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Observational Cohort Study**

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Summary

769 patients with conjunctivitis were treated either with Oculoheel (n = 456) or tetryzoline (n = 313) in a prospective, controlled cohort study. The treatments were compared by an analysis of variance with baseline values of efficacy parameters as covariates. Efficacy parameters were the mean symptom score and the sum of 5-point rating scale scores of 9 specific conjunctivitis symptoms and the global assessment of the investigators. For both the mean symptom score and the sum of score, the intensity of the baseline symptoms was reduced significantly during the treatment. The analysis of variance revealed with a probability of 95% that the difference between the treatments was less than 5% of the maximum score range. Thus, Oculoheel was shown not to be inferior to tetryzoline with regard to a clinically relevant reduction of the specific conjunctivitis symptoms. The global assessment revealed that a treatment with Oculoheel was rated as "very good" or "good" in 88% of the cases (tetryzoline group: 95%). Tolerability was excellent for both treatment groups.

Keywords: Antihomotoxic medicine, conjunctivitis, homeopathy, observational cohort study, Oculoheel, tetryzoline

Introduction

Many patients present to the general practitioner or ophthalmologist with a red and painful eye, often associated with ocular discharge (1). A frequent cause for these complaints is an inflammation of the conjunctiva, a thin and transparent mucous membrane that covers the inner surface of the upper and lower eyelids and extends to the limbus of the cornea on the surface of the globe (2). Together with the surface of the cornea this non-keratinizing epithelium forms the conjunctival sac.

The conjunctiva is of prime importance in the maintenance of the optimal physiological environment of the eye and thus to the preservation of vision (3). Major functions of the conjunctiva are to provide a tear film, which is essential for eye movement, and to protect the ocular surface against pathogens by providing immuno-active and anti-microbial agents. Conjunctival inflammation may therefore cause imbalance of these processes.

In general, conjunctivitis may be of infectious (predominantly bacterial or viral) or non-infectious origin. Allergic conjunctivitis, permanent irritation, and toxic reactions present the most important non-infectious causes of inflammation.

The incidence of allergic diseases of the eye has been increasing, affecting approximately 20% of the general population (4). The typical symptoms of seasonal allergic conjunctivitis often occur in combination with rhinitis symptoms and include intensive ocular itching, hyperemia, lacrimation, and discharge, frequently accompanied by nasal congestion and sneezing (2).

Because these symptoms affect patients'

quality of life, a symptomatic therapeutic approach is often considered adequate (5, 6, 7). Several classes of medications are currently prescribed. Topical or oral ophthalmic antihistamines compete with histamine for receptors on effector cells and thus suppress the immune response and the manifestation of clinical symptoms. The most prevalent sign of conjunctivitis, red eye, is frequently treated with vasoconstrictors. These drugs decrease conjunctival edema and hyperemia by activating α -adrenergic receptors and thus providing symptomatic relief (4). In addition to antihistamines and vasoconstrictors, non-steroidal anti-inflammatory drugs, mast cell stabilizers, and corticosteroids may be used for specific treatment.

A further therapeutic option is the use of the antihomotoxic remedy Oculoheel (manufactured by Biologische Heilmittel Heel GmbH, Baden-Baden, Germany). This preparation has been approved in several countries and is used to treat conjunctivitis, blepharitis, and dacryocystitis. Based on its individual homeopathic constituents, Oculoheel is assumed to have general anti-inflammatory and detoxifying activities specifically intended for the treatment of the eyes.

Methods

Study design

We sought to obtain additional data on the efficacy, safety, and mode of application of Oculoheel (eye drops) under the conditions of daily routine treatment. For this reason, a prospective, controlled, observational cohort study was performed by comparing disease-specific efficacy parameters and safety between patients treated with the antihomotoxic remedy and those

		Oculoheel	Tetryzoline
Demographic data	Age (years)		
	• mean	39.1	44.3
	• range	6–89	6–94
	• SD	19.8	18.6
	Sex		
	• male	162 (35.5)	147 (47.0)
	• female	292 (64.0)	164 (52.4)
	• not specified	2 (0.4)	2 (0.6)
Localisation and specification	Conjunctivitis		
	• with reddening	389 (88.0)	283 (92.8)
	• without reddening	38 (8.6)	16 (5.2)
	• not specified	15 (3.4)	6 (2.0)
	Marginal blepharitis		
	• with reddening	64 (58.7)	68 (68.0)
	• without reddening	44 (40.4)	30 (30.0)
	• not specified	1 (0.9)	2 (2.0)
Cause of conjunctivitis	Irritation	167 (36.6)	147 (47.0)
	Allergic inflammation	165 (36.2)	125 (39.9)
	Infection	99 (21.7)	45 (14.4)
	Systemic disease	8 (1.8)	2 (0.6)
	Others	37 (8.1)	13 (4.2)
Mode of conjunctivitis	Acute	218 (47.8)	234 (74.8)
	Chronic	144 (31.6)	33 (10.5)
	Recurrent	76 (16.7)	31 (9.9)
	Not specified	18 (3.9)	15 (4.8)
Intensity of conjunctivitis	Slight	188 (41.2)	94 (30.0)
	Moderate	239 (52.4)	196 (62.6)
	Severe	25 (5.7)	21 (6.7)
	Not specified	3 (0.7)	2 (0.6)
Duration of conjunctivitis [weeks]	< 1	187 (41.0)	196 (62.6)
	1–2	97 (21.3)	74 (23.6)
	2–4	59 (12.9)	12 (3.8)
	> 4	102 (22.4)	19 (6.1)
	Not specified	11 (2.4)	12 (3.8)

Tab. 1: Baseline parameters of patients entered into the observational study. Data are number of patients and percentage (%). Oculoheel: n = 456; tetryzoline: n = 313; n may be smaller due to single patients with missing data. Multiple assignment was possible for the parameters localisation/specification and cause of conjunctivitis. SD = standard deviation

treated with tetryzoline, a local vasoconstrictor frequently used in the treatment of conjunctivitis (8, 9, 10).

Patients and treatment

According to the character of an observational study, the investigators were free to enroll any patient with conjunctivitis or related eye diseases without any further inclusion or exclusion criteria, to reflect the real treatment situation of such patients. An exception was made with regard to the intended comparison of the homeopathic remedy with the vasoconstrictor. Patients were to be treated with either Oculoheel (containing *Euphrasia officinalis* D5, *Cochlearia officinalis* D5, *Pilocarpus jaborandi* D5, *Echinacea angustifolia* D5) or

with a standardized tetryzoline dosage (0,5 mg) as monotherapy. Oculoheel is prepared without preservatives.

Patients could be included only if they were at least 6 years old. During the initiation of this study two monodose preparations containing tetryzoline 0,5 mg were available in Germany (Berberil® N eye drops, Yxin®). The investigators were free to choose either for treatment.

Intervention and assessment

Individual patient and treatment data were ascertained during a screening and a termination visit and entered into a specific document form. The regular study treatment period was 2 weeks. If considered

necessary, interim visits were made and the respective data were also documented (results reported herein were documented in the treatment of conjunctivitis as the most prevalent indication).

During the screening visit the following data were collected: demographic data, possible risk factors, diagnosis, localization, specification, and cause of the eye irritation. To document baseline data for the assessment of efficacy, the intensity of the general conjunctivitis complaints was assessed according to the following scale: slight, moderate, severe, and the character of the disease as acute, chronic, or recurrent. More detailed information was obtained by ascertaining the intensity (scale: none, slight, moderate, severe, very severe) of the following specific symptoms: pain/burning, itching, reddening, light sensitivity, swelling, lacrimation, foreign-body sensation, and stabbing, retrobulbar pain. Further data were ascertained with regard to the duration of the examined disease, possible pre-treatment, the dosage to be used, and the occurrence of concomitant conditions.

During the termination visit investigators asked about possible premature termination of the treatment and reason, time of first improvement of the symptoms, occurrence of side effects, and possible dosage changes. The specific symptoms were again assessed as described above.

At the same visit the investigators assessed the efficacy of the treatment according to a 5-point rating scale: very good (no more complaints), good (significant improvement), moderate (slight improvement), without success (no change), or deterioration. For the assessment of tolerability and patients' compliance a 4-point rating scale was used (very good, good, moderate, bad).

Statistics

The following statistics were calculated for score variables and continuous variables: mean, median, standard deviation, minimum, and maximum; for categorical and ordinal variables: absolute and relative fre-

quencies. With regard to the comparability of the treatment groups, demographic data and all baseline parameters were compared descriptively, and a *t*-test or Fisher's exact test was performed.

Our objective was to demonstrate therapeutical equivalence between the treatments, particularly "non-inferiority" of Oculoheel. For the efficacy parameters, a tabular comparison was performed concerning the course of the scores of the single symptoms, the course of the mean symptom scores, and the course of the sum of scores.

The analysis of statistical relevance of possible differences was done using analysis of variance by including the baseline values as covariates and on the basis of adjusted means.

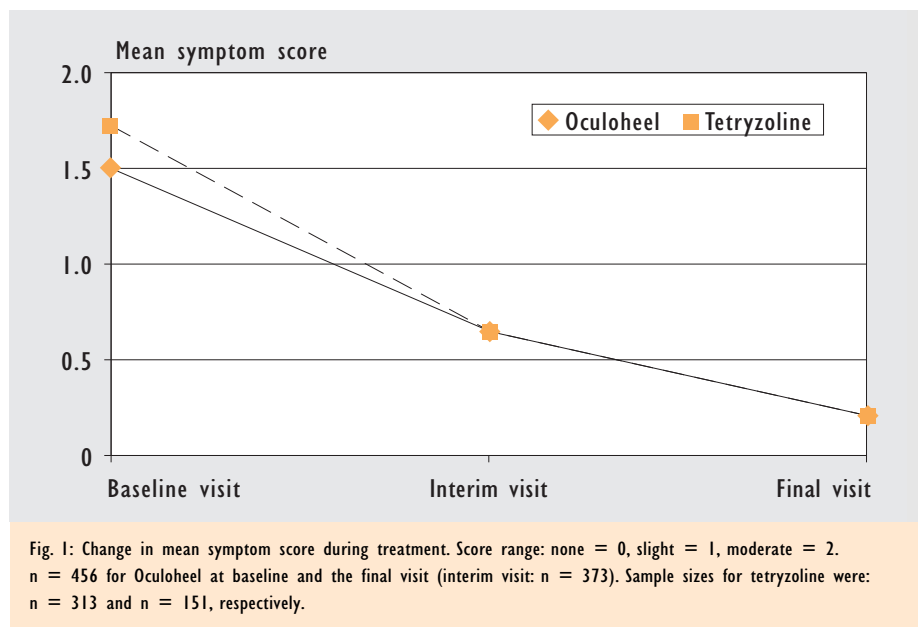
This observational study was planned, conducted, and analyzed following Standard Operating Procedures and in compliance with specific guidelines (11). All Case Record Forms were reviewed for completeness and consistency. Double-data entry was performed for all numerical data. The statistical analysis was carried out by using the validated software SAS, version 6.12.

Results

Patients

In total, 790 patients with conjunctivitis took part in the observational studies. Twenty-one were excluded because they were not at least 6 years old or had missing data, resulting in 769 total patients: 456 treated with Oculoheel and 313 treated with tetryzoline. In the following, percentage values are related to the total patient population in the respective treatment group. Values not totaling to 100% are due to missing data.

Twenty-nine percent of the patients in the Oculoheel group and 16% of the patients in the Tetryzoline group terminated their treatment prematurely. In most cases (Oculoheel: 24%, tetryzoline: 14%) this was due to cure with no need for further



therapy. Further termination reasons were insufficient efficacy (Oculoheel: 5%, tetryzoline: 1%) and the occurrence of adverse events or lack of compliance (Oculoheel: 1%, tetryzoline: 1%).

A summary of specific disease data at baseline is given in Table 1. The mean age in the Oculoheel group was 39.1 years, compared with 44.3 years in the tetryzoline group. More female than male patients were included. The investigators were asked to specify the reasons that presumably caused the conjunctivitis. Irritation, allergic inflammation, and infection were reported most frequently as the underlying etiologies.

The "red eye" was the most common symptom, with an intensity predominantly assessed as moderate or slight. The documentation of the duration of disease revealed that in most cases the conjunctivitis was acute, but there was also a considerable number of patients with chronic and recurrent complaints (Tab. 1). In the Oculoheel group the number of patients with chronic complaints was higher than in tetryzoline patients (32% vs. 11%, respectively). This finding is also reflected by the duration of the disease. In both treatment groups, a duration of < 1 week was most common, but in the Oculoheel group again there were approximately three times

more patients with disease duration of > 4 weeks (Tab. 1). The majority of patients did not have any pre-treatment with other ophthalmologic medications before enrolling (Oculoheel: 83%, tetryzoline: 98%).

Treatment

The applied dosage was predominantly 1 drop t.i.d. at study onset for both groups (Oculoheel: 74%, tetryzoline: 70%; *U*-test: *p* = 0.78). Changes in the dosage scheme during treatment occurred more frequently in the Oculoheel group (41%) than in the tetryzoline group (14%). Dosage changes were almost exclusively reported as dose reductions.

The mean treatment duration was 12.5 days in the Oculoheel group and 15.9 days in the tetryzoline group. Most patients in both treatments had a treatment duration of 8–14 days (Oculoheel: 55%, tetryzoline: 49%).

Assessments

Symptom score: At each visit the investigators assessed the intensity of specific conjunctivitis symptoms. With these data a mean symptom score (score range: 0–4) was calculated to assess the general reduction in symptom severity during the course and at the end of the treatment (Fig. 1).

The evaluation revealed a relevant and almost linear reduction in both treatment groups. At baseline the mean symptom score in the Oculoheel group was 1.45. At an interim visit this score decreased to 0.56 and further decreased to 0.1 at the end of the treatment. The respective values in the tetryzoline group were comparable (1.71 to 0.7 to 0.3).

The analysis of variance revealed with a probability of 95% that the difference between the treatments was less than 5% of the maximum score range (Tab. 2). Thus, it can be stated that Oculoheel is not inferior (i.e. equal or superior) to tetryzoline.

When analyzing subgroups according to the severity of the complaints at baseline (slight, moderate, severe) the same results were obtained for each of these groups. The reduction in mean symptom score was similar in both treatment groups. The comparison of the treatments revealed improving results for Oculoheel with an increase in the severity of symptoms. Best results were obtained for the intensity “severe” (actual equivalence limit: 1.25% of the maximum score range).

Sum of score: When comparing the respective data at baseline, highest values were obtained in the tetryzoline group (Fig. 2). During the treatment phase, the sum of score of the eye symptoms was significantly reduced. In the Oculoheel group the respective values decreased from 7.5 (baseline visit) to 3.0 (interim visit) to 1.0 (final visit). In the tetryzoline group a decrease from 11.5 to 4.2 to 1.1 was determined. Also, for this parameter the analysis of variance revealed with a probability of 95% that the difference between the treatments was less than 5% of the maximum range of sum of score (Tab. 2).

Subgroup analyses were performed to obtain further information on possible treatment differences. For both parameters described above, therapeutic equivalence between Oculoheel and tetryzoline was obtained for the subgroup of patients with allergic inflammation as the underlying cause of conjunctivitis (actual equivalence

Mean symptom score			
	Baseline visit	Interim visit	Final visit
Mean (Oculoheel)	1.45	-0.89	-1.35
Mean (Tetryzoline)	1.71	-1.01	-1.41
Difference (Oculoheel – Tetryzoline)	-0.26	0.11	0.06
95% confidence interval of the difference	-0.34 – -0.18	0.04 – 0.19	0.01 – 0.11
Common standard deviation	0.527	0.392	0.342
Standardized difference ¹	-0.49	0.28	0.18
t-test	0.0001		
Actual limit of equivalence (score-points)		0.19	0.11
Standardized limit of equivalence ²		0.48	0.32
Sum of symptom score			
	Baseline visit	Interim visit	Final visit
Mean (Oculoheel)	7.51	-5.19	-7.99
Mean (Tetryzoline)	11.51	-5.74	-8.31
Difference (Oculoheel – Tetryzoline)	-4.00	0.55	0.32
95% confidence interval of the difference	-4.75 – -3.26	0.03 – 1.07	-0.01 – 0.65
Common standard deviation	5.182	2.443	2.139
Standardized difference ¹	-0.77	0.23	0.15
t-test	0.0001		
Actual limit of equivalence (score-points)		1.07	0.65
Standardized limit of equivalence ²		0.44	0.30

¹ Standardized difference: ratio of difference and standard deviation
² Standardized limit of equivalence: ratio of actual limit of equivalence and standard deviation.
 Effect size according to Cohen: 0.2 = small, 0.5 = medium, 0.8 = large difference (16)

Tab. 2: Analysis of variance. Reduction of the mean symptom score and the sum of symptom score by including the baseline scores as a covariate.

limit: mean symptom score 2.8% of the maximum score range, sum of score 2.6% of range of sum of score). Additionally, the stratification was extended to the nine single conjunctivitis symptoms. For each single analysis the results suggest therapeutic equivalence between the treatments, whereas Oculoheel showed best results concerning the symptom “pain/burning” (actual equivalence limit: 1.8% of the maximum score range).

Therapy Results

As a further parameter, the time of first improvement of the symptoms was documented. For 83% of the patients treated with Oculoheel and 97% of the patients treated with tetryzoline, global improvement of the symptoms was ascertained within days 4 to 7 of treatment. Differences between the groups may be due to

the considerably higher number of chronic cases in the Oculoheel group (Tab. 1).

At the termination visit investigators assessed the success of the therapies according to a 5-point rating scale. This global assessment revealed that treatment with Oculoheel was rated as “very good” or “good” in 88% of the cases. The respective value for tetryzoline was 95% (Fig. 3).

Tolerance and Compliance

The tolerability assessment of both treatments was excellent. For 98% of the Oculoheel patients and 100% of the tetryzoline patients a “very good” or “good” tolerance was reported. There were no concerns with regard to patients’ compliance. In both treatment groups compliance was considered by the investigators as “very good” or “good” in 96% of the patients.

Discussion

Disorders of the ocular surface affect most individuals at some time in their lives. Thus, red eye is a common clinical problem in most medical practices and is frequently a result of conjunctivitis. While most ocular complaints associated with conjunctivitis are benign, others can lead to serious sequelae. Therefore, an approach to treatment should be based on the severity of symptoms, the magnitude of possible consequences, and the risk potential of the medication to be administered (1). Anti-histamines and vasoconstrictors are widely used to relieve symptoms, especially in the treatment of allergic conjunctivitis (7, 12).

It has been shown recently that observational studies are reliable tools in the investigation of drug safety and efficacy. Comparing the results of observational studies and randomized controlled trials in 19 treatments, differences in the estimates of the effects were found in only 2 (13). Carefully planned, conducted, and statistically evaluated observational studies generally provide valid data for the assessment of therapies.

Demographic data, documented clinical symptoms, and other baseline characteristics of the patients treated in this study are representative of the patient population who present to general practitioners and ophthalmologists. The specific treatment focused on irritations and allergic conditions as the most prevalent underlying causes of the conjunctivitis symptoms. Some imbalances were found with regard to single baseline parameters between the treatment groups. In both groups the cases were predominantly acute, but in the patients treated with Oculoheel a higher proportion of chronic conditions was reported. In conjunction, the mean symptom intensity at baseline slightly differed. Therefore, an analysis of covariance with the baseline values as covariates was performed to adequately consider these findings.

Both parameters, the mean symptom score and the sum of score, revealed a clinically relevant reduction of baseline values to al-

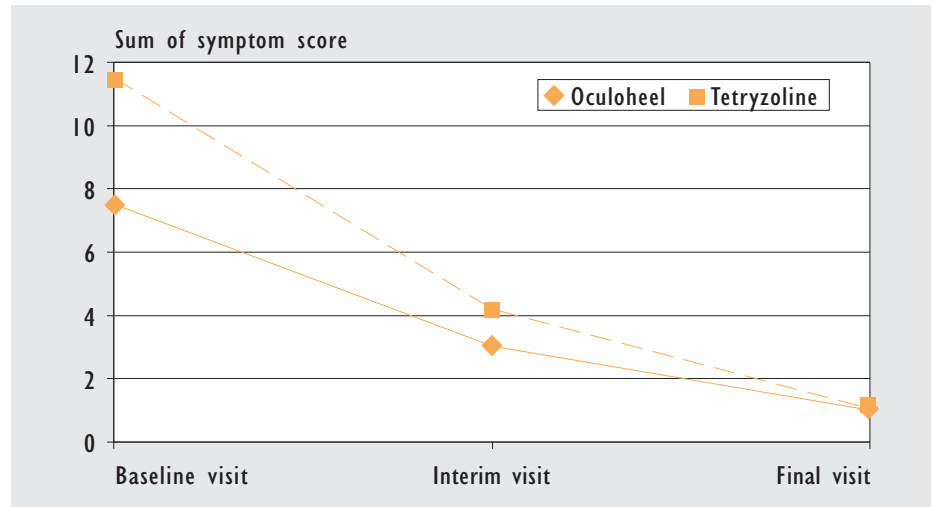


Fig. 2: Change in sum of symptom score during treatment. $n = 456$ for Oculoheel at baseline and the final visit (interim visit: $n = 373$). Sample sizes for tetryzoline were: $n = 313$ and $n = 151$, respectively.

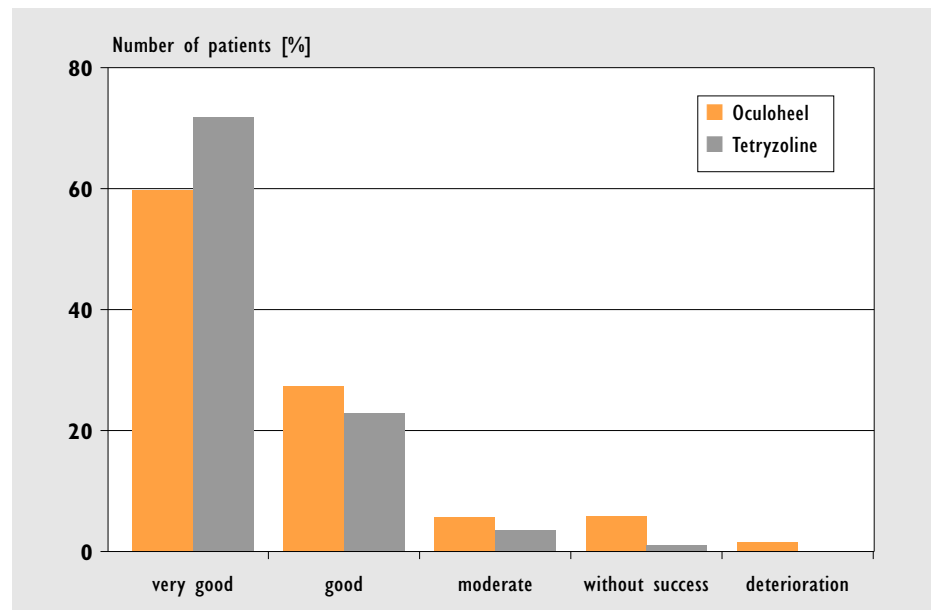


Fig. 3: Investigators' global assessment of the efficacy of the treatments

most zero at the end of the treatment. Statistical analysis revealed that the efficacy of Oculoheel and tetryzoline in the treatment of conjunctivitis was comparable. No relevant differences were found for the summarizing parameters or in the evaluation of single symptoms such as pain/burning, itching, or reddening. These results were also confirmed by the investigators' global assessment of efficacy.

In addition to efficacy, drug tolerance should be considered as a key factor when selecting the choice of therapy. Both treatments were well tolerated in this study.

Although no adverse events were reported, possible side effects generally have to be considered in the case of treatment with vasoconstrictors. Adverse systemic reactions such as circulatory disturbances (14) and local side effects such as ocular stinging (15) and risk of glaucoma are possible sequelae associated with vasoconstrictor treatment.

Because we have demonstrated therapeutic equivalence for Oculoheel, it can be regarded as a valuable and safe homeopathic remedy in the treatment of conjunctivitis.

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