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Noninvasive Electrical Stimulation for the Treatment of Chronic Ocular Pain and Photophobia

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Abstract

Introduction—"Dry eye" or "keratoconjunctivitis sicca" is a multifactorial disease estimated to have a worldwide prevalence of 5–33% (1). Conventional therapies targeting the ocular surface with artificial tears, anti-inflammatories, punctal closure, eyelid hygiene, and antibiotics do not provide relief in all patients, especially those with neuropathic like ocular complaints (wind hyperalgesia and photophobia) (2–5). We anticipated that ocular TENS would alleviate symptoms of ocular pain, photophobia, and dryness in these latter individuals.

Methods—All individuals who received electrical stimulation between May 10, 2016 and April 6, 2017 for the treatment of chronic ocular pain at the oculofacial pain clinic of the Miami Veterans Administration (VA) Hospital were included in this retrospective review. All patients had symptoms of dryness along with other neuropathic-like symptoms (e.g. photophobia) and minimal signs of tear dysfunction. Ocular pain intensity, symptoms of dryness, and light sensitivity were compared pre-treatment and 5 minutes post-treatment via a two-tailed paired Student's *t* test.

Results—The use of TENS significantly reduced the mean pain intensity in both the right and left eyes 5 minutes after treatment compared to prior to treatment ($P < 0.05$, paired *t* test). The use of TENS significantly decreased light sensitivity in both eyes ($P < 0.05$). The findings for symptoms of dryness, however, were equivocal with a significant decrease in the left eye but not the right ($P < 0.05$, paired *t* test).

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Discussion—Our data indicate that TENS may similarly provide analgesia in patients with dry eye symptoms as it does for many other chronic pain conditions. Furthermore, the noted effect on symptoms of photophobia and dryness suggest that all may be linked by similar trigeminal–thalamic–cortical pathways. Prospective studies with electrical stimulation of dry eye are needed to further elucidate its benefit and mechanism of action.

Keywords

ocular pain; transcutaneous electrical stimulation; neuromodulation; photophobia; dry eye

Introduction

Chronic pain is estimated to affect 11.2% or 25.3 million adults within the United States when defined by the National Health Interview Survey as daily pain experienced over the past 3 months (6). Within pain, the American Academy of Pain Medicine reports that back pain is most common (27%), followed by severe headache or migraine pain (15%), neck pain (15%) and facial ache or pain (4%) (7). A less well-studied aspect of chronic pain is ocular pain. While ocular pain after trauma, inflammation, and infection have been well described, there is a growing understanding that the entity referred to as “dry eye” or “keratoconjunctivitis sicca” involves similar neuroanatomical pain pathways within the trigeminal system (8,9). Similar to chronic pain outside the eye, studies estimate a worldwide prevalence of 5–33% for symptoms of dry eye (1).

Traditional treatments for dry eye target the ocular surface and tear film, and include artificial tears, anti-inflammatories, punctal closure, eyelid hygiene, and antibiotics (2–4). Yet many patients, especially those with ocular complaints consistent with neuropathic pain (i.e. hot burning pain, allodynia and hyperalgesia in the form of sensitivity to light and wind), report less improvement in eye pain with topical therapies (5). In such patients, scattered reports have described partial improvement with agents used to treat neuropathic pain such as tricyclic antidepressants, serotonin reuptake inhibitors, and anticonvulsants including gabapentinoids (4,10–12). Given the side effects of these medications, there is keen interest in evaluating the potential of low risk adjuvant treatments in patients whose ocular pain is refractory to topical ocular therapy.

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive form of neuromodulation that has demonstrated effectiveness in numerous pain conditions (13–16). Specifically, peripheral stimulation including TENS has established utility in alleviating multiple oral and facial pain conditions (17–21). TENS involves the transmission of electrical current to the peripheral nervous system through electrodes placed on the skin surface. The typical modifiable parameters of a TENS device are the intensity (mA), pulse width (ms), and the frequency (Hz). While lower intensities stimulate sensory nerves, higher intensity settings will progressively stimulate an increasing motor nerve response. There are two major theories that explain the analgesic mechanism of TENS: 1) Gate Control Theory and 2) Descending pain inhibitory pathway modulation (22,23). Although now further refined, the Gate Control Theory originally described by Melzack and Wall posited that activation of large diameter afferent fibers results in presynaptic nociceptor inhibition and

activation of inhibitory interneurons, which suppress the transmission of ascending pain signals (22). Later findings that unilateral TENS treatment causes bilateral analgesic effects prompted investigations revealing that TENS exerts descending modulation through activation of inhibitory pathways or inhibition of facilitatory pathways (23,24).

The RS Medical RS-4i Plus Sequential Stimulator® is an electrical stimulation device that delivers current through gel electrodes placed transcutaneously around the site of pain. This device has proven successful in treating a number of pain conditions including knee and back pain (25–29). The device applies conventional TENS and a technology known as interferential current therapy (ICT), which occurs when the two electrodes are set at slightly differing frequencies, for example 5000Hz and 5100Hz. The two frequencies are thought to interfere with one another and create a beat frequency, 100Hz, at points of intersection (30,31). ICT is among the most commonly used electrical modalities employed by physiotherapists and previous limitations of its use were the device bulk and expense compared to many simple TENS devices (31,32). New innovations have made ICT portable, less expensive, and treatments can be performed at home rather than scheduled in clinic. This higher frequency is often preferred since reports of varying modalities have noted less dysesthesia compared to lower frequencies while still exerting the 100Hz treatment at the target site.

While no studies have reported on an ICT modality for ocular pain, we found 4 reports describing the use of TENS for in the setting of ocular pathology and two that studied the effects of TENS in ocular pain (33–36). Although the latter two reported pain relief, the first of these investigated the more invasive subcutaneous application of electrical current and the second from 1991 involved only ten cases in the setting of acute surgical pain (33,34). This study was performed to expand our understanding of electrical stimulation treatment for ocular pain and light sensitivity (e.g. photophobia).

Materials and Methods

All individuals who received electrical stimulation for the treatment of ocular pain at the oculofacial pain clinic of the Miami Veterans Administration (VA) Hospital were included in this retrospective review. Institutional Review Board approval was obtained for the retrospective review of patient records. Data was collected from VistA/CPRS, the VA health care system's centralized electronic medical record as routine in each patient's clinical care.

Patient population

All patients seen in the VA Oculofacial Pain Clinic between May 10, 2016 and April 6, 2017 with chronic ocular pain (>3 months duration) suspected to have a neuropathic component [determined by specific descriptors such as burning, sensitivity to light (e.g. photophobia) and wind and/or discordance between symptoms and signs, that is a high level of symptoms with minimal signs of tear dysfunction] were offered TENS therapeutic treatment. Patients were not offered this therapeutic option if they had a history of a: biomedical electronic devices including a cardiac pacemaker or automatic internal defibrillator, cerebrovascular condition, epilepsy, pregnancy, acute pain of unknown etiology, and skin lesion or injury at the sites of electrode placement. All patients were informed of potential complications to

this type of treatment including but not limited to the following: electrical burns, irritation of skin, exacerbation of pain, and interference with biomedical electronic devices.

Treatment Procedure

All treatments were performed at the VA Oculofacial Pain Clinic. The skin overlying the sites of electrode placement was first cleansed with alcohol pads and allowed to dry. One electrode was placed along the ocular midline above the brow and the second electrode was placed on the temple or lateral ocular region. This placement was performed bilaterally with a total of four electrodes (Figure 1). With this placement, the electrodes were in close proximity to branches of the ophthalmic (V1) and maxillary (V2) nerves of the trigeminal system, including those supplying corneal sensation. The device was then turned on and the preprogrammed therapy started. This program was set to deliver interferential 5000/5100 Hz frequencies, 100 Hz beat frequency, with a variable pulse width and amplitude for 30 minutes. The amplitude was increased manually until the point of discomfort and then set to one level directly below this point. This amplitude adjustment was performed bilaterally and the selected amplitude noted by the technician.

Outcome measures

Utilizing standardized values provided by the RS Medical Engineering Division, the selected level for stimulus intensity in each eye was recorded by conversion to milliamperes (Supplemental Table 1). Ocular pain intensity was assessed with the Defense and Veterans Pain Rating Scale (DVPRS) (Figure 2) developed in 2010 by a Pain Management Task Force of the Department of Defense and Veterans Health Administration as an alternative to the traditional Numeric Rating Scale (37). Assessment occurred immediately prior to treatment, 20 minutes into treatment, 25 minutes into treatment, immediately prior to the end of treatment, and five minutes post-treatment. Dryness and light sensitivity were assessed on a 11-point scale with zero representing none and ten representing the most intense possible.

Five minutes post-treatment, patients were asked to note any side effects or complications on a comments form. Patients were then called the day after treatment to assess any side effects or complications within 24 hours of treatment. They were also asked to describe their pain intensity the day after treatment.

The same ocular technician oversaw all clinical treatments and data collection.

Dry Eye Ocular Examination

In addition to the numeric dry eye pain assessment throughout treatment, dry eye assessment prior to treatment included standardized questionnaires regarding ocular dryness, the Dry Eye Questionnaire 5 (DEQ5) (score 0–22) and Ocular Surface Disease Index (OSDI) (score 0–100), higher scores indicate more severe symptoms (38,39). A value of 6 or greater on the DEQ5 indicates mild or greater dry eye symptoms and a value of 12 or greater indicates severe symptoms (40). OSDI scores over 30 indicate severe dry eye symptoms (41). A Schirmer’s test was performed to measure tear production. During this test, a paper strip is placed into the corner of the eye and the amount of moisture on the strip is measured in

millimeters (mm) after 5 minutes. Normal tear production is indicated at values greater than 10 mm and severely reduced tear production at values less than 5 mm (42).

Statistical Analysis

Data are reported as mean and SD (continuous variables) unless otherwise noted. All parameters were compared pre-treatment and 5 minutes post-treatment via a two-tailed paired Student's *t* test. A $P < 0.05$ was considered statistically significant.

Results

Population

A total of 14 patients were treated. All had dry eye symptoms and most had normal tear production based on the Schirmer's test (Table 1). 1 patient did not complete the full course of treatment due to worsening pain. The remaining 13 patients undertook the full prescribed 30-minute course of treatment noting non-painful paresthesias. Data was analyzed only for those patients who completed the treatment. Age, gender, ethnicity, non-ocular chronic pain conditions, mental health disorders, systemic pain medications, and ocular medications were assessed from the medical record during the visit (Table 2).

TENS settings

We employed a beat frequency of 100 Hz from a 5000 Hz sine wave mixed with another 5100 Hz sine wave. The pulse width was variable dependent on a proprietary algorithm modified by the amplitude. The mean amplitude (standard deviation) empirically determined sub pain threshold for treatment of the right eye was 52.38 (11.09) milliamps (mA) and 48.08 (11.40) mA for the left eye.

Effects of TENS therapy on ocular pain

The use of TENS significantly reduced the mean pain intensity in both the right and left eyes 5 minutes after treatment compared to prior to treatment ($P < 0.05$, paired *t* test) (Figure 3). Pain intensity in the right eye decreased by 57.63% ($P=0.01$) from a mean value of 4.54 (3.18) to 1.92 (2.50). Pain intensity in the left eye decreased by 55.17% ($P=0.01$) from a mean value of 4.46 (3.36) to 2.00 (2.38).

Dryness and light sensitivity were frequently noted eye symptoms with 11 of 13 and 8 of 13 patients, respectively, reporting values greater than 0 prior to treatment. The use of TENS significantly decreased light sensitivity in both eyes ($P < 0.05$). Light sensitivity in the right eye decreased by 27.14% ($P=0.01$) from a mean value of 5.83 (2.95) to 4.25 (3.83). Light sensitivity in the left eye decreased by 28.95% ($P=0.004$) from a mean value of 6.33 (2.91) to 4.50 (3.70). The findings for dryness, however, were equivocal with a significant decrease in the left eye but not the right ($P < 0.05$, paired *t* test). Specifically, dryness in the right eye decreased by 35.90% ($P=0.11$) from a mean value of 3.00 (3.04) to 1.92 (2.81). Dryness in the left eye decreased by 48.89% ($P=0.04$) from a mean value of 3.46 (3.37) to 1.77 (2.89).

Only two of the 14 patients noted any side effects when asked 5 minutes post-treatment. One patient noted epiphora (e.g. excessive tearing) during treatment and the other noted an exacerbation of pain requiring premature cessation of treatment.

None of the patients reported any new side effects or complications the day after treatment. All the patients reported that their pain intensity had returned to the pretreatment baseline by the day after treatment.

Discussion

In this case series, we found that electrical stimulation of the ocular region decreased overall ocular pain intensity by an average of 57.63% (P=0.01) (Right) and 55.17% (P=0.01) (Left), decreased the intensity of light sensitivity by an average of 27.14% (P=0.01) (Right) and 28.95% (P=0.004) (Left), and produced equivocal effects on the intensity of dryness. Our data compares favorably with TENS therapy for other facial pain conditions. TENS has been well investigated as a dental analgesic and demonstrated efficacy in procedures including: rubber dam placement, cavity preparation, pulp capping and other endodontic procedures, prosthetic tooth preparations, and extractions (17). A randomized control trial by Hanson et al. examined TENS (2–100 Hz) in acute oro-facial pain and observed that 38% of the 64 patients experienced a decrease in pain intensity by greater than 50% (21). Two additional studies examined the effect of multiple TENS treatments for facial pain over a period of three weeks to two years (20,43). Although the magnitude was not measured, the first study found that 32% of the 50 patients treated with TENS (20–100 Hz) daily for three months experienced successful or moderately successful pain relief (20). The second study by Bremerich et al found a mean Visual Analog Scale (VAS) reduction of 6.2 after several weeks of daily (5–100 Hz) treatment (43). A separate study conducted on 30 patients with trigeminal neuralgia who were given repeated treatments of TENS (1–150 Hz) found that mean VAS scores decreased from 8.9 (Pre TENS) to 3.1 at 1 month and 1.3 at 3 months (44). None of these previous studies utilized ICT and none used TENS frequencies higher than 150 Hz making comparisons with our study difficult (20,21,43,44).

Dry eye is a common condition, with 12% of males and 22% of females carrying this diagnosis in a South Florida veteran population (45). In a separate study of veterans, we found that the majority of individuals with dry eye symptoms also reported ocular pain; 37% described spontaneous burning ocular pain, 47% reported sensitivity to wind, and 37% reported sensitivity to light (10). In many individuals, treatment of ocular pain is refractory to standard topical therapies (e.g. artificial tears, anti-inflammatories) suggesting a neuropathic component. Since treatment is applied transcutaneously, TENS is less invasive than surgical therapy and relatively inexpensive compared to pharmaceutical therapies.

Supporting this idea, all our patients had concomitant chronic non-ocular pain conditions, most frequently chronic low back. This is not surprising given the concept that some forms of chronic pain do not exist in isolation and individuals with these chronic pain conditions tend to have other concomitant pain conditions, a concept termed chronic overlapping pain conditions (46). In fact, pain mechanisms driving symptoms in these different sites are likely similar (e.g. peripheral and central sensitization, glial activation, inflammation). As such,

therapies effective in the treatment of non-ocular pain may be useful to treat ocular pain, given the likelihood of shared underlying mechanisms (47).

Several pathways may mediate chronic ocular pain (4,8,48). Components of these pathways may be amenable to TENS (with or without ICT) treatment resulting in clinical benefit for dry eye symptoms (e.g. pain and photophobia). These neuroanatomical pathways of corneal sensation travel from the nasociliary branch of the trigeminal ophthalmic division (V1) to the spinal trigeminal nuclear complex (Vi/Vc, Vc/C1). Second order axons then join the contralateral spinothalamic pathway which projects to the thalamus prior to synapsing with third order neurons ascending to supraspinal centers including the somatosensory cortex (48). Chronicity of ocular pain develops as a result of peripheral or central sensitization that are also observed in neuropathic pain conditions outside of the eye (4). Corneal polymodal nociceptors are known to develop features of sensitization (e.g. increased transduction and conduction) after injury and exposure to an inflammatory milieu (49). In support of this, many mediators involved in the generation of peripheral sensitization, such as TNFα, IL1, IL6, PGE_2, MMP-9, and NGF are elevated in the tears of patients with dry eye. Investigators also observed sensitization of central somatosensory nerves with connections to the eye (50). Specifically, sensitization was observed in trigeminal nucleus caudalis neurons as demonstrated by increased sensitivity to ocular stimulus and increased convergent input from periocular skin in models of lacrimal gland resection, uveitis and photokeratitis (50–52). Thus, it is plausible that like neuropathic pain elsewhere in the body, ocular pain associated with sensitization of the trigeminal system may be responsive to TENS therapy.

Photophobia or extreme light sensitivity is similarly linked to trigeminal–thalamic–cortical pathways (53,54). Okamoto et al. found that light responsive retinal photodetectors activated the superior salivatory nucleus which then evoked ocular vasodilation and activation of ocular trigeminal afferent neurons on blood vessels (55). Concomitantly, Noseda et al., found in a rat model that select intrinsically photosensitive retinal ganglion cells (IPRGCs) directly synapse with discrete regions of the posterior thalamus which are associated with somatosensation and pain (56).

Keeping this anatomy and pathophysiology in mind, the reduction in ocular pain intensity and light sensitivity may be related to modulation of these trigeminal–thalamic–cortical pathways. Since TENS is applied peripherally, it may modulate photophobia through an effect on the distal components of these circuits such as the retinal photodetectors, trigeminal afferents, or IPRGCs. Retinal cells can be activated directly through electrical stimulation and a rabbit model has demonstrated a decreasing amplitude of extracellular action potentials with increasing frequencies of repetitive stimulation (57). Thus, it is possible that TENS may desensitize the ability of retinal cells to respond to stimuli, such as light, and thereby reduce photophobia. Another possible site of action is the trigeminal-cervical complex where the photophobia and pain pathways converge. There is no data on ICT for ocular pain and it is not known whether the overlying 5000–5100Hz tonic frequencies had an independent effect on ocular pain, beyond the proposed delivered frequency of 100 Hz.

Our findings need to be considered bearing in mind the limitations of this retrospective case series, which included a small population, a specific machine and treatment protocol, lack of a control group, and no data on the effect of repeated TENS therapy on ocular pain and photophobia reduction. Furthermore, based on this case series, we cannot comment on the durability of this treatment response as data were not collected between 5 minutes and one-day post treatment. Nonetheless, we do know that our patients' ocular symptoms returned to baseline by the first day follow up. This is not surprising given that an animal model of TENS has noted that the effects on dorsal horn cells are short lasting (58). Additionally, we used a single waveform and electrode location and it is not known if these are optimal for trigeminal mediated ocular pain. As such, we may be able to increase treatment effect through further optimization of stimulation parameters and dosing interval.

Despite these limitations, we found that noninvasive transcutaneous electrical nerve stimulation of the trigeminal nerve provided short-term reductions in ocular pain and photophobia. This study is novel as we examined the use of TENS to alleviate symptoms co-morbid with sensations of dryness, namely ocular pain intensity and photophobia, and delivered therapy with a high (kHz) frequency based ICT. Further studies will be required to elucidate optimal techniques, identify which patients are most likely to benefit, and evaluate long-term effects of similar treatments. Given what is known about the use of neuromodulation therapies for non-ocular pain, continuous daily treatment or intermittent treatment during pain exacerbation may be optimal for clinically meaningful pain relief.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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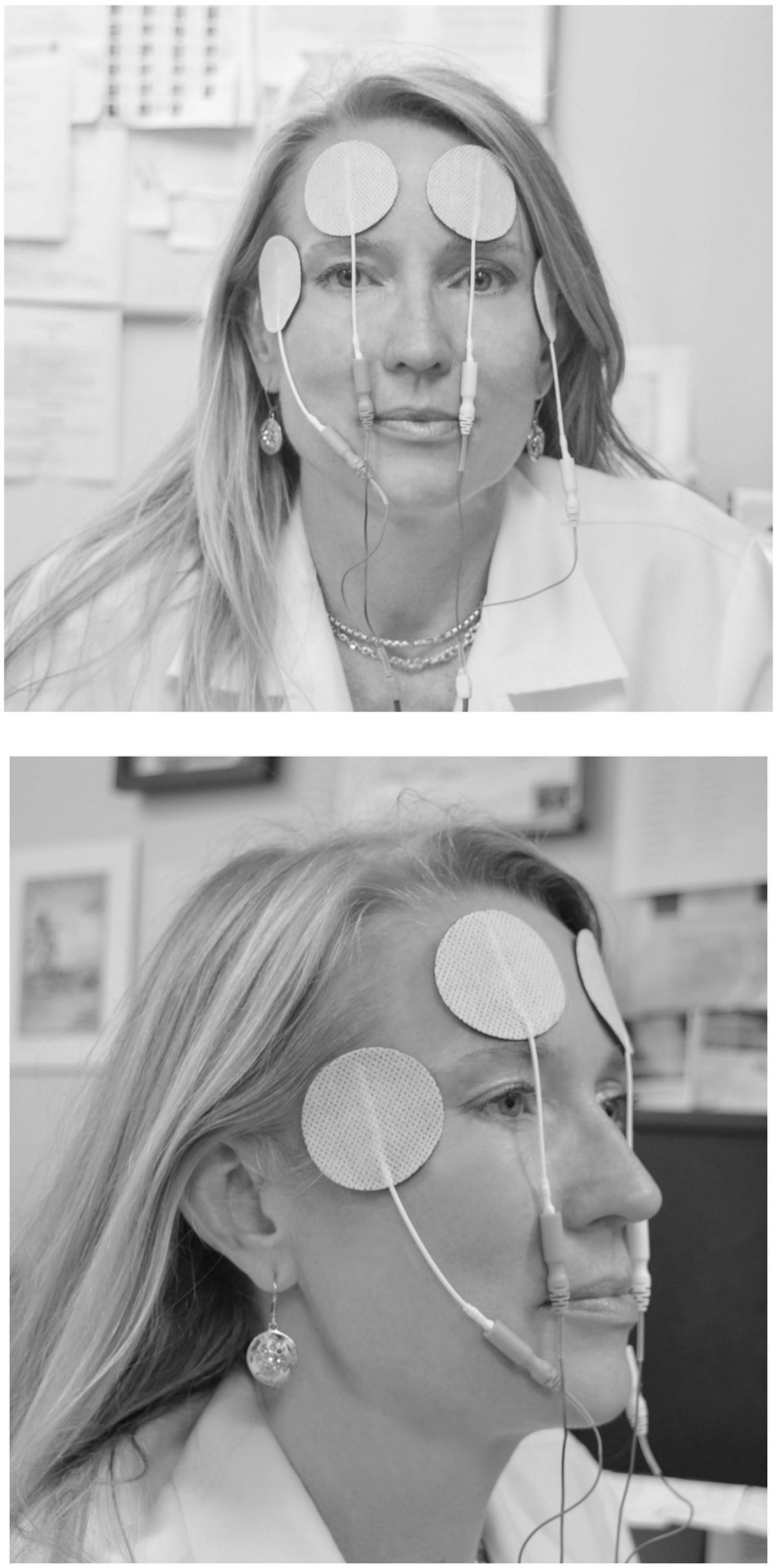

Figure 1.

(A, B). Electrode Placement for Chronic Ocular Pain. One electrode was placed along the ocular midline above the brow and the second electrode was placed on the temple or lateral ocular region. This placement was performed bilaterally with a total of four electrodes.

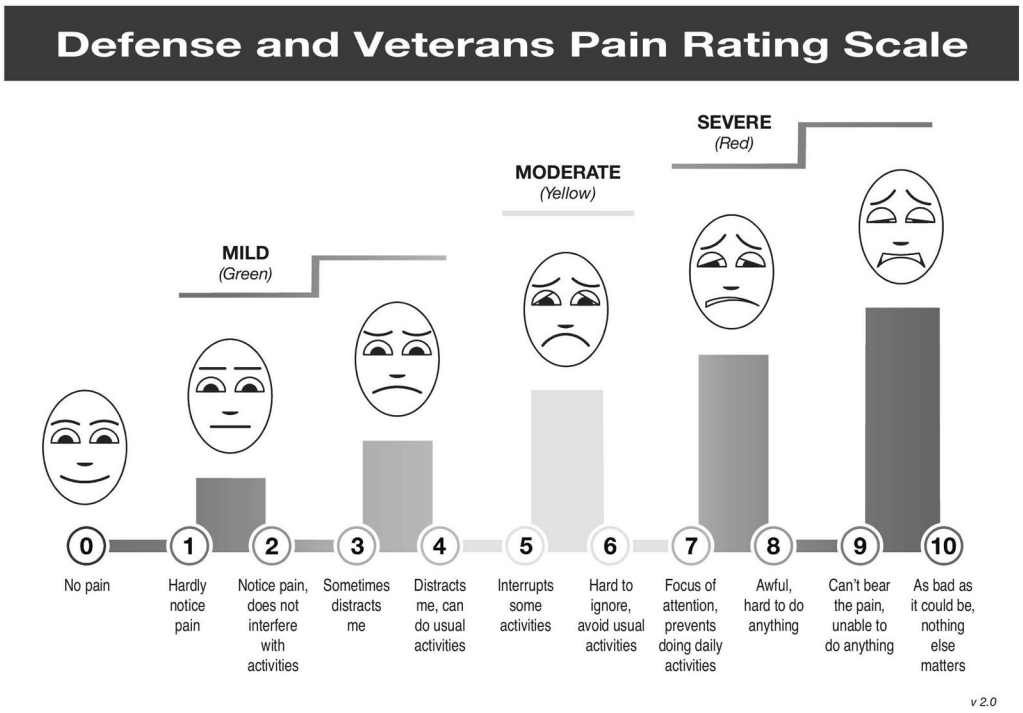

Figure 2.

The Defense and Veterans Pain Rating Scale (DVPRS), developed by the Army Surgeon General Pain Management Task Force (37,59).

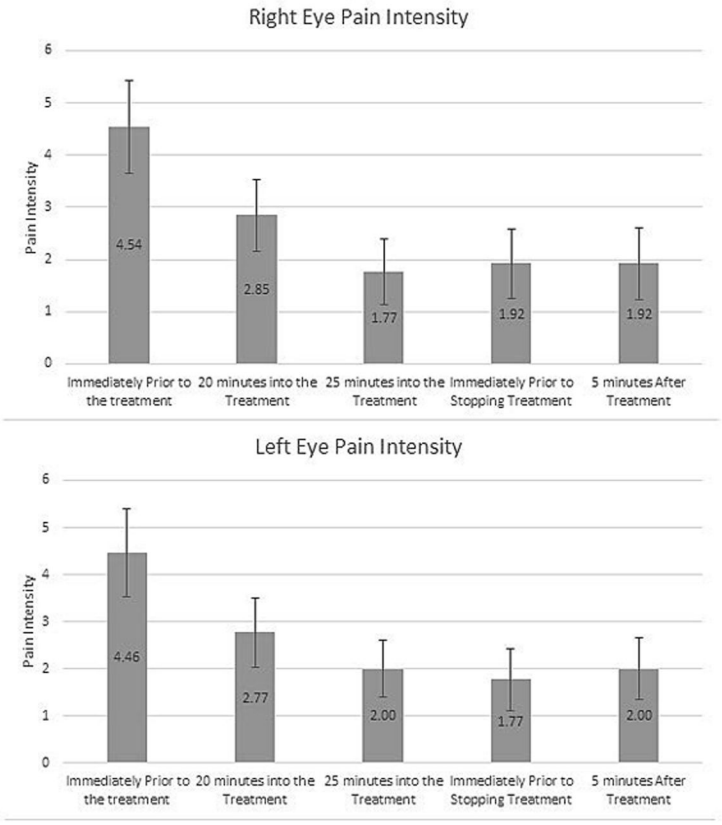

Figure 3.

Mean ocular pain intensity (N=13) in the right and left eye immediately prior to treatment, 20 minutes into treatment, 25 minutes into treatment, immediately prior to the end of treatment, and five minutes post-treatment (Standard error denoted by brackets). Ocular pain intensity was assessed with the Defense and Veterans Pain Rating Scale (DVPRS).

Table 1

Dry Eye Ocular Examination

Patient #	DEQ5	OSDI	Schirmer's (Right) (mm)	Schirmer's (Left) (mm)
1	8	50	6	5
2	14	50	12	12
3	15	83	16	22
4	18	92	13	9
5	20	N/A	10	10
6	18	26	25	15
7	18	63	13	13
8	N/A	21	33	28
9	15	56	14	12
10	18	79	12	9
11	14	35	12	10
12	14	56	10	14
13	21	96	17	9

Pt=patient number; DEQ5=dry eye questionnaire 5 (score 0–22); OSDI= ocular surface disease index (score 0–100); OD=right; OS=left

*N/A=not applicable due to incomplete or empty questionnaire

Table 2

Demographics, Past Medical History, Systemic pain medications, and Ocular medications

Pt	Age	Sex	Race/ ethnicity	Non-ocular chronic pain conditions	Mental health disorders	Systemic pain medications	Ocular medication
1	58	F	W/NH	Ankle Pain, Shoulder Pain,	Depression	Cyclobenzaprine, Ibuprofen, Tramadol	Cyclosporine, Fluorometholone
2	36	F	W/H	Chronic Low Back Pain, Fibromyalgia, Migraine, Insomnia, IBS, Carpal Tunnel	Depression	Acetaminopen, Oxycodone, Lidocaine Topical, Meloxicam, Methocarbamol, Pregabalin	Olopatadine
3	57	M	B/NH	Chronic Low Back Pain, Knee Pain, Inflammatory Arthritis, Carpal Tunnel	Depression	Cyclobenzaprine, Diclofenac Topical, Tramadol	Cyclosporine, Artificial tears
4	34	M	B/NH	Chronic Low Back Pain, Shoulder Pain, Headache		Gabapentin	Lubricating Solution
5	46	M	W/NH	Chronic Low Back Pain, Knee Pain, Migraine	Anxiety Personality Disorder	Acetaminophen, Codeine, Capsaicin, Chlorzoxazone, Ibuprofen, Lidocaine Topical, Pregabalin, Tramadol	Fluoromethalone, Artificial tears
6	46	F	W/H	Chronic Low Back Pain, Fibromyalgia, IBS	PTSD, Depression, Anxiety	Capsaicin, Ibuprofen, Menthol/Salicylate Topical	Cyclosporine, Artificial tears
7	52	M	W/H	Chronic Low Back Pain	None	Gabapentin, Codeine/Acetaminophen	Lubricating Solution,
8	30	M	W/NH	Chronic Low Back Pain, Migraine, TBI	PTSD	Menthol/M-Salicylate Topical, Ibuprofen, Naproxen	None
9	32	M	W/H	Chronic Low Back Pain, Migraine, TBI	PTSD	Diclofenac, Amitriptyline	None
10	61	M	W/NH	Chronic Neck Pain, Opioid Dependence	None	Gabapentin, Diclofenac Topical, Buprenorphine/Naloxone	Cyclosporine
11	65	M	W/H	Chronic Low Back Pain, Opioid Dependence, IBS, OA	Depression	Baclofen, Celecoxib, Duloxetine, Gabapentin, Lidocaine Topical, Meloxicam	Lifitegrast, Artificial tears
12	47	M	W/H	Chronic Low Back Pain, Migraine, TBI	PTSD	Gabapentin, Meloxicam	None
13	62	M	W/NH	Peripheral Neuropathy	Schizophrenia	None	Dorzolamide/Timolol, Artificial tears
14	34	M	W/H	Chronic Low Back Pain, Knee Pain	PTSD, Depression	Naproxen	Lubricating Solution

Pt=patient number; F=female; M=male; W=white; B=black, NH=not hispanic