Meta-analysis

Efficacy of cryoneurolysis in the management of chronic non-cancer pain: A systematic review and meta-analysis

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ABSTRACT

Background and Aims: Cryoneurolysis, a neuroablative technique, is used in the event of failure of conservative treatment in chronic pain conditions. To date, no systematic review has been published to demonstrate its effectiveness in managing chronic non-cancer pain. Therefore, this review was done to ascertain the efficacy of cryoneurolysis and describe its role in chronic non-cancer pain management. **Methods:** We searched PubMed, Cochrane, Embase, Scopus, and Google Scholar databases for articles published between January 2011 and September 2021. Two independent reviewers extracted the data from the included studies. Assessment of risk of bias of included randomised controlled trials (RCTs) was done using RevMan 5.4.1 software and Newcastle-Ottawa scale was used for non-randomised studies. **Results:** Ten studies enroling a total of 425 patients were included in the qualitative analysis. Eight studies were assessed quantitatively. RCTs were found only for cervicogenic headache and knee osteoarthritis management. The rest of the included studies were prospective non-controlled and retrospective studies. A significant pain reduction was seen at seven-day [Standardised Mean Difference (SMD) 1.77 (1.07, 2.46)], $P < 0.00001$, $I^2 = 79\%$), one-month (SMD 3.26 [2.60, 3.92], $P < 0.00001$, $I^2 = 45\%$), three-month (SMD 2.58 [1.46, 3.70], $P < 0.00001$, $I^2 = 93\%$), six-month (SMD 2.38 [0.97, 3.79], $P = 0.001$, $I^2 = 86\%$) follow-ups. Improved disability and no serious complications were noted. **Conclusion:** Cryoneurolysis appeared to be effective in pain alleviation in refractory painful conditions for up to six months. It is safe and well-tolerated with an excellent safety profile but the quality of evidence is limited by substantial heterogeneity between trials. Therefore, more comparative clinical trials on a larger sample size are needed to provide more concrete evidence.

Key words: Chronic pain, freezing, intractable, neural conduction, pain, pain management

INTRODUCTION

Pain persisting for longer than three months is defined as chronic pain.[1] Chronic non-cancer pain refers to persistent pain not associated with cancer or cancer-related treatment. It can affect any region of the body with pain severity that varies from mild to excruciating and includes both neuropathic and nociceptive components. The management of chronic non-cancer pain continues to challenge pain physicians. Multimodal pain management techniques are preferred in the management of chronic non-cancer pain. In case of failure of non-invasive therapies, neuroablative techniques can be used. Cold temperature-mediated ablation of sensory nerve fibres is a minimally invasive and relatively safe neuroablative technique. Cryoablation is the destruction of tissues by freezing, and when it is done to ablate a nerve to relieve pain, it is called cryoneurolysis. It is also known as cryoneuroablation or cryoanalgesia.[2,3] Cryoablation involves using a metallic cryoprobe that is cooled by the rapid expansion of pressurised gas, causing

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freezing-induced cell death by ice crystals formation. Nerve damage mechanisms following the cryoablation involve Wallerian degeneration, ice-crystal mediated damage to vasa vasorum and endoneural oedema, direct injury to axons and disintegration of microtubules halting the axonal transport.[4-6] These mechanisms lead to cessation of conduction, activation of descending inhibitory pathway, inhibition of the release of excitatory neurotransmitters and sodium channel blockade. Either of these mechanisms or their combination results in inhibition of pain transmission.[7] It is a relatively safer way of neurolysis. The complication rate is minimal compared to thermal ablation. Following cryoablation, the basal lamina of the Schwann cells and the endoneurium remain intact, indicating that the nerve can regenerate.[6] Cryoneurolysis has been demonstrated to be safe for the affected nerve as well as the surrounding tissues, such as blood vessels and muscles.[3] A few studies have reported the role of cryoneurolysis in various chronic pain conditions. However, more substantial evidence is still needed to reach a consensus on its analgesic efficacy and duration of pain alleviation. To date, no systematic review demonstrating the effectiveness of cryoneurolysis in chronic non-cancer pain management has been published. Therefore, this review was done to ascertain the efficacy of cryoneurolysis intervention and describe the currently available evidence regarding its role in managing chronic non-cancer pain.

METHODS

Study design

The study protocol was registered in PROSPERO (registration number CRD42021278143). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed while reporting this systematic review and meta-analysis.

Eligibility criteria

The studies that evaluated the role of cryoneurolysis in managing chronic non-cancer pain were included in this review. A well-formulated Population, Intervention, Control, Outcome, Study (PICOS) design has been used for the inclusion of promising studies [Table 1]. Animal studies, articles not published in English, articles whose full-text was not available were not included. Systematic review, literature review, scoping reviews, case reports, editorials and conference abstracts were excluded. Children, acute pain patients, patients with active infection, coagulopathies and bleeding abnormalities, cancer pain patients, postsurgical patients and psychiatric patients were excluded. The studies were also excluded if the study methods and design were not properly stated and reported inadequate data.

Table 1: PICOS framework

Criteria	Determinants
Population	Adults with non-cancer chronic pain:
	CEH
	Occipital neuralgia
	TMJ pain
	Lumbar Facet joint pain
	Knee osteoarthritis
	Painful neuromas
	Peripheral neuropathic pain
	PLP
Interventions	Percutaneous cryoneurolysis
Controls	Varies from study to study, compared to control groups and/or placebo group
Outcomes	Primary objective
	Estimation of pain score (VAS)
	Secondary objective
	Effect on the quality of life
	Duration of pain relief
	Adverse effect
Study design	Prospective randomised and non-randomised controlled trials, Cohort studies, Retrospective studies

PICOS: P=Population, I=Intervention, C=Control, O=Outcomes, S=Study design; CEH=Cervicogenic headache, TMJ=Temporomandibular joint, PLP=Phantom limb pain; VAS=Visual Analogue Scale score

Electronic literature search and study selection

A database search of PubMed, Cochrane, Embase, Scopus and Google Scholar was done for articles published between January 2011 and September 2021. The terms used to carry out e-search were "cryoneurolysis," "cryoablation," "percutaneous cryoablation," "cryoanalgesia," "chronic pain," "chronic non-cancer pain" [Annexure 1]. Two reviewers independently performed an online literature search by using the different combinations of the search terms. Manual screening of references and bibliographies of selected articles was performed. Once the abstract was analysed and found appropriate, the full text of selected articles was studied. Another reviewer independently assessed and decided the articles, to be included in the final analysis.

Data extraction

Two independent reviewers went through all the selected articles. Reviewers did independent and thorough data extraction from the articles and summarised it in a Microsoft Excel spreadsheet using a standardised data extraction form. The following data were extracted: study characteristics (author,

publication year, study design, sample size), patient demographics, the target area for cryoneurolysis, outcome [pain score, disability, duration of analgesia and procedure-related complication (if any)]. Patients were considered responsive if the visual analogue scale (VAS) score was reduced to 50% of the baseline value. Included studies evaluated the pain scores at different follow-up intervals. Pooled analyses were conducted if at least three studies were available at any follow-up interval. Means and standard deviation (SD) were extracted directly from the studies wherever possible. Data extraction for quantitative analysis was done for pain outcome at seven days, one, one and a half to two, three and six months follow-up and compared with baseline mean. We provided a qualitative synthesis where high heterogeneity did not allow for quantitative synthesis.

Quality assessment of individual studies

The risk of bias assessment for included randomised controlled trials (RCTs) was done using Review Manager Software version 5.4.1 (The Cochrane Collaboration, Copenhagen, Denmark, 2014). Two independent reviewers assessed the included studies regarding selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias by evaluating random-sequence generation, allocation concealment, participant blinding, blinding of outcome assessor, incomplete outcome data and selective reporting in individual studies. The internal validity of the study was assessed by rating the above parameters as either "high," "low," "unclear" risk of bias. A quality assessment of non-randomised studies was performed using the Newcastle-Ottawa scale (NOS).

Statistical analysis

Data analysis was performed using RevMan 5.4.1 (The Cochrane Collaboration, Copenhagen, Denmark, 2014). VAS scores were converted from 0-100 mm into 0-10 cm scale if needed. A random-effect model with an inverse variance method was applied. For pain outcome, standardised mean differences (SMDs) with 95% confidence intervals (CIs) were calculated. SMD contributes to express the size of the intervention effect in an individual study relative to the observed variability in that study and additionally allows for before and after comparisons, independent of specific units of measures in them. We have presented the results with 95% CI, *P* values and associated forest plots. Egger's test and funnel plot-based analysis of the possibility of publication bias was not performed. We only did meta-analysis (quantitative synthesis) for pain outcomes as sufficient data was unavailable for other variables.

Assessment of heterogeneity

Statistical heterogeneity between the studies was expressed using the I^2 statistic. I^2 represents percentage of variability in the treatment estimates and interpreted as 0-40%: might not be important heterogeneity; 30-60%: moderate heterogeneity; 50-90%: substantial heterogeneity; 75-100%: considerable heterogeneity. A *P* value 0.10 for the Cochran Q statistics indicates significant heterogeneity.[8,9]

RESULTS

Search results and study selection

A database search was performed in September 2021, and total 78 studies were assessed for eligibility. After excluding review articles, case reports, editorials, conference abstracts, clinical opinions and comments, total 10 articles were included in the final analysis as outlined in the PRISMA flowchart [Figure 1]. Eight articles were used for quantitative analysis.

Study characteristics

RCTs were found only for cryoneurolysis in cervicogenic headache and knee osteoarthritis management among the included studies. Cryo-intervention for refractory occipital neuralgia, phantom limb pain (PLP) and peripheral neuropathy was assessed in prospective non-randomised trials. Retrospective trials for lumbar facet pain, refractory temporomandibular joint (TMJ) pain, and painful neuropathies were also included. This review includes a total of 425 patients who met our inclusion criteria [Table 2].[10-18]

Risk of bias assessment

Both the included RCTs demonstrated a low risk of bias in most of the categories [Figure 2]. Low risk of bias was given eleven times and unclear risk of bias was given three times using RevMan risk of bias assessment tool. Seven of the non-randomised studies were scored good quality whereas one was fair quality based on NOS [Table 3].

Results of individual studies

Primary outcome

Comparison of pain scores

Five of the included studies assessed the pain scores within seven days of cryoneurolysis intervention, and a significant reduction in pain scores was seen as compared to baseline score (SMD1.77 [1.07, 2.46], $P < 0.00001$, $I^2 = 79\%$). Three studies evaluated the

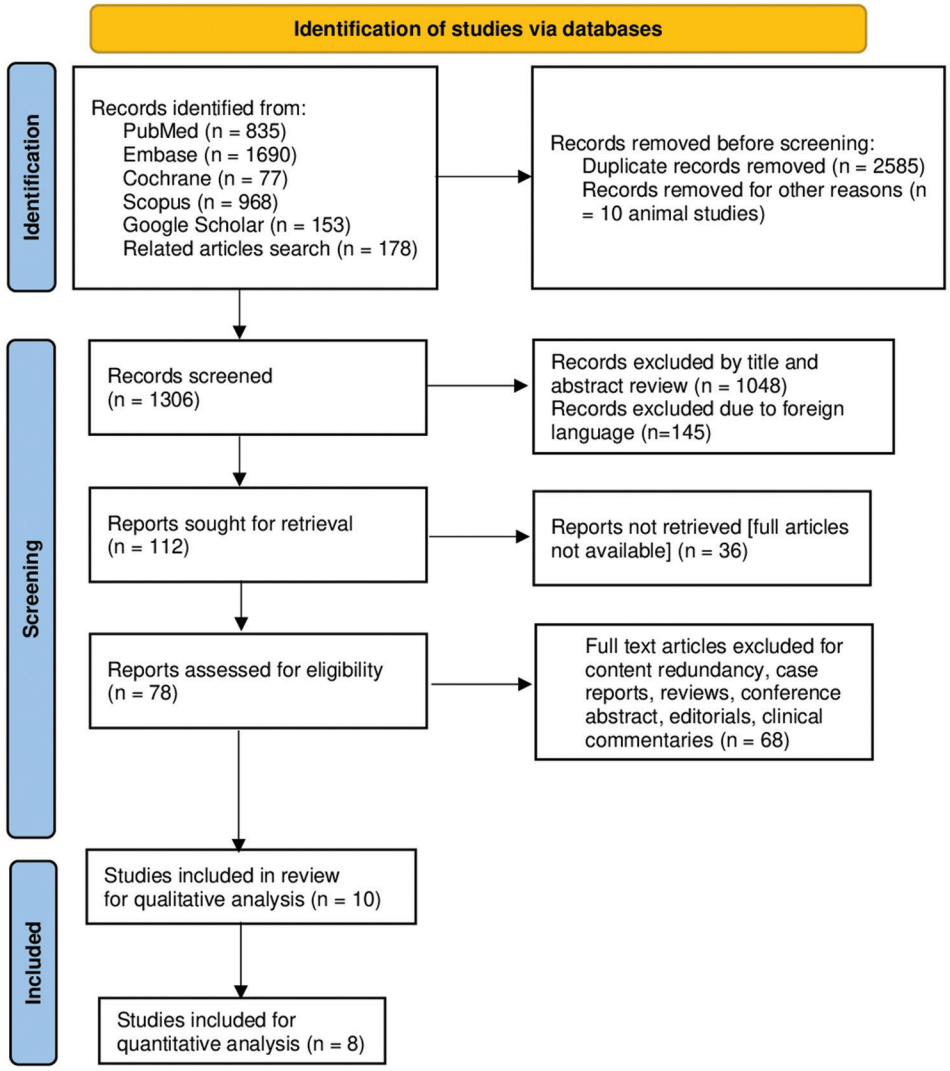

Figure 1: PRISMA flow diagram

pain scores at one month (SMD 3.26 [2.60, 3.92], $P < 0.00001$, $I^2 = 45\%$) and five studies evaluated the scores between one and a half and two months interval (SMD 2.48[1.65, 3.30], $P < 0.00001$, $I^2 = 86\%$) and found significant reduction in pain scores as compared to pre-intervention score. Four studies evaluated the pain scores at three months (SMD 2.58 [1.46, 3.70], $P < 0.00001$, $I^2 = 93\%$) and three studies evaluated at six months of follow-up (SMD 2.38 [0.97, 3.79], $P = 0.001$, $I^2 = 86\%$) and favourable pain reduction was seen [Figure 3 (a-e)]. Long-term follow-up assessment was done by three of the included studies, but data was not sufficient for quantitative analysis. Sidebottom *et al*. reported that 17.6% of patients were pain-free after 12 months,[11] Yoon *et al*. reported significant post-intervention pain reduction (P = 0.03) by the end of one year,[14] and Moesker *et al*. reported pain relief of 90-95% after two and a half years in a patient and after five years in two patients.[5] Substantial heterogeneity (I^2 varied between 79-86%) was seen at most of the follow-up intervals.

Secondary outcome

Comparison of disability

Functional disability assessment following cryoneurolysis intervention and its impact on health-related quality of life (Research and development (RAND) 36 Questionnaire) was evaluated by Kvarstein *et al*.[18] and minimal improvement was seen from baseline at six weeks of follow-up. Global impression of change of participants (on a 5-point scale where 1 = much better, 5 = much worse) and neck movements was reported "moderately to much improved" in 61.3% and 29% of patients, respectively, at 18 weeks of follow-up. Pain disability

Table 2: Summary of studies evaluating the effects of various interventions

Author; Year	Study design	Condition treated	Cryoneurolysis target	Primary outcome	Conclusion	Comment
Wolter *et al*., 2011[10]	Retrospective	Lumbar facet joint syndrome; *n*=91	Lumbar medial branch	Mean pain score decreased from 7.7 before treatment to 3.7 immediately after treatment and 4.22 at three-month follow-up; significant improvement in pain disability index	Sustained pain relief; ameliorates pain related disability and depression	No complication reported
Sidebottom *et al*., 2011[11]	Retrospective	TMJ pain; *n*=17	Auriculotemporal nerve and TMJ capsule	Significant improvement in VAS score (P<0.001); complete pain resolution in 2 patients and no change seen in 2 patients; mean number of pain free months after treatment=7; 3 patients showed long-term pain relief till the end of 12 months studied	Useful adjunct to treat intractable TMJ pain with definite short-term pain relief; long-term relief may be possible	Only 2 cases reported temporary complication; 12 patients showed temporary relief, 6 of them underwent TMJ replacement, 1 had repeat cryoanalgesia, 1 -referred to pain specialist, 1- controlled on nortriptyline
Friedman *et al*., 2012[12]	Retrospective	Painful Morton neuroma (*n*=5), Stump neuroma (*n*=12), other (*n*=7)	Various lower extremity nerves	Marked or total pain relief in 11 patients; moderate relief in 3 patients; mild relief in 1; no relief in 5 patients	Substantial pain reduction and improvement in quality of life; hence, can be a reasonable therapy	None reported
Moesker *et al*., 2014[5]	Prospective	PLP; *n*=5	Affected nerve after positive diagnostic block	3 patients showed excellent pain relief (100%, 95%, 90% relief), 1 patient showed acceptable relief (40%), 1 patient showed 20% relief	Long-term pain relief in PLP; can be considered as a part of multimodal treatment	Both central and peripheral components are involved in PLP but identification and treatment of peripheral trigger can be considered for treatment
Prologo *et al*., 2015[13]	Retrospective	Refractory pudendal neuralgia; *n*=11	Pudendal nerve	Decrease in mean pain score from 7.6 (baseline) to 2.6 (24 hours), 3.5 (45 days) and 3.1 (6 months) after treatment	Safe and effective in refractory pudendal neuralgia	None reported
Yoon *et al*., 2016[14]	Prospective non-randomised	Refractory peripheral neuropathy; *n*=22	Affected nerve after positive diagnostic nerve block; 3 plantar neuromas, 3 ilioinguinal, 4 posterior tibial, 7 saphenous, 1 gluteal, 1 sural, 1 geniculate and 2 digital nerves	Statistically significant decrease in pre-procedure mean pain score from 8.3±1.9 to 2.3±2.5 at 1 month, 3.2±2.5 at 3 months, 4.7±2.7 at 6 months and5.1±3.7 at 12 months post-procedure	Safe and effective therapy in chronic refractory neuropathic pain with moderately long-term pain relief	None reported
Prologo *et al*., 2017[15]	Prospective Non-randomised	Refractory PLP; *n*=21	Upper extremity (*n*=4) and lower extremity (*n*=17) Peripheral nerve	Technical success rate of procedure was 100%. Mean pain score decreased from 6.2 (baseline) to 2.3 (at 45 days) and to 2 (at mean long-term follow-up of 196 days±99~6.5 months) (P<0.0001). Disability scores decrease from 11.3 (baseline) to 3.3 (45 days follow-up) (P<0.0001)	Percutaneous cryoablation is a safe, feasible and efficacious therapy for PLP	Minor procedure related complication reported in 6 (29%) patients

Contd...

Table 2: Contd...

Author; Year	Study design	Condition treated	Cryoneurolysis target	Primary outcome	Conclusion	Comment
Radnovich *et al*., 2017[16]	RCT	Grade 2/3 knee OA; *n*=161	Infrapatellar branch of saphenous nerve after positive diagnostic nerve block	Significantly improved WOMAC pain score at day 30 (*P*=0.0004) and up to day 90 after treatment (*P*=0.0061) in treatment group than sham group; Functional score significantly improved at day 30 (*P*=0.0012) and day 90 (*P*=0.0172) in treatment group	Safe, well-tolerated and effective to treat chronic knee OA pain	Mild, self-resolving side-effects with no significant group difference
Kastler *et al*., 2018[17]	Observational	Unilateral refractory greater occipital neuralgia; *n*=6	Greater occipital nerve	>50% pain relief in all cases at day 7, and in 5 of 6 cases at 1 and 3 months. Pre-procedure Mean pain score (7.8±1.17) decreases to (2.6±1.3) day 7, (2.75±1.25) 1 month, (3.9±0.74) 3 months follow-up; 1 patient benefited from second session after pain recurrence after first session	Feasible and effective option for intractable refractory greater occipital nerve neuralgia	No complication reported; Small sample size and brief follow-up period (3 months) limits study outcome
Kvarstein *et al*., 2019[18]	Randomised double blind trial	CEH patients were allocated to two groups (3:2); Occipital cryoneurolysis (*n*=31) and Injection group (*n*=21)	Greater and lesser occipital nerve after positive diagnostic block (>50% pain relief)	Significant pain reduction >50% and reduced number of opioid consumers in both groups; After 6-7 weeks, pain intensity increased, but did not reach baseline within 18 weeks; No significant difference seen between the groups	Cryoneurolysis provided substantial, but temporary pain relief, and the effect was not significantly different between groups	Various transient/ minor side effects reported, but no significant difference was seen between the groups

TMJ=temporomandibular joint; VAS=visual analogue score; PLP=phantom limb pain; OA=osteoarthritis; CEH=cervicogenic headache; n=number; RCT=randomised controlled trial

index (PDI) was assessed following cryoablation of lumbar facet joint by Wolter *et al*.,[10] and significant improvement ($P < 0.05$) was seen in familiar/domestic duties, recreation, social activities, profession and vitally dispensable activities component of PDI. Western Ontario and McMaster Universities Arthritis Index (WOMAC) physical function and stiffness subscale was assessed by Radnovich *et al*.[16] in patients post-cryotherapy for knee osteoarthritis, and significant improvement was seen at day 30, day 150, but non-significant improvement was seen at day 60 compared to the sham group. At day 90, the physical function subscale but not the stiffness subscale showed a significant decrease in the treatment group than the sham group. Improved functional outcome was also reported by Friedman *et al*.[12] and Moesker *et al*.[5] Prologo *et al*.[15] reported a significant decrease in disability score at day 45 of follow-up from baseline (mean of 11.3 to 3.3; $P < 0.0001$).

Duration of relief

The included studies reported variable duration of relief. Most of the studies demonstrated significant pain reduction at three- and six-months of follow-up. Three studies did long term follow-up for ≥ 12 months. Yoon *et al*.[14] showed 12 months of pain relief in 50% of patients. The mean (SD) duration of pain relief demonstrated by Sidebottom *et al*.[11] was 14.7 (20.26) months (range 0-68 months, skewed distribution). The study by Moesker *et al*.[5] showed 90-95% pain relief even at five years in two patients.

Safety

Three out of ten studies reported no procedure-related complications.[12-14] Mild transient complications like local pain/tenderness, bleeding at the puncture site, numbness, bruising, redness was reported in five studies.[11,12,15,16,18] These complications were self-resolving. Two studies did not report the safety of the cryoneurolysis procedure.[5,17]

Table 3: Risk of bias assessment (Newcastle-Ottawa quality assessment scale criteria) for non-randomised studies

Study ID	Selection				Comparability		Outcome			Total scores	Quality
	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest	Most important factor	Additional factor	Assessment of outcome	Length of follow-up	Adequacy of follow-up		
Wolter *et al*. 2011[10]	*		*	*	*	*	*	*	*	8	Good
Sidebottom *et al*. 2011[11]	*		*	*	*		*	*	*	7	Good
Friedman *et al*. 2012[12]	*		*	*	*	*	*	*	*	8	Good
Moesker *et al*. 2014[5]			*	*	*		*	*	*	6	Fair
Prologo *et al*. 2015[13]	*		*	*	*			*	*	6	Good
Yoon *et al*. 2016[14]	*		*	*	*		*	*	*	7	Good
Prologo *et al*. 2017[15]	*		*	*	*	*		*	*	7	Good
Kastler *et al*. 2018[17]	*		*	*	*			*	*	6	Good

Good quality: 3 or 4 stars (★) in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

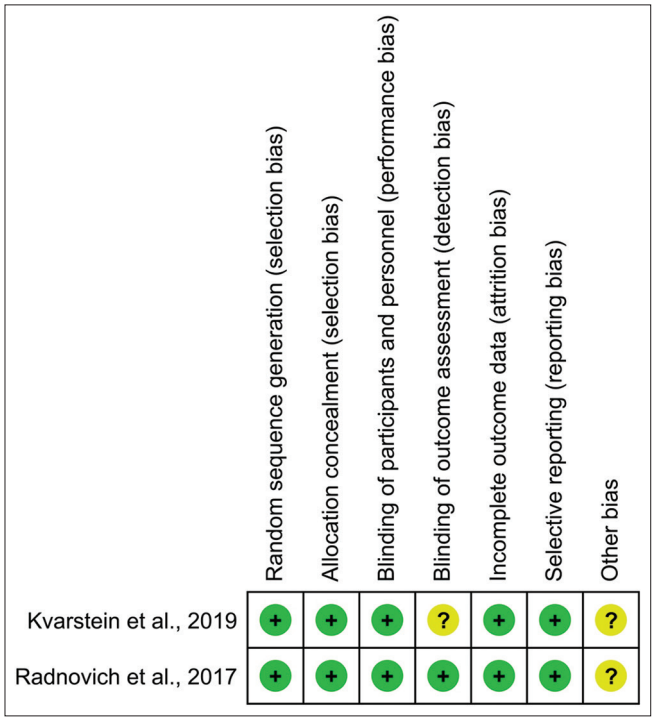

Figure 2: Risk of bias assessment. Authors' judgments about each risk of bias item is presented as percentages across all included studies

DISCUSSION

Cryoneurolysis has been utilised to treat a wide range of neuropathic pain disorders related to neoplastic and non-neoplastic diseases. It is done by putting cryoprobes in the vicinity of the targeted nerve(s) under imaging guidance so that the ablation zone includes the target nerve. A diagnostic local anaesthetic injection before the cryoablation confirms the target and defines the approach for ablation. The safety and analgesic efficacy of cryoneurolysis in various chronic pain conditions have been documented in recent years.

The main findings of this review were that significant pain reduction was demonstrated at seven-days, one, three and six months evaluation. Despite substantial heterogeneity between the studies, considerable pain relief up to six months post-intervention was observed. Although three studies demonstrated long-term therapeutic benefit, the data was not sufficient. Analysis for disability outcome could not be performed due to insufficient data, but qualitative assessment demonstrated improved global status and functional outcome varying from minimal to improved. No or minimal transient procedure-related complication was noted.

Destruction of pain carrying fibres by freezing is usually performed in refractory cases of chronic

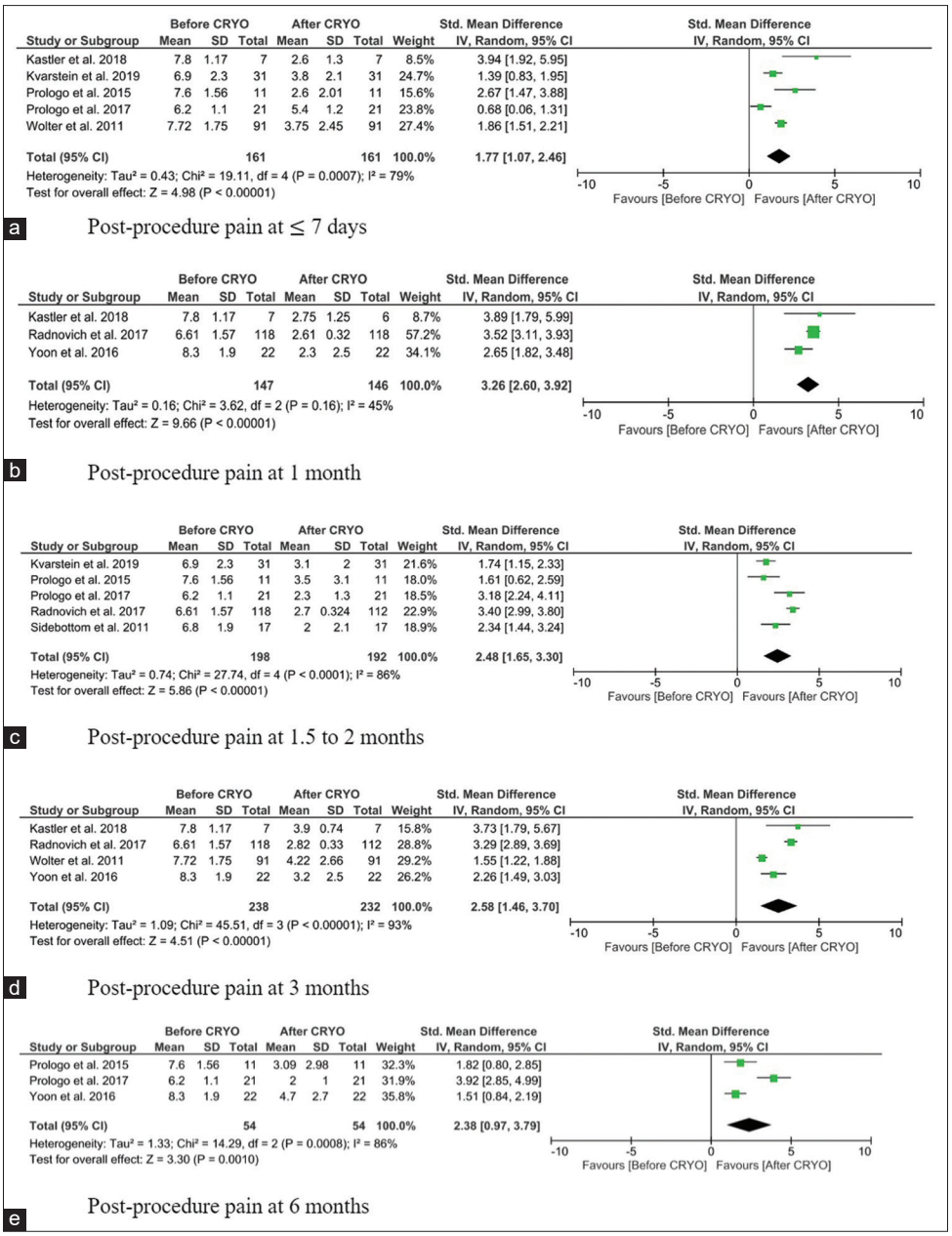

Figure 3: Forest plot for pain outcome- (a) post-procedure pain at ≤1 week, (b) post-procedure pain at 1 month, (c) post-procedure pain at 1.5-2, months, (d) post-procedure pain at 3 months, (e) post-procedure pain at 6 months. CI, Confidence interval; SD, Standard deviation; CRYO, Cryoneurolysis

pain that are not responsive to conservative therapies. The role of cryo-denervation in lumbar facet joint pain has been described in the past in few studies,[19-21] but these studies only focused on pain scores. A study by Wolter *et al*.[10] demonstrated considerable improvement in disability index and amelioration of depression along with sustained pain relief following cryoneurolysis of lumbar medial branches in facet joint pain. A study by Sidebottom *et al*.[11] showed the effectiveness of cryoablation of auriculotemporal nerve and TMJ capsule in intractable TMJ pain.

Cryoneurolysis for peripheral neuritis was first described in 1976.[2] Despite being an older technique, limited literature is available on its efficacy to treat chronic peripheral neuropathies. Friedman *et al*.[12] and Prologo *et al*.[13] demonstrated significant pain relief and improved quality of life in refractory cases of painful neuromas and peripheral neuritis. A small sample size, retrospective nature of study, short and variable follow-up period limit the quality of the outcomes.[12,13] Long term pain relief was assessed in another study by Yoon *et al*.[14] who reported a significant relief at intervals as long as one year

after the cryoneurolysis. Although positive outcome was reported, further study on a larger sample size is needed to generalise this result. PLP following amputation of a body part is the clinical manifestation of ectopic signalling along an altered pathway due to the reorganisation and sensitisation of neural inputs from transacted peripheral somatosensory afferent fibres to the brain.[22-24] Numerous interventions, ranging from cortical modulation to surgical excision of the residual nerve, have been tried and reported at different locations down this transformed pathway.[24-27] Still, no treatment guidelines have been approved. Cryoneurolysis and other peripheral nerve-targeting therapies have been reported to be efficacious.[5,28-30] Mechanisms like plasticity and "wind-up" support peripheral intervention in amputation-related nerve transection.[24] Two small case-series have demonstrated the safe use of cryoanalgesia to manage stump neuromas in residual limb pain and PLP.[5,29] Moesker *et al*.[5] and Prologo *et al*.[15] also reported significant pain reduction following nerve stump cryoneurolysis demonstrating the role of targeting peripheral pain locus in PLP. No procedure-related complication was seen. Long-term pain reduction was reported by both the studies lasting for at least six months to two and a half to five years. The study outcome of both the studies was limited by their design (exploratory study with no control group, no randomisation, no blinding) and variability in the final follow-up point.

Cryoneurolysis has been an addition to a multimodal regimen for treating pain in chronic knee osteoarthritis.[31] Radnovich *et al*.[16] demonstrated safety and tolerability of infrapatellar branch of saphenous nerve cryoneurolysis and found a significant decrease in pain score and improvement in symptoms compared to sham treatment for up to 150 days.

The role of occipital cryoneurolysis in refractory cases of cervicogenic headache and occipital neuralgia was successfully demonstrated with pain alleviation lasting from three to four and a half months.[17,18] A RCT by Kvarstein *et al*.[18] showed no benefit of cryoneurolysis over local anaesthetic and steroid injection. The study outcome was limited by a small sample size which increases the risk of type-II error, short follow-up period, biasing due to self-assessment of pain and lack of an effective blinding process.

All the included studies show some level of efficacy, varying from partial to complete pain relief and a variable duration of pain relief, which is explained by the variability in nerve regeneration following cryoneurolysis. The procedure appeared safe and well-tolerated with an excellent safety profile based on the reports of included trials, though a few studies reported an isolated event of serious complication, that is, myonecrosis and abscess formation.[32] No other reports of permanent nerve damage, neuroma formation, or deafferentation pain have been published.[33-35]

Cryoneurolysis showed various advantages over other neuroablative techniques such as reduced risk of neuroma formation as it does 'not interrupt the perineurium or epineurium, and hence, nerve regeneration can occur,[36] there is no risk of deafferentiation pain as is seen with conventional thermal radiofrequency, and there is no risk of systemic toxicity unlike chemical neurolysis.[37] There are other clinical advantages like simultaneous use of multiple probes in dynamic configuration to produce large superimposing ablation zones, direct visualisation of the ablation zone, and decreased risk of intra- and post-procedural complications.[38,39] Cryoneurolysis is a relatively painless technique and there is no risk of transient excruciating pain as seen with thermal ablation, and therefore is well tolerable.[3] It is a durable treatment, but it is not permanent, as the ablated sensory nerve will regenerate and revive its function.[36] Still, its excellent safety profile allows repeated therapy without increasing the risks.

There are several limitations to this review. Most of the included studies were retrospective, or non-randomised trials, leading to significant risk of bias that hampers the quality of studies. The considerable heterogeneity due to the above methodological issues is another limitation of the review. Variable outcome measures, varying time frames and discrepancies in the study design of the included studies provide only limited concrete evidence.

This systematic review provides an updated report regarding the available literature on cryoneurolysis intervention. Though the technique appeared to be effective, safe and well-tolerated, the quality of evidence is poor. Further studies, preferably large-scale RCTs, are needed to elucidate its analgesic effects and compare with other interventional techniques, to give more substantial evidence regarding its comparative efficacy. A strong need for strengthening research and

techniques related to chronic pain exists; nevertheless, novel nerve block techniques for chronic pain keep getting devised.[40,41]

CONCLUSION

The available evidence suggests that percutaneous image-guided cryoneurolysis effectively alleviates pain in refractory chronic pain conditions like cervicogenic headache, occipital neuralgia, peripheral neuropathies, PLP, knee osteoarthritis, lumbar facet joint pain and TMJ joint pain for up to six months. It appeared safe and improved the functional disability.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Treede RD, Rief W, Barke A, Aziz Q, Bennett M, Benoliel R, *et al*. Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). PAIN 2019;160:19-27.
2. Lloyd JW, Barnard JD, Glynn CJ. Cryoanalgesia: A new approach to pain relief. Lancet 1976;2:932–4.
3. Trescot AM. Cryoanalgesia in interventional pain management. Pain Physician 2003;6:345-60.
4. Wagner R, DeLeo JA, Heckman HM, Myers RR. Peripheral nerve pathology following sciatic cryoneurolysis: Relationship to neuropathic behaviors in the rat. Exp Neurol 1995;133:256–64.
5. Moesker AA, Karl HW, Trescot AM. Treatment of phantom limb pain by cryoneurolysis of the amputated nerve. Pain Pract 2014;14:52–6.
6. Myers RR, Powell HC, Heckman HM, Costello ML, Katz J. Biophysical and pathological effects of cryogenic nerve lesion. Ann Neurol 1981;10:478–85.
7. Zhou L, Shao Z, Ou S. Cryoanalgesia: Electrophysiology at different temperatures. Cryobiology 2003;46:26–32.
8. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
9. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration. The Cochrane Collaboration; 2011.
10. Wolter T, Deininger M, Hubbe U, Mohadjer M, Knoeller S. Cryoneurolysis for zygapophyseal joint pain: A retrospective analysis of 117 interventions. Acta Neurochir (Wien) 2011;153:1011–9.
11. Sidebottom AJ, Carey EC, Madahar AK. Cryoanalgesia in the management of intractable pain in the temporomandibular joint: A five-year retrospective review, Br J Oral Maxillofac Surg 2011;49:653-6.
12. Friedman T, Richman D, Adler R. Sonographically guided cryoneurolysis: Preliminary experience and clinical outcomes. J Ultrasound Med 2012;31:2025–34.
13. Prologo JD, Lin RC, Williams R, Corn D. Percutaneous CT-guided cryoablation for the treatment of refractory pudendal neuralgia. Skeletal Radiol 2015;44:709–14.
14. Yoon JH, Grechushkin V, Chaudhry A, Bhattacharji P, Durkin B, Moore W. Cryoneurolysis in patients with refractory chronic peripheral neuropathic pain. J Vasc Interv Radiol 2016;27:239–43.
15. Prologo JD, Gilliland CA, Miller M, Harkey P, Knight J, Kies D, *et al*. Percutaneous image-guided cryoablation for the treatment of phantom limb pain in amputees: A pilot study. J Vasc Interv Radiol 2017;28:24-34.
16. Radnovich R, Scott D, Patel AT, Olson R, Dasa V, Segal N, *et al*. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: A multicenter, randomised, double-blind, sham-controlled trial. Osteoarthritis Cartilage 2017;25:1247-56.
17. Kastler A, Attyé A, Maindet C, Nicot B, Gay E, Kastler B, *et al*. Greater occipital nerve cryoneurolysis in the management of intractable occipital neuralgia. J Neuroradiol 2018;45:386-90.
18. Kvarstein G, Högström H, Allen SM, Rosland JH. Cryoneurolysis for cervicogenic headache - A double blinded randomised controlled study. Scand J Pain 2019;18;20:39-50.
19. Bärlocher CB, Krauss JK, Seiler RW. Kryorhizotomy: An alternative technique for lumbar medial branch rhizotomy in lumbar facet syndrome. J Neurosurg 2003;98:14–20.
20. Birkenmaier C, Veihelmann A, Trouillier H, Hausdorf J, Devens C, Wegener B, *et al*. Percutaneous cryodenervation of lumbar facet joints: A prospective clinical trial. Int Orthop 2007;31:525–30.
21. Staender M, Maerz U, Tonn JC, Steude U. Computerized tomography-guided kryorhizotomy in 76 patients with lumbar facet joint syndrome. J Neurosurg Spine 2005;3:444–9.
22. Flor H. Phantom-limb pain: Characteristics, causes, and treatment. Lancet Neurol 2002;1:182-9.
23. Griffin SC, Tsao JW. A mechanism-based classification of phantom limb pain. PAIN 2014;155:2236-42.
24. Subedi B, Grossberg GT. Phantom limb pain: Mechanisms and treatment approaches. Pain Res Treat 2011;2011:864605.
25. Weeks SR, Anderson-Barnes VC, Tsao JW. Phantom limb pain: Theories and therapies. Neurologist 2010;16:277-86.
26. Foell J, Bekrater-Bodmann R, Flor H, Cole J. Phantom limb pain after lower limb trauma: Origins and treatments. Int J Low Extrem Wounds 2011;10:224-35.
27. Foell J, Bekrater-Bodmann R, Diers M, Flor H. Mirror therapy for phantom limb pain. Eur J Pain 2014;18:729-39.
28. Cornish P, Wall C. Successful peripheral neuromodulation for phantom limb pain. Pain Medicine 2015;16:761–4.
29. Borghi B, D'Addabbo M, White PF, Gallerani P, Toccaceli L, Raffaeli W, *et al*. The use of prolonged peripheral neural blockade after lower extremity amputation: The effect on symptoms associated with phantom limb syndrome. Anesth Analg 2010;111:1308-15.
30. Neumann V, O'Connor RJ, Bush D. Cryoprobe treatment: An alternative to phenol injections for painful neuromas after amputation. AJR Am J Roentgenol 2008;191:W313;author reply W314.
31. Dasa V, Lensing G, Parsons M, Bliss R, Preciado J, Guirguis M, *et al*. An ancient treatment for present-day surgery: Percutaneously freezing sensory nerves for treatment of postsurgical knee pain. Tech Reg Anesth Pain Manag 2014;18:145-9.
32. Cahani D, Chacko J, Hahn B. Myonecrosis: A rare complication of cryoneurolysis. J Emerg Med 2019;57:73-6.
33. Djebbar S, Rossi IM, Adler RS. Ultrasound-guided cryoanalgesia of peripheral nerve lesions. Semin Musculoskelet Radio 2016;20:461-71.
34. Shah SB, Bremner S, Esparza M, Dom S, Orozco E, Haghshenas C, *et al*. Does cryoneurolysis result in persistent motor deficits? A controlled study using a rat peroneal nerve injury model. Reg Anesth Pain Med 2020;45:287-92.
35. Ramirez M, Ravichandran S, Ronald L. Pabon-Ramos WM, Smith TP, Kim CY, *et al*. Recognition and management of dermatologic complications from interventional radiology procedures. Diagn Interv Imaging 2019;100:659-70.
36. Hsu M, Stevenson FF. Wallerian degeneration and recovery

of motor nerves after multiple focused cold therapies. Muscle Nerve 2015;51:268–75.
37. Jones WB, Jordan P, Pudi M. Pain management of pancreatic head adenocarcinomas that are unresectable: Celiac plexus neurolysis and splanchnicectomy. J Gastrointest Oncol 2015;6:445–55.
38. Thacker PG, Callstrom MR, Curry TB, Mandrekar JN, Atwell TD, Goetz MP, *et al*. Palliation of painful metastatic disease involving bone with imaging-guided treatment: Comparison of patients' immediate response to radiofrequency ablation and cryoablation. AJR 2011;197:510–5.
39. Erinjeri JP, Clark TW. Cryoablation: Mechanism of action and devices. J Vasc Interv Radiol 2010;21:187–91.
40. Malhotra N, Joshi M, Gehdoo RP, Usmani H, Sharma G. Pain medicine as a career. Indian J Anaesth 2021;65:73-8.
41. Kose SG, Kose HC, Tulgar S, Akkaya OT. Ultrasound guided pulsed radiofrequency between the popliteal artery and capsule of the knee (RPACK); A new technique for relief of chronic posterior knee pain. Indian J Anaesth 2022;66:474-5.

ANNEXURE 1. DETAILED SEARCH STRATEGY

PubMed

	Query
#1	(cryoneurolysis)
#2	(Percutaneous cryoablation)
#3	(cryoanalgesia)
#4	((#1) OR (#2) OR (#3))
#5	(chronic pain)
#6	((#4) AND (#5))
#7	(chronic non cancer pain)
#8	((#6) OR (#7))
#9	((#6) OR (#7)) from 2011/1/1-2021/9/30
#10	((((Cryoneurolysis) OR (percutaneous cryoablation)) OR (cryoanalgesia)) AND (chronic pain)) OR (chronic non-cancer pain) from 2011/1/1-2021/9/30

EMBASE

	Query
#1	'cryoneurolysis'/exp OR cryoneurolysis
#2	percutaneous AND cryoablation
#3	cryoanalgesia
#4	cryoneurolysis OR (percutaneous AND cryoablation) OR cryoanalgesia
#5	(cryoneurolysis OR (percutaneous AND cryoablation) OR cryoanalgesia) AND chronic AND pain
#6	(cryoneurolysis OR (percutaneous AND cryoablation) OR cryoanalgesia) AND chronic AND pain OR (chronic AND 'non cancer' AND pain)
#7	((cryoneurolysis OR (percutaneous AND cryoablation) OR cryoanalgesia) AND chronic AND pain OR (chronic AND 'non cancer' AND pain)) AND [2011-2021]/py
#8	(('cryoneurolysis'/exp OR cryoneurolysis OR (percutaneous AND ('cryoablation'/exp OR cryoablation)) OR 'cryoanalgesia'/exp OR cryoanalgesia) AND chronic AND ('pain'/exp OR pain) OR (chronic AND 'non cancer' AND ('pain'/exp OR pain))) AND [2011-2021]/py

SCOPUS

	Query
#1	TITLE-ABS-KEY (cryoneurolysis)
#2	TITLE-ABS-KEY (percutaneous AND cryoablation)
#3	TITLE-ABS-KEY (cryoanalgesia)
#4	(TITLE-ABS-KEY (cryoneurolysis) OR TITLE-ABS-KEY (percutaneous AND cryoablation) OR TITLE-ABS-KEY (cryoanalgesia))
#5	(TITLE-ABS-KEY (cryoneurolysis) OR TITLE-ABS-KEY (percutaneous AND cryoablation) OR TITLE-ABS-KEY (cryoanalgesia) AND TITLE-ABS-KEY (chronic AND pain))
#6	(TITLE-ABS-KEY (cryoneurolysis) OR TITLE-ABS-KEY (percutaneous AND cryoablation) OR TITLE-ABS-KEY (cryoanalgesia) AND TITLE-ABS-KEY (chronic AND pain) OR TITLE-ABS-KEY (chronic AND non-cancer AND pain))
#7	TITLE-ABS-KEY (((((cryoneurolysis) OR (percutaneous AND cryoablation)) OR (cryoanalgesia)) AND (chronic AND pain)) OR (chronic AND non-cancer AND pain)) AND PUBYEAR >2010 AND PUBYEAR <2021

COCHRANE	
	Query
#1	(cryoneurolysis):ti, ab, kw OR (percutaneous cryoablation):ti, ab, kw OR (cryoanalgesia):ti, ab, kw
#2	(cryoneurolysis)):ti, ab, kw OR (percutaneous cryoablation):ti, ab, kw OR (cryoanalgesia):ti, ab, kw AND (chronic pain):ti, ab, kw
#3	(cryoneurolysis):ti, ab, kw OR (percutaneous cryoablation):ti, ab, kw OR (cryoanalgesia):ti, ab, kw AND (chronic pain):ti, ab, kw AND (chronic non cancer pain):ti, ab, kw with Cochrane Library publication date Between Jan 2011 and Sep 2021 (Word variations have been searched)