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ORIGINAL ARTICLE

Is gabapentin effective in dry eye disease and neuropathic ocular pain?

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Abstract

This study aims to evaluate the efficacy of gabapentin treatment in dry eye disease (DED) and neuropathic ocular pain. Our study was performed with 72 patients. The painDETECT questionnaire was used for neuropathic pain screening. Patients who were thought to have severe DED according to ocular surface disease index (OSDI) questionnaire, Schirmer's test type 1 and tear break up time test results were treated with artificial tear and cyclosporine drops. Gabapentin treatment was also initiated in addition to artificial tear and cyclosporine drops treatments to the patients with neuropathic component and DED findings. We divided the patients into two groups: group 1 (n: 36), patients treated with artificial tear and cyclosporine drops and group 2 (n: 36), patients treated with artificial tear, cyclosporine drops and gabapentin. In the first evaluation, no significant differences were found between groups in terms of OSDI score, Schirmer's test result and TBUT. After the 6 weeks of treatment, in both groups OSDI score, Schirmer's test result and TBUT statistically significantly improved. OSDI score, Schirmer's test result and TBUT significantly improved after the 6 weeks of gabapentin treatment than artificial tear and cyclosporine treatment group ($p < 0.001$). Dry eye patients should be screened for neuropathic ocular pain symptoms and individualized treatment has to be applied. Our study showed that the use of gabapentin is effective in severe dry eye patients with neuropathic ocular pain.

Keywords Gabapentin · Dry eye disease · Neuropathic ocular pain

Introduction

Dry eye disease (DED) is a common cause of chronic ocular pain [1]. It is associated with ocular discomfort, pain and visual impairment due to tear dysfunction and ocular surface damage [2]. Due to the high density and superficial location of corneal nociceptors, damage or dysfunction in the corneal somatosensory pathway is considered to be a part of DED in some patients [3]. Persistent damage or inflammation on the ocular surface as a repetitive injury to the corneal nerves may result in abnormal activation of the sensory fibers of the eye resulting in chronic neuropathic ocular pain [4]. Neuropathic ocular pain is characterized by symptoms such as dysesthesia (unpleasant abnormal sensations), spontaneous pain, allodynia (pain response to innoxious stimuli including light and wind) and hyperalgesia (exaggerated pain to noxious stimuli) [5, 6]. Inadequate response to tear dysfunction therapies should require consideration of neuropathic mechanisms. Neuropathic symptoms are caused by a lesion or disease of the somatosensory nervous system and may be occurred by hypersensitization of peripheral or central corneal and conjunctival somatosensory nerves.

Central sensitization may occur as a result of the continuous activation of nociceptors and the progression of peripheral sensitivity [5]. Persistent activity of corneal nociceptors promotes the release of glutamate from presynaptic afferent neurons, leading to the activation of *N*-methyl-D-aspartic acid (NMDA) receptors [7]. Chronic neuropathic pain is often treated with gabapentinoids due to its effects on central pain pathways. Gabapentin is a molecule with class 1 and A levels in neuropathic pain treatment, which reduces the release of multiple excitatory neurotransmitters and increases the concentration of γ-aminobutyric acid (GABA) by binding to the α2δ subunit of presynaptic N type voltage-gated calcium channels [8]. In a study, it was shown that pain

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was significantly reduced after photorefractive keratectomy operation with gabapentin use [9]. Gabapentin may likewise be useful for the treatment of DED.

The aim of this study was to evaluate the efficacy of gabapentin treatment in DED and neuropathic ocular pain.

Methods

Our study was performed with 72 patients in Burdur State Hospital Neurology and Ophthalmology Clinics. This study was approved by Pamukkale University Medical School Non-Interventional Clinical Trials Ethics Committee. It has been conducted in accordance with the principles of Helsinki Declaration. All participants were informed about the purpose and procedures and their written informed consent was obtained to participate in this study. Participation in this study was voluntary and patients were free to withdraw from the project at any time.

The painDETECT questionnaire (PD-Q) was used for neuropathic pain screening in patients admitted to the neurology clinic. PD-Q is designed to screen for neuropathic signs and symptoms without physical examination and it was shown as a reliable and valid scale to determine neuropathic component of chronic pain in Turkish patients [10]. Patients with PD-Q score > 18 were considered positive for neuropathic component. All patients enrolled in the study were evaluated in terms of dry eye findings after routine examination in ophthalmology clinic. Patients who were thought to have severe DED according to ocular surface disease index (OSDI) questionnaire (score 0–100, higher scores representing greater disability) [11], Schirmer's test type 1 (result of < 5 mm at 5 min.) and tear break up time (TBUT < 5 s) test results and who had symptoms for more than 6 months were treated with artificial tear and cyclosporine drops. Gabapentin treatment was also initiated in addition to artificial tear and cyclosporine drops treatments to the patients with neuropathic component and DED findings. Gabapentin therapy was initiated 600 mg/day (300 mg, two times a day) on day 1, 900 mg/day (300 mg, three times a day) on day 2 and the dose was titrated up to 1800–2400 mg/day as needed for pain relief.

We divided the patients into two groups: group 1 (*n*: 36), patients treated with artificial tear and cyclosporine drops and group 2 (*n*: 36), patients treated with artificial tear, cyclosporine drops and gabapentin.

Patients who had ocular diseases (glaucoma, keratitis, corneal scar, retinopathy, contact lens use, and recent ocular surgery in 3 months), diabetes (with or without retinopathy and/or neuropathy), rheumatological diseases (arthritis, SLE, Sjogren, and scleroderma), oncological diseases, hyperthyroidism, hypothyroidism, vitamin B and vitamin D deficiencies, hepatic or renal failure were excluded. Also patients who use analgesic or antiinflammatory drugs or who can not tolerate gabapentin because of the side effects or failed during the follow-up were excluded.

Patients were examined by the same neurologist and ophthalmologist at the first visit and after 6 weeks of daily artificial tear and cyclosporine drops treatment and gabapentin treatment. OSDI scores, Schirmer's test and TBUT scores were compared between the groups at the first visit and after 6 weeks follow-up. SPSS software version 21 (IBM, Chicago, IL, USA) was used for the analysis. Numerical variables were indicated as mean and standard deviation (SD). The Kolmogorov–Smirnov test was applied to determine the normality of the distribution and independent samples *t* test was used for the comparison of the scores. Statistical significance was set at $p < 0.05$.

Results

72 patients were enrolled in the study (36 patients in each group). Group 1 consisted of 20 female and 16 male; group 2 consisted of 21 female and 15 male. The mean age of the group 1 was 43.2 ± 6.3 years and the mean age of group 2 was 46.1 ± 6.9 years. No significant difference was observed between the groups in terms of gender and age. The characteristics of the groups are shown in Table 1.

In the first evaluation, no significant differences were found between groups in terms of OSDI score, Schirmer's test result and TBUT [group 1: OSDI score 70.11 ± 18.04, Schirmer's test (mm) 3.12 ± 1.01, TBUT (s) 3.69 ± 1.14; group 2: OSDI score 66.82 ± 16.10, Schirmer's test (mm) 3.80 ± 1.43, TBUT (s) 3.91 ± 1.31] (Table 2). After the 6 weeks of treatment, in both groups OSDI score, Schirmer's test result and TBUT statistically significantly improve. [Group 1: OSDI score 49.41 ± 16.70, Schirmer's test (mm) 10.09 ± 2.63, TBUT (s) 9.94 ± 1.73; Group 2: OSDI score 31.13 ± 11.52, Schirmer's test (mm) 14.17 ± 2.95, TBUT (s) 12.84 ± 1.98] (Table 3). Anterior segment photos that illustrate the improvement of DED are shown in Fig. 1.

Comparison of OSDI score, Schirmer's test result and TBUT between groups after the 6 weeks of treatment is

Table 1 Characteristics of the patients

	Group 1 (*n*: 36)	Group 2 (*n*: 36)	*p* value
Age, years (mean ± SD)	43.2 ± 6.3	46.1 ± 6.9	0.39[a]
Gender			
Male (*n*, %)	16	15	0.27[b]
Female (*n*, %)	20	21	

SD standard deviation

[a]Independent samples *t* test

[b]Chi square test

Table 2 Comparison of dry eye tests at the first evaluation

	Group 1	Group 2	*p* value
OSDI score (mean ± SD)	70.11 ± 18.04	66.82 ± 16.10	0.14
Schirmer's test, mm (mean ± SD)	3.12 ± 1.01	3.80 ± 1.43	0.29
TBUT, s (mean ± SD)	3.69 ± 1.14	3.91 ± 1.31	0.11

SD standard deviation, *OSDI* ocular surface disease index, *mm* millimeters, *s* seconds

shown in Table 4. Statistically significantly improved results were determined in gabapentin treatment group than group 1 ($p < 0.001$).

Discussion

According to the data we obtained in our study, although topical surface treatment in DED and neuropathic ocular pain was found to be beneficial alone, addition of gabapentin to treatment resulted in significant improvement in dry eye evaluation test scores and ocular pain compared to topical surface treatment.

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory system [12]. Symptoms of neuropathic pain such as dysesthesia, hyperalgesia and allodynia are caused by peripheral and central somatosensory changes and sensitization due to recurrent neurogenic damage [7]. A similar description is used by DED patients including dryness, burning, aching, grittiness, jabbing and foreign body sensation which may occur spontaneously or triggered by innoxious stimuli. Chronic severe or recurrent axonal damage may lead to regeneration of corneal nociceptors. With regeneration, the injured nerve can develop some changes that may be a source of spontaneous pain [7]. These features suggest a pathophysiological relation between DED and other neuropathic pain conditions. A study revealed that the severity and persistence of dry eye symptoms were related to the symptoms of neuropathic ocular pain [13]. In a study, after laser in situ keratomileusis (LASIK), the cause of dry eye symptoms were thought to be pathological neuroplasticity in peripheral and central sensitization [14]. In another study, mechanical detection and pain thresholds measured on the cornea were associated with dry eye symptoms and ocular pain. These findings propose hypersensitivity within the corneal somatosensory pathways in patients with severe dry eye and ocular pain complaints as underlying pathology [15]. In our study, first time in literature, we used gabapentin to ameliorate symptoms of neuropathic ocular pain in DED. Our results also can be an evidence for a central disorder perhaps with central sensitization as the underlying mechanism for neuropathic ocular pain in dry eye patients. Therefore, treatment in severe DED patients should target central sensitization with centrally acting drugs like gabapentin. Our findings suggest that dry eye disease should not only be considered as limited to the eye, but also systemic therapies should be thought.

The relationship between dry eye disease and chronic pain syndromes has been shown in clinical studies. In these studies, more severe dry eye symptoms and neuropathic ocular pain scores were reported in dry eye disease patients who were accompanied by comorbid chronic pain syndromes [16, 17]. In case of inadequate response to topical surface treatment in dry eye symptoms, neurological factors should be considered [18]. The evaluation of non-ocular neuropathic symptoms may indicate the presence of systemic neuropathy, as well as central sensitization, which is the cause of ocular pain [19]. Identification of such neuropathy might suggest a pathway for management of ocular symptoms and the treatment of accompanying neurological condition can help to control DED. In our study, the presence of neuropathic symptoms was evaluated with PD-Q. The PD-Q is a reliable screening questionnaire that was designed to detect the presence of a neuropathic component. Patients who have a probable neuropathic component were treated with gabapentin together with topical surface therapy. Although there was no difference in dry eye findings at the beginning, significantly improved results were obtained in the group treated with gabapentin than the group treated with topical

Table 3 Comparison of dry eye severity at enrollment and after 6 weeks of therapy

	Before treatment	After treatment	*p* value
Group 1			
OSDI score (mean ± SD)	70.11 ± 18.04	49.41 ± 16.70	< 0.001
Schirmer's test, mm (mean ± SD)	3.12 ± 1.01	10.09 ± 2.63	< 0.001
TBUT, s (mean ± SD)	3.69 ± 1.14	9.94 ± 1.73	< 0.001
Group 2			
OSDI score (mean ± SD)	66.82 ± 16.10	31.13 ± 11.52	< 0.001
Schirmer's test, mm (mean ± SD)	3.80 ± 1.43	14.17 ± 2.95	< 0.001
TBUT, s (mean ± SD)	3.91 ± 1.31	12.84 ± 1.98	< 0.001

SD standard deviation, *OSDI* ocular surface disease index, *mm* millimeters, *s* seconds

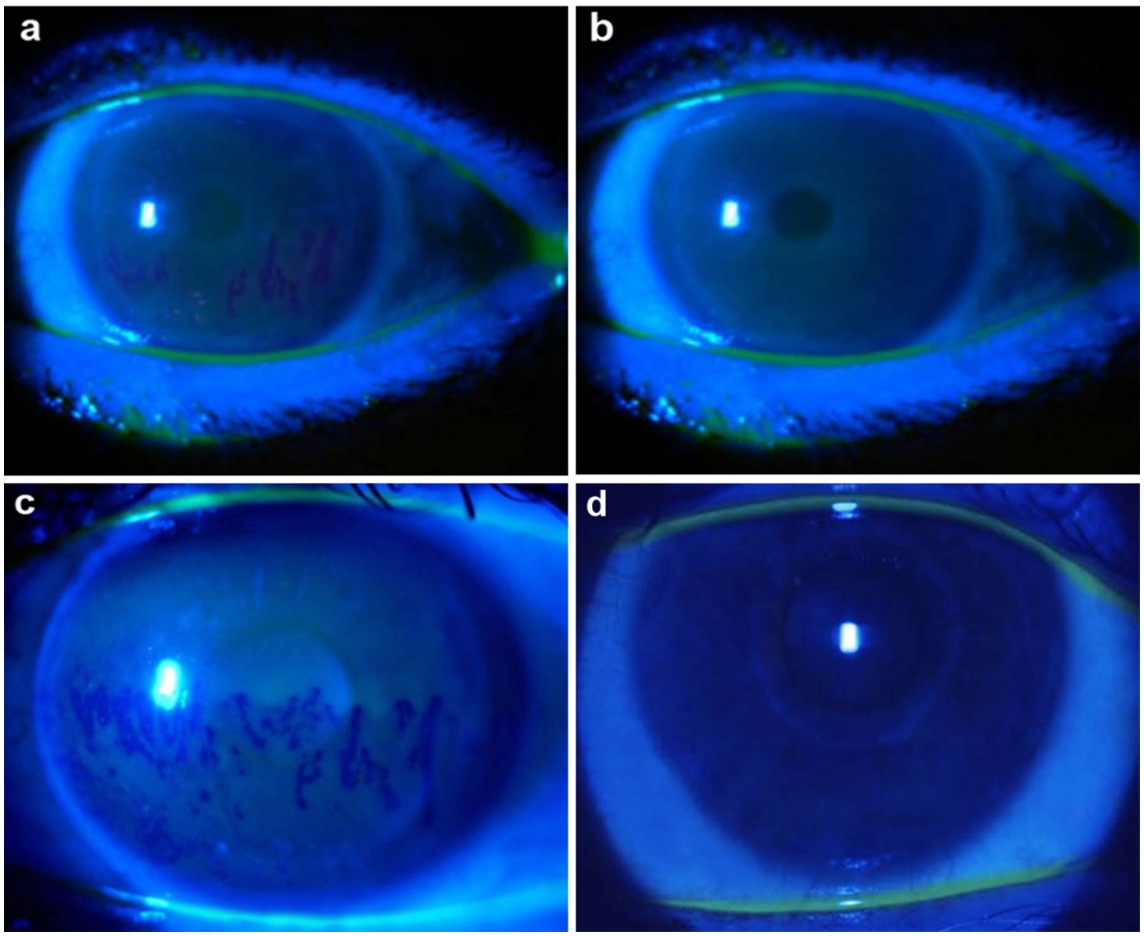

Fig. 1 Anterior segment photos that illustrate the improvement of DED. **a** Group 1 first visit. **b** Group 1 after treatment with artificial tear and cyclosporine drops. **c** Group 2 first visit. **d** Group 2 after treatment with artificial tear, cyclosporine drops and gabapentin

Table 4 Comparison of dry eye tests after 6 weeks of treatment

	Group 1	Group 2	*p* value
OSDI score (mean ± SD)	49.41 ± 16.70	31.13 ± 11.52	< 0.001
Schirmer's test, mm (mean ± SD)	10.09 ± 2.63	14.17 ± 2.95	< 0.001
TBUT, s (mean ± SD)	9.94 ± 1.73	12.84 ± 1.98	< 0.001

SD standard deviation, *OSDI* ocular surface disease index, *mm* millimeters, *s* seconds

surface agents alone. It is important to use systemic therapies from early stages of neuropathic ocular pain especially in patients with neuropathic symptoms.

Clinical manifestations of neuropathic ocular pain may be caused by multiple pathologies in the corneal somatosensory pathway. Therefore, treatments targeting different regions of the pain pathway should be used together [20]. Chronic neuropathic pain is often treated with gabapentinoids due to its effects on central pain pathways. Gabapentin is a first line recommended drug for the treatment of neuropathic pain and frequently used in neurology practice. It inhibits the release of excitatory neurotransmitters by blocking the voltage-gated calcium channels [8]. Despite evidence that dry eye disease symptoms may be associated with neuropathic pain, limited data are available to support the use of neuropathic pain therapy in dry eye management. Some studies report the use of topical non-steroidal antiinflammatory drugs and opioids in ocular pain patients [5, 21, 22]. In a prospective, placebo-controlled study, gabapentin was shown to reduce postoperative pain significantly after photorefractive surgery [9]. There is no previous study on the use of gabapentin in neuropathic ocular pain in DED. To our knowledge, this is the first study about using a centrally acting neuromodulator drug in DED. Also our results provide evidence that ocular symptoms are associated with underlying central pain-processing disorder in dry eye patients.

There are some limitations in our study. First, our sample size is small. Although our results are important, generalization may not be done about using a systemic neuropathic

pain drug in all severe dry eye patients. Second, only severe DED patients were enrolled in our study. Further studies are needed about the treatment of neuropathic symptoms in patients with tear dysfunction and mild-moderate dry eye.

DED is an important health problem due to its significant morbidity. Effective and appropriate treatment depends on new studies about the complex pathophysiology behind the disease. Our study is important because our data showed that appropriate treatment of symptoms affect clinical outcomes. An integrated treatment approach would be useful in dry eye patients, especially with neuropathic symptoms. Therefore, we recommend that dry eye patients should be screened for neuropathic ocular pain symptoms and individualized treatment has to be applied. To our knowledge, this is the first study in the literature showing that the use of gabapentin is effective in severe dry eye patients with neuropathic ocular pain.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval This study was approved by Pamukkale University Medical School Non-Interventional Clinical Trials Ethics Committee.

References

1. The epidemiology of dry eye disease (2007) Report of the epidemiology subcommittee of the international dry eye workshop. Ocul Surf 5:93–107
2. Galor A, Feuer W, Lee DJ, Florez H, Venincasa VD, Perez VL (2013) Ocular surface parameters in older male veterans. Investig Ophthalmol Vis Sci 54:1426–1433
3. Guthoff RF, Wienss H, Hahnel C, Wree A (2005) Epithelial innervation of human cornea: a three-dimensional study using confocal laser scanning fluorescence microscopy. Cornea 24:608–613
4. Belmonte C, Acosta MC, Merayo-Lloves J et al (2015) What causes eye pain? Curr Ophthalmol Rep 3:111–121
5. Kalangara JP, Galor A, Levitt RC, Felix ER, Alegret R, Sarantopoulos CD (2016) Burning eye syndrome: do neuropathic pain mechanisms underlie chronic dry eye? Pain Med 17(4):746–755
6. Galor A, Levitt RC, Felix ER, Martin ER, Sarantopoulos CD (2015) Neuropathic ocular pain: an important yet underevaluated feature of dry eye. Eye (Lond) 29(3):301–312
7. Goyal S, Hamrah P (2016) Understanding neuropathic corneal pain—gaps and current therapeutic approaches. Semin Ophthalmol 31(1–2):59–70
8. Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P (2006) EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 13:1153–1169
9. Lichtinger A, Purcell TL, Schanzlin DJ, Chayet AS (2011) Gabapentin for postoperative pain after photorefractive keratectomy: a prospective, randomized, double-blind, placebo-controlled trial. J Refract Surg 27(8):613–617
10. Alkan H, Ardıc F, Erdogan C, Sahin F, Sarsan A, Findikoglu G (2013) Turkish Version of the painDETECT Questionnaire in the assessment of neuropathic pain: a validity and reliability study. Pain Med 14:1933–1943
11. Irkec MT, Turkish OSDI Study Group (2007) Reliability and validity of turkish translation of the ocular surface disease index (OSDI) in dry eye syndrome. Investig Ophthalmol Vis Sci 48(13):408
12. Jensen TS, Baron R, Haanpaa M et al (2011) A new definition of neuropathic pain. Pain 152(10):2204–2205
13. Galor A, Zlotcavitch L, Walter SD et al (2015) Dry eye symptom severity and persistence are associated with symptoms of neuropathic pain. Br J Ophthalmol 99(5):665–668
14. Chao C, Golebiowski B, Stapleton F (2014) The role of corneal innervation in LASIK-induced neuropathic dry eye. Ocul Surf 12(1):32–45
15. Spierer O, Felix ER, McClellan AL et al (2016) Corneal mechanical thresholds negatively associate with dry eye and ocular pain symptoms. Investig Ophthalmol Vis Sci 57(2):617–625
16. Vehof J, Kozareva D, Hysi PG et al (2013) Relationship between dry eye symptoms and pain sensitivity. JAMA Ophthalmol 131(10):1304–1308
17. Crane AM, Levitt RC, Felix ER, Sarantopoulos KD, McClellan AL, Galor A (2017) Patients with more severe symptoms of neuropathic ocular pain report more frequent and severe chronic overlapping pain conditions and psychiatric disease. Br J Ophthalmol 101(2):227–231
18. McMonnies CW (2017) The potential role of neuropathic mechanisms in dry eye syndromes. J Optom 10(1):5–13
19. Crane AM, Feuer W, Felix ER, Levitt RC, McClellan AL, Sarantopoulos KD, Galor A (2017) Evidence of central sensitisation in those with dry eye symptoms and neuropathic-like ocular pain complaints: incomplete response to topical anaesthesia and generalised heightened sensitivity to evoked pain. Br J Ophthalmol 101(9):1238–1243
20. McGreevy K, Bottros MM, Raja SN (2011) Preventing chronic pain following acute pain: risk factors, preventive strategies, and their efficacy. Eur J Pain Suppl 5:365–372
21. Zollner C, Mousa S, Klinger A, Förster M, Schäfer M (2008) Topical fentanyl in a randomized, double-blind study in patients with corneal damage. Clin J Pain 24(8):690–696
22. Wenk HN, Nannenga MN, Honda CN (2003) Effect of morphine sulphate eye drops on hyperalgesia in the rat cornea. Pain 105(3):455–465