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Comparative efficacy of the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract, and sulfur preparations in the treatment of patients with chronic blepharitis on the background of meibomian gland dysfunction

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ABSTRACT

BACKGROUND: Meibomian gland dysfunction (MGD) and chronic blepharitis remain significant challenges in ophthalmology. Standard therapy comprises phytoblepharohygiene and eyelid massage, with anti-inflammatory and tear substitutes. However, the efficacy of the sequential use of phytoblepharohygiene and the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract and sulfur preparations (Blepharogel Forte®; Geltek-Medica, Russia) for chronic blepharitis and MGD, remains underexplored.

AIM: To evaluate the therapeutic effect of a sequential regimen comprising a line of phytoblepharohygiene products, including the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract and sulfur preparations (in patients with prolonged chronic blepharitis and MGD).

MATERIALS AND METHODS: The study involved 42 patients (84 eyes) aged 16–73 years, including 30 men (60 eyes, 71.4%) and 12 women (24 eyes, 28.6%), diagnosed with chronic blepharitis, MGD, and dry eye syndrome. Depending on the treatment method, two groups were formed. Patients of control group I (20 subjects, 40 eyes, 47.6%) received eyelid massage and phytoblepharohygiene with the ophthalmic gel containing hyaluronic acid and *Aloe vera* extract (agent 1) or the ophthalmic gel containing hyaluronic acid, *Aloe vera* extract, and sulphur preparations (agent 2) (in case of confirmed demodicosis). The comparison group II (22 subjects, 44 eyes, 52.4%) underwent eyelid massage and phytoblepharohygiene, which was completed by applying the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract, and sulfur preparations (agent 3) (irrespective of a positive or negative test for demodicosis).

RESULTS: From the first week onwards, the indices characterizing hyposecretion of meibomian glands in groups I and II were already 1.9±0.2 and 1.1±0.3 points lower than the initial values of 2.6±0.2 and 2.4±0.3 points, respectively (p <0.05). Furthermore, the dynamics of hypersecretion indices exhibited a comparable trend, with values of 1.6±0.2 and 1.5±0.2 points recorded after a week in comparison with the initial values of 2.3±0.3 and 2.2±0.2 points, respectively (p <0.05). The index characterizing eyelid edema at this stage of the study exhibited a statistically significant decrease only in group II of patients who received the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract and sulfur preparations (1.4±0.2 points after a week in comparison with the initial 2.3±0.2 points) (p <0.05). In group I, only the initial results were maintained, whereas in group II, a stable increase was observed.

CONCLUSION: The ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract and sulfur preparations can be effective in the treatment of patients with blepharitis and MGD due to its superior therapeutic effectiveness compared with the standard blepharohygiene and phytoblepharohygiene regimens.

Keywords: blepharitis; meibomian glands; metronidazole; Blepharogel Forte; *Aloe vera*; ophthalmic gel.

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Сравнительная эффективность глазного геля, содержащего метронидазол, гиалуроновую кислоту, экстракт *Aloe vera* и препараты серы, в лечении пациентов с хроническим блефаритом на фоне дисфункции мейбомиевых желёз

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АННОТАЦИЯ

Обоснование. Известно, что дисфункция мейбомиевых желёз (ДМЖ) и хронический блефарит сегодня остаются одними из наиболее актуальных проблем офтальмологии. Базовая терапия включает фитоблефарогигиену и массаж век на фоне использования противовоспалительных средств и слезозаменителей. При этом результативность последовательного использования средств блефарогигиены с включением глазного геля, содержащего метронидазол, гиалуроновую кислоту, экстракт *Aloe vera* и препараты серы (Блефарогеля Форте®; «Гельтек-Медика», Россия), в лечении пациентов с хроническим блефаритом на фоне ДМЖ мало изучена.

Цель исследования — оценить терапевтический эффект последовательного использования линейки средств фитоблефарогигиены с включением глазного геля, содержащего метронидазол, гиалуроновую кислоту, экстракт *Aloe vera* и препараты серы, у больных с затяжным хроническим блефаритом на фоне ДМЖ.

Материалы и методы. В исследовании участвовали 42 пациента (84 глаза), из них 30 мужчин (60 глаз, 71,4%) и 12 женщин (24 глаза, 28,6%), с хроническим блефаритом на фоне ДМЖ и синдромом «сухого глаза» в возрасте 16–73 лет.

В зависимости от способа лечения сформированы 2 группы. Пациенты I, контрольной, группы (20 человек, 40 глаз, 47,6%) получали массаж век, фитоблефарогигиену с глазным гелем, содержащим гиалуроновую кислоту и экстракт *Aloe vera* (препарат 1), или глазным гелем, содержащим гиалуроновую кислоту, экстракт *Aloe vera* и препараты серы (препарат 2), — при подтверждённом демодекозе. Пациентам II группы, основной, которую составили 22 человека (44 глаза, 52,4%), выполняли массаж век, а фитоблефарогигиену завершали нанесением на веки глазного геля, содержащего метронидазол, гиалуроновую кислоту, экстракт *Aloe vera* и препараты серы (препарат 3), независимо от положительного или отрицательного теста на демодекоз.

Результаты. Уже с первой недели в I и II группах показатели, характеризующие гипосекрецию мейбомиевых желёз, составили 1,9±0,2 и 1,1±0,3 балла в сравнении с исходными — 2,6±0,2 и 2,4±0,3 балла соответственно (p <0,05). Сходной оказалась и динамика показателей гиперсекреции: 1,6±0,2 и 1,5±0,2 балла через неделю в сравнении с исходными — 2,3±0,3 и 2,2±0,2 балла соответственно (p <0,05). Показатель, характеризующий отёк век, на данном этапе исследования статистически значимо уменьшился лишь во II группе больных, которые получали препарат 3 (1,4±0,2 балла через неделю в сравнении с исходными 2,3±0,2 балла) (p <0,05). В I группе отмечено лишь стойкое сохранение полученных результатов, во II группе — стабильное нарастание.

Заключение. Использование глазного геля, содержащего метронидазол, может быть рекомендовано к применению в лечении больных с блефаритом и ДМЖ в связи с более значимым терапевтическим эффектом в сравнении с базовой линейкой блефарогигиены и фитоблефарогигиены.

Ключевые слова: блефарит; мейбомиевы железы; метронидазол; Блефарогель Форте; *Aloe vera*; глазной гель.

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BACKGROUND

Meibomian gland dysfunction (MGD) is one of the pressing issues of today's ophthalmology [1–3]. Mild MGD is typical for 70.0% of patients with primary dry eye disease (DED), 47.0% of patients with chronic blepharitis, and 46.7% of patients with DED accompanied by gland hypersecretion [4]. Severe MGD, mainly hyposecretory, leads to secondary DED in 80% of cases and is associated with plugs of dried discharge or thick meibum in the ducts [5].

Moderate MGD is more often associated with hypersecretion leading to maceration of the eyelid skin, itching, and keratoconjunctivitis sicca (50% of cases). It also occurs in 10% of patients with DED not caused by blepharitis [5]. Blepharitis is often complicated by concomitant conditions, such as gastroenterological disorders (biliary dyskinesia, constipation), rosacea, and allergies. Patients with rosacea complicated by demodicosis have an increased recurrence rate and greater affected skin area compared to uncomplicated disease [6].

Demodex mites (*Demodex folliculorum*, *Demodex brevis*) live in the sebaceous and meibomian glands creating favorable conditions for inflammation. The prevalence of demodicosis reaches from 2% to 5%, and it is the 7th among skin diseases [7–9]. Optimal growth temperature for the mites is 30–40 °C, and they survive off the host for up to 9 days at room temperature and up to 25 days in water [10]. Lipid meibum supports the *Demodex* life cycle, which worsens inflammation [11].

Skin-surface biopsy is considered the gold standard for the diagnosis of demodicosis [12–14]. Skin scrapings and adhesive tape impressions have low specificity and are of little value [5]. Background therapy includes lid hygiene using first-line products such as blefarogels containing hyaluronic acid, Aloe vera extract and sulfur preparations. This improves MGD symptoms and prepares the eyelid skin for anti-inflammatory and antiseptic agents [15–18].

Doxycycline has an anti-inflammatory effect by inhibiting phospholipase A2 and matrix metalloproteinases, which benefits tissues and reduces inflammation [19–21]. In studies, long-term doxycycline administration (16 weeks) led to clinical remission in 75.9% of patients; however, the recurrence rate at 3 months was 5.6% [22]. The drug is well tolerated, but can cause dyspepsia.

Retinoids (isotretinoin in particular) have proven their efficacy in treatment of severe rosacea associated with demodicosis. They reduce the proliferation of gland duct epithelium, reduce keratinization, and have an anti-inflammatory effect [23]. However, their use is limited due to side effects, such as dry skin and mucous membranes, and they are also contraindicated in children under 12 years of age.

Metronidazole is intended for systemic and topical treatment of blepharitis and demodicosis. Long-term metronidazole therapy improves clinical and microbiological parameters [24]. Topical metronidazole (from 0.75 to 1.0% gel) is less toxic and well tolerated by patients.

Combination treatment, including herbal products for eyelid care and medicinal products, effectively improves the MGD and demodex blepharitis symptoms. The study confirms the need to inverstigate the effect of the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract, and sulfur preparations, especially in chronic inflammation.

The aim of the study is to evaluate the therapeutic effect of consecutive herbal lid hygiene products, including the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract, and sulfur preparations, in patients with long-lasting chronic blepharitis associated with MGD.

MATERIALS AND METHODS

Study design

It was a prospective, parallel, non-randomized, single-center study.

The study examined 42 patients (84 eyes) with chronic blepharitis associated with low-to-moderate MGD. The study included 30 (71.4%) men and 12 (28.6%) women, aged 16 to 73 years, with DED, hypersecretory (42.9%) and hyposecretory (57.1%) MGD. Medical record review was confidential, the samples were examined anonymously; patients or their legally authorized representatives voluntarily signed an informed consent form. The study was conducted according to the ethical principles stated in the Helsinki Declaration (2013) and the principles of bioethics; the results may be published in scientific journals.

In this study, an objective sign of hyposecretory MGD was plugging of excretory duct orifices with dried meibum or thick toothpaste-like meibum when pressing on the lid. For patients with hypersecretory MGD, the inclusion criteria and objective sign of hypersecretion were skin irritation caused by meibomian gland secretion or irritation of marginal conjunctiva where the secretion is accumulated, generally in the outer and/or inner canthus.

The MGD severity was assessed using the previously proposed point scale [2, 5] based on the cumulative estimate of secretory function of the meibomian glands (total meibomian index, TMI). The index is the sum of the deformation index (DI) of the lid margin and the occlusion index (OI). Mild, moderate, severe, and extremely severe grades of MGD correspond to 1, 2, 3–6, and 7–12 points, respectively.

Eligibility criteria

The study inclusion criteria were the following:

- no deformation of the lid margin (DI=0) or the presence of single/multiple scars on the lid margin or palpebral conjunctiva when the lids are completely closed (ID=1–2);
- single or multiple obstructed meibomian gland ducts or ductules, accounting for not more than 50% of the total ducts and ductules on the lid margin (OI=1–2);

- diagnosed moderate or severe MGD according to the previously proposed point scale (TMI ≥2) [2, 5];
- signs of hyposecretory MGD (plugs of dried meibum in the ducts) or hypersecretory MGD (skin irritation caused by meibum);
- DED in combination with chronic blepharitis;
- six or more *Demodex* mites in the sample of 16 eyelashes (during the diagnosis of demodicosis).

Exclusion criteria:

- severe deformation of the lid margin preventing the lid closure;
- over 50% of obstructed meibomian gland ducts or ductules;
- progressive or acute inflammation in the anterior segment;
- intolerance to the components of the drugs used;
- co-morbidities which can affect the results (e.g., diabetes mellitus, severe allergic reactions).

Study setting

The study was performed in the ophthalmology department of the Children's Clinical Hospital at Saint-Petersburg State Pediatric Medical University.

Study duration

The study was conducted from September 2023 to December 2023.

Intervention description

All patients had lid massage twice a week (the course consisted of 10 sessions), low viscosity artificial tears 4 times a day, and an artificial tear gel at night. In addition, all patients used herbal lid hygiene products at home twice a day for 8 weeks.

The study subjects were divided into 2 groups by the treatment method. Control patients in Group I (20 subjects, 40 eyes, 47.6%) had eyelid massage using the above lid care procedure, followed by the ophthalmic gel containing hyaluronic acid, *Aloe vera* extract, and sulphur preparations (agent 2), twice a day if demodicosis was confirmed or the ophthalmic gel containing hyaluronic acid and *Aloe vera* extract (agent 1) in case of negative results for demodicosis.

In addition to lid massage, all patients in comparison Group II (22 subjects, 44 eyes, 52.4%) used herbal lid hygiene products daily, followed by application of the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract, and sulfur preparations (agent 3 — Blepharogel Forte®; Geltek-Medica, Russia), on the lids twice a day (regardless of the test result for demodicosis).

Objective (hyperemia of the lid margins, edema of the lid margins, plugs of dried meibum or toothpaste-like meibum in the meibomian gland ducts or ductules (hyposecretory MGD), areas of skin irritation in the outer and/or inner canthus caused by meibum (hypersecretory MGD)) and subjective (eyelid heaviness, tenderness of the lid margins, eyelid itching and burning sensation, subjective discomfort) signs were assessed using a 4-point scale where:

- 0: no signs;
- 1: subtle signs;
- 2: clear signs;
- 3: significant signs.

This method helped standardize the strategy for treatment and assessment of the patients' condition and provided objective comparison of the efficacy of different treatment methods.

Patients were followed up for 8 weeks (at Weeks 1, 2, 4, and 8); the first examination was performed to obtain baseline data, and each subsequent examination included control of objective clinical signs of MGD.

Acaricidal effect was evaluated twice, to obtain baseline data and at Week 8.

Statistical analysis

The sample size was not pre-calculated. Statistical processing of results was carried out using Statistica 12.0 (StatSoft, USA). The normal distribution was assessed with the Kolmogorov–Smirnov test. Mean and mean error were calculated (M±m). Two-tailed Student's t-test (parametric method) was used to assess the significance of differences. Critical level of significance in testing statistical hypotheses was set at 0.05, 0.01, or 0.001.

RESULTS

All patients with chronic blepharitis associated with MGD had a similar reduction of objective and subjective signs over time, regardless of the severity and nature of secretions. Clinical signs of MGD improved as early as Week 1 and included decreased hyposecretion (plugs in the meibomian gland ducts or ductules) and hypersecretion (skin irritation). However, there was no statistically significant change in hyperemia of the lid margins after the first week. Eyelid edema was significantly reduced only in Group II, where agent 3 was used (Table 1).

A statistically significant reduction in all signs of blepharitis, including hyperemia, was observed from Week 2. These changes were maintained throughout the follow-up period (up to Week 8). A significant increase in the treatment effect was observed in Group II from Week 2 to Week 4 for hyperemia, eyelid edema, and signs of secretion, especially with agent 3 (Fig. 1, 2). The results in Group II were stable.

The inter-group comparison showed that the clinical effect on most signs was higher in patients using agent 3. The exception was hyperemia of the lid margins, where no significant difference was noted between the groups. Subjective symptoms, such as itching, burning, and eyelid heaviness, reduced as soon as by Week 2 in both groups, with a more significant effect in Group II. By Week 8, symptoms in patients using agent 3 were statistically significantly better than in Group I (Table 2).

Table 1. Dynamics of expression of objective clinical signs of meibomian gland dysfunction in patients treated with different therapies (*n*=42, 84 eyes) (points, M±m)

Symptom	Group	Number of eyes	Initial data	Stages of observation (wk)			
				1	2	4	8
Hyperemia of the eyelid margins	I	40	2.1±0.2	2.1±0.3	1.6±0.2*	0.6±0.3* #	0.4±0.3*
	II	44	2.6±0.2	2.3±0.2	1.6±0.2* #	0.4±0.2* #	0.3±0.2*
Edema of the costal margin of the eyelids	I	40	2.4±0.2	2.5±0.2	2.0±0.3*	1.3±0.1* #	1.4±0.1*
	II	44	2.3±0.2	1.4±0.2*	0.7±0.2* # †	0.1±0.1* # †	0.3±0.2* †
Presence of plugs of dried secretion or pasty secretion in the ducts of the meibomian glands (dysfunction of the meibomian glands with hyposecretion)	I	16	2.6±0.2	1.9±0.2*	1.3±0.1* #	0.4±0.3* #	1.1±0.3*
	II	32	2.4±0.3	1.1±0.3*	0.4±0.1* # †	0.5±0.3*	0.4±0.1* †
Presence of areas of skin irritation in the area of the external and|or internal adhesion with caustic secretion (dysfunction of the meibomian glands with hyposecretion)	I	24	2.3±0.3	1.6±0.2*	1.5±0.2*	0.8±0.2* #	1.3±0.3*
	II	12	2.2±0.2	1.5±0.2*	0.8±0.1* # †	0.2±0.1* # †	0.5±0.2* †

* differences are statistically significant compared to baseline data; # compared to the corresponding data of the previous observation stage; † compared to the data of the control group; in all cases p <0.05–0.001.

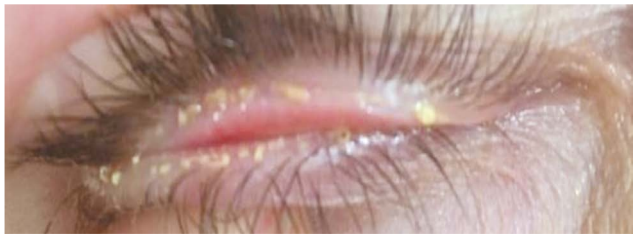

Fig. 1. Presence of thick, pasty meibomian gland secretion in patient D. with hyposecretory meibomian gland dysfunction before treatment.

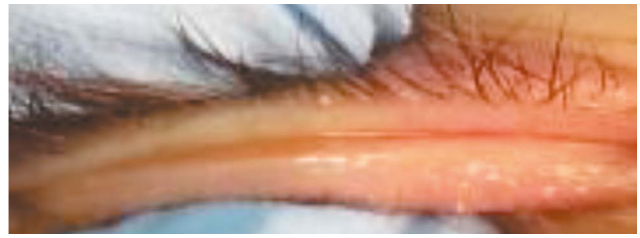

Fig. 2. Picture of the eyelid rib margin with almost complete absence of thick secretion in patient D. at the 4th week of follow-up.

Table 2. Dynamics of severity of clinical symptoms (subjective signs) of meibomian gland dysfunction in patients receiving different therapy (*n*=42, 84 eyes) (points, M±m)

Symptom	Group	Number of eyes	Initial data	Stages of observation (wk)			
				1	2	4	8
Feeling of heaviness of the eyelids	I	40	2.4±0.3	2.2±0.3	1.5±0.3*	0.7±0.1* #	0.7±0.1*
	II	44	2.6±0.2	2.1±0.3	1.1±0.2*	0.3±0.1* †	0.2±0.1* †
Feeling of pain in the edges of the eyelids	I	40	1.8±0.3	1.0±0.3*	0.6±0.4*	0.6±0.2*	0.2±0.1*
	II	44	1.6±0.1	1.1±0.1*	0.5±0.1* #	0.3±0.1*	0.4±0.2*
Feeling of itching and burning of the eyelids	I	40	2.8±0.2	2.3±0.4	1.6±0.2*	0.7±0.1* #	0.6±0.1*
	II	44	2.7±0.3	2.7±0.1	1.7±0.2*	0.2±0.1* # †	0.2±0.1* †
Subjective discomfort	I	40	2.5±0.4	1.6±0.1*	1.1±0.1* #	1.1±0.2*	0.6±0.1* #
	II	44	2.6±0.3	1.9±0.1*	1.0±0.1* #	0.4±0.1* †	0.2±0.1* †

* differences are statistically significant compared to baseline data; # compared to the corresponding data of the previous observation stage; † compared to the data of the control group; in all cases p <0.05–0.001.

By Week 8, an acaricidal effect was achieved in both groups, with a more significant effect in Group II (Table 3). The results were confirmed by evaluation of acaricidal activity, showing the significantly decreased number of mites. The difference between the groups is shown in Fig. 3.

DISCUSSION

The study evaluated the therapeutic effect of agent 3 in patients with long-lasting chronic blepharitis associated with MGD. The dosage form selection remains an important therapeutic challenge in these patients. Given the side

Table 3. Comparative evaluation of acarograms in patients of study groups with chronic blepharitis and meibomian gland dysfunction on the background of different therapy regimens (*n*=28, 56 eyes) (points, M±m)

Acarogram dynamics	Group I (13 patients, 26 eyes) Phytoblepharocleaning + eyelid massage + artificial tears				Group II (15 patients, 30 eyes) Phytoblepharocleaning + eyelid massage + artificial tears + agent 3			
	Hyposecretion of meibomian glands, 10 eyes		Hypersecretion of meibomian glands, 16 eyes		Hyposecretion of meibomian glands, 22 eyes		Hypersecretion of meibomian glands, 8 eyes	
Stages of observation	Initial data	Week 8	Initial data	Week 8	Initial data	Week 8	Initial data	Week 8
The number of *Demodex* mites in a preparation from 16 eyelashes	10.3±0.2	3.4±0.2*	8.7±0.3	4.4±0.3*	8.9±0.2	2.3±0.4* †	9.6±0.3	2.5±0.5* †

* differences are statistically significant compared with baseline data; † compared with control group data; in all cases p <0.05–0.001.

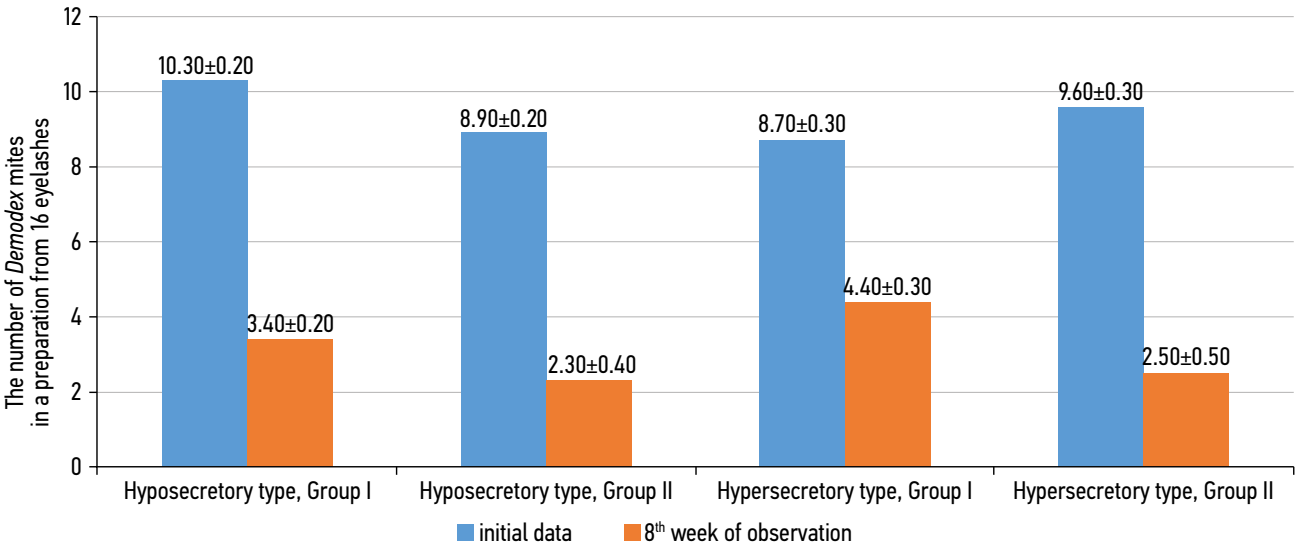

Fig. 3. Comparative characterization of acaricidal effect in subjects receiving different therapies depending on the nature of meibomian gland secretion (*n*=28, 56 eyes).

effects and risks of concomitant use of agent 3 with other drugs during systemic therapy with metronidazole, including long-term use for 16 weeks with tapering, as well as certain disadvantages of metronidazole ointments (a favorite medium for *D. folliculorum*), metronidazole topical gels offer some benefits in ophthalmology. In addition, it has a clear benefit of no age restrictions for therapy compared to gel products used in dermatology.

Treatment regimens used in ophthalmology, based on herbal lid hygiene products in combination with therapeutic lid massage, provide a positive therapeutic effect in patients. However, the most rapid and beneficial clinical effect, its prolongation, and acaricidal effect of the therapy remain important issues, since diagnosed demodicosis in patients with chronic blepharitis associated with MGD requires therapy adjustments.

Therefore, this study of the the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract, and sulfur preparations efficacy (a topical gel for herbal lid hygiene) demonstrated that it was more beneficial compared to other dosage forms of metronidazole and also provided the most significant clinical effect compared to the baseline herbal lid hygiene products.

Study limitations

Not found.

CONCLUSION

Addition of metronidazole to the topical gel products for the lid margins (the ophthalmic gel containing metronidazole, hyaluronic acid, *Aloe vera* extract, and sulfur preparations) resulted in a statistically significant difference in the clinical effect compared to the baseline therapy at Week 4 and also helped maintain a stable therapy effect during the following 4 weeks. Thus, topical gels for lid hygiene containing metronidazole as part of combination therapy can be recommended for patients with blepharitis and MGD due to a more significant therapeutic effect compared to the baseline herbal lid hygiene products. In our opinion, when choosing combined therapy for patients with blepharitis associated with MGD, it is important to focus on preliminary diagnosis in order to confirm or rule out demodicosis.

ADDITIONAL INFORMATION

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