CLINICAL STUDY

Comparison of the efficacy and safety of two eye gels in the treatment of dry eyes: Lacrinorm and Viscotears

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Abstract

Purpose **To compare the efficacy and safety of two carbomer 940 eye gels in the treatment of dry eyes: Lacrinorm (also called GelTears), a recently introduced eye gel, and Viscotears (also called Vidisic or Lacrigel), used as a reference gel. The main difference between the two gels is in the preservative, respectively benzalkonium chloride and cetrimide.**

Methods **A double-masked, randomised, parallel-group study was conducted in 16 centres in four European countries. A total of 179 patients suffering from aqueous-deficient dry eye were enrolled, of whom 92 were randomised to treatment with Lacrinorm and 87 to the reference gel. Gel was instilled four times a day for a period of 30 days.**

Results **After 30 days of treatment, subjective symptoms (the combined scores of foreign body sensation, ocular dryness, burning or pain, and photophobia) had improved by 50% in the Lacrinorm group and by 45% in the reference gel group, and objective test results (break-up time, fluorescein test, Schirmer test, Lissamine Green test) by 35–36% in the Lacrinorm group and 25–45% in the reference group. The improvements were significant in both treatment groups ($p < 0.001$), with no significant differences between the treatment groups. Subjective local tolerability upon instillation on day 30 was rated 'good' or 'very good' by 91% of patients in both treatment groups. Adverse events were reported for 21 patients in the Lacrinorm group and 17 in the reference group, the most frequent being discomfort, blurred vision, hyperaemia, burning and itching. The frequency and descriptions of adverse events did not differ significantly between the two treatment groups. No serious adverse events were reported.**

Conclusions **Over the period of study, Lacrinorm eye gel was as effective and safe as Viscotears/Lacrigel in the treatment of dry eye.**

Key words Benzalkonium chloride, Carbomer 940, Cetrimide, Dry eye, Lacrinorm, Viscotears

There has been an increasing demand for the treatment of dry eyes, probably influenced by the higher proportion of elderly people in the population and to a lesser extent by environmental factors and the side effects of certain systemic medicines.[1]

Artificial tears provide the main form of symptomatic treatment. Early saline solutions required frequent instillation, but current formulations provide an increased contact time on the ocular surface.

Polyacrylic acid can be formulated at high viscosity for the topical treatment of dry eye.[2] This gel is well tolerated and has lubricating properties, with an extended ocular surface residence time.[3] Its non-Newtonian properties, which cause it to 'shear-thin' during the blink or saccade, minimise the symptoms of viscous drag that would otherwise occur.[4–6] Polyacrylic acids of differing molecular weights are available. The most widely used is carbomer 940, whose efficacy and good tolerance in the treatment of dry eyes has been established.[7–11]

Viscotears (marketed as Viscotears in Switzerland and the United Kingdom, as Vidisic in Belgium, the Netherlands and Germany, and as Lacrigel in France) is a carbomer 940 eye gel used in the treatment of dry eye. In a study by Brodwall *et al.*[12] it was shown to be as safe as, better tolerated and more effective than polyvinylalcohol 1.4%. Lacrinorm (code number 221-A; Laboratoire·Chauvin, marketed at GelTears in the United Kingdom) is a new carbomer 940 gel product that has recently been introduced in France, Belgium and Switzerland.

The difference between Lacrinorm and Viscotears is the preservative, respectively benzalkonium chloride and cetrimide. They are both ionically charged, surfactant quaternary ammonium compounds. The ocular toxicity of benzalkonium chloride has been extensively

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studied and its effects on the eye are well known. Published information about cetrimide is more limited. Since toxicity can arise with any preservative in use, formulations using different preservatives are of potential clinical value. Carbomer 934P with benzalkonium chloride 0.008% as preservative was studied and shown to be as safe as and more efficacious than placebo.[13]

Previous studies with Lacrinorm have shown that this gel is effective in the treatment of several forms of dry eye and that it is well tolerated.[8,14] The aim of the present study was to assess the efficacy and safety of Lacrinorm compared with that of the reference gel, Viscotears, over a period of 30 days.

Patients and methods

A multicentre, randomised, double-masked, parallel-group study was performed in 16 centres in four European countries (seven centres in France, four in Belgium, four in the United Kingdom and one in Switzerland). The protocol was approved in each country by an independent ethics committee. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Informed consent was obtained from patients prior to enrolment.

Patients

Patients were of either sex, aged over 18 years, and suffering from aqueous-deficient dry eye[15] as defined by the presence of two out of four specified symptoms (foreign body sensation, ocular dryness, burning or pain, and photophobia) and conformity with at least two of the following test results: tear film break-up time (BUT) $\leqslant$10 s, fluorescein staining $\geqslant$2 on a scale of 0–5, Schirmer 1 test without anaesthesia $\leqslant$6 mm in 5 min, Lissamine Green staining $\geqslant$4 according to the criteria of van Bijsterveld (0 to 9).[16]

The main exclusion criteria were: concomitant ocular pathology other than dry eye; the wearing of moisture-conserving spectacles or contact lenses; use of ocular inserts for dry eye; past history of intolerance or allergy to one of the study components (carbomer 940, cetrimide or benzalkonium chloride); and pregnancy in women.

Patients using a tear substitute prior to recruitment underwent a washout period with preservative-free saline *ad libitum* (Minims), for a minimum of 7 days before commencing double-masked treatment. Patients who had not been previously treated received no washout.

Systemic drugs were allowed before and during the study, but the name and dosage were recorded. Patients were asked to maintain the same levels of systemic therapy throughout the study period or to inform the investigator of any change. If other drugs were instilled via the ocular route during the study, this was considered to be a major protocol deviation (4 for Viscotears, 3 for Lacrinorm).

Study treatments and schedule

Lacrinorm (Laboratoire Chauvin) is a sterile, colourless, liquid gel containing 2.0 mg/g carbomer 940, and 0.1 mg/g benzalkonium chloride as preservative. The reference gel (Viscotears in Belgium, the UK and Switzerland, and Lacrigel in France) is a sterile, colourless, liquid gel containing 2.0 mg/g carbomer 940, and 0.1 mg/g cetrimide as preservative. The two treatments were supplied in identical, coded 10 g tubes.

The gel was to be administered topically four times a day from day 0 to day 30. If both eyes needed treatment, the eye gel could be instilled in both eyes, but only the more severely affected eye at recruitment was used for the analysis.

Patients attended at: the recruitment visit, the baseline visit on day 0, and study visits on days 15 and 30. Patients who discontinued treatment prematurely were assessed upon withdrawal. At the recruitment visit, past medical history was recorded, written informed consent obtained, and inclusion criteria checked. After a washout period of 7 days for patients using a tear substitute prior to recruitment, patients were randomly allocated to double-masked treatment on day 0 for a period of 30 days. At each of the four visits, four subjective symptoms were assessed and four objective tests performed. The four subjective symptoms (foreign body sensation, ocular dryness, burning or pain (including any stinging sensation), and photophobia) were each graded on a scale of 0–3: 0 = none; 1 = mild; 2 = moderate; 3 = severe. The overall subjective score was then calculated as the sum of the scores of the four symptoms, ranging from 0 to a maximum of 12. The four objective ophthalmic tests were BUT, fluorescein staining, Schirmer test and Lissamine Green staining, performed in this sequence after the subjective evaluation.

For the break-up test, a single drop of saline was applied to a Fluorets paper and the excess shaken off. The wetted strip was then touched briefly onto each lower tarsal plate. The patient was asked to blink several times to distribute the fluorescein. The time between the last blink and the first dry spot on the cornea, using the diffuse, cobalt blue illumination of the slit lamp, was taken to be the BUT. A second measurement was made within 20 s of the first and the values averaged.

Fluorescein staining (0.5%) on the cornea was graded just after the break-up test using the same illumination. The degree of staining of the cornea was assessed as follows: 0 = no fluorescein stain, or <5 superficial punctate erosions; 1 = $\geqslant$5 erosions affecting less than 10% of the surface; 1.5 = erosions affecting 10–25% of the surface; 2 = erosions affecting 25–50% of the surface; 3 = erosions affecting >50% of the surface; 4 = presence of confluent erosions affecting one or more zones; micro-ulcerations; 5 = presence of one or more wide and deep corneal ulcers.

Table 1. *Demography and baseline characteristics*

	All randomised patients (n = 179)			Efficacy analysis population (n = 160)		
	Lacrinorm (n = 92)	Reference gel (n = 87)	p value	Lacrinorm (n = 83)	Reference gel (n = 77)	p value
Age (years)						
Mean	58.6	64.0	0.02[c]	58.7	64.8	0.01[c]
SD	16.2	14.0		16.5	13.2	
Sex (n)						
Male	17	14	0.67[b]	16	11	0.40[b]
Female	75	73		67	66	
Dry eye duration (months)						
Mean	36	60	0.01[c]	36	61	0.01[c]
SD	45	73		46	75	
Tear substitute[a]						
Yes	44	50	0.20[b]	39	46	0.11[b]
No	48	37		44	31	

[a]Prior to study enrolment. [b]Chi-squared test. [c]t-test.

The Schirmer test was performed without anaesthesia, with the papers inserted at the junction of middle and lateral third of the lids and with the eyes closed. After 5 min the length of wetting was marked and measured in millimetres.

For the Lissamine Green test, a single drop (about 50 μl) of Lissamine Green (Pharma Plus, Jargeau, France) was instilled. The patient was asked to blink several times to distribute the stain. The degree of staining on the interpalpebral nasal and temporal conjunctiva and the cornea was recorded as follows: 0 = no stain; 1 = slight stain; 2 = moderate stain; 3 = intense stain. The scores were summed, to give a range from 0 to 9 as previously described.[16]

On day 30, patients and investigators were asked to rate the efficacy of the treatment as 'good', 'fairly good' or 'poor'.

The primary efficacy variable was the sum of the score of the four subjective symptoms. The protocol stated that 80 patients per group were needed to detect a difference of 0.78 between groups with a standard deviation of 1.5 (the scale ranged from 0 to 12, with $\alpha = 0.05$ and $\beta = 0.10$). The secondary efficacy variables were the four objective tests, and the patients' and investigators' opinions on the efficacy of the treatments.

Safety variables were: tolerance upon instillation, visual acuity and reporting of adverse events. Patients were asked to identify symptoms that occurred within 10 min of instillation; symptoms appearing after this time were also noted. The duration and nature of significant symptoms were documented. Ocular tolerance was also assessed by measuring distance visual acuity at recruitment and on day 30, using the Snellen scale. All adverse events occurring during the study, from patient inclusion to withdrawal or completion, were recorded in the Case Report Form.

Treatment compliance was assessed on day 15 and day 30 and was rated as: 'very good' if all instillations were performed, 'good' if 1 or 2 instillations were forgotten per week, 'fairly good' if 3–7 instillations were forgotten per week and 'poor' if more than 7 instillations were forgotten per week. If the compliance was poor, the mean instillation frequency of the gel per week was recorded.

Statistical methods and data sets analysed

Statistical analysis was performed on the more severely affected eye at recruitment. Comparison of patient characteristics at baseline used chi-squared tests for qualitative data and t-tests for quantitative data (Table 1). For efficacy results, a statistical analysis was performed on the individual differences between the baseline visit (day 0) and the study visit (day 15 or day 30). In addition, tests were performed on the progression of the mean of the scores on days 0, 15 and 30. For the primary efficacy variable (sum of the subjective symptom scores) and the objective ophthalmic tests (fluorescein test and Lissamine Green), a discrete repeated measures analysis was applied for all the visits (CATMOD procedure, SAS Institute).[17] The effects of three factors (treatment, time, time × treatment interaction) were studied; t-tests were performed for Schirmer test and break-up time. In addition, adjustment was made at each centre to take into account inter-observer variability. The statistical analysis was performed using the software package SAS, version 6.08.

Results

Patient characteristics

A total of 179 patients with aqueous-deficient dry eye were recruited to the study, of whom 92 were randomised to treatment with Lacrinorm and 87 to the reference gel (Viscotears or Lacrigel depending on the country). No attempt was made to assess the presence of Meibomian gland disease. Since the efficacy analysis did not take into account the data for patients with missing visits, comparison between treatment groups of the major demographic parameters and baseline characteristics was performed on all randomised patients and separately on each of the evaluable sets of patients (83 patients in the Lacrinorm group and 77 in the

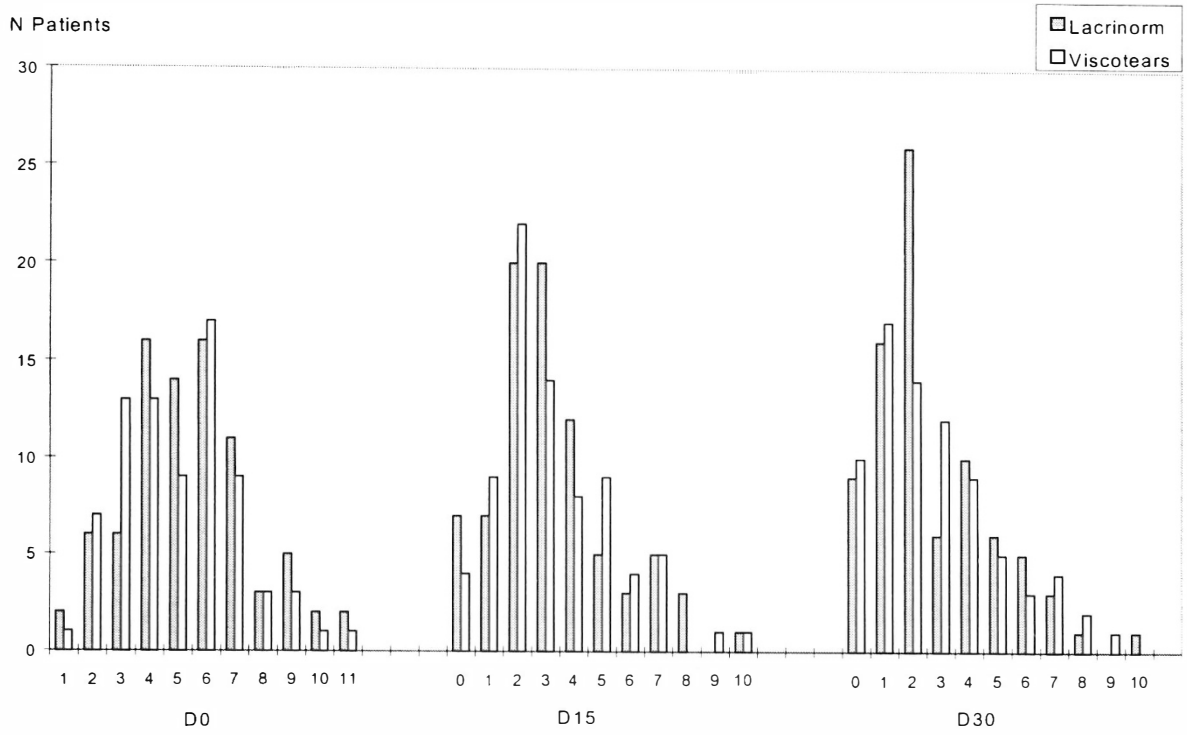

Fig. 1. *Sum of symptom scores*

reference group) (Table 1). There were no statistically significant differences between the treatment groups at baseline in either patient population, except for age and duration of dry eye. Patients in the reference gel group were older and had a longer known duration of dry eye.

The most frequent subjective symptoms at baseline were foreign body sensation and ocular dryness, which were present in 82–88% of all randomised patients in each treatment group. Burning or pain was present in 77% of randomised patients in the Lacrinorm group and 70% in the reference group, and photophobia in 54% of randomised patients in the Lacrinorm group and 67% in the reference group. In the majority of cases, symptoms were described as of mild or moderate intensity. The aetiology of dry eye was unclassified in 67% of all randomised patients. In cases where the aetiology was known, the most frequent cause was Sjögren's syndrome, which was presented by slightly more patients in the reference gel group (13 patients compared with 8 in the Lacrinorm group).

There were no statistically significant differences between the treatment groups in the scores of the subjective symptoms or objective ophthalmic tests at baseline in either patient population.

Concomitant therapies that might have influenced the dry eye syndrome were comparable between treatment groups, except for beta-blockers, which were used at a stable level throughout the study by two patients in the Lacrinorm group compared with 12 patients in the reference gel group.

Premature discontinuation

Ten patients in each treatment group discontinued the study prematurely. In the Lacrinorm group the reasons were: consent withdrawn (5 patients), adverse event (4 patients) and other (adverse event plus worsening of the disease; 1 patient stopped the treatment at day 23; after evaluation he was kept in the efficacy analysis). In the reference gel group, the reasons were: consent withdrawn (4 patients), adverse event (4 patients), lost to follow-up (1 patient) and other (used up all treatment by day 15; 1 patient).

Compliance

Treatment compliance was evaluated by the investigators as 'very good' for the majority of patients: 128 (74.4%) on day 15 and 105 (65.6%) on day 30. There was no statistically significant difference between the treatment groups in the level of compliance at either visit. The time intervals between the visits were close to the planned intervals of 15 and 30 days, with no significant difference between the treatment groups.

Efficacy

The primary efficacy variable was the sum of the scores of the four subjective symptoms (foreign body sensation, ocular dryness, burning or pain, and photophobia). The values of the ordinal variable (1–12) are shown in Fig. 1. In both treatment groups, the score of subjective symptoms improved most rapidly over the first 15 days, and then at a slower rate until day 30. The initial median score was 5 for both groups and the median change over

Table 2. *Score of subjective symptoms*

		Lacrinorm	Reference gel
Day 0	*N*	83	77
	Mean	5.42	5.05
	Q1	4	3
	Median	5	5
	Q3	7	6
Day 15	*N*	83	77
	Mean	3.22	3.25
	Q1	2	2
	Median	3	3
	Q3	4	5
Day 30	*N*	83	77
	Mean	2.71	2.77
	Q1	1	1
	Median	2	2
	Q3	4	4

time was identical for each group (Table 2). Although the mean reduction from baseline in the Lacrinorm group was slightly greater on both day 15 and day 30, the improvement in the subjective symptoms did not differ significantly between the two treatments ($p = 0.18$; no treatment effect). For both treatments combined, the change was significantly greater after 30 days than after 15 days ($p < 0.001$; time effect). Comparison of the two treatment groups over time showed that improvements in score in each group were comparable after 15 days, as well as after 30 days (CATMOD procedure, $p = 0.92$; no treatment × time interaction). When adjusted for centre, the conclusions were unchanged.

Analysis of the progression of the mean scores on days 0, 15 and 30 showed a statistically significant decrease over time for the two treatment groups combined ($p < 0.001$). When adjusted for centre, the conclusions were unchanged.

Due to the baseline differences in age and dry eye duration between the treatment groups, adjustments were performed for these co-variates. When adjusted for age, there was a statistically significant difference between the two treatment groups ($p = 0.039$; treatment effect), with the improvement in subjective scores being slightly better in the Lacrinorm group (2.7 vs 2.3 on average). When adjusted for dry eye duration, the greater improvement after 30 days than after 15 days in both treatment groups was not significant ($p = 0.052$). When adjustment was made for dry eye duration (<12 months; at least 12 months but <60 months; ⩾60 months), the score improvement in the two treatment groups combined was significant over time ($p = 0.008$). No further differences in the conclusions were revealed by adjustments for age or dry eye duration.

The results of the objective ophthalmic tests (BUT, fluorescein test, Schirmer test and Lissamine Green test) are presented in Figs. 2–5. After 30 days of treatment the improvements in each of the four tests ranged from 35% to 36% in the Lacrinorm group and from 25% to 45% in the reference gel group. For both treatment groups combined, the improvement in mean scores was statistically significant for each of the four ophthalmic tests ($p < 0.001$ in all four cases). There were no

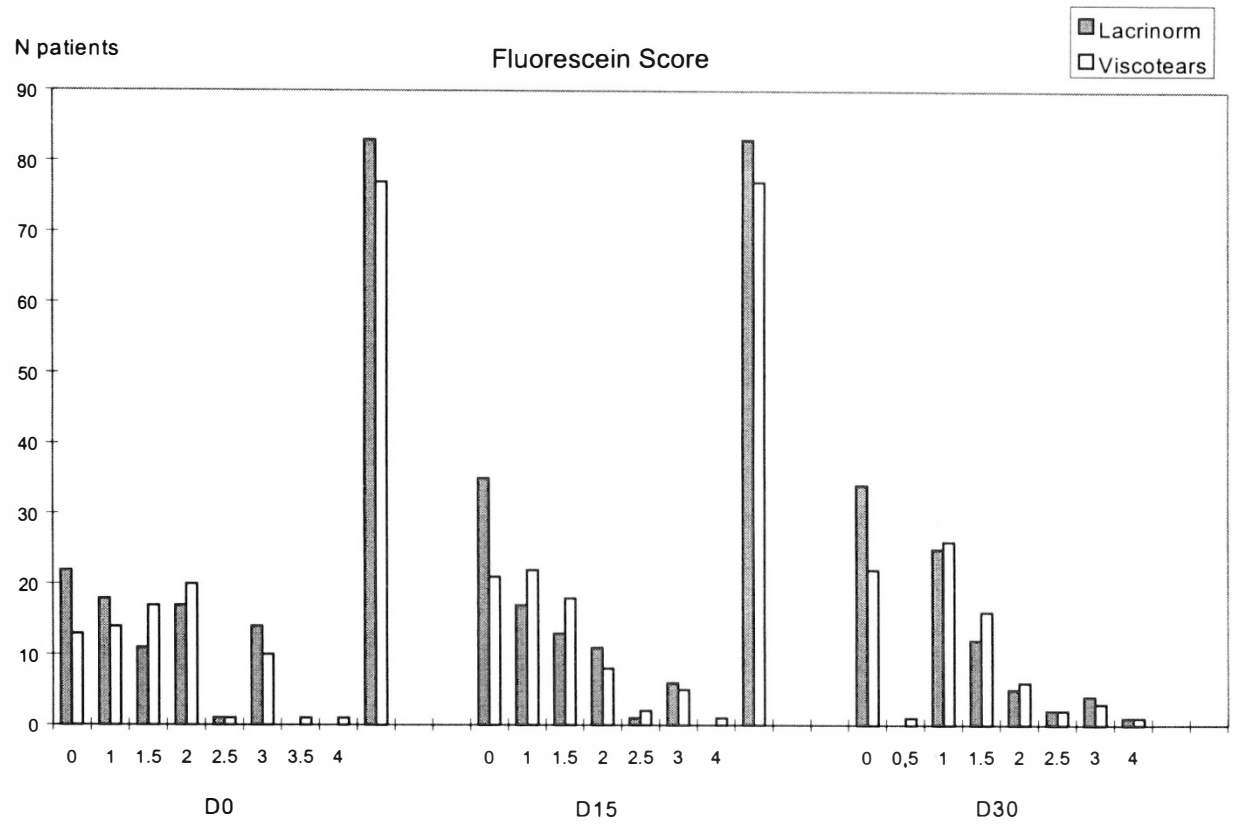

Fig. 2 *Fluorescein scores.*

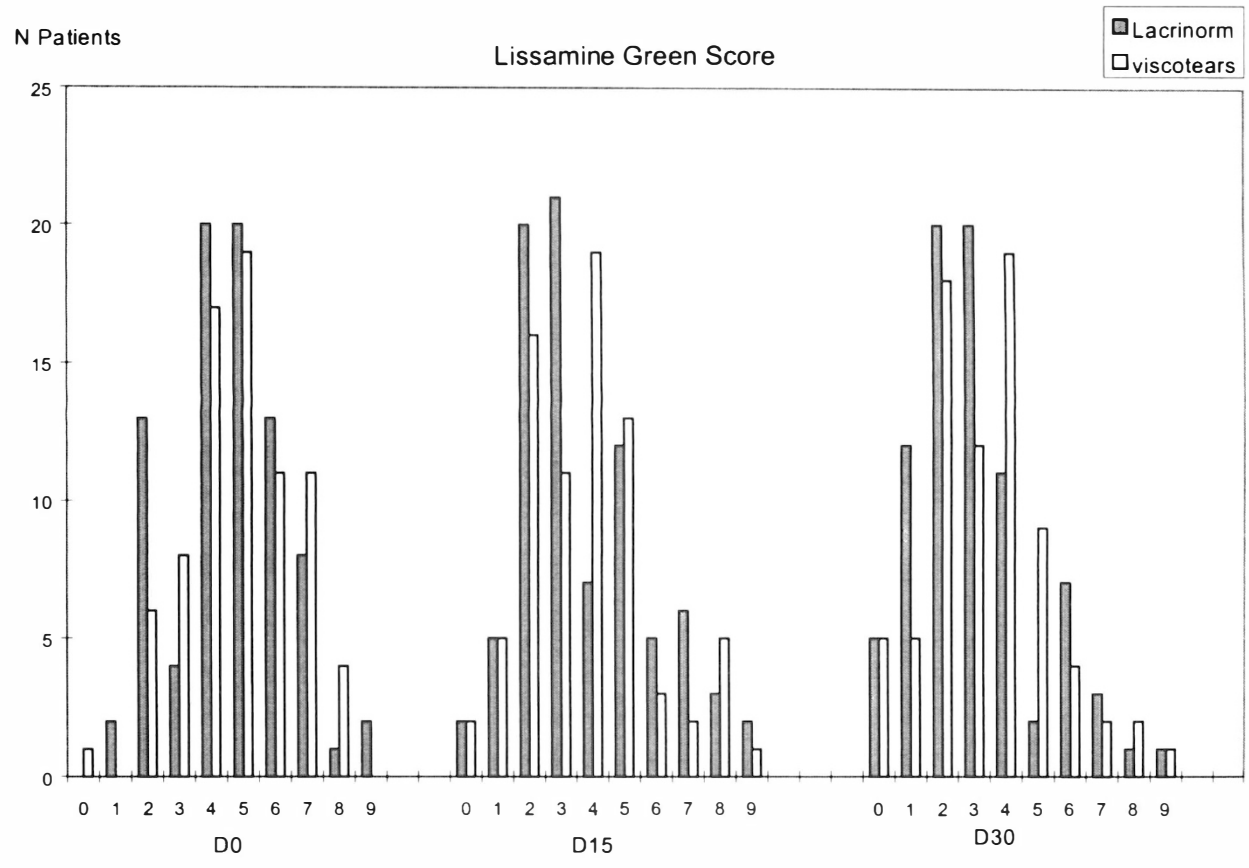

Fig. 3. *Lissamine Green scores.*

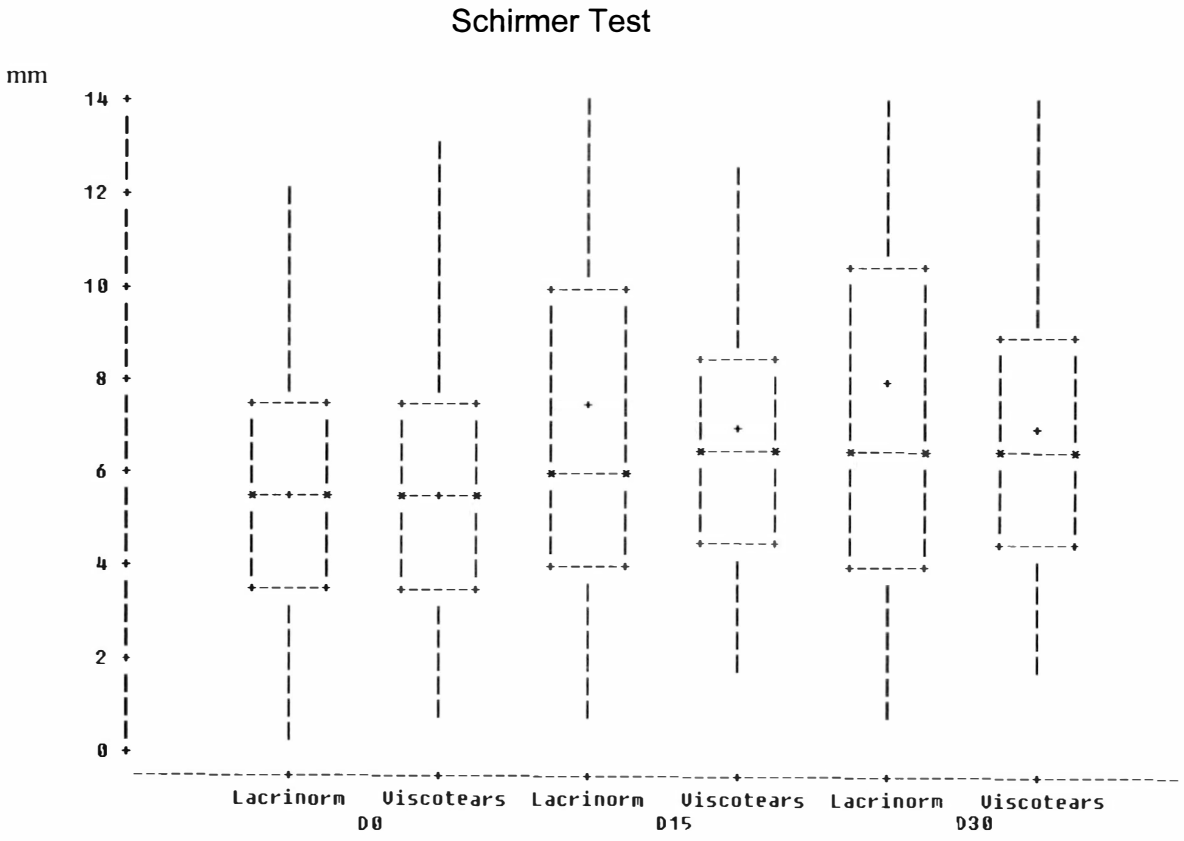

Fig. 4. *Schirmer test results (box plots).*

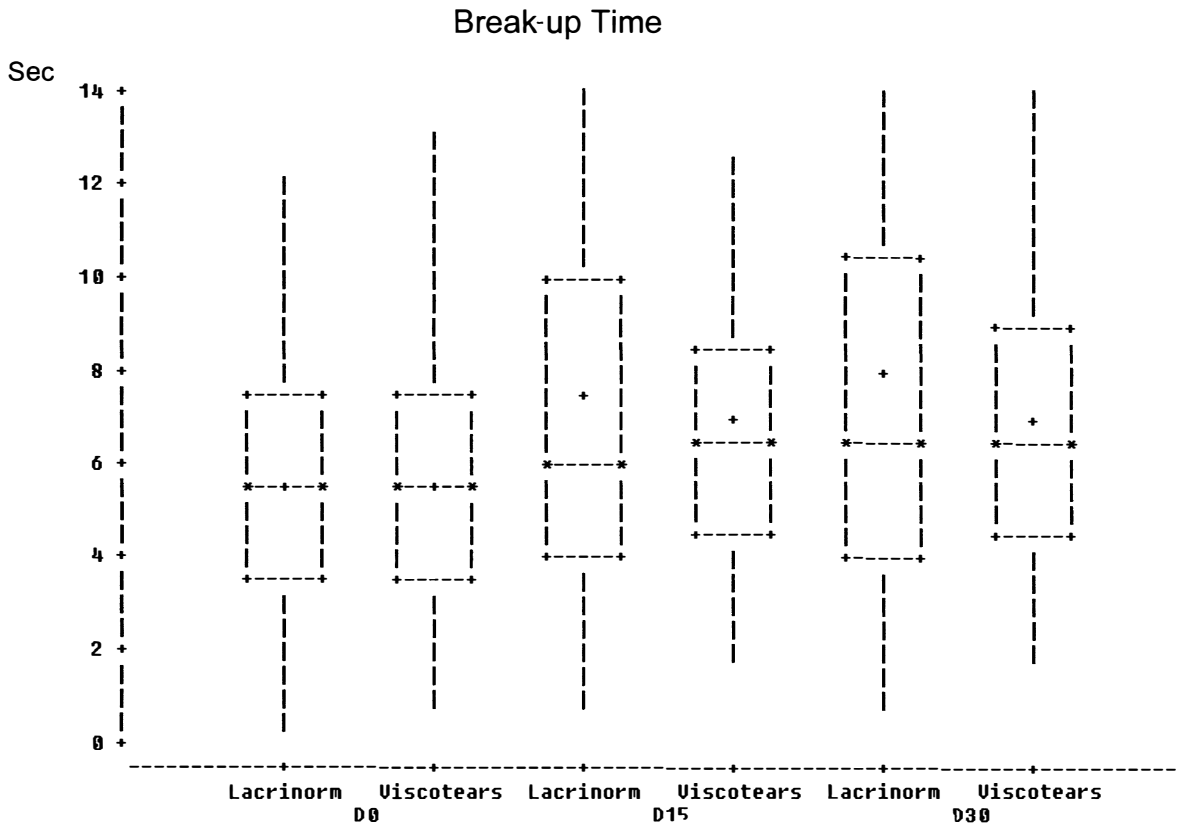

Fig. 5 *Break-up time results (box plots).*

statistically significant differences between the two treatment groups for any of the four ophthalmic tests (no treatment effect or treatment × time interaction).

The patients' and investigators' opinions of the efficacy of the treatments, on day 30 are given in Table 3. For 50–67% of patients the rating was 'good', with no statistically significant difference between the treatment groups.

Safety

The mean treatment duration was 27.8 ± 6.5 days in the Lacrinorm group and 27.7 ± 6.7 days in the reference group. For treatment dosage, most patients received four instillations per day, as required by the protocol, but a total of 8 patients (4 in each group) received two or three instillations per day.

Table 3. *Patients' and investigators' opinions of the efficacy of the treatments*

Opinion	Lacrinorm *n* (%)	Reference gel *n* (%)
Patients' opinion		
Good	56 (67)	45 (58)
Fairly good	20 (24)	23 (29)
Poor	8 (9)	10 (13)
Investigators' opinion		
Good	43 (51)	39 (50)
Fairly good	33 (39)	30 (38)
Poor	8 (10)	9 (12)

Subjective local tolerance upon instillation was rated as 'very good' or 'good' by 90% of patients in the Lacrinorm group and 87% of patients in the reference group on day 15, and by 91% of patients in both treatment groups on day 30. There was no significant difference between the treatment groups at either visit. Blurred vision reported due to the eye gel was the most frequent symptom (14 patients in the Lacrinorm group and 11 in the reference group). Other symptoms reported were indissociable from the dry eye pathology (Table 4). The frequency of events was comparable in the two treatment groups, and there was no significant difference between the groups in the duration of symptoms.

Analysis of the difference in Snellen acuity between the recruitment visit and the day 30 visit, performed as an objective assessment of ocular tolerance, showed no statistically significant difference between the treatment groups. The mean difference was −0.15 ± 3.2 for the Lacrinorm group and 0.12 ± 0.8 for the reference group.

A total of 57 adverse events (24 in the Lacrinorm group and 33 in the reference group) were reported for 21 patients (23%) in the Lacrinorm group and 17 (20%) in

Table 4. *Subjective tolerance upon instillation*

	Lacrinorm (*n*)	Reference gel (*n*)
Blurred vision	14	11
Burning sensation	5	3
Stinging/itching	4	4
Foreign body sensation	2	3
Grittiness	1	2

the reference group. There were no significant differences between the treatment groups in the percentage of patients with at least one adverse event at either visit. Of the 57 adverse events, 14 events reported by 14 different patients were classified as related to the study treatment: Lacrinorm: blurred vision = 3, stinging = 3, hyperaemia = 1; reference gel: blurred vision = 1, grittiness = 1, soreness = 1, stinging = 1, sticky eyes = 2, redness = 1. All these events resolved on stopping treatment. Only three treatment-related adverse events were described as severe: 2 in the Lacrinorm group and 1 in the reference group. A total of 9 patients, 5 in the Lacrinorm group and 4 in the reference group, discontinued the study treatment due to adverse events. No serious adverse events were reported.

Discussion

In this randomised trial, comparing Lacrinorm with Viscotears, the baseline characteristics of the two groups of patients (92 in the Lacrinorm group and 87 in the reference group) were comparable except for age, duration of dry eye syndrome and intake of a systemic beta-blocker. The longer known duration of dry eye in the reference group might have been related to their older age, since the use of beta-blockers is also more frequent in older people. However, these differences had no influence on the mean score of subjective symptoms, which was slightly higher in the Lacrinorm group at the baseline visit (5.4 vs 5.1).

The subjective symptoms improved significantly in both groups after treatment, with no statistically significant difference between groups. Improvements of 50% and 45% were obtained in the Lacrinorm and reference groups respectively, after 30 days of treatment.

When the baseline difference in age was taken into account there was a statistically significant difference in favour of the Lacrinorm group. However, although the score improvement in this group was slightly higher than in the reference group, the difference was too small to be clinically significant. When the adjustment was performed for dry eye duration, there was no difference between the two treatments.

These results are comparable to those of Brodwall *et al*.[12] and of Leibowitz *et al*.,[7] in which each of these subjective symptoms was significantly relieved.

The results of objective tests (BUT, fluorescein, Schirmer and Lissamine Green tests) suggested significant improvement with both treatments over time, with no statistically significant difference between the two groups. The greatest improvement in the BUT and fluorescein tests occurred during the first 15 days, whereas the Schirmer test and Lissamine Green test results improved steadily throughout the study. It is recognised that a component of these improvements may be due to a placebo effect.

Subjective tolerance upon instillation was rated 'very good' or 'good' by the large majority of patients in each treatment group. The most frequently reported symptom was transitory blurred vision, probably due to prolonged contact with the ophthalmic gel. As noted with many ophthalmic treatments, transient burning was also reported. Some symptoms reported were indissociable from the current dry eye symptoms.

Adverse events were reported for 23% of patients in the Lacrinorm group and 20% of patients in the reference group. Side effects were generally mild. The nature and frequency of these events were not significantly different between the two treatment groups, and events classified as related to the study treatment were rarely described as severe. The most frequent adverse events were discomfort, blurred vision, hyperaemia, and burning and itching, and were similar to other reports of ophthalmic symptoms described upon instillation of eye gels.[7,12,13] Most patients showed very good compliance.

In conclusion, this study has shown that Lacrinorm eye gel is as effective as the reference gel (Viscotears/ Lacrigel) for the treatment of dry eye, even though different preservatives (benzalkonium chloride versus cetrimide) are present in these gels. Both treatments produced significant improvements in the subjective symptoms of foreign body sensation, ocular dryness, burning or pain, and photophobia, as well as in objective tests. Over the 30 days of the trial, tolerance was very good, and the majority of patients were satisfied with the treatments. Lacrinorm eye gel can therefore be of value for the relief of patients suffering from dry eye.

Appendix. Lacrinorm Study Group

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