulsed radio-frequency; RFN –radiofrequency neurotomy; CHA – cervicogenic headache; CZJP – cervical zygapophysial joint pain; CZJ – cervical zygapophysial joint; VRS – Verbal Rating Scale, PT – Physical Therapy; TENS – Transcutaneous electrical nerve stimulation; VAS- visual analogue scale; MQS – Medication Quantification Scale; BMI – Body Mass Index; DRG – dorsal root ganglion; GON – greater occipital nerve. (*) = Due to low CHA population in study has been considered as poor evidence for CHA

Table 5 (cont.). Detailed description of all the 4 randomized trials.

Study	Participants	Demography	Intervention	Control group	Follow-up	Outcome measured	Result(s)	Conclusion(s)
PRF ABLATION								
RANDOMIZED								
Gabrhelík et al, 2011 (52) Blind, randomized clinical pilot study	30 patients (13 men, 17 women) suffering from refractory CHA. Patients were randomly allocated into 2 groups of 15.	Group A Gender (M/F): 7/8 Age (yrs): 45.90 (12.8) [22–73] BMI kg/m2: 27.61 (3.10) [23.60–32.80] VAS before treatment: 5.50 (1.13) [4–7] MQS before treatment: 8.88 (2.98) [4.8–14.8] Group B Gender (M/F): 6/9 Age (yrs): 43.60 (9.2) [28–65] BMI kg/m2: 27.14 (3.15) [20.4–32.4] VAS before treatment: 5.90 (1.2) [4–8] MQS before treatment: 9.05 (2.93) [4.6–13.6]	GON block with steroid was utilized in group A, while a PRF treatment was employed in group B.	No	Yes	Success of both procedures was evaluated by comparing pre and post interventions VAS of pain, MQS - III and Global Perceived Effect at 3 and 9 minutes after the procedures.	At 3 mts post therapy a significant decrease in VAS ($P < 0.001$) was identified (3.2 points in group A, 3.3 points in group B respectively). In group B pain remained reduced even after 9 mts ($P < 0.001$) when compared to pretreatment scores. The consumption of analgesic medication was reduced significantly in both groups at three mts ($P < 0.001$) and 9 mts ($P < 0.01$). No serious complication	GON block is a safe, efficient technique in the management of CHA.

Years – yrs; Weeks –Wk; Months – mts; RF – radio-frequency; PRF – Pulsed radio-frequency; RFN –radiofrequency neurotomy; CHA – cervicogenic headache; CZJP – cervical zygapophysial joint pain; CZJ – cervical zygapophysial joint; VRS – Verbal Rating Scale, PT – Physical Therapy; TENS – Transcutaneous electrical nerve stimulation; VAS- visual analogue scale; MQS – Medication Quantification Scale; BMI – Body Mass Index; DRG – dorsal root ganglion; GON – greater occipital nerve. (*) = Due to low CHA population in study has been considered as poor evidence for CHA

3.2 Study Characteristics

A detailed description of all nine studies can be seen in Tables 5-7, and a list of excluded studies (23,39,40, 60-70) is provided in Table 8. There are 3 RCTs and 4 non-RCTs investigating RF on CHA. There is one RCT and one non-RCT investigating pulsed RF on CHA. The 4 RCTs were analyzed for risk of bias using Cochrane criteria (Table 2) and the 5 non- RCTs were analyzed for methodological quality using the Newcastle-Ottawa quality assessment scale (Table 3).

3.3 Clinical Relevance

Clinical relevance of the selected articles was based on effectiveness of RF and pulsed RF for CHA, based on patient description, description of interventions and treatment settings, clinically relevant outcomes, and clinical importance and benefits versus potential harms. Six of 9 studies met the criteria (Table 5).

3.4 Analysis of Evidence

The evidence was synthesized based on the USPSTF criteria (47,51) as shown in Table 4. There are no high quality studies to show good evidence for better outcomes of RFA for CHA. There is limited evidence as there are no high quality studies to support RF and pulsed RF as effective interventions for CHA.

Table 6. *Detailed description of the 5 non-randomized trials.*

Study	Participants	Demography	Intervention	Control group	Follow-up	Outcome measured	Result(s)	Conclusion(s)
RF ablation NON-RANDOMIZED								
Govind et al, 2003 (28) Prospective study	Forty-nine patients diagnosed as suffering from third occipital headache, 51 nerves	Men (n) 21 Median age (years) 41 Women (n) 28 Median age (years) 45 Median pain intensity 80 Median duration of symptoms (months) 24 Range (months) 6 to 240 Compensation claim 33	RF neurotomy for third occipital headache	No	No	Primary outcome – complete relief of pain, such that the patient did not require any drug treatment or other treatment for their headache. Secondary outcome was patient had resumed normal daily activities unaffected by headache. Other outcomes were any side effects that the patient attributed to the operation.	Forty-three (88%) achieved successful outcome. Median duration of relief in these patients was 297 days, with 8 patients continuing to have ongoing relief. Fourteen patients underwent a repeat neurotomy to reinstate relief, with 12 (86%) achieving a successful outcome.	RF neurotomy greatly improved the low success rate previously encountered with third occipital neurotomy. Although the relief of headache is limited in duration, it is profound and can be reinstated by repeat neurotomy.
van Suijlekom et al, 1998 (56) Prospective study	Fifteen patients with CHA were treated and then assessed one wk prior to treatment and, at short-term (8 wks), intermediate (mean 8.8 mts), and long-term (mean 16.8 mts) follow-ups.	Men: 4 (33-68 yrs); Women: 11 (25-65 yrs); Duration of pain in mts: 6 to >60 CHA: unilateral -12; Bilateral - 3	RFN of CZJ	No	Yes	VAS, 7-point VRS, number of headache days per week and analgesic intake per week	The RFN of CZJ significantly reduced headache severity in 12 (80%) patients, both at short-term and long-term follow-up assessed by 7-point VRS. Mean VAS decrease was 31.4 mm ($P < 0.001$) and 53.5 mm ($P < 0.0001$) respectively in this period. The average mean number of headache days per wk decreased from 5.8 days to 2.8 days ($P = 0.001$) and average analgesic intake per wk showed a reduction from mean of 17.5 tablets to mean of 3.4 tablets ($p = 0.003$).	Definitive conclusion about the clinical efficacy of this treatment can only be drawn from a randomized controlled trial.

Years – yrs; Weeks – Wk; Months – mts; RF – radio-frequency; PRF – Pulsed radiofrequency; RFN – radiofrequency neurotomy; CHA – cervicogenic headache; CZJP – cervical zygapophysial joint pain; CZJ – cervical zygapophysial joint; VRS – Verbal Rating Scale, PT – Physical Therapy; TENS – Transcutaneous electrical nerve stimulation; VAS – visual analogue scale; MQS – Medication Quantification Scale; BMI – Body Mass Index; DRG – dorsal root ganglion; GON – greater occipital nerve

Table 6 (cont.). *Detailed description of the 5 non-randomized trials.*

Study	Participants	Demography	Intervention	Control group	Follow-up	Outcome measured	Result(s)	Conclusion(s)
Hamer and Purath, 2014 (57) Retrospective observational study	Forty patients with refractory CHA and or occipital neuralgia	Average age 46.9 years with a female to male ratio of 39:5. Prior to treatment, 30 of the included patients (75%) self-reported migraine headaches. Ten patients (25%) self-reported a history of whiplash injury; one patient had an established diagnosis of fibromyalgia	RFN of the C2 DRG and/or third occipital nerves	No	Yes. After treatment, patients were followed for a minimum of 6 mts to a yr.	Patient demographics and the results of RFN were recorded on the same day, after 3-4 days, and at 6 mts to 1 yr following treatment. % Pain Reduction; Duration (wks) of pain reduction; Complications	35% of patients reported 100% pain relief and 70% reported 80% or greater pain relief. The mean duration of improvement is 22.35 wks. Complication rate was 12-13%. 92.5% of patients reported they would undergo the procedure again if severe symptoms returned.	RFN of the C2 DRG and/or third occipital nerve can provide many mts of greater than 50% pain relief in the vast majority of recipients with an expected length of symptom improvement of 5-6 mts.
Lee et al, 2007 (58) Prospective observational study	Thirty patients suffering from chronic CHA for longer than 6 mts and showing a pain relief by greater than 50% from diagnostic/ prognostic blocks	Gender (men:women) 16:14 Mean age 54 yrs Preoperative VAS 6.8 Average number of headache-day/wk (mean) preoperative 6.2	RFN of CZJ in patients with CHA	No	Yes, assessed at 1 wk, 1 mt, 6 mts, and at 12 mts	VAS, number of headache-days per wk and amount of analgesic intake per wk. Results were defined as successful if preoperative pain was relieved by more than 75%.	RFN of the CZJ significantly reduced the headache severity in 22 patients (73.3%) at 12 mts after the treatment. Number of patients showed pain relief by greater than 75% at 1 wk - 18 (60.0%) 1 mt - 25 (83.3%) 6 mts - 23 (76.7%) 12 mts - 22 (73.3%) Average number of headache-day/wk Postoperative 2.8 Reduction of analgesic intake/ wk 70%	RFN of CZJ has shown to provide substantial pain relief in patients with chronic CHA when carefully selected.
PRFA NON-RANDOMIZED								
Halim et al, 2010 (59) Retrospective study	Eighty-six patients who had undergone lateral C1-2 joint PRF application, for CHA in a single pain center from March 2007 to December 2008	Men - 37% (32/86); Women - 63% (54/86) Age (yrs) Mean ± SD: 50 ± 2.1 Duration of headache (yrs) Mean ± SD: 9.4 ± 1.1 VAS before C1-2 PRF Mean ± SD: 8.5 ± 0.1 History of previous percutaneous interventions: 90.7% (78/86) Insurance claims: 48.8% (42/86)	The C1-2 PRF application was performed using the intra-articular anterolateral approach under fluoroscopic guidance.	No	Yes	Percentage of patients who had ≥ 50% pain relief at 2 mts, 6 mts, and 1 yr.	The percentage of patients who had ≥ 50% pain relief at 2 mts, 6 mts, and 1 yr were 50% (43/86), 50% (43/86), and 44.2% (38/86), respectively. Long-term pain relief at 6 mts and 1 yr were predicted reliably by ≥ 50% pain relief at 2 mts ($P < 0.001$). Apart from one patient that complained of increased severity of occipital headache lasting several hrs, no other reported complications.	PRF application of the lateral C1-2 facet joint is a feasible and safe technique in patients with CHA that are nonresponsive to other techniques such as RFN of lower cervical facet joints and cervical epidural injections. However, further prospective trials are required to validate.

Years – yrs; Weeks – Wk; Months – mts; RF – radio-frequency; PRF – Pulsed radiofrequency; RFN – radiofrequency neurotomy; CHA – cervicogenic headache; CZJP – cervical zygapophysial joint pain; CZJ – cervical zygapophysial joint; VRS – Verbal Rating Scale, PT – Physical Therapy; TENS – Transcutaneous electrical nerve stimulation; VAS – visual analogue scale; MQS – Medication Quantification Scale; BMI – Body Mass Index; DRG – dorsal root ganglion; GON – greater occipital nerve

Table 7. *All nine studies with methodological scores, design, results and review outcome.*

Study	Study Design	MQ Score	Participants	Outcomes tested	Results
Radiofrequency Ablation					
Lord et al, 1996 (55) (*)	Randomized, double-blind study	11	12 pts received percutaneous RFN in multiple lesions made, temperature of electrode raised to 80 deg C with 12 controls an identical procedure except that RF current was not turned on	100-mm VAS, McGill Pain Questionnaire, four ADLs affected by pain, SCL-90-R	P(*)
Stovner et al, 2004 (53) (*)	Randomized, double-blind study	8	6 pts were randomized to RFN of facet joints C2-C6 ipsilateral to the pain, and 6 pts were to sham treatment.	Days with intense headache; hrs with pain; Neck, Shoulder/arm pain days; Headache, Neck, Shoulder/arm pain intensity; Analgesics intake; Neck flexion/extension, lateral flexion and rotation; Algometry	N(*)
Haspeslagh et al, 2006 (54)	Randomized controlled study	9	15 pts received sequence of RFN (cervical facet joint denervation, followed by cervical DRG lesions when necessary), and 15 control pts underwent local injections with steroid and anesthetic at GON, followed by TENS.	VAS for pain, GPE scores, quality of life scores were assessed at T0, T1 (8 wks), T2 (16 wks), T3 (6 mts), and T6 (12 mts).	N
Govind et al, 2003 (28)	Prospective study	7/13	49 pts RFN for third occipital headache	Primary- complete relief of pain Secondary- pt had resumed normal daily activities. Other outcomes - side effects	P
van Suijlekom et al, 1998 (56)	Prospective study	6/13	15 pts with CHA were treated with RFN of CZJ	VAS, 7-point VRS, number of headache days per wk & analgesic intake per wk	P
Hamer and Purath, 2014 (57)	Retrospective observational study	6/13	40 pts with refractory CHA and or occipital neuralgia	% Pain Reduction; Duration (wks) of pain reduction; Complications on the same day, after 3-4 days, and at 6 mts to 1 yr following treatment	P
Lee et al, 2007 (58)	Prospective observational study	7/13	30 pts suffering from chronic CHA for longer than 6 mts got RFN of CZJ	VAS, number of headache-days per wk and amount of analgesic intake per wk	P
PRF Ablation					
Gabrhelík et al, 2011 (52)	Blind, randomized clinical pilot study	8	A GON block with steroid was utilised in gp A (15 pts), pulsed RF treatment was employed in gp B (15 pts).	VAS of pain, MQS - III and GPE at 3 and 9 mts after the procedures	P
Halim et al, 2010 (59)	Retrospective study	7/13	86 pts who had lateral C1-2 joint pulsed RF application, for CHA	percentage of patients who had ≥ 50% pain relief at 2 mts, 6 mts, 1 yr	P

Years – yrs; Weeks – Wk; Months – mts; RF – radiofrequency; PRF – Pulsed radiofrequency; RFN – radiofrequency neurotomy; CHA – cervicogenic headache; CZJP – cervical zygapophysial joint pain; CZJ – cervical zygapophysial joint; VRS – Verbal Rating Scale, PT – Physical Therapy; TENS – Transcutaneous electrical nerve stimulation; MQS – Medication Quantification Scale; BMI – Body Mass Index; DRG – dorsal root ganglion; greater GON – occipital nerve ; Group – Gp; vs – versus; P – positive results in study; N – Negative result in study; Pts – patients; MQ – Methodological Quality; VAS – visual analogue scale; activities of daily living (ADL); GPE – global perceived effects; DRG – dorsal root ganglion. Based on Furlan AD et al., 2009 (45). (*) = Due to the low CHA population, this study has been considered as poor evidence for CHA.

4.0 Discussion

The evidence for RFA is limited, based on one high quality randomized trial with an inadequate number of patients to be considered for appropriate experimental power (55) and multiple moderate quality non-randomized studies (28,56, 58) suggesting effectiveness for CHA. Based on our review one randomized trial with high quality (54), one randomized trial with moderate quality but a limited number of patients (53), and one low quality non-randomized trial (57) showed negative evidence. The evidence for pulsed RFA is limited based on one moderate quality randomized trial (52) and one moderate quality non-randomized study (59) suggesting effectiveness for CHA. The results showed somewhat similar findings as that of a previous review (39); however, they were discordant to another past review (23). Furthermore, we have performed a methodological quality assessment of the studies which has not been done in the other 2 reviews. Evidence is insufficient to assess the effects on the health outcomes because of the limited number of studies or the low power of the studies, unexplained inconsistency between RCTs, flaws in trial design, gaps in the chain of evidence, and lack of detailed information on desired health outcomes.

Even though there are multiple studies evaluating various aspects of CHA intervention with RFA and pulsed RFA, most studies failed to meet the inclusion criteria. The

Table 8. *List of excluded studies which were considered as possibly relevant.*

Manuscript Author(s)	Reason for Exclusion	Conclusion
Radiofrequency ablation		
McDonald et al, 1999 (60)	Data was projected from Lord et al 1996 with extension of more patients; Neurotomy at C3/4 and C6/7	RFN provides clinically significant and satisfying periods of freedom from pain, and its effects can be reinstated if pain recurs.
van Kleef et al, 1996 (61)	Even though prospective double blind randomized study, study has investigated levels C4, C5, and C6; dorsal root ganglion for cervicobrachial pain	67 degrees C RF lesion adjacent to the DRG can result in a significant alleviation of pain in chronic cervicobrachial pain.
Park et al, 2011 (62)	Effect of RF neurotomy (RFN) for lower cervical (C4-7) medial branches on CGH was evaluated.	Lower cervical disorders can play a role in the genesis of headache in addition to the upper cervical disorders or independently.
Bovaira et al, 2013 (63)	Case series with 3 pts	RF is a satisfactory treatment option, affording adequate analgesia, though the effects are sometimes temporary.
Giblin et al, 2014 (64)	Case report	The diagnostic and therapeutic complexity of CHA and the overlap with other headache types, including trigeminal autonomic cephalgias and migraine. It represents a unique proof of principle in that not only trigeminal nerve pain but also presumed neurogenic inflammation can be relieved by blockade of cervical nociceptive inputs.
Sjaastad et al, 1995 (65)	Case series of 7 pts	In the future RF treatment of the planum nuchale will probably be one of the therapeutic options for CHA.
Munglani and Stauffer, 2003 (70)	Case series of 6pts	The cervical DRG category contained 6 pts. Three of the pts in this category presented with neck pain and 2 presented with CHAs. The cervical DRG pts were sent the questionnaire containing neck and back disability questions.
Pulsed Radiofrequency ablation		
Van Zundert et al, 2003 (66)	Clinical audit 6 pts had chronic CHA (C2,3) and 12 cervicobrachialgia, duration of which ranged from < 1–40 years	Satisfactory pain relief of at least 50% was achieved in 13 of 18 (72%) patients at 8 weeks. More than one yr after treatment, 6 patients (33%) continue to rate treatment outcome as good or very good. No side effects were reported.
Kim et al, 2013 (67)	Case series of 2pts	Two successful ultrasound-guided pulsed radiofrequencies on 2 pts, who complained occipital headache and posterior neck pain.
Zhang et al, 2011 (68)	Case series of 2pts	Study demonstrates the effectiveness of PRF to treat CHA originating from the C2 nerve.
Review		
Mehnert and Freedman, 2013 (23)	Comprehensive review	RF neurotomy may provide the most sustained relief of headache symptoms although the relief typically is not permanent. Pulsed RF, a nondestructive modality, may also have benefit for CHAs.
van Suijlekom et al, 2010 (69)	Comprehensive review	Injection of the nervus occipitalis major is recommended after unsatisfactory results with conservative treatments (1 B+). In the case of an unsatisfactory outcome after injection of the nervus occipitalis major, RF treatment of the ramus medialis (medial branch) of the cervical ramus dorsalis can be considered (2 B+/-). If the result is unsatisfactory pulsed RF treatment of the ganglion spinale (dorsal root ganglion) of C2 and/or C3 can be considered in a study context (O).
van Boxem et al, 2008 (39)	Narrative review	There is not sufficient evidence supporting the use of RF facet denervation for the management of CHA. The studies examining the management of cervical radicular pain suggest a comparable efficacy for RF and pulsed RF (PRF). The PRF treatment is supposed to be safer and therefore should be preferred.
van Kleef and van Suiljekom, 2002 (40)	Narrative review	Definite conclusion about the clinical efficacy of the treatment of chronic cervical pain, brachialgia, and CHAheadache by means of radiofrequency procedures can only be drawn from a randomized controlled trial.

included studies were randomized control studies, case controls, prospective non-randomized cohort studies, retrospective cohort studies, and cross-sectional studies. Thus, evidence from this systematic review, applying strict and contemporary criteria with robust outcomes, provides appropriate and sound guidance in managing CHA in practical settings. Furthermore, this is updated evidence using the latest trials with strict adherence to systematic methodological assessment of the evaluation. Unfortunately, there were not enough homogenous studies to provide meta-analysis in an appropriate manner.

In this systematic assessment, 3 randomized trials and 4 observational studies were included in assessing the effectiveness of RFA for CHA. The randomized trial by Lord et al (55) is a double-blind clinical trial that included 24 patients comparing percutaneous RF neurotomy to a sham treatment wherein the procedural technique was the same but RF was not applied to the control group. Patients with cervical spine pain from automobile accidents were included in the study after comparative diagnostic blocks identified patients with cervical facet joint derived neck pain. At 3 months all patients were formally interviewed by completing the visual analogue scale (VAS) and the McGill Pain Questionnaire. Among the 24 patients, one patient in each treatment and control group had C2-C3 and ipsilateral C4-C5 pain; one patient in each treatment and control group had C2-C3 and contralateral C5-C6 pain; one patient in the control group had C2-C3 and ipsilateral C4-C5 and C5-C6 pain; and one patient in the control group had bilateral C2-C3 and C5-C6 and contralateral C6-C7 facet joint derived pain. The median time for return of pain to at least 50% of the preoperative level was 263 days in the active group and 8 days in the placebo group. This study found that RF neurotomy can provide pain relief for a moderate proportion of patients lasting from months to over a year. Even though it is a meticulously performed study on a small number of patients, some authors have noted that the technique is not commonly utilized in the United States (51), while others have criticized the differences in baseline characteristics of patients among both groups and the nature of the blinding (71). Even though the study met inclusion criteria, the small number of patients with CHA included in this study has been of concern and has been considered as low evidence for the CHA population.

There were 2 RCTs (53,54) which did not show significant benefits with RFA. Stovner et al (53), in a moderate quality RCT, investigated RFA treatment for facet joints C2 through C6 for CHA and had a 2-year follow-up to enable detection of possible long-term beneficial and/or harmful effects. The study, which proposed the intended patient number to be ≥ 24 based on power calculations to detect a marked treatment effect (> 50% improvement), had only 12 patients enrolled in study. However, only one patient each in the RFA and sham groups had C2-C3 originated pain while other pain generators were below C3. Due to lower the CHA population in the study, it has been considered as poor evidence against RFA on CHA.

The other study by Haspeslagh et al (54) is a high quality RCT which did not show evidence that RFA of cervical facet joints and dorsal root ganglion is an effective treatment for patients fulfilling the clinical criteria of CHA. This study compared 15 patients with RFA of cervical facet joints and upper dorsal root ganglion with injection (primary rami of the facet joints C3-C4, C4-C5, and C5-C6) with 15 patients with local anesthetic block of the GON. The VAS for pain, global perceived effects scores, and quality of life scores were assessed at T0, T1 (8 weeks), T2 (16 weeks), T3 (6 months), and T6 (12 months). However, there were 3 people who were lost to follow-up in the RFA group by 16 weeks and one person was lost to follow-up in the injection group. Finally, by 12 months there were 11 patients in the RFA group and 10 in the injection group. They have not discussed the prospective power analysis, and around 8 weeks, there were 7 patients who received at least 2 diagnostic segmental blocks of cervical nerves (C2, C3 and seldom others) of them one received RF of the DRG of C2 and two received RF of the DRG of C3. Even though this is a high quality study against RFA for CHA, it has a small patient population, up to one year follow-up, and non-standardized algorithms of treatment.

In one of the moderate quality prospective non-RCTs, van Suijlekom et al (56) assessed the clinical efficacy of RF cervical z-joint neurotomy (RFA of C3 through C6 on the affected side) in patients with CHA. Fifteen consecutive patients with CHA were treated and then assessed one week prior to treatment, and at short-term (8 weeks), intermediate (mean 8.8 months), and long-term (mean 16.8 months) follow-ups. The VAS, 7-point Verbal Rating Scale (VRS), number of headache days per week, and analgesic intake per week were compared. The results of this study showed that RFA of the cervical z-joints significantly reduced headache severity in 12 (80%) patients assessed by 7-point VRS; the mean VAS decrease was 31.4 mm and 53.5 mm both at short-term and long-term follow-ups. In this study investigators performed multilevel RFA and also stated that a definitive conclusion about the clinical efficacy can only be drawn from a RCT.

Govind et al (28), in moderate quality non-RCT, evaluated RFA for the treatment of third occipital headache with a revised technique using a large gauge electrode ensuring minimum separation between 3 electrode placements, and holding the electrode in place by hand. This revised technique was used to treat 51 nerves in 49 patients diagnosed as suffering from third occipital headache on the basis of controlled diagnostic blocks of the TON. The criteria for successful outcome was complete relief of pain for at least 90 days associated with restoration of normal activities of daily living, and no use of drug treatment for headache. Among the 49 patients, 43 (88%) achieved a successful outcome. The median duration of pain relief in these patients was 297 days, and 8 patients had continued relief. Fourteen patients underwent a repeat neurotomy to reinstate relief with 12 (86%) achieving a successful outcome with a median duration of pain relief of 217 days, and 6 patients had continued relief. This study showed that the revised technique provided relief of headache which was limited in duration; however, the relief could be reinstated by repeat neurotomy.

Lee et al (58), in prospective moderate quality non-RCT, investigated 30 patients suffering from chronic CHA for longer than 6 months who had showed a pain relief of greater than 50% from diagnostic/prognostic C3-C4 cervical medial branch blocks. The patients who needed multi-level cervical blocks and those who were involved in litigation or compensational programs were excluded. These patients were treated with RFA of the cervical z-joints and were subsequently assessed at one week, one month, 6 months, and 12 months following the treatment. The results of this study showed that RFA of the cervical z-joints significantly reduced the headache severity in 22 patients (73.3%) at 12 months after the treatment. The average headache days per week decreased from 6.2 days to 2.8 days, and the average analgesic intake per week showed a 70% reduction. There were no major complications related to the procedures. Limitations of this study were no control group, not a randomized study, the number of patients was small, and data from long-term follow-up evaluation were not included. This study found RFA of cervical z-joint can provide substantial pain relief in patients with chronic CHA when carefully selected.

Hamer and Purath (57), in low quality retrospective non-RCT, reviewed 40 patients with refractory CHA and/or occipital neuralgia. Patients were all referred by a headache specialty clinic for evaluation for RFA of the C2 dorsal root ganglion and/or TONs. After treatment, patients were followed for a minimum of 6 months to a year. Thirty-five percent of patients reported 100% pain relief and 70% reported 80% or greater pain relief. The mean duration of improvement is 22.35 weeks. About 92.5% of patients reported that they would undergo the procedure again if severe symptoms returned. The most frequent procedure performed on patients with greater than 50% pain reduction was bilateral C2 ganglion RFA accounting for 53% or 22 patients. The next most common was bilateral C2 ganglion and TON ablations, followed by bilateral TON ablation. The limitations of the study are its retrospective nature, lack of standardization of treatment, selection bias by including a patient in which success was very likely given previous positive results, and a patient population with multifactorial headaches, specifically a large percent of patients with migraine headaches were included.

Among the excluded studies for RFA, the studies by McDonald et al (60) and Park SW (62) are noteworthy as they showed significant improvement, even though they failed to meet the inclusion criteria. Thus, overall RF neurotomy for CHA showed poor evidence based on the strict criteria.

Among the pulsedRFA studies for CHA, Gabrhelík et al (52) performed a moderate quality blind pilot randomized study. In this study, 15 patients underwent a blockade of the GON, a branch of the C2, with administration of local anesthetic and corticosteroids, while another 15 patients had a pulsed RFA to the GON. Median VAS before treatment was 5.5 which significantly decreased to 2.3 in the anesthetic and corticosteroids group, while in the GON group it was 5.9 which significantly decreased to 2.6 at 3 months. Before treatment, the median index Medication Quantification Scale III was 9.2 in both groups. Three months after treatment the median index decreased significantly to 4.8 in anesthetic and corticosteroids group, and to 3.2 in the GON group. The limitations of this study are a small sample size, pilot study design, and no control group.

In a moderate quality non-RCT retrospective study, Halim et al (59) investigated 86 patients who had undergone lateral C1-C2 joint pulsed RFA for CHA in a single pain center. The C1-C2 pulsed RF application was performed using the intra-articular anterolateral approach under fluoroscopic guidance. The duration of pain before the procedure was 9.4 ± 1.1 years (mean ± SE), while the baseline pain score was 8.5 ± 0.1. There were 48.8% (42/86) of patients with ongoing insurance claims while 90.7% (78/86) had undergone a previous nonsurgical procedure for similar complaints. The

percentage of patients who had ≥ 50% pain relief at 2 months, 6 months, and one year were 50% (43/86), 50% (43/86), and 44.2% (38/86), respectively. The limitations of this study are its retrospective nature and less than one year of follow-up.

Among the excluded studies of pulsed RFA for CHA, the studies by Van Zundert et al. (66) and Zhang et al (68) are noteworthy as they showed significant improvement, even though they failed to meet the inclusion criteria. Thus, overall pulsed RF neurotomy for CHA showed poor evidence based on the strict criteria.

Regeneration of the afferent neural structures does occur. If the thermal lesion to the nerve is incomplete, distal sprouting of axons may begin days after the RF lesion (72,73). The relief of pain after RF neurotomy is typically of limited duration, even with careful patient selection and use of proper technique (36,74). Fig. 5 shows the lateral view of a fluoroscopic image with the placement of the needle. Investigators have noted that with repeated interventions for recurrent patients, relief of CHA for longer than 2 years can be achieved (28). Additional blocks are usually not necessary before repeat neurotomy for patients who respond well to an initial procedure (12,28).

Investigators have described several adverse effects associated with neurotomy such as ataxia, hypersensitivity, numbness, itching, and paresthesias following RFA for CHA (2). Numbness that is limited in duration in the cutaneous distribution of a targeted nerve has been described (34,51,55). Also it should be pointed out that there are no well-established techniques regarding denervation for A-O or A-A joints. The characteristic anatomy of these joints carries additional risk when neurotomy of these structures is contemplated (60). Denervation of a portion of the multifidus muscle and the semispinalis cervicis is an expected consequence of the procedure, and improves with time as the nerve regenerates; there is no risk for charcot arthropathy and no microvascular disease results from the procedure (10,60).

Even though there are several studies which have discussed pulsed RF techniques (75), it is associated with complications such as several hours of an increased occipital headache (23). Pulsed RF is not equivalent to thermal RF neurotomy (in terms of physiology or clinical utility), and available data for efficacy have not been as compelling as those for thermal RF (59).

The limitation of this systematic review is in the selected studies. There were inconsistencies between randomized trials, flaws in the design of both randomized and non-randomized trials, and gaps in the chain of evidence with regard to the interventional treatment of CHA. The studies include few RCTs and several non-RCTs. While the evidence that is available is promising, additional carefully designed trials to investigate side effects and long-term outcomes of RF and pulsed RF for CHA would further clarify the potential of the application of this established ablation therapy. Future research should focus on prospective randomized blind control studies to investigate standardized techniques for effective management of CHA for better long-term outcomes and to better define the symptom clusters which might predict treatment success.

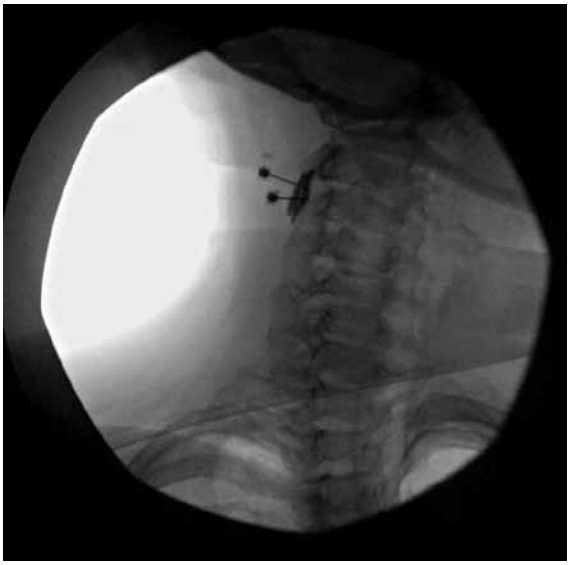

Fig. 5. *C2-C3 junction and upper 1/3 of C3 waist. AP view of fluoroscopic image with the placement of the needle.*

5.0 Conclusion

There is limited evidence for RF and pulsed RFA therapies for management of CHA. There is a need for high quality RCTs and/or multiple consistent non-RCTs without methodological flaws to evaluate the efficacy of RF and pulsed RFA therapies for CHA. Therefore clinicians should perform specific testing to investigate the cause of CHA and venture to treat it after weighing the risks and benefits.

Conflict of interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

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