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Original Research Article

Efficacy of diquafosol sodium combined with M22 optimized pulsed light in the treatment of dry eye due to meibomian gland dysfunction

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Abstract

Purpose: *To determine the efficacy and safety of 3 % diquafosol sodium combined with M22 optimized pulse light (OPT) in the treatment of dry eye due to meibomian gland dysfunction (MGD).*
Methods: *Data from 97 dry eye patients admitted to Shantou Balder Eye Hospital with MGD-induced dry eye illness between August 2019 and June 2021 were retrospectively reviewed and analyzed. Patients meeting MGD diagnostic criteria in ophthalmology and exhibiting MGD-induced dry eye signs were split into two groups. The medication group (43 cases) received 3 % diquafosol sodium eye drops six times a day for three months, while the pulsed light group (44 cases) underwent three M22 OPT sessions at one-month intervals. Treatment efficacy of the two methods were compared by assessing changes in ocular surface, symptom severity, inflammatory factors (hs-CRP, IL-8, IL-1β), and quality of life before and three months after treatment commenced. Adverse reactions were also recorded.*
Results: *Pulsed light group showed a slightly higher (but not significant) total effective rate (95.45 %) than the medication group (93.02 %; $p > 0.05$). Three months post-treatment, both groups exhibited significant improvements in various indicators such as FL, OSDI, symptom scores, tear biomarker levels, and overall eye health ($p < 0.05$). The incidence of adverse reactions was similar between the medication (4.65 %) and pulsed light (9.09 %) groups.*
Conclusion: *Treatment with 3 % diquafosol sodium and M22 OPT for MGD-induced dry eye yields comparable efficacy and safety, improving symptoms, ocular surface function, reducing inflammation, and enhancing quality of life. However, 3 % diquafosol sodium shows better patient tolerance and fewer adverse reactions, but further research is needed due to the limited number of patients in this study.*

Keywords: *Meibomian gland dysfunction, Dry eye, Diquafosol sodium eye drops, Optimized pulsed light, Quality of life*

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INTRODUCTION

Meibomian gland dysfunction (MGD) is an ocular surface disorder that is characterized by abnormal lid gland secretion. This abnormal secretion causes varying degrees of discomfort, such as a burning sensation, fluctuating vision, increased secretion, reduced tear film stability, ocular surface inflammation, and even corneal damage, which impairs vision [1]. According to

epidemiological studies, MGD is one of the major causes of dry eyes, and accounts for 50 % to 65 % of dry eye cases in Asia [2]. Dry eye caused by MGD has a negative impact on patients' quality of life and has become a public health issue. Local heat compresses, meibomian massage, medicines, intense pulsed light, thermal pulses, and meibomian gland probing (MGP) are being used in clinical treatment for individuals with dry eyes caused by MGD [3]. Varying therapeutic techniques have different outcomes, such as local heat compresses that require repetitive heating or constantly changing towels, has frequently demonstrated minimal efficacy. MGP opens the clogged terminal ducts of the meibomian gland but may cause eyelid bleeding. Therefore, an effective therapy for treatment of MGD-induced dry eye remains a hot topic of research.

Purinergic P2Y2 receptor (P2Y2) agonist is a novel drug for treatment of dry eye. It activates P2Y2 receptor on the ocular surface in order to promote the secretion of tears from conjunctival epithelial cells, and the secretion of mucin from conjunctival cup cells, thereby enhancing the stability of tear film and improving dry eye symptoms. Diquafosol sodium 3 % eye drop is currently the only marketed P2Y2 receptor agonist that has been used in clinical practice for treatment of dry eyes [4]. As a synthetic derivative of uridine triphosphate, diquafosol sodium effectively treats MGD-induced dry eye by regulating tear mucin secretion. Yin Liang *et al* [5] found that diquafosol sodium was beneficial in treating dry eye by increasing ocular surface function, decreasing clinical symptoms, and lowering inflammatory factor levels. M22 optimized pulse light (OPT) is a broad-spectrum light that emits controlled, high-intensity pulses that effectively eliminate energy fluctuations and exert an effect of unblocking the blocked lid glands by liquefying viscous lid fat, and it has been used frequently in patients with MGD dry eye in recent years [6]. Although both diquafosol sodium and M22 OPT effectively cures MGD dry eye, there have been few clinical studies that compare their efficacy. The present study compared the efficacy of 3 % diquafosol sodium eye drops and M22 OPT in treatment of MGD-induced dry eye, with the aim of providing a reference for patients to choose an appropriate treatment option.

METHODS

General data

Clinical data of 97 patients admitted to Shantou Balder Eye Hospital with MGD-induced dry eye illness between August 2019 and June 2021 were retrospectively reviewed. This study was approved by the Ethics Committee of Shantou Balder Eye Hospital, China ({2019} no. 1). The patients were informed and they signed a fully-informed consent form.

Meibomian gland dysfunction was diagnosed according to the diagnostic criteria of Ophthalmology to include: abnormal openings of the meibomian gland and lid margin, abnormal quality and quantity of meibomian gland secretions, and absence of tarsal glands. MGD was diagnosed when one or more of these three conditions were met, accompanied by symptoms such as blurred vision and a sensation of a foreign body and dryness in the eyes.

Inclusion criteria

All patients were eligible for inclusion if they met the following criteria: first diagnosis as MGD-induced dry eye, absence of meibomian gland, morphological changes of lid margin, including lid margin thickening, neovascularization, disappearance of gland orifice, distortion of posterior lid margin, abnormal secretions of meibomian gland, and any of the above signs combined with abnormal tear film diagnosed as MGD-induced dry eye. Patients aged 18 - 60 years, who suffered from the disease in both eyes, with mild to moderate dry eye, who had been previously diagnosed with MGD-induced dry eye, had not received physical therapy within 1 month, and had complete clinical data were also included in the study.

Exclusion criteria

Patients with the following conditions were excluded: Stevens-Johnson syndrome, eye infections, trauma, and allergies. Contact lens wearers, patients who had undergone eye surgery within the past 3 months, patients with systemic or ocular diseases that may affect the tear film and patients that are allergic to 3 % diquafosol sodium eye drops were also excluded from the study.

Patients were divided into two groups comprising medication group (n = 43), and pulsed light group (n = 44) based on their treatment methods. All 97 patients had the illness in both eyes and received treatment for both eyes. However, for the convenience of data analysis, the right eye of each patient was chosen for study.

Treatment protocols

Medication group received meibomian gland

massage at the first visit, and repeated the meibomian gland massage during each monthly follow-up visit. They were treated with 3 % diquafosol sodium eye drops daily (Santen Pharmaceutical Co., Ltd., no. J20180008) for 3 consecutive months. During the first visit, the ophthalmologist used a meibomian gland forceps to perform meibomian gland massage and prescribed local application of 3 % diquafosol sodium eye drops 6 times a day. During the follow-up visits every month, meibomian gland massage was repeated and local medication was continued for 3 months.

The pulse light group received OPT therapy using M22 model IPL device (Lumenis intense light and laser system, Lumenis Ltd., Yokneam, Israel). Treatment was administered 3 times, with an interval of 1 month (3 – 4 weeks) between each session. Optimized pulse light treatment was performed by an ophthalmologist, with the treatment area being the lower eyelid. A metal cushion plate was placed in the conjunctival sac to cover the cornea and sclera to adequately protect the eye, and a layer of gel was applied to the treated skin area.

OPT parameters

Toyos treatment parameters were used, with 590 nm optical filter, pulse emission time of 6.0 milli sec, the pulse delay time of 50 milli sec, and the energy adjustable from 10 - 14 J/cm^2. After OPT treatment, meibomian gland massage was performed by the ophthalmologist using a meibomian gland forceps. A localized cold compress was applied to the treatment area after treatment, and patients were instructed to protect themselves from the sun.

Evaluation of parameters/indices

Clinical efficacy was evaluated 3 months after treatment. It is said to be *markedly effective* (ME) when the clinical symptoms are either significantly relieved or disappears. Fluorescence staining (FL) is negative, break-up time (BUT) is greater than 10 sec and tear secretion (ST) is greater than 10 mm/5 min.

It is termed *effective* (E) when the clinical symptoms are relieved, FL grading decreased by 1-2 grades; TBUT greater than 5 seconds and ST greater than 5-10 mm/5 min.

It is *Ineffective* (I) when clinical symptoms are not relieved or are worsened, while FL, BUT and ST do not reach the above criteria. Total effective rate (TE) is computed using Eq 1.

TE = ME+E …….. (1)

Ocular surface function

The indicators of FL, BUT and ST were tested in the two groups before and 3 months after treatment, respectively, where FL: fluorescence staining score was performed in 4 quadrants with a total score of 0 - 12, and was categorized as mild, moderate and severe; BUT: corneal staining was performed using test paper, and patients were instructed to blink 3 - 5 times and observed under the slit lamp and BUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film; ST: filter paper strips were placed in the lower conjunctival sac of the affected eye after local anesthesia, and the wet length of the paper strips was recorded after 5 min.

Symptom severity

The subjective symptom questionnaire and the ocular surface disease index (OSDI) [7] were used to assess the severity of symptoms in the two groups before and after treatment. The OSDI scale has 12 evaluation items and a score range of 0 - 100. Low scores are suggestive of mild symptoms. There are eight items on the subjective symptom questionnaire, including impaired vision, photophobia, and eye tiredness. Each item is scored from 0 to 4 points based on its frequency of occurrence.

Inflammatory factors

A total of 15 µL of tear fluid was collected from both groups by capillary pipette method [8] before and 3 months after treatment, and the levels of hypersensitive C-reactive protein (hs-CRP), interleukin-8 (IL-8) and interleukin-1β (IL-1β) were measured by enzyme-linked immunosorbent assay.

Quality of life

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) [9] was used to assess the quality of life of the two groups before and 3 months after treatment, respectively, in terms of visual condition, activity impairment and general health, with high scores indicating good quality of life.

Adverse reactions

The occurrence of adverse reactions during treatment was recorded in both groups.

Statistical analysis

The SPSS 16.0 software was used, and the measurement data conforming to normal distribution were expressed as mean ± standard deviation (SD). The *t*-test for independent samples was used for comparison between groups, and *t*-test for paired samples was used for comparison within groups. Wilcoxon signed-rank test was used for data not conforming to normal distribution. Count data were expressed as number of cases or percentage (n, %), and chi-square test was used for comparison, and the difference was considered statistically significant when $p < 0.05$.

RESULTS

The baseline data (age, sex, body mass index, disease duration and severity) were comparable between the two groups ($p > 0.05$; Table 1).

Table 1: Comparison of baseline data of disease

Group	Sex (male/ female)	Age (yr)	Dura-tion (months)	Body mass index (kg/m^2)	Severi-ty (mild/ moderate)
Medication (n=43)	25/18	52.4±7.2	42.8±5.0	23.84±2.7	20/23
Pulsed light (n=44)	24/20	52.9±7.7	42.0±6.4	24.0±2.5	19/25

Values are mean ± SD

Clinical efficacy

The total effective rate of the pulsed light group (95.45 %) was slightly higher than that of the medication group (93.02 %), but the difference was not statistically significant ($p > 0.05$; Table 2).

Table 2: Comparison of clinical efficacy

Group	Markedly effective	Effective	Ineffective	Total effective
medication group (n = 43)	28 (65.12)	12 (27.91)	3 (6.98)	40 (93.02)
Pulsed light group (n = 44)	29 (65.91)	13 (29.55)	2 (4.55)	42 (95.45)

Values are n (%)

Ocular surface function

The differences in FL, BUT and ST between the two groups before treatment were not statistically significant ($p > 0.05$), however 3 months after treatment, FL decreased significantly ($p < 0.05$) in both groups, while BUT and ST increased significantly ($p < 0.05$) in both groups. However the differences between the two groups in the above indexes were not statistically significant following treatment ($p > 0.05$; Figure 1).

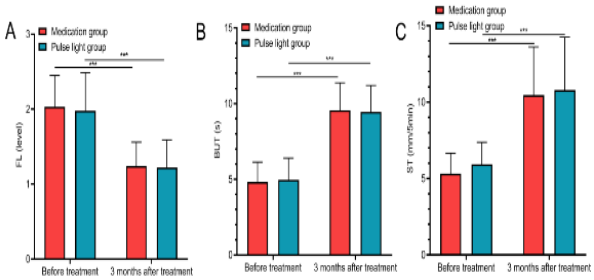

Figure 1: Comparison of ocular surface function. (A) FL (grade); (B) BUT(s); (C) ST (mm/5 min). Note: Compared within same group before treatment, ***$p < 0.001$

Symptom severity

There was no statistically significant difference in OSDI and self-conscious symptom scores between the two groups before treatment ($p > 0.05$), however 3 months after treatment, OSDI and self-conscious symptom scores decreased significantly ($p < 0.05$) in both groups, but there was no statistically significant difference between groups in the above indices ($p > 0.05$) (Figure 2).

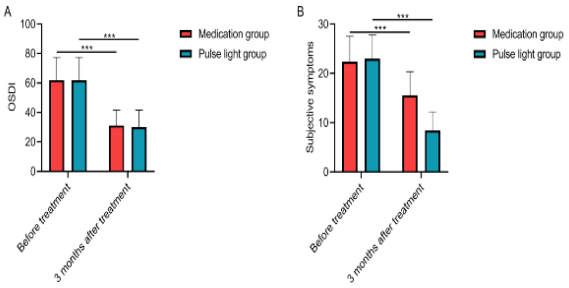

Figure 2: Comparison of symptom severity. (A) OSDI; (B) self-conscious symptoms. Note: Compared within same group before treatment, ***$p < 0.001$

Inflammatory factors

The differences in hs-CRP, IL-8 and IL-1β levels between the two groups before treatment were not statistically significant ($p > 0.05$) however 3 months after treatment, hs-CRP, IL-8 and IL-1β levels decreased significantly ($p < 0.05$) in both groups, but the differences between groups in the above indexes were not statistically significant ($p > 0.05$; Figure 3).

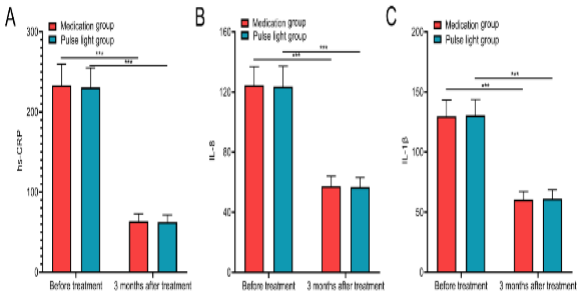

Figure 3: Comparison of inflammatory factor levels (ng/L). (A) hs-CRP; (B) IL-8; (C) IL-1β. Note: Compared within same group before treatment, ***p < 0.001

Quality of life

There were no statistically significant differences in visual status, activity impairment and general health scores between the two groups before treatment (p > 0.05) however 3 months following treatment, visual status, activity impairment and general health scores increased significantly (p < 0.05) in both groups, but there was no statistically significant difference between groups in the above indexes (p > 0.05; Figure 4).

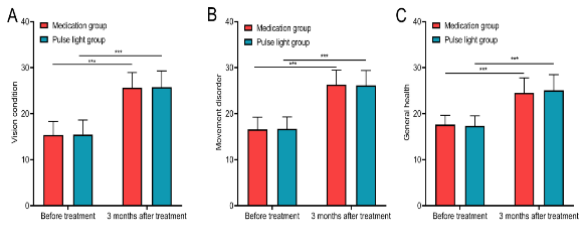

Figure 4: Comparison of quality of life (score). (A) visual acuity; (B) activity impairment; (C) general health. Note: Compared within same group before treatment, ***p < 0.001

Adverse reactions

The incidence of adverse reactions in the medication group (4.65 %) was slightly lower than that in the pulsed light group (9.09 %) though not statistically significant (p > 0.05) (Table 3).

Table 3 Comparison of adverse reactions n (%)

Group	IOP elevation	Conjunctival congestion	Pruritus	Total
medication group	1 (2.33)	0	1 (2.33)	2 (4.65)
Pulsed light group	1 (2.27)	2 (4.55)	1 (2.27)	4 (9.09)

Data are presented as n (%). IOP: intraocular pressure

DISCUSSION

Clinical signs of multifactorial ocular disease occur rather slowly, and are connected to ocular disease, dry reaction, tear film failure, and tear hypertonicity [10]. MGD is a significant contributor to dry eye. Meibomian glands are responsible for secreting oil, limiting tear outflow, and preventing excessive evaporation. When the function of the meibomian glands is impaired, the secretion of the tear film's lipid layer is diminished, and the tear is excessively evaporated, resulting in tear film instability and corneal exposure, resulting in dry eye illness [11]. Presently there is no effective treatment for MGD-induced dry eye, and only local massage, hot compresses, eye drops, intense pulsed light, and other methods can relieve clinical symptoms and slow disease development [12].

The efficacy and safety of 3 % diquafosol sodium was compared with M22 OPT in treatment of MGD-induced dry eye. After treatment, ocular surface function, symptom severity, and quality of life improved in both groups, but the differences between the groups in these indicators were not statistically significant (p > 0.05). Both treatments are thought to be safe and effective for treating MGD-induced dry eye disease, relieving clinical symptoms, and improving quality of life. Diquafosol sodium is a P2Y2 receptor agonist that increases intracellular calcium ion content by activating the P2Y2 receptor on the conjunctival epithelial cell membrane and goblet cell membrane, as well as promote water secretion in the conjunctival epithelial cell membrane, thus alleviating MGD-related clinical symptoms associated with dry eye [13]. Simultaneously, diquafosol sodium stimulates lipid production, raises phospholipid and cholesterol levels, boosts the expression of mucin-related genes on corneal epithelial cells, and accelerates the development of lipid vesicles. Moreover, diquafosol sodium also promotes rapid recovery of corneal epithelial barrier function and prevent corneal dryness [14]. M22 maximizes the energy of pulsed light to penetrate the skin, allowing it to accurately target the pigment in the deeper layers of the skin, thus preventing injury to the normal skin during the pigment group decomposition process. Simultaneously, M22 optimized pulsed light causes vasospasm, vascular endothelial cell swelling, tissue hypoxia, coagulation, and necrosis via photothermal action, which shrinks and occludes abnormal new blood vessels, limiting the entry of inflammatory factors, viruses, and bacteria into the meibomian glands [15]. Furthermore, the M22 tailored pulsed light raises the local temperature of the meibomian glands,

melts the viscous meibum, and dredges the meibomian glands [16].

Researchers are discovering that inflammatory response play significant role in MGD-induced dry eye [17]. MGD-induced hypertonic tear film causes ocular surface inflammation, epithelial cell injury, and decreased release of watery fluid in tears, lowering tear film stability. Yan *et al* [18] found that there is a significant inflammatory response in patients with MGD-induced dry eye. hs-CRP, IL-8, and IL-1β are common inflammatory factors, and their levels effectively reflect the degree of inflammatory response. For example, IL-1 limits the release of neurotransmitters like acetylcholine and norepinephrine, as well as diminishes tear secretion and promote dry eye. The results of this study showed that hs-CRP, IL-8 and IL-1β levels were significantly decreased in both groups after treatment, but the differences between the groups of the above indicators were not statistically significant ($p > 0.05$). This thus indicates that both 3 % diquafosol sodium and M22 optimized pulsed light were effective in reducing inflammatory response and promoting recovery and rehabilitation.

Limitations of this study

This is a single-center, small-sample retrospective study. The results may be biased, and the study did not test and analyze the long-term recurrence of dry eye induced by MGD. Multi-center, large-sample prospective studies will need to be conducted in the future to validate the claim in this study.

CONCLUSION

The efficacy and safety of 3 % diquafosol sodium and M22 OPT treatment for MGD-induced dry eye are comparable, and both effectively relieve patients' clinical symptoms, improve ocular surface function, reduce inflammatory response and improve quality of life.

DECLARATIONS

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Funding

None provided.

Ethical approval

This study was approved by the Ethics Committee of Shantou Balder Eye Hospital, China ({2019} no. 1).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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