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Interventional Management Of Neuropathic Ocular Pain – A Scoping Review

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Abstract

Neuropathic Ocular Pain (NOP) is a debilitating and refractory pain condition. This scoping review is the first to summarize the current evidence of efficacy of interventional treatment options for NOP. Databases were searched for studies published up to March 31, 2023. Two reviewers screened and extracted data, and performed the risk of bias analysis. Twelve studies were included, consisting of 4 cohort studies and 8 case series/reports, with a total of 87 patients. Eight interventions were defined: stellate ganglion block (n=1), trigeminal nerve blocks (n=3), retrobulbar block (n=1), pulsed radiofrequency of sphenopalatine ganglion (n=1), Onabotulinum-Toxin A(n=1), trigeminal nerve stimulation (n=1), intrathecal drug delivery (n=1) and transcutaneous electrical trigeminal nerve stimulation (n=3). Procedures were found to be safe and demonstrated analgesic effect. Follow-up ranged from 24h to 12 months. Substantial heterogeneity across studies was found, and quality was deemed low and of moderate risk of bias. High-quality studies are urgently needed.

Introduction

The cornea is one of the most densely innervated tissues in the body.[1] Ocular surface pain is a condition that is characterized by discomfort, irritation, or burning sensation in the eyes. This condition was usually grouped under the umbrella term "dry eye (DE)", but recent research has shown that it can occur independently of tear dysfunction. [2] The prevalence of ocular surface pain varies depending on the definition of symptoms and the studied population, ranging from 5% to 50%. [3, 4] This is a complicated and multifaceted condition that is linked to multiple risk factors, which can significantly disrupt an individual's daily life both physically and mentally, resulting in a poor quality of life. [5-7] Ocular surface pain can be classified into nociceptive and neuropathic pain based on their respective causes and presentations. This review primarily focused on a discussion of Neuropathic Ocular Pain (NOP), also known as Corneal Neuralgia, Keratoneuralgia, or Burning Eye Syndrome. [8] NOP can be further classified based on the location of the nerve lesion within the somatosensory system: "peripheral", which is characterized by dysfunction of corneal sensory nerves and/or periocular nerve fibers; "central", involving dysfunction in ascending and descending central nervous system (CNS) fibers, and "autonomic", which affects the autonomic nervous system (ANS). [9] The etiologies of NOP include ocular diseases (dry eye disease,[5, 10, 11] herpetic keratitis, [12] recurrent erosion syndrome [8]), post-traumatic (radiation keratopathy [2], post-chemotherapy [13], trauma [11], post-refractive surgery [14, 15]), systemic diseases (Sjögren's syndrome, lupus) [11], and psychological comorbidities (anxiety, depression, and history of posttraumatic stress disorders). [16, 17]

The symptoms of NOP can vary and may include aching, burning, foreign body-like, dryness, irritation, discomfort, squeezing, pressure, itchy, light sensitivity, allodynia, and hyperalgesia. [18] Some patients may also experience periocular pain, facial pain, migraine headaches, and hyperacusis. Visual disturbances have also been reported.

Several pharmacological and non-pharmacological options for NOP have been investigated, including antidepressants and anticonvulsants. However, a significant proportion of patients remain refractory to treatments. [8, 9, 17] Several interventional (percutaneous) procedures have been successfully used in the treatment of complex chronic pain states such as complex regional pain syndrome and neuropathic pain [19-23], but their therapeutic role for NOP have not been completely established. Therefore, the objective of this scoping review is to evaluate the efficacy of these interventional options for the treatment of NOP.

Methods

This scoping review was performed according to the Arksey and O'Malley's framework for conducting a scoping review, with modifications proposed by Levac et al. We specified the research questions, identified the relevant literature, selected the studies, mapped the data, and synthesized the data to report the results.

Search Strategies And Terms

We conducted a comprehensive search of the literature from database inception to March 31, 2023, with the assistance of a medical information specialist (M.E.). The following databases were searched: MEDLINE, 1946 onward; MEDLINE Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations; Embase Classic/ Embase, 1947 onward; Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science, and

Scopus. The search was restricted to human subjects. We searched for randomized and nonrandomized trials, case series and case reports, systematic reviews and meta-analyses by using combinations of subject headings and keyword terms for "eye or ocular" and "neuropathic pain" and "interventions". Details of the search strategies are provided in Supplement 1, and a summary of the search history record is presented in Supplement 2.

Eligibility Criteria

A population, concept, and context (PCC) approach was followed for this scoping review. [24, 25]

Population

Studies included in the clinical analysis focused on adult patients (age 18 years and older) who suffered from NOP.

Concept

The concept of interest was the role of (percutaneous) pain interventions in the treatment of NOP.

Context

The context of interest was to assess the efficacy in terms of change in pain intensity, improvement of functional and psychological outcomes, and quality of life. Sustainability of analgesic benefit and adverse effects were also noted.

Study Selection Process

All citations were independently screened on title and abstract for eligibility by two reviewers (S.A.A. and T.S.) as per the inclusion criteria. Covidence® was used as a management tool. Papers of interest were then full text screened. Data was independently extracted by two reviewers (S.A.A. and T.S.). Any disagreement was resolved through discussion with senior author (Y.H.).

Data extraction

Extracted data included number of patients, type of study, patient characteristics, details of pain condition, details of interventions and comparators (type of injectate, dose, guidance technique), follow up time points, outcomes, and adverse effects of the interventions. The data was entered into prespecified tables on a standardized data extraction form. The data collection form was pilot-tested before its use.

Assessment Of The Risk Of Bias

Two reviewers (S.A.A. and T.S.) independently evaluated risk of bias for non-randomized trials and case series using ROBINS-I [26] and IHE's quality appraisal checklist for assessing case series studies [27], respectively. Any disagreement was resolved through discussion with the senior author (Y.H.).

Data Synthesis

We narratively synthetized the characteristics of all studies that met inclusion criteria. Study characteristics and treatment details were summarized. For continuous data, means (or medians) and standard deviations (or interquartile ranges or ranges) were extracted.

Results

Search Results

A total of 3925 unique articles were retrieved from the search, of which 3879 were excluded at the screening stage. Full texts of the remaining 46 articles were assessed with 12 studies meeting eligibility criteria (***Figure 1***). Four retrospective cohort studies [28-31], three case series [32-34], and five case reports [35-39] were included.

Risk Of Bias

The risk of bias assessment of the included non-randomized trials showed one study of low risk of bias [30], one study of moderate risk of bias [31], and two studies deemed to have a serious risk for bias [28, 29] (***Table 9***). The quality of case series

was deemed low in two studies [29, 32], moderate in one study [33], and high in one study [34] (***Table 10***).

Interventions For NOP

From these 12 studies, eight interventions were identified for the treatment of NOP and listed below. We provide a concise rationale and indication for each intervention, summarize the data on treatment specifics and outcomes, and suggest potential areas for further research in this review.

Intervention 1: Stellate Ganglion Block (SGB) for NOP

Rationale:

The cervical sympathetic nervous system is responsible for the innervation of various structures in the body including blood vessels, sweat glands, eyes, face, head, neck, heart, and upper extremities. Several studies have shown that SGB may offer potential benefits for both painful and non-painful medical conditions. [40-42]

Details Of The Studies And Outcomes:

We only found one case series on the use of SGB for NOP (***Table 1***). [32] This small case series (n=6) investigated the effect of a course of six weekly sessions of SGB using landmark technique (LMT), injecting 4 ml of 0.5% bupivacaine and clonidine 1 mcg/kg, for participants suffering from NOP, caused by glaucoma. Participants' preprocedural VAS (Visual Analogue Scale for Pain Assessment in which 0 is the absence of pain and 10 is the worst pain ever experienced) was high, averaging between 7-10/10. Four out of six participants reported a significant improvement. Two participants had complete pain relief up to one year after the procedure. Two other participants reported to only have mild pain, rated at 3/10, up to 12 months post-procedure. The latter group continued to take gabapentin simultaneously. Two of the six participants could not be evaluated due to loss of follow-up. There was no report on adverse events (AE).

Intervention 2: Peripheral Branches of Trigeminal Nerve Block (TNS) in NOP

Rationale:

Targeting the peripheral branches of the trigeminal nerve, including supraorbital, supratrochlear, infraorbital, and infratrochlear nerve, has been found to be an effective treatment for various conditions, such as migraine headaches, supratrochlear neuralgia, infratrochlear neuralgia, infraorbital neuralgia, and lacrimal neuralgia. [43-45] These periocular nerve blocks (PNB) have been suggested for the treatment of NOP based on the hypothesis that suggests that pain signals may arise due to the abnormal regeneration of damaged corneal nerve endings. This abnormal regeneration could lead to abnormal connections with adjacent nerve endings, resulting in spontaneous activity. The tissues surrounding the cornea, such as the palpebral conjunctiva, skin, or fornix, receive innervation from the supraorbital, supratrochlear, infratrochlear, and infraorbital nerves. [17] Therefore, blocking the periorbital nerves next to the injured corneal nerves could reduce ectopic activity and decrease pain signaling to the spinal trigeminal nucleus, leading to a reduction in eye pain perception. [29]

Details Of The Studies And Outcomes:

We found two retrospective cohort studies, [28, 29] and one case report [35] on the use of PNB for NOP (***Table 2***). The studies have included participants ranging from 37 to 69 years of age with moderate to severe intensity of NOP from different causes. Injectates consisted of local anesthetics alone or in combination with steroids. All procedures were done using LMT. In one study conducted by Lee et al., nineteen participants were given a total of 94 peripheral trigeminal nerve blocks. [28] The number of injections varied among the participants, with a median of 4.9 (range 1-17) injections per

patient and a median of 84.7 days (range 7-455 days) between each injection. At a median follow-up period of 2.4 years (range 7 days – 4.6 years), the majority of participants (84.2%) reported that the injections continued to provide partial or complete pain improvement. Over half of those assessed reported effects lasting more than six weeks. Injections containing dexamethasone did not increase the odds of prolonged duration (relative risk, 0.88; 95% CI, 0.81-0.97).

In a complex study by Small et al., patients with severe NOP were treated with multi-modal analgesia including gabapentin. They found that adding gabapentin to multi-modal treatment regimen provided significant pain relief. [29] Eleven individuals who did not benefit from gabapentin, underwent PNB. Greater occipital nerve block or sphenopalatine ganglion block were added in case of occipital pain or sympathetically-mediated pain, respectively. Seven out of eleven individuals experienced complete resolution of pain lasting from 1.5 hours to 7 months. Repeated blocks were considered at weeks to months after initial blocks, if the pain recurred. No AE were reported.

Lastly, one participant reported by Duerr and colleagues in 2019 stated that they experienced significant pain relief and improvement of photophobia that lasted for several months (range 4-7) after each procedure. [35]

Intervention 3: Inferotemporal Retrobulbar Injection in NOP

Rationale:

The retrobulbar block (RBB) was once the gold standard for akinesia and anesthesia in intraocular surgery, but its use has decreased due to newer techniques with similar efficacy and fewer complications. Although rare, complications such as retrobulbar hemorrhage, optic nerve damage, and central spread of local anesthetic and brainstem anesthesia can have severe consequences. [46]

Details Of The Studies And Outcomes:

We found one case report of a young patient with NOP receiving landmark-guided (LMG) RBB. [36] (***Table 3***) Following a positive diagnostic block, he received 8 therapeutic injections over the course of 3.5 years, each providing him with significant pain reduction (VAS baseline 7-9/10 versus VAS post 1-3/10), lasting 4-9 months. The study reported longer duration of pain relief with dexamethasone as compared to triamcinolone acetonide (9 months versus 4-6 months). No complications were noted.

Intervention 4: Sphenopalatine Ganglion (SPG) Pulsed Radiofrequency Neuromodulation (PRFN) for NOP

Rationale:

The trigeminal-autonomic reflex is the most relevant signaling pathway in relation to SPG-mediated pain. Activation of this pathway leads to the release of vasoactive peptides that cause the extravasation of plasma proteins and neurogenic inflammation. [47, 48] Targeting the SPG with peri-target injection, radiofrequency ablation, and neurostimulation, have been studied and show promise in treating headache disorders, facial pain syndromes, and other facial neuralgias. [22, 49]

Details Of The Studies And Outcomes:

We only found one case report on the use of PRFN of SPG for NOP. [37] (***Table 4***) The procedure was performed under fluoroscopic guidance on a 53-year-old male, who experienced refractory NOP with blepharospasm following caustic injury. Two sessions of PRFN of SPG were completed within 4 months' time. The first session was performed for 120 seconds at 45 V for two cycles, and the second session performed for 90 seconds at 60 V for two cycles. After completion of both sessions, the participant reported a significant improvement in pain and blepharospasm symptoms, with still

ongoing partial benefit at 3 years post-procedure.

Intervention 5: BoNT-A Injection for NOP

Rationale:

Onabotulinum toxin A (BoNT-A) is a type of neurotoxin that is derived from Clostridium botulinum. It has been used as a therapeutic agent for a wide range of disorders such as cervical dystonia, chronic migraine, hyperhidrosis, urinary incontinence, strabismus, and blepharospasm. [50] Moreover, BoNT-A has been found to inhibit the release of local nociceptive neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), and glutamate. [51] It also reduces the expression of transient receptor potential vanilloid 1 (TRPV1), thereby dampening neurogenic inflammation and peripheral sensitization. [52] Given these effects, BoNT-A has increasingly been used to treat a variety of neuropathic facial pain disorders, including post-herpetic neuralgia, trigeminal neuralgia, and occipital neuralgia. [53] One published case series [54], demonstrating that patients receiving BoNT-A injections for chronic migraine also experienced significant improvement in photophobia and DE, led to the hypothesis that individuals with NOP may experience similar symptomatic improvement with periocular BoNT-A injection.

Details Of The Studies And Outcomes:

We found one case series on the use of BoNT-A for refractory NOP (***Table 5***). [33] Patients received one session of periocular BoNT-A injection, using modified migraine protocol, targeting procerus, corrugators, and frontalis muscles. The rationale was to target the muscles closest to trigeminal afferents on the corneal surface. The severity and frequency of photophobia and eye discomfort were assessed, using the Visual Light Sensitivity Questionnaire-8 (VLSQ-8) [55] and Dry Eye Questionnaire-5 (DEQ-5) [56]. Both parameters were demonstrated to be significantly decreased (VLSQ-8 scores pre: 26-40/40, post: 18-23/40; DEQ-5 scores pre:13-19/22, post: 5-11/22). Tear film parameters, eyelid, and eyebrow anatomy were also evaluated but deemed unchanged.

Intervention 6: Trigeminal Nerve Stimulation (TNS) for NOP

Rationale:

According to the neurophysiological gate-control theory proposed by Melzack and Wall, the stimulation of large-diameter afferent fibers inhibits the transmission of noxious stimuli by small-diameter fibers. [57] Subsequently, invasive stimulation of the trigeminal nerves through the Gasserian ganglion has been investigated for the treatment of chronic atypical trigeminal neuralgia. [58] Similarly, NOP has been suggested as a possible indication for TNS.

Details Of The Studies And Outcomes:

We found one case report describing a 30-year-old woman experiencing severe DE-like symptoms and NOP post laser in situ keratomileusis surgery (LASIK). [38] (***Table 6***) The participant underwent fluoroscopic-guided implantation of an electrode close to the first trigeminal branch (V1). This procedure provided significant pain control until lead migration at 8 months post-implant. Further attempts to revise the implant failed to provide adequate pain control, and the device was explanted. The same patient then received an intrathecal drug delivery system (IDDS) with fentanyl and bupivacaine at C1-C2 level, providing adequate symptom control for over a year. It is worth noting that this study was related to another publication by Hayek et al., [39] but the latter focused more on intrathecal drug delivery system, discussed in Intervention 7 section.

Intervention 7: Intrathecal Drug Delivery System (IDDS) for NOP

Rationale:

Lundborg et al. conducted a study from 1990 to 2005 on use of continuous high intrathecal bupivacaine administration to treat 40 patients with refractory pain in the head, neck, mouth,

and shoulder regions; cancer-related (n=25) and non-cancer (n=15). [59] The study was based on clinical experiences and promising results from case reports. [60-62] They concluded that cervical high spinal analgesia is a safe and effective treatment for refractory pain in areas innervated by cranial and upper cervical nerves. The results showed significant pain relief and reduced opioid requirement with few side effects.

Details Of The Studies And Outcomes:
We only found one case report on the use of IDDS for NOP. [39] (***Table 7***) The tip of the intrathecal catheter was located at C1-C2 level. Patient satisfaction was high with over 50% pain relief for more than a year. The continuous infusion was started at fentanyl 5 mcg/day and bupivacaine 3 mg/day, and titrated up to fentanyl 26 mcg/day and bupivacaine 16 mg/day. Average frequency of bolus use was 20-24 times per day. Documented complications included post-dural puncture headache and catheter migration. It is crucial to note that appropriate catheter positioning at the C1-C2 level was vital for relieving NOP in this case, as evidenced by the loss of analgesia when the catheter migrated 2 cm caudad.

Intervention 8: Transcutaneous Electrical Nerve Stimulation (TENS) for NOP
Rationale:
Studies have shown that TENS is effective in treating various pain conditions, including fibromyalgia, painful diabetic neuropathy, migraines, facial pain. [63-70] There are two major theories explaining TENS' analgesic mechanism: Gate Control Theory and descending inhibitory pathway modulation. [57, 71] High frequency TENS (>60 Hz) has been shown to activate supraspinal delta-opioid and cholinergic receptors, modifying the release of gamma-aminobutyric acid (GABA) and enkephalins, which facilitate inhibition of interneurons within the trigeminal-thalamic tract in the context of ocular pain. [72-74]

Details Of The Studies And Outcomes:
We came across two retrospective studies [30, 31] and a case series [34] on use of TENS for NOP. (***Table 8***) Two studies utilized the RS Medical RS-4i Plus Sequential Stimulator, a device that combines traditional TENS technology with interferential current therapy (ICT) to potentially reduce adverse dysesthesias that are commonly associated with traditional TENS stimulation. [31, 34] The other study used the Compact Trigeminal NeuroStimulator (TNS) device (Cefaly®) with a single electrode. [30] Electrodes were attached to the forehead and temples for RS-4i, and center of the forehead for TNS device, covering the ophthalmic (V1) and maxillary (V2) branches.

In one retrospective cohort study (n=18) investigating the use of Cefaly® TENS device, patients were instructed to use the device daily for at least 20 minutes, continued for at least 3 months. [30] Ocular symptom intensity including dryness, pain, light sensitivity, wind sensitivity, and burning were evaluated monthly for 6 months. Except for dryness, all other ocular symptoms were significantly decreased up to 6 months. Mean weekly frequency use of TNS decreased over time, though therapeutic effect remained. Interestingly, the majority of participants (15/18) reported feeling sedated when TNS use. A second retrospective cohort study (n=10) investigated the use of RS-4i. [31] Follow-up ranged from 3 to 14 months. Nine out of ten patients reported significant pain relief at last follow-up. Interestingly, both studies reported that mean weekly frequency use of TENS decreased over time, indicative of a lower need for treatment.

Finally, we found one case series (n=13) reporting significant but short-lasing decrease in ocular pain intensity following a single episode of 30-minute session with the RS-4i device. [34]

Participants' ocular symptoms returned to baseline within 24 hours post-treatment. Adverse effects reported were epiphora (n = 1) and exacerbation of pain (n = 1).

Discussion

NOP is a highly complex and refractory pain condition. To our knowledge, this is the first scoping review providing a detailed summary of the rationale and current evidence for the use of various pain interventions to manage NOP. We only found low-quality evidence to support the use of eight interventions, with moderate risks of bias.

The study of NOP is becoming increasingly important as we seek to understand its complex underlying mechanism. This may include autonomic, peripheral and central sensitization components, or a combination of all three. Despite an extensive list of non-pharmacological options (such as lifestyle modification and cognitive behavioral therapy), pharmacological options (such as topical therapy, gabapentinoid, serotonin and norepinephrine reuptake inhibitor, tricyclic antidepressant, anti-convulsant, low-dose naltrexone) and the included interventional options, finding the optimal treatment for these refractory patients remains challenging and is probably multi-faceted and multidisciplinary. Therefore, encouraging collaboration amongst different specialties and adopting a multimodality approach would be the most effective strategy at this time. In that context, we hope our scoping review will bring some new insights.

This review has several limitations. All reported evidence stems from observational data, that is flawed by high risk of confounding and bias. This becomes even more apparent due to significant heterogeneity, lack of long-term follow-up and a low number of studies for each intervention. This prohibits us from making any recommendations at this time.

Nevertheless, this review has revealed some promising data and should be seen as a boost and call for development of high-quality evidence with monitoring of long-term outcomes and adverse effects to clearly delineate the role of these treatments in this refractory patient population that is desperately in need of better pain control.

Conclusion

NOP is a complex and refractory pain condition. The current evidence for interventional treatment for NOP is limited and of low quality, offering insufficient support to provide recommendations. Given the debilitating character of this disease, there is an urgent need for high-quality studies, including monitoring of long-term outcomes and adverse effects, to clearly establish the efficacy of included pain interventions for NOP.

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Declarations/Disclosures

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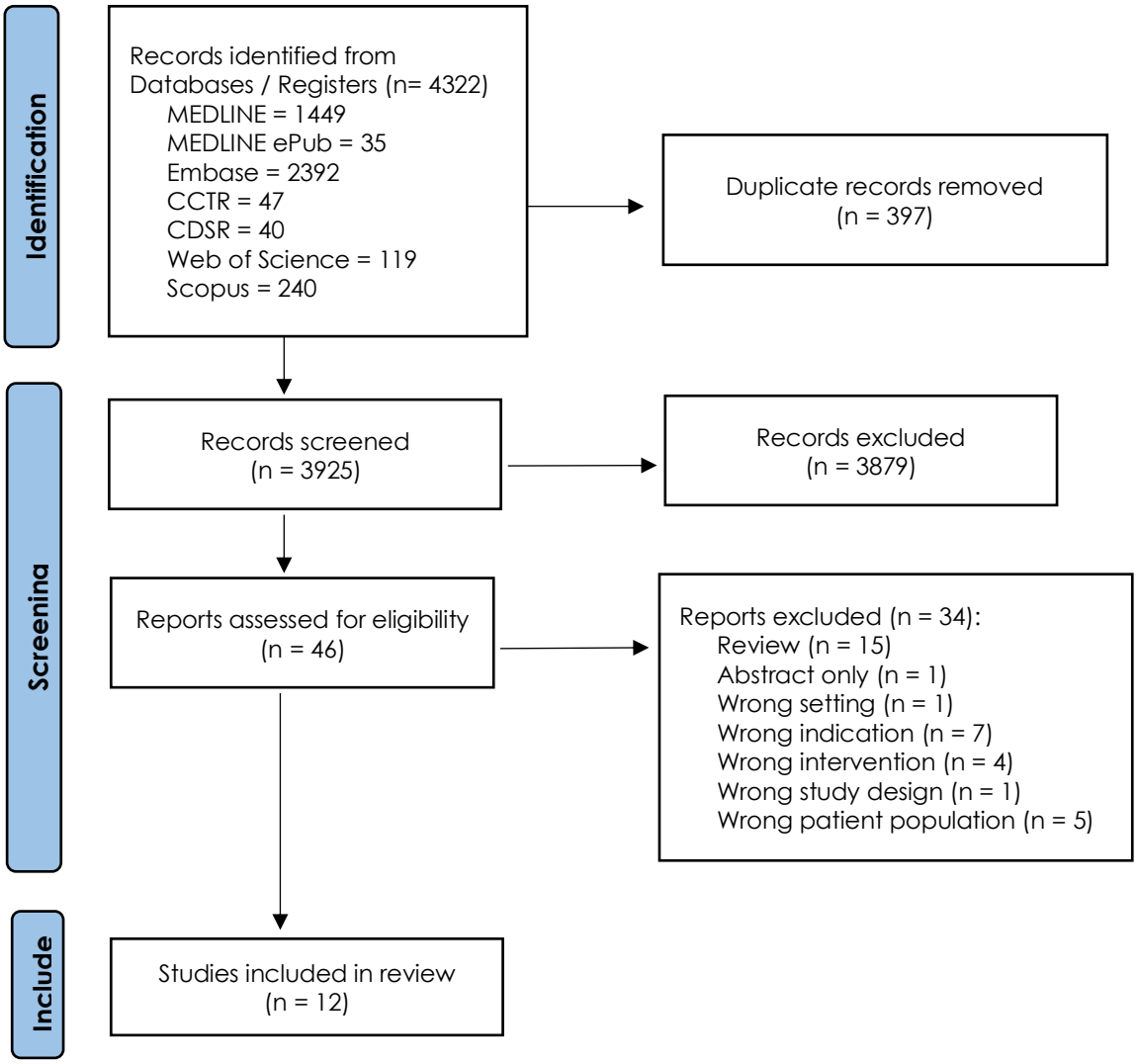
REB: Not indicated based on the type of manuscript

Figures

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.



CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews

Tables

Table 1. Data Extraction Table for Stellate Ganglion Block in NOP

1st Author, Year, Number of participants, Study type	Participants: Indication, Age, Gender, Preprocedural pain intensity, Duration of pain	Details of Intervention	Comparator	Outcomes assessed, Follow-up	Results, Adverse events
Xavier, 2016 N = 6 CS	*NOP: post-glaucoma *Age in yrs, mean (range): NP *M/F: NP *VAS pain: 7-10/10 *Duration: NP	*Weekly sessions of SGB with 4 mL of bupi (0.5%) w/o vasoconstrictor and clonidine 1 mcg/kg. *LMT	None	*Outcome: pain intensity (VAS) *FU: 1 yr	*n=4: excellent response - 2/4: asymptomatic at 1 yr - 2/4: VAS 3/10 at 1 yr *n=2: no FU

Bupi: bupivacaine; CS: case series; FU: follow-up; LMT: landmark technique; M/F: Male/Female; n: number; NOP: neuropathic ocular pain; NP: not provided; SGB: stellate ganglion block; VAS: Visual Analogue Scale for pain assessment, in which 0 is the absence of pain and 10 is the worst pain ever experienced; W/O: without; yrs: years

Table 2. Data Extraction Table for Peripheral Branches of Trigeminal Nerve Block (TNB) or Periocular Nerve Block (PNB) in NOP

1st Author, Year, Number of participants, Study type	Participants: Indication, Age, Gender, Preprocedural pain intensity, Duration of pain	Details of Intervention	Comparator	Outcomes assessed, Follow-up	Results, Adverse events
Lee, 2022 N = 19 Cohort Study (R)	*NOP: ocular surface disease, post-trauma, and scleritis *Age in yrs, median (range): 53.7 (25-83) *M/F: 4/15 *VAS pain: NP *Duration, median (range): 37.7m (11 days-25 yrs)	*PNB: ST, SO, lacrimal nerve *LMT *2% lido w/ epi + 0.5% bupi w/ or w/o DXM, 0.5-1 ml/nerve *Number of injections/participant, median (range): 4.9 (1-17) *Interval between injections, median (range): 84.7 days (7-455) *94 block total	None	*Outcomes: Primary 1. Response to injection (Efficacy) 2. Duration of effect 3. Overall efficacy Secondary: LA+DXM vs LA only: Effectiveness , duration of pain relief *Median (range) FU: 2.4 yrs (7 days–4.6 yrs)	*Response to injection No efficacy 8% Moderate 54.5% High 37.5% *Duration of effect No effect: 14% 0-2 wks: 26.3% 2-6 wks: 8.7% > 6 wks: 50.9% *Overall efficacy No improvement: 15.8% Partial: 57.9% Complete or near complete: 26.3% * LA only: 31.8% of total injections * Addition of DXM did not increase odds of prolonged duration (odds ratio, 0.63; 95% CI, 0.16–2.50) *AE: temporary bruising (n=2/19)
Small, 2020 N=11 Cohort study (R)	*NOP: post-ocular surgery (n=4), trauma (n=1), radiation (n=1), zoster ophthalmicus (n=1), post-pituitary adenoma resection (n=1), postseptoplasty (n=1), neuromyelitis optica (n=1), unknown (n=1) *Age in yrs, mean (SD): 54 (NP) *M/F: 7/4 *VAS pain: 5-9/10 *Duration: 0.3-7 yrs	*PNB:SO, ST, IO, ITR *LMT *4 mL of 0.5% bupi + 1 mL of 80 mg DM, 0.5-1 ml/nerve *If occipital pain: +GON (LA 3-5 ml) *If SMP: +XRGSPG	None	Outcomes: pain intensity FU: up to 7m	* 7/11: complete resolution of pain *duration: range 1.5 hrs – 7 m 5/7 had repeated blocks at wks-months after initial blocks * 4/11: no improvement * No AE

Duerr, 2019 N= 1 CR	*NOP: post-retinal detachment repair *Age in yrs, mean (SD): 66 (NP) *M *VAS pain: 8/10 *Duration: 7 yrs	*Series of 3 PNB; -1st (SO, ST, IO, ITR): 0.5% bupi 4 ml + DM 80 mg, 0.5-1 ml/ nerve -2nd (ITR, IO), at one-wk post 1st PNB: 0.5% bupi 2 ml+ DM (dose NP), 1 ml/nerve -3rd (SO, ST, IO, ITR), after 7m post 2nd PNB: details NP * LMT	None	Outcomes: Pain intensity (VAS), photophobia intensity FU: *After 1st PNB: immediately, post-one wk *After 2nd PNB: at 7m *After 3rd PNB: at 4m	Results: *After 1st PNB: Postprocedure: VAS 0/10, resolution of photophobia, At 1 wk: VAS 1-2/10 *After 2nd PNB: VAS 0/10 for 7 m then VAS 1-2/10 (duration NP) *After 3rd PNB: VAS 0/10 for 4 m + mild photophobia * No AE

AE: adverse event; Bupi: bupivacaine; CR: case report; DM: Depo-Medrol; DXM: dexamethasone; epi: epinephrine; FU: follow-up; GON: Greater Occipital Nerve block; hrs: hours; IO: infraorbital; ITR: infratrochlear; LA: local anesthetic; Lido: lidocaine; LMT: landmark technique; M/F: Male/Female; m: months; mg: milligram; ml; milliliter; n: number; NOP: neuropathic ocular pain; NP: not provided; PNB: periocular nerve block; R: retrospective; SD: Standard deviation; SMP: sympathetically-mediated pain; SO: supraorbital; SPG: sphenopalatine ganglion block; ST: supratrochlear; TNB: trigeminal nerve block; VAS: Visual Analogue Scale for pain assessment, in which 0 is the absence of pain and 10 is the worst pain ever experienced; VS: versus; wks: weeks; W/: with; W/O: without; XRG: fluoroscopic-guided; yrs: years

Table 3. Data Extraction Table for Inferotemporal Retrobulbar Injection in NOP

1st Author, Year, Number of participants, Study type	Participants: Indication, Age, Gender, Preprocedural pain intensity, Duration of pain	Details of Intervention	Comparator	Outcomes assessed, Follow-up	Results, Adverse events
Yalamanchili, 2019 N = 1 CR	*NOP: postkeratectomy *Age (yrs): 21 *M *VAS pain: 7-9/10 *Duration: > 2 yrs	*Diagnostic block: 0.25% bupi *Rx regularly performed over 3.5 yrs: 0.25% bupi + TA 40 mg/ml (50:50), 3-4 ml/each orbit, 27G ¾ inch needle *Last two injections performed differently: 0.25% bupi + DXM implant *LMT	None	Outcomes: *Pain intensity (VAS) *Duration of pain relief FU: > 3 yrs	*8 injections over 3.5 yrs *Pain intensity, duration of pain relief: - LA + TA (6/8 injections): 7-9/10 (pre) *vs* 1-3/10 (post), lasted 4-6m - LA + DXM (2/8 injections): VAS 7-9/10 (pre) *vs* VAS 1-2/10 (post), lasted 9m *No AE

AE: adverse event; Bupi: bupivacaine; CR: case report; DXM: dexamethasone; FU: follow-up; G: Gauge; LA: local anesthetic; LMT: landmark technique; M: Male; m: months; mg: milligram; ml: milliliter; N: number; NOP: neuropathic ocular pain; Rx: treatment; TA: triamcinolone acetonide; VAS: Visual Analogue Scale for pain assessment, in which 0 is the absence of pain and 10 is the worst pain ever experienced; VS: versus; yrs: years

Table 4. Data Extraction Table for Sphenopalatine Ganglion Pulsed Radiofrequency in NOP

1st Author, Year, Number of participants, Study type	**Participants: Indication, Age, Gender, Preprocedural pain intensity, Duration of pain**	**Details of Intervention**	**Comparator**	**Outcomes assessed, Follow-up**	**Results, Adverse events**
Rectoret, 2021 N = 1 CR	*NOP: post-caustic injury *Age (yrs): 53 *M *VAS pain: 7/10 *Duration: 2 yrs	* Diagnostic block, successful: 2% lido 2 ml, XRG (infrazygomatic) *Rx: - XRG- PRF, 22 G 10 cm cannula with 2 mm active blunt tip. - 2 sessions within 4m (interval NP): 1st :120 sec at 45 V *2 cycles 2nd :90 sec at 60 V *2 cycles	None	Outcomes: Pain intensity FU: up to 3 yrs	* > 50% decrease in pain intensity and blepharospasm *At 3 yrs post-Rx participant reported daily pricking and pressure sensation, but intensity of pain experienced was acceptable. *No AE

AE: adverse event; cm: centimeter; CR: case report; FU: follow-up; G: Gauge; Lido: lidocaine; M: Male; m: months; ml: milliliter; mm: millimeter; N: number; NOP: neuropathic ocular pain; NP: not provided; PRF: pulsed radiofrequency neuromodulation; Rx: treatment; Sec: seconds; V: Volt; VAS: Visual Analogue Scale for pain assessment, in which 0 is the absence of pain and 10 is the worst pain ever experienced; XRG: fluoroscopic-guided; yrs: years

Table 5. Data Extraction Table for BoNT-A Injection in NOP

1st Author, Year, Number of participants, Study type	**Participants: Indication, Age, Gender, Preprocedural pain intensity, Duration of pain**	**Details of Intervention**	**Comparator**	**Outcomes assessed, Follow-up**	**Results, Adverse events**
Venkateswaran, 2020 N = 4 CS	*NOP *Age (yrs): 35, 55, 57, 69 *M/F: 3/1 *VAS pain: NP *Duration: NP *VLSQ-8 Pre: 26-40/40 *DEQ-5 Pre: 1319/22	* BoNT-A, modified migraine protocol *35 units, 7 injection sites (5 units in procerus, 10 units in corrugators, 20 units in frontalis muscles) * LMT	None	Outcomes: *Photophobia and Dry eye symptoms (VLSQ-8, DEQ-5) *Tear film parameters, eyelid anatomy and function, eyebrow anatomy *FU: > 1 m	*VLSQ-8 at 1m: 26-40/40 (pre) to 18-23/40 (post) *DEQ-5 at 1m: 13-19/22 (pre) to 5-11/22 (post) *Tearfilm/eyelid/eyebrow anatomy: slightly different or unchanged *No AE

AE: adverse event; BoNT-A: Onabotulinum toxin A; CS: case series; DEQ-5: Dry eye Questionnaire-5 score; LMT: landmark technique; M/F: Male/Female; m: months; N: number; NOP: neuropathic ocular pain; NP: not provided; VAS: Visual Analogue Scale for pain assessment, in which 0 is the absence of pain and 10 is the worst pain ever experienced; VLSQ-8: Visual Light Sensitivity Questionnaire-8 score; yrs: years

Table 6. Data Extraction Table for Trigeminal Nerve Stimulation (TNS) in NOP

1st Author, Year, Number of participants, Study type	Participants: Indication, Age, Gender, Preprocedural pain intensity, Duration of pain	Details of Intervention	Comparator	Outcomes assessed, Follow-up	Results, Adverse events
Sayegh, 2016 N = 1 CR	* NOP: post-LASIK *Age (yrs): 30 *F *VAS pain: NP *Duration: 9 yrs	*XRG modified Haertl approach: Implantation of electrode into trigeminal ganglion via left foramen ovale *Deep Brain Stimulator electrode, toward V1 branch *Rechargeable generator *Setting: bipolar configuration involving contact 1 (cathode) and contact 2 (anode), freq 85 Hz, PW 150 µS, amp 0.06 V	None	Outcomes: Pain intensity FU: up to 8m	*Pain well controlled up postop, pain relapsed at 8m due to lead migration *After revision, pain remained inadequately controlled: explant *Followed by successful trial of high cervical IT infusion of bupi +fentanyl, IT pump implanted

AE: adverse event; Bupi: bupivacaine; CR: case report; F: Female; freq: frequency; FU: Follow up; Hz: Hertz; IT: intrathecal; LASIK: Laser in situ keratomileusis surgery; m: months; N: number; NOP: neuropathic ocular pain; NP: not provided; PW: pulse width; S: sec; TNS: trigeminal nerve stimulation; V: Volt; VAS: Visual Analogue Scale for pain assessment, in which 0 is the absence of pain and 10 is the worst pain ever experienced; V1 branch: ophthalmic branch of trigeminal nerve; XRG: fluoroscopic-guided; yrs: years

Table 7. Data Extraction Table for Intrathecal Drug Delivery System (IDDS) in NOP

1st Author, Year, Number of participants, Study type	**Participants: Indication, Age, Gender, Preprocedural pain intensity, Duration of pain**	**Details of Intervention**	**Comparator**	**Outcomes assessed, Follow-up**	**Results, Adverse events**
Hayek, 2016 N = 1 CR	*NOP: post-LASIK *Age (yrs): 30 *F *VAS pain: 6-10/10 *Duration: 7 yrs	*IDDS *XRG, tip at C1C2 *IT solution: fentanyl 50 mcg/ml and bupi 30 mg/ml. *Initial setting: fentanyl 5 mcg/day and bupi 3 mg/day, PTM provided	None	Outcomes: Pain intensity FU: > 1 yr	* > 50% pain relief for >1 yr *Fentanyl 26 mcg/day and bupi 16mg/day *PTM bolus: fentanyl 0.6mcg and bupi 0.36 mg, max 30 bolus per 24H (average use of 20-24 PTM boluses/day) *AE: - PDPH, Rx with EBP 1 wk later, resolution of headache - Catheter migration + CSF collection around the pump, successful revision

AE: adverse event; Bupi: bupivacaine; C: cervical; CR: case report; CSF: cerebrospinal fluid; EBP: epidural blood patch; F: Female; FU: Follow up; H: hours; IDDS: intrathecal drug delivery system; IT: intrathecal; LASIK: Laser in situ keratomileusis surgery; m: months; mg/ml: milligram per milliliter; mcg/ml: microgram per milliliter; N: number; NOP: neuropathic ocular pain; PDPH: postdural puncture headache; PTM: personal therapy manager; Rx: treatment; VAS: Visual Analogue Scale for pain assessment, in which 0 is the absence of pain and 10 is the worst pain ever experienced; wks: weeks; XRG: fluoroscopic-guided; yrs: years

Table 8. Data Extraction Table for Transcutaneous Electrical Nerve Stimulation (TENS) in NOP

1st Author, Year, Number of participants, Study type	Participants: Indication, Age, Gender, Preprocedural pain intensity, Duration of pain	Details of Intervention	Comparator	Outcomes assessed, Follow-up	Results, Adverse events
Mehra, 2021 N = 18 Cohort study (R)	*NOP: NP *Age in yrs, mean (SD): 57.5 (14.5) *M/F: 12/6 *VAS pain: 3.8±3.5 *Duration: > 6m	* TENS device (Cefaly®) with one electrode *Use of TENS ≥ 3m *Location: forehead (ST and SO) * Freq 60 Hz, PW 250 µS, amp increase from 1 to 16 mA over 14 min, then at 16 mA for 20-min *Single sessions	None	Outcomes: *Primary: Ocular symptom intensity, mean (SD) (dryness, pain, light sensitivity, wind sensitivity, burning) *Secondary: Freq and Duration of TNS use FU: up to 6m postTNS	Ocular symptom intensity *Dryness Pre: 6.2±2.6 At 6m: 5.0±3.2, p=0.13 *Pain Pre: 6.2±2.1 At 6m: 4.3±3.0, p < 0.01 *Light sensitivity Pre: 7.2±2.5 At 6m: 4.6±3.1, p <0.01 *Wind sensitivity Pre: 6.3±2.7 At 6m: 4.3±3.1, p <0.01 *Burning Pre: 6.2±2.3 At 6m: 2.87±3.42, p < 0.01 *Overall reduction in symptoms at 6m: - n=11: >30% reduction - n=7: ≥50% reduction *Better response in individuals w/ migraine *Mean (SD) weekly freq TNS use - 1st m: 3.7±1.9 sessions/wk, average 25.8 min/session - 3rd m: 3.6±2.0 sessions/wk, mean 29.7 min/session - 6th m: 2.7± 2.3 sessions/wk, mean 28.0 min/session *2/18 participants discontinued at 4th and 5th m: lack of efficacy *AE: 15/18 subjects: sedative effect

Zayan, 2020 N = 10 Cohort study (R)	* NOP: NP * Age in yrs, mean(SD): 47.5 (NP) *M/F: 8/2 *VAS pain: 4-10/10 *Duration: >6m (NS)	*RS Medical RS4i Plus Sequential Stimulator; combined the conventional TENS technology with interferential current therapy (ICT) *Use of TENS > 3m *Location: Four electrodes, TN branches *Use of device up to 3 times/day at amp of choice * Device programmed at 5000/5100 Hz freq,100 Hz beat freq	None	Outcomes: 1. Freq of use 2. Ocular pain intensity (VAS) FU: 3-14m	*Initial: mean usage 14 times/wk, frequency decreased over time as need decreased. At last FU: Mean usage of 3 times/wk *Median (range) duration of use: 6.5m (3-14) *Ocular pain intensity - n=9: 4-10/10 (pre) to 3-8/10 (post), p = 0.02 *AE: increased pain (n=1)
Sivanesan, 2017 N = 14 CS	*NOP: NP * Age in yrs, mean (SD): 47 (NP) *M/F: 11/3 *VAS pain: 4.46/10 (Left), 4.54/10 (Right) *Duration: >3m	*RS Medical RS4i Plus Sequential Stimulator with ICT *Location: bilateral V1 and V2 *Device programmed: 5000/5100 Hz, 100 Hz beat freq, with a variable PW and amp for 30 min. Amp of sub-maximal	None	Outcomes: *Pain intensity, using Defense and Veterans Pain Rating Scale *Dryness and light sensitivity FU: 5 min post-Rx, 1-day post-Rx	*Pain intensity (mean) RE: 4.54 (pre) to 1.92 (5min post-Rx); p=0.01 LE: 4.46 (pre) to 2.00 (5 min post-Rx); p=0.01 For all (n=14): pain returned to baseline at 24h post-Rx *Dryness (mean) RE: 3.00 (pre) to 1.92 (5min); p=0.11 LE: 3.46 (pre) to 1.77 (5min); p=0.04 *Light sensitivity (mean) RE: 5.83(pre) to 4.25 (5min); p=0.01 LE: 6.33(pre) to 4.50(5min), p=0.004 *AE: Epiphora (N=1), Exacerbation of pain (N=1)

AE: adverse event; amp: amplitude; Bupi: bupivacaine; C: cervical; CR: case report; CS: case series; CSF: cerebrospinal fluid; EBP: epidural blood patch; freq: frequency; FU: Follow up; H: hours; Hz: Hertz; ICT: interferential current therapy; IDDS: intrathecal drug delivery system; IT: intrathecal; LASIK: Laser in situ keratomileusis surgery; LE: left eye; m: months; M/F: Male/Female; mA: milliamps; mcg/ml: microgram per milliliter; mg/ml: milligram per milliliter; min: minutes; N: number; NOP: neuropathic ocular pain; NP: not provided; NS: not specified; PW: pulse width; PTM: personal therapy manager; R: retrospective; RE: right eye; Rx: treatment; S: seconds; SD: Standard deviation; SO: supraorbital; ST: supratrochlear TENS: transcutaneous electrical nerve stimulation; TN: trigeminal nerve; TNS: trigeminal nerve stimulation; VAS: Visual Analogue Scale for pain assessment, in which 0 is the absence of pain and 10 is the worst pain ever experienced; V1 branch: ophthalmic branch of trigeminal nerve; V2 branch: maxillary branch of trigeminal nerve; wks: weeks; W/: with; XRG: fluoroscopic-guided; yrs: years

Table 9. Risk of Bias in Non-randomized Studies using ROBINS-I

1st author and year	Confounding	Participant selection	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall risk
Lee 2022	High	Low	High	Moderate	Low	Moderate	Moderate	High
Small 2020	High	Moderate	Moderate	High	High	High	Moderate	High
Mehra 2021	Low	Low	Low	Low	Low	Low	Low	Low
Zayan 2020	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate

Table 10. Case Series Studies Quality Appraisal Checklist using The Institute of Health Economics (IHE) Form

1st Author and year Checklist	Xavier 2016	Venkateswaran 2020	Sivanesan 2017	Small 2020
Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes
Was the study conducted prospectively?	Unclear	Unclear	No	No
Were the cases collected in more than one centre?	Unclear	Unclear	No	No
Were patients recruited consecutively?	Unclear	Unclear	Yes	Unclear
Were the characteristics of the patients included in the study described?	No	Yes	Yes	Yes
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Unclear	Unclear	Yes	No
Did patients enter the study at a similar point in the disease?	Unclear	No	Unclear	No
Was the intervention of interest clearly described?	Unclear	Yes	Yes	Yes
Were additional interventions (cointerventions) clearly described?	No	No	No	Yes
Were relevant outcome measures established a priori?	Unclear	Yes	Yes	Unclear
Were outcome assessors blinded to the intervention that patients received?	Unclear	Unclear	No	Unclear
Were the relevant outcomes measured using appropriate objective/subjective methods?	Unclear	Yes	Yes	No
Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Unclear
Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear	Unclear	Yes	Unclear
Was follow-up long enough for important events and outcomes to occur?	Yes	No	No	Unclear
Were losses to follow-up reported?	Yes	Yes	Yes	Yes
Did the study provided estimates of random variability in the data analysis of relevant outcomes?	No	No	Yes	No
Were the adverse events reported?	No	No	Yes	No
Were the conclusions of the study supported by the results?	Unclear	Yes	Yes	Unclear
Were both competing interests and sources of support for the study reported?	Unclear	Yes	Yes	Yes

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