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The efficacy of a netilmicin/dexamethasone gel combination in the treatment of posterior blepharitis in moderate-severe dry eye patients

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Abstract

Purpose: To evaluate the safety and efficacy of netilmicin/dexamethasone combination in the treatment of meibomian gland dysfunction (MGD)-associated posterior blepharitis.

Methods: In this prospective and controlled study were enrolled 40 patients with MGD and symptoms of dry eye disease. Two groups were established: 20 patients (group 1) received netilmicin 3 mg/ml and dexamethasone 1 mg/ml eye gel, whereas in group 2 (20 patients) received vehicle for 15 days. Patients were evaluated at baseline, 15 and 45 days, including SANDE and VARS questionnaire, non-invasive tear film breakup time (NIBUT), tear meniscus height (TMH), ocular redness and meibography score. Moreover, fluorescein tear-film breakup time (TBUT), fluorescein ocular surface staining, lid margin evaluation including hyperemia, edema and meibum expressibility and quality examinations were carried out. Furthermore, intraocular pressure (IOP) and best-corrected visual acuity (BCVA) were considered as safety parameters.

Results: In group 1, at 15 and 45 days there were statistically significant changes in VARS and SANDE score ($p < 0.0001$) as well as lid margin parameters, TBUT and fluorescein ocular surface staining ($p < 0.0001$). Comparing the two groups, a significant improvement of SANDE score was observed at 15 days in group 1 as well as lid margin parameters, TBUT and fluorescein ocular surface staining at 15 and 45 days (all $p < 0.0001$).

Conclusion: Netilmicin/dexamethasone combination is effective and safe to treat MGD-associated posterior blepharitis improving both symptoms and ocular surface signs.

Keywords

Ocular surface agents < CORNEA / EXTERNAL DISEASE, eyelid disease: infections/inflammations < OCULOPLASTIC EYELID /LACRIMAL DISEASE, diseases of the ocular surface: lid inflammation affecting the ocular surface < CORNEA / EXTERNAL DISEASE, diseases of the ocular surface: persistent corneal epithelial defects < CORNEA / EXTERNAL DISEASE, drug delivery systems / pharmacokinetics < CORNEA / EXTERNAL DISEASE

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Introduction

Posterior blepharitis describes inflammation of the meibomian glands and their orifices and may be a result of or cause of meibomian gland dysfunction (MGD).[1–4] MGD refers to a diffuse abnormality of the meibomian glands resulting in duct obstruction, alteration of the tear film and dry eye disease (DED).[1] MGD is the main cause of posterior blepharitis, but others include infections, allergic conjunctivitis, and rosacea.[1–6]

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Available previous clinical data indicate that dexamethasone could be effective in the treatment of patients with posterior blepharitis.[2–4,6,7]

In particular, the association with antibiotics is able to achieve complete clinical resolution of the signs and symptoms in patients with posterior blepharitis and MGD, reducing both the bacterial load and the eyelid inflammation.[2–4,6,7]

Netilmicin is an aminoglycoside, a widely used antibiotic in ophthalmology, with a well-established efficacy in treatment of infectious ocular surface diseases; however, there are few clinical data about the effectiveness in treatment of blepharitis and MGD.[8]

A novel netilmicin/dexamethasone gel combination has been developed and recent data demonstrated that increases the permanency of the drugs on the eyelid and ocular surface improving the clinical efficacy, suggesting therefore a potential treatment also for blepharitis.[9]

Furthermore, the presence of xanthan gum as viscosity enhancer with anti-oxidant and mucoadhesive properties could ameliorate conjunctival and corneal epithelium damages also in patients with MGD and DED.[9–11]

The proposed clinical study intends to evaluate the efficacy and safety of the netilmicin/dexamethasone gel formulation in the treatment of posterior blepharitis and compared to vehicle for a treatment period of 4 weeks.

Methods

In this prospective, observational and controlled study were enrolled 40 patients with posterior blepharitis and symptoms of dry eye disease.

The research protocol received approval from the local institutional review board at the University of Messina and adhered to the principles of the Helsinki declaration. Prior to enrollment, all patients provided informed consent following a discussion on the potential risks and benefits as well as the study's nature.

The inclusion criteria encompassed individuals aged 18 years or older with a clinical diagnosis of bilateral MGD and Dry Eye Disease, Tear Break-up Time less than 10 s, a meibomian gland expressibility score ranging from 1 to 2, an OSDI score exceeding 12, and a documented lack of response to previous treatments such as eyelid hygiene, warm compresses, topical antibiotics, and steroids drops within the past 6 months.

Two groups were established: 20 patients (group 1) received netilmicin 3 mg/ml and dexamethasone 1 mg/ml eye gel (Netildex gel®, SIFI, Italy), whereas in group 2 (20 patients) received vehicle two times daily for 15 days.

Patients were evaluated at baseline, 15 and 45 days, including:

- Dry Eye (SANDE) questionnaire;
- Visual Analogue Rating Scale (VARS) for dry eye symptoms;
- Keratograph 5 M (Oculus, Germany) was used to assess non-invasive tear film breakup time (NIBUT), tear-meniscus height (TMH), ocular redness and meibography.
- TBUT was measured 3 consecutive times after the instillation of fluorescein, and the average result was considered;
- The modified Oxford scale was considered for the grading of fuorescein ocular surface staining;[12]
- Lid margin evaluation established on the presence of 4 criteria each one scored from 0 to 4: lid margin hyperemia, lid margin edema, lid margin debris, and meibum expressibility.[13–15]

Furthermore, intraocular pressure (IOP) and best-corrected visual acuity (BCVA) were considered as safety parameters.

Statistical analysis

Numeric data are presented as the mean and standard deviation, while categorical data are depicted as absolute rate and percentage. The Kolmogorov-Smirnov test was employed to assess the conformity of the data to a normal distribution.

Within each group, the significance of differences between baseline and measurements taken at 15 and 45 days was evaluated using the Student's T-test for parametric data and the Wilcoxon signed-rank test for non-parametric data.

Furthermore, a statistical analysis was conducted to compare groups, employing the Chi-Square test for categorical variables, the Student's t-test for parametric data, and the Mann-Whitney U test for non-parametric data. Statistical significance was set at a p-value < 0.05, and values from the eye with the most severe condition at baseline were utilized for analysis.

Statistics were performed using GraphPad Prism version 9.3 for MacOS.

To estimate the population size, we assumed a 50% improvement in Tear Break-up Time (TBUT). With an alpha error of 0.05 and a beta error of 80%, the calculated population number was 16. Consequently, we enrolled 20 patients to accommodate for potential dropouts. However, no dropouts were observed. The main outcome measures included TBUT and corneal-conjunctival staining.

Results

Twenty patients (6 males and 14 females; mean age 63.8 ± 14.5 years) were included in group 1, while 20 patients (5 males and 15 females; mean age 65.4 ± 14.1 years) were included in group 2.

The clinical parameters of the two groups were reported in Table 1; no significant differences in gender distribution, mean age were observed between these groups.

Table 1. Clinical characteristics of the study population.

	Group 1	Group 2	p-value
Age, years	63.8 ± 14.5	65.4 ± 14.1	0.73
Male/Female	6/14	5/15	0.91
BCVA, LogMAR	− 0.1 ± 0.1	0.05 ± 0.09	0.1
IOP, mmHg	14.7 ± 0.9	14.1 ± 1.6	0.12

BCVA- Best Corrected Visual Acuity; IOP- Intraocular Pressure. All data are reported as mean ± standard deviation. Results were considered statistical significant for $p < 0.05$.

Ocular discomfort symptoms assessment:

In group 1, at 15 and 45 days there were statistically significant changes in mean VARS and both SANDE frequency and severity scores decreased ($p < 0.0001$, respectively). In groups 2, at 15 and 45 days there were statistically significant changes in mean VARS and SANDE frequency ($p < 0.0001$, respectively); however, there was not significant changes of SANDE severity score (Table 2).

Additionally, at 15 days comparing the two groups statistically significant differences were observed in numerous symptoms evaluated and mean VARS score ($p < 0.0001$), as well as SANDE frequency ($p = 0.0007$) and severity scores ($p = 0.012$). However, these changes were not significant at 45 days (Table 2).

Lid margin evaluation

At 15 and 45 days, in group 1 there were significant changes of eyelid redness and swelling ($p < 0.0001$, respectively), as well as eyelid debris and meibomian gland expressibility improved ($p < 0.0001$, respectively).

In group 2 there was a significant change of eyelid debris ($p = 0.04$) at 15 days (Table 3).

Statistically significant differences were noted in all assessed lid margin parameters at both the 15-day and 45-day intervals when comparing the two groups.

Ocular surface and tear film parameters:

TBUT and staining score improved significantly in group 1 after 15 and 45 days ($p < 0.0001$, respectively), whereas in group 2 only TBUT improved ($p = 0.001$ and $p = 0.005$) (Table 4). When comparing the two groups, both parameters showed significant improvement in Group 1 ($p < 0.0001$ for both) (Table 4). No significant changes of TMH were observed in both groups throughout the follow-up period.

Safety parameters:

No adverse events were reported during the treatment and follow-up periods in the two groups.

No significant changes of IOP and BCVA were observed in both groups throughout the follow-up period (Table 1).

Discussion

Although numerous treatments have been proposed for posterior blepharitis, including local and systemic therapies, none of them is ideal to allow a complete and persistent clinical resolution.[2–8] Warm compresses and massage for eyelid, lid scrub, together with topical antibiotics and antinflammatory agents like corticosteroids are the most common strategies to manage posterior blepharitis and MGD.[2–4] Several studies demonstrated the effectiveness of topical macrolides such as azithromycin, or tetracycline to improve the signs and symptoms in patients with MGD.[16] Furthermore, the association with topical corticosteroids improves significantly the efficacy of azithromycin, as reported in previous trials.[7,16] The role of bacteria is unclear, indeed the pathogenic mechanisms involved in posterior blepharitis and MGD are different, including eyelid and conjunctival inflammation, corneal damage, microbiological changes and tear film instability-associated DED.[17] The stasis of the meibum, caused by the meibomian glands obstruction, dropout or inflammation can stimulate the bacteria overgrowth on the eyelid, and a consequent increased release of esterases and lipases, generating free fatty acids, which in turn causes inflammation and hyperkeratinisation.[17] These changes in lipid composition are responsible for the instability of the tear film and the ocular discomfort experienced by patients.[17] Moreover, studies demonstrated the high prevalence of *Demodex folliculorum* infestation in patients with MGD, reporting also a significant association between the severity of the infestation and meibomian gland loss as well as the symptoms of eye discomfort.[18] Previous studies evaluated the effects of topical netilmicin on human ocular surface bacteria, reporting an effective and rapid onset of action in reducing the conjunctival and eyelid surface flora.[8] Although topical netilmicin is a widely used antibiotic for ocular surface infections, there are few clinical data about the treatments of posterior blepharitis.[8] In this study, we have demonstrated the clinical effectiveness of a combination netilmicin/dexamethasone gel formulation to treat posterior blepharitis, reporting a significant improvement of lid margin inflammation, tear film stability, as well as reduced corneal and conjunctival epithelial cells damages. Actually, the gel formulation increases the permanency of the both netilmicin and dexamethasone on the eyelid, improving the antinflammatory effects, as well as the reduction of the microbial flora. Our findings demonstrate a rapid efficacy of this formulation in reduction of lid margin signs, and these changes were maintained after 1 months. Xanthan gum is a polysaccharide with antioxidant properties that could ameliorate the conjunctival and corneal epithelium damages in patients with DED. The improvements of TBUT and ocular surface staining

Table 2. Symptoms evaluation.

	Group 1					Group 2					Group 2 vs Group 1		
	Baseline	15 days	45 days	p-value 15days vs baseline	p-value 45 days vs baseline	Baseline	15 days	45 days	P 15days vs baseline	P 45 days VS baseline	p-value baseline	p-value 15 days	p-value 45 days
Foreign body	35.9 ± 25.2	27.1 ± 18.3	30.4 ± 29.8	<0.0001	0.0378	38.25 ± 10.8	34.95 ± 10.5	25.9 ± 21.7	0.0032	0.0032	0.5961	0.0230	0.4519
Burning	35.0 ± 18.1	27.2 ± 23.4	31.1 ± 29.5	0.0059	0.2249	36.8 ± 17.9	33.8 ± 15.7	35.1 ± 26.9	0.0131	0.6445	0.6649	0.1431	0.5481
Itchiness	38.9 ± 20.6	21.8 ± 11.1	33.6 ± 28.8	<0.0001	0.4158	39.5 ± 19.6	35.1 ± 15.8	34.7 ± 23.1	0.0021	0.3579	0.9002	<0.0001	0.8420
Pain	14.9 ± 11.4	9.2 ± 6.4	17.1 ± 25.6	<0.0001	0.5897	16.6 ± 10.2	16 ± 9.7	18.9 ± 22	0.3372	0.5406	0.4746	0.0006	0.7330
Sticky Eye	42.5 ± 13.1	23.5 ± 20.6	13.8 ± 12.9	<0.0001	<0.0001	40.5 ± 13.1	38.4 ± 11.9	17.4 ± 16.3	0.2672	<0.0001	0.5290	0.0002	0.2836
Blurred Vision	37.3 ± 23.1	14.5 ± 16	20.3 ± 21.7	<0.0001	0.0082	39.4 ± 16.4	33.2 ± 14.2	25.4 ± 17.9	<0.0001	<0.0001	0.6351	<0.0001	0.2662
Photophobia	44.4 ± 18.5	11.1 ± 14	24.1 ± 20.7	<0.0001	<0.0001	44.5 ± 17	44.5 ± 17	25.4 ± 17.9	0.87	<0.0001	0.9892	<0.0001	0.8374
Mean	35.6 ± 12.3	19.2 ± 10.4	24.3 ± 21.1	<0.0001	<0.0001	37.8 ± 9.5	35.4 ± 9	24.5 ± 16.7	<0.0001	<0.0001	0.3700	<0.0001	0.9700
SANDE frequency	46.5 ± 25.9	25.1 ± 18.1	24.3 ± 21.1	<0.0001	<0.0001	47.3 ± 18.2	38.2 ± 13.4	21.1 ± 18.1	<0.0001	<0.0001	0.8762	0.0007	0.6612
SANDE severity	48.9 ± 23.9	29.3 ± 21.7	19.1 ± 19.7	<0.0001	<0.0001	45 ± 22.2	41.2 ± 20.8	38.5 ± 19.5	0.04	0.1687	0.4619	0.0119	0.7952

All data are reported as mean ± standard deviation. Results were considered statistical significant for $p < 0.05$.

Table 3. Eyelid margin parameters.

	Group 1					Group 2					Group 2 vs Group 1		
	Baseline	15 days	45 days	p-value 15days vs baseline	p-value 45 days vs baseline	Baseline	15 days	45 days	p-value 15days vs baseline	p-value 45 days vs baseline	p-value baseline	p-value 15 days	p-value 45 days
Expressibility	2.6 ± 1	1 ± 0.2	1.4 ± 0.7	<0.0001	<0.0001	2.2 ± 0.7	2.2 ± 0.7	2.1 ± 0.7	0.08	0.06	0.35	<0.0001	0.06
Hyperemia	2.7 ± 1	1.5 ± 0.6	1.4 ± 0.7	<0.0001	<0.0001	2.4 ± 0.7	2.4 ± 0.6	2.1 ± 0.6	0.4	0.02	0.84	<0.0001	<0.0001
Edema	2.5 ± 1.1	1.3 ± 0.8	1.5 ± 0.8	<0.0001	<0.0001	2.5 ± 0.7	2.5 ± 0.7	2.3 ± 0.7	0.82	0.07	0.88	<0.0001	<0.0001
Debris	2.3 ± 0.6	1.6 ± 1.1	1.6 ± 1.1	<0.0001	<0.0001	2.3 ± 0.6	2.3 ± 0.6	1.5 ± 0.5	0.37	<0.0001	0.85	<0.0001	<0.0001

All data are reported as mean ± standard deviation. Results were considered statistical significant for $p < 0.05$.

Table 4. Ocular surface and tear film parameters.

	Group 1					Group 2					Group 2 vs Group 1		
	Baseline	15 days	45 days	p-value 15days vs baseline	p-value 45 days vs baseline	Baseline	15 days	45 days	p-value 15 days vs baseline	p-value 45 days vs baseline	p-value baseline	p-value 15 days	p-value 45 days
TBUT	2 ± 1.2	3.5 ± 0.9	3.7 ± 0.5	<0.0001	<0.0001	2 ± 0.8	2.2 ± 0.7	2.5 ± 0.8	0.001	0.005	0.91	<0.0001	<0.0001
Staining	1.5 ± 0.9	0.7 ± 0.5	0.5 ± 0.5	<0.0001	<0.0001	1.6 ± 0.7	2.5 ± 0.7	1.7 ± 0.6	0.26	0.66	0.51	<0.0001	<0.0001
TMH	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.5	0.37	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.05	0.12	0.67	0.29	0.47
NIKBUT	3.6 ± 2.7	3.7 ± 1.9	7.4 ± 4.9	0.77	0.002	3.9 ± 1.8	2.3 ± 0.6	4.1 ± 1.3	0.03	0.35	0.55	0.15	0.0001
Hyperemia	1.7 ± 0.7	1.3 ± 5.2	1.4 ± 0.8	0.07	0.05	1.7 ± 0.5	2.4 ± 0.5	1.9 ± 0.4	0.001	0.008	0.84	0.09	0.0003
Meibography	2.2 ± 0.4	2.2 ± 1.1	2.3 ± 0.9	0.21	0.17	2.1 ± 0.5	2.1 ± 0.6	2.2 ± 0.6	0.16	0.12	0.36	0.001	0.01

All data are reported as mean ± standard deviation. Results were considered statistical significant for $p < 0.05$.

observed at 15 and 45 days could be related also to the xanthan gum activity, that together with the antinflamatory property of dexamethasone and the reduction of microbial flora, could ameliorate the corneal and conjunctival epithelial damages and the lid margin inflammation. However, this study has some limitations, in particular the small sample size of the groups and the short term follow-up, may represents a boundary to generalize the effectiveness of this treatment in a long period. Although in our group there were no significant changes of the intraocular pressure, this could be a possible side effect of a prolonged treatment with dexamethasone, in particular in responders to corticosteroids. Furthermore, the comparison with a group treated with netilmicin alone, and the evaluation of the microbial flora changes on the eyelids after treatments, could be helpful to understand the role of netilmicin on posterior blepharitis and MGD, and its profile of efficacy.

Author contributions

Giovanni W Oliverio: Conceptualization, Writing, Review, Editing, Data analysis.
Leandro Inferrera and Elisa I Postorino: Conceptualization, Data collection.
Paola Palino: Data collection.
Pasquale Aragona: Conceptualization, Writing, Review, Editing; Original draft preparation, Data analysis and Supervision.

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Data availability

Data are available upon reasonable request.

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