*Acri.Tec GmbH

11. Januar 2011

ANHANG 2

STUDY REPORT

A randomised, comparative study to determine the safety and efficacy of "OPHTHALIN" versus Healonid® (both 1% w/v Sodium Hyaluronate solutions) during intraocular surgery

Report No. CT 9101E

Edition: Final

26 August 1994

Authors: P I Condon

L J Aikman

Sponsor:

Fermentech Medical Limited
Research Avenue South
Heriot Watt Research Park
Edinburgh
EH14 4AP
UK

R196/A/10

CONTENTS

CONTENTS (continued)

DECLARATION

We, the undersigned, hereby declare that this study was performed in accordance with the principles of Good Clinical Practice. The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained.

Date: 30/8/94

Mr P I Condon
Waterford Regional Hospital
Ardkeen
Waterford
Ireland

Date: 1/9/94

Laraine J Aikman
Clinical Research Manager
Fermentech Medical Limited
Edinburgh
UK

REPORT NO CT 9101E

The data presented in this report have been audited against the Case Report Forms, by the Quality Assurance Unit of Inveresk Research International. This report accurately reflects the data generated during the conduct of the study.

Signed: D Watson Date: 13th September 1994

(Quality Assurance)

SUMMARY

A randomised, comparative study to determine the safety and efficacy of "OPHTHALIN" versus Healonid® (both 1% w/v Sodium Hyaluronate solutions) during intraocular surgery

STUDY OBJECTIVES

To compare the safety and efficacy of "OPHTHALIN", a bacterially derived sodium hyaluronate solution (1% w/v), with that of Healonid® a licensed sodium hyaluronate solution (1% w/v) derived from a biological source.

STUDY DESIGN

This was a single blind (double blind to assessing investigator) randomised, comparator controlled, single centre study.

SITE:

The study was performed at a single site:

Waterford Regional Hospital
Ardkeen
Waterford
Ireland

PATIENTS:

A total of 42 patients were enroled and evaluated. Twenty-eight patients were treated using "OPHTHALIN" whilst the remaining 14 were treated using the comparator product (Healonid®).

TRIAL MEDICATION:

Patients were randomised to receive either "OPHTHALIN" (consisting of 0.5 ml of a 1% w/v solution of bacterially derived sodium hyaluronate in buffered saline) or the comparator product (consisting of 0.5 ml of a 1% w/v solution of biologically derived sodium hyaluronate in buffered saline). Both products were supplied in sterile syringes.

CLINICAL MEASUREMENTS:

The primary variable was the investigator's assessment of the success of the operative procedure. Other measurements made were intraocular pressure, corneal thickness,

endothelial cell count (and percentage cell loss). Sodium hyaluronate performance, patient recovery and adverse events were also monitored.

RESULTS:

The operative procedure was successful in all patients except for one (number 13) treated with "OPHTHALIN". There were no significant differences in intraocular pressure, corneal thickness or corneal endothelial cell counts between groups. The performance of the sodium hyaluronate was assessed as "good" or "very good" in all patients and there was no difference between treatment groups. Patient recovery was "good" or "very good" in almost all cases with no difference between products.

CONCLUSIONS:

"OPHTHALIN" (a 1% w/v solution of bacterially derived sodium hyaluronate) appeared to be as safe and as clinically useful as the product currently licensed for sale, Healonid® (a 1% w/v solution of biologically derived sodium hyaluronate)

1. INTRODUCTION

Sodium hyaluronate, a large polysaccaride molecule, is present in nearly all connective tissue matrices of vertebrate organisms (1). In the human body, it is an important structural element of the skin, subcutaneous and interstitial connective tissues, synovial tissue and fluid, umbilical cord, and the vitreous. In the eye, sodium hyaluronate is found not only in the vitreous but also, at a much lower concentration, in the aqueous humour and in the connective tissues of the angle (2).

During eye surgery to replace a lens made opaque by cataract, the eyeball must be penetrated to remove the lens and replace it with an artificial one. Sodium hyaluronate is introduced into the anterior chamber through a small cannula, before lens extraction, in order to protect the corneal endothelium and to maintain a deep anterior chamber. The maintenance of a deep anterior chamber during surgery allows efficient manipulation during surgery and produces less trauma to the corneal endothelium and other surrounding tissues (3). In order to implant an intraocular lens an additional amount of sodium hyaluronate may be introduced before insertion of the intraocular lens and it may also be used to coat the artificial lens and surgical instruments. Once the intraocular lens has been implanted in the anterior chamber the sodium hyaluronate is removed by irrigation with sterile solution of isotonic saline to avoid elevated intraocular pressure in the postoperative period (4, 5).

The amount of sodium hyaluronate administered during surgery should be sufficient to maintain the integrity and depth of the anterior chamber and to enable safe insertion of the lens, without leaving any excess material in the eye.

The rationale behind this study was to compare a currently licensed sodium hyaluronate product Pharmacia's Healonid® (derived from the combs of cockerels) with a bacterially derived hyaluronate product ("OPHTHALIN"). The objective of this study was to compare the safety and efficacy of these two sources of sodium hyaluronate.

The title of the clinical trial protocol was:

> "A double-blind, randomised single centre study to determine the bioequivalence and assess the efficacy of a 1% w/v Sodium Hyaluronate solution, from two separate sources, during intraocular surgery".

However, this does not truly reflect the purpose of the study. As sodium hyaluronate is not a pharmacologically active substance, but rather a relatively inert material used clinically for its physical property of viscoelasticity, the use of the term "bioequivalence" is not considered appropriate. Rather, the study was a randomised study to determine the comparative safety and efficacy of "OPHTHALIN" when compared with Healonid® (both 1% w/v sodium hyaluronate solutions) during intraocular surgery.

It is the viscoelastic property of sodium hyaluronate that makes it an ideal support material in ophthalmic surgery. Used during surgery as a 1% w/v solution (in phosphate buffered saline) it not only maintains a deep anterior chamber, affording valuable space during operative procedures, but also reduces post-operative problems. Reported post-operative corneal endothelial cell loss following extracapsular cataract extraction has been found to average 14% when Ringer's lactate was used but averaged 6% when sodium hyaluronate has been used. The difference was significant ($p < 0.01$) (6).

2. PATIENTS AND METHODS

2.1 Study Design

This study was a randomised study designed to demonstrate the safety and efficacy of "OPHTHALIN" in comparison to a licensed sodium hyaluronate product. Parameters utilised to judge the comparative efficacy of "OPHTHALIN" with the licensed product were:

i) the investigator's (operating surgeon's) assessment of the handling characteristics of the products during surgery and initial success of the operation;

ii) the co-investigator's subsequent assessment of the success of the operation.

The study was open with respect to the first of these assessments and double-blind with respect to the second. The evaluation of the subsequent success of the operation was carried out by a second investigator (co-investigator) who was unaware of the treatment received by each patient.

In addition to the above, the following measurements were carried out:

i) intra-ocular pressure;
ii) corneal endothelial cell count;
iii) corneal thickness;
iv) adverse events;
v) patient recovery.

2.2 Patient Population

The study population consisted of adult patients with proven cataract requiring lens replacement surgery. Patients had previously presented at, or been referred to, the Waterford Regional Hospital and had a well documented history of cataract.

2.2.1 Inclusion Criteria:

a. Adult males, or post menopausal females (or females using a recognised reliable form of contraception) with proven cataract who would normally be considered eligible for surgery to replace the affected lens.
b. Patients of either sex aged 18 or over.

2.2.2 Exclusion Criteria:

a. Patients whose intraocular pressure was $\geq$22 mm Hg.
b. Patients with glaucoma, a personal history of glaucoma or an anatomic anomaly causing glaucoma.

c. Patients receiving any topically applied drugs which influence intraocular pressure (ie timolol, acetazolamide).
d. Patients with previous anterior segment inflammation or trauma (surgical or otherwise).
e. Patients with a known corneal endothelial cell count of ≤ 1000 cells.mm^{-2}.
f. Patients who had received anticoagulant 4 days prior to surgery.
g. Patients who had received another experimental drug within the previous six weeks.
h. Patients with a known hypersensitivity to sodium hyaluronate.
i. Positive pregnancy test, unreliable contraception, lactating mothers.
j. Patients incapable of giving written informed consent or complying with the protocol.
k. Patients who regularly came into contact with horses.

2.3 Drugs and Dosage

2.3.1 Study Medication

Both the study and reference medications were 1% solutions of sodium hyaluronate in phosphate buffered saline supplied in sterile disposable syringes with a cannula. Syringes were capable of delivering 0.5 ml.

2.3.2 Formulation

Test medication ("OPHTHALIN")	Reference medication (Healonid®)
Sodium hyaluronate 10 mg	Sodium hyaluronate 10 mg
Sodium chloride 8.5 mg	Sodium chloride 8.5 mg
Disodium hydrogen phosphate dihydrate 0.28 mg	Disodium hydrogen phosphate dihydrate 0.28 mg
Sodium dihydrogen phosphate dihydrate 0.045 mg	Sodium dihydrogen phosphate hydrate 0.04 mg
Water for injection to 0.5 ml	Water for injection to 0.5 ml

2.3.3 Batch Numbers

Batch numbers of material used were:

"OPHTHALIN" - 512111 (expiry date 14 October 1995)

Healonid® - TE 47615 (expiry date October 1994)

The Certificate of Analysis for the "OPHTHALIN" test substance is included in Appendix C.

2.3.4 Storage Instructions

The medication was stored at 2-8°C and protected from light and freezing.

2.3.5 Labelling, Emergency Code Break and Dispensing Instructions

The outer package and syringe were labelled with the patient number. The label on the outer packaging employed a tear off portion bearing the patients number and was affixed to the appropriate page of the Case Record Form.

A sealed randomisation envelope accompanied the trial medication containing the identity of the contents. This envelope was only to be opened in an emergency to reveal the identity of the patient's medication.

2.3.6 Dosage Schedule

The sodium hyaluronate solution was administered by injection into the anterior chamber of the eye during surgery on Day 2 of the study. The time of administration was recorded. All patients received treatment with 0.5 ml of 1.0% w/v sodium hyaluronate administered intraocularly using a 27 gauge Rycroft cannula. The precise amount of sodium hyaluronate used during surgery was determined by the specific clinical requirements for each individual patient. However, 4 patients (numbers 3, 16, 25 and 28) received more than 0.5 ml of 1.0% sodium hyaluronate solution.

2.4 Study Procedures and Measurements

Visit - 1 Preliminary examination

It was planned that patients would attend an out-patient clinic for complete eye examination including an ultrasound A-scan. A baseline measurement of corneal thickness and endothelial cell count was also to be performed. In the event this test was performed for the majority of patients on Day 1. Endothelial cell counts and corneal thickness were determined by specular microscopy (7).

The equipment used for this assessment consisted of two specular microscopes, a widefield Pocklington keeler and a narrowfield Bio-Optics Microscope, both of which used contact techniques. Endothelial cell analysis was carried out using the Bio-Optics computerised video digitizing system. Corneal thickness was measured using the Cilco Sonometrics Villa-sensor ultrasonic pachymeter.

On admission to hospital a patient considered eligible for recruitment into the study was examined and questioned about their medical history. If he/she was eligible for the study they were given the patient information leaflet (see Appendix A) and the opportunity to ask questions. The patient was then asked to give their informed consent and details of the physical examination and medical history were transcribed onto the Case Record Forms.

Visit 2 - Day 2

The patient underwent surgery to remove the lens affected by cataract and replace this with a prosthesis. During the operative procedure the surgeon used the test or comparator material as per normal procedure. After the surgery had been completed the surgeon made an assessment of the efficacy of the sodium hyaluronate and noted any relevant points concerning the operative procedure. The patient had their eye examined and IOP measured using a slit lamp microscope (applanation tonometry) 4 hours after surgery, and the patient was then asked if they had suffered any Adverse Events or had any comments.

Visit 3 - Day 3

The patient was asked if he/she had suffered any Adverse Events or had any comments. They then had their eye examined and IOP measured. The Investigator made further assessment of the success of the operative procedure, noted any changes in IOP, inflammation, and details of any drugs administered or changes in concomitant medication. If the investigator considered that the patient's progress was satisfactory then the patient was discharged.

Visit 4 - Day 14

The patient was asked if he/she had suffered any Adverse Event or had any comments. They then had their eye examined, IOP and corneal thickness measured and corneal endothelial cell count determined. Patient recovery was assessed. In most cases this examination was performed 14 days after surgery (ie Day 16).

Visit 5 - Day 90 (± 5)

Procedures as for Visit 4. In addition the Investigator made a final overall assessment of the efficacy of sodium hyaluronate. The percentage loss of endothelial cells and corneal thickness were measured and recorded at this visit and the Study Completion Forms were completed.

2.5 Adverse Events

All adverse events were recorded on Adverse Event Forms and those which were classified as serious were reported to the study sponsor immediately. Adverse events were classified by intensity (mild, moderate, severe) and by causality (probable, possible, unrelated, insufficient evidence).

2.6 Randomisation Methods

A randomisation scheme was produced by the Production Department, Fermentech Medical Limited to comply with protocol design. A total of 42 patients received treatment in a random manner so that 28 patients received the test substance,

"OPHTHALIN", and 14 the comparator product, Healonid®. A block size of 6 was selected and, of every 6 patients recruited, 4 received "OPHTHALIN" and 2 received Healonid®.

A copy of the randomisation list is included in Appendix D.

2.7 Data Management

At the study initiation the CRA reviewed facilities for suitability and ensured that the Investigators and other relevant staff understood the study protocol. During the study the CRA monitored study progress and data collection. A total of 9 monitoring visits were undertaken. A source data verification check was performed on 48% of patients recruited.

A computer database, for both Case Record Form and Adverse Event Form data, was set up for this study using Microsoft Access. Relevant data were exported from this system in d-Base IV format to a SAS system for statistical analysis.

2.8 Statistical Methods

Data were supplied as a d-Base IV file to Dr R Prescott, Medical Statistics Unit, University of Edinburgh for analysis. This was converted to a SAS-PC file using DBMS/COPY(8). With the exceptions noted below, all subsequent calculations were undertaken using SAS version 6.4 on a DCS 486 microcomputer operating under OS-2.

Comparisons between the two treatment groups, of mean changes from baseline in outcome variables, were made using the two-sample t-test, with the calculation of 95% confidence intervals being based on mean $\pm$ t (standard error of mean).

Confidence limits for the success of the operative procedure within each treatment group employed the tables for exact confidence limits published in Documenta Geigy Scientific Tables(9).

Comparisons of patient recovery, for which the responses form a short ordered scale, were by an exact version of Mantel-Haenszel test for trend in a 2x2 contingency table. Scores of 1 to 4 were allocated to the outcome categories. Exact probabilities were calculated using a calculator in the first instance, and were checked using the StatXact package. In this package the test is described as the Trend Test with Equally Spaced Scores(10).

2.9 Drug Analysis

No drug analyses were performed as the test and comparator materials are not bioavailable.

2.10 Study Conduct

The study was performed under regulatory approval from the Irish authorities (CT 106/92). A copy of the Department of Health letter is included as Appendix E.

The protocol, Patient Consent Form and Patient Information Sheet (included as Appendix A) were submitted for consideration by the Ethics Review Committee of the study centre. The approval letter and composition of the Committee are included in Appendix F.

The study was conducted in accordance with the provisions of the Declaration of Helsinki and the Tokyo (1975), Venice (1983) and Hong Kong (1989) revisions. Informed consent was obtained from each patient before study entry.

2.11 Archives

All data generated and recorded during this study, including a copy of the final report, will be stored in the Scientific Archives of Fermentech Medical Limited for 15 years after issue of the final report.

The investigator will retain copies of all CRFs at the institution at which the study was conducted for 15 years.

3. RESULTS

3.1 Patient Population

A total of 42 patients were recruited at the one centre participating in this study. The patients were randomised into 2 unequal groups with 28 patients receiving the test substance, "OPHTHALIN", and 14 patients receiving the reference substance, Healonid®. The first patient entered the study on 31 March 1993 and the final patient completed the study on 30 December 1993. Full details of patient randomisation are given in Appendix D. There were no patient withdrawals during the study.

3.2 Protocol Violations and Deviations

One protocol violation was recorded, patient number 3 was treated with both "OPHTHALIN" and the reference treatment (the latter being used to delineate the ciliary sulcus). However, this patient was not excluded from the statistical analysis.

The following deviations from the trial protocol occurred:

- a total of 42 patients entered the study (and not 32 as planned);
- in most cases surgery was performed on the first day of attendance and not on the second day (Visit 2) as stated in the protocol;
- visits 4 was normally 14 or 15 days after surgery and not 12 days after as implied by the protocol;
- percentage loss of endothelial cells was not calculated at visit 4 as required by the protocol.

Formal protocol amendments were not issued for these deviations.

3.3 Demography

Demographics of the treatment groups at the time of randomisation are given overleaf. A more complete listing is given in Appendix G.

TABLE 1

Number of Patients	"OPHTHALIN"	Reference Treatment
	28	14
Male Female	11 (39%) 17 (61%)	3 (21%) 11 (79%)
Parameter	Mean (S.D.)	Mean (S.D.)
Age (years)	73.5 (7.3)	73.9 (12.1)
Height (cm)	166.1 (7.0)	161.8 (7.4)
Weight (Kg)	65.8 (12.8)	62.9 (11.9)

Concomitant disease was present in the majority of patients (full details are given in Patient Data Listings included as Appendix H). The most common concomitant diseases are given below.

Disease	"OPHTHALIN"	Reference Treatment
Hypertension	4	4
Arthritis	4	0

3.4 Treatment details

All patients recruited into this trial had their lens replacement surgery performed under local anaesthetic. A lid speculum was placed in the eye and superior rectus stay suture inserted to help immobilise the eye. The cornea was kept moist and clear by regular application of sterile isotonic saline.

A 7 mm limbal conjunctival incision was made, followed by a half thickness straight scleral 6 mm incision (after suitable wetfield cautery to close the limbal blood vessels). The scleral incision was undermined to the anterior surgical limbus and a 3.5 mm keratome angled incision made into the anterior chamber to produce a valvular type wound. A capsulorhexis of the anterior capsule was carried out with a 25 gauge bent needle and Uttrata forceps. Hydro-dissection and hydro-delineation was carried out by injecting a balanced salt solution and the nucleus freed from its surrounding cortex.

Phacoemulsfication was then performed using the O.M.S. Diplomat instrument and the nucleus removed using the "chip/flip" techniques for immature cataracts or a "divide and conquer" technique for hard cataracts. Using a balanced salt solution, the cortex was

aspirated and the anterior capsule flap and posterior capsule cleaned of cells. Sodium hyaluronate was then injected into the anterior chamber and bag, and the artificial lens implanted. The loops of the lens were positioned and the sodium hyaluronate removed by irrigation with a balanced salt solution prior to suturing the wound. A subconjunctival injection of gentamicin and decadron was made into the conjunctival flap adjacent to the wound. The infusion solution used during the course of phacoemulsification and removal of the cortex consisted of Hartman's solution mixed with a small amount of adrenaline and gentamicin to maintain pupil dilation and to prevent infection during surgery.

3.5 Clinical Results

3.5.1 The primary measure of efficacy was the investigator's assessment of the operative procedure (ie the physical success of maintaining a deep anterior chamber enabling the artificial lens to be implanted). In all but one case the operation was regarded as a success (in 96% of "OPHTHALIN" and 100% of Healonid® cases). In one case, using "OPHTHALIN", the operation was judged unsuccessful.

With 28 patients in the group treated with "OPHTHALIN" it can be calculated that the population success rate with "OPHTHALIN" lies between 81.7% and 99.9% (with a 95% confidence limit). With 14 patients treated in the comparator group the population success rate with Healonid® is at least 80.7%.

3.5.2 Other parameters assessed were intraocular pressure, corneal thickness, corneal endothelial cell counts, sodium hyaluronate performance and patient recovery.

Change in Intraocular Pressure

The intraocular pressures throughout the study are summarised in Table 2. Responses were quite variable, with one patient in each treatment group having a rise of more than 20 mmHg on the first postoperative day (Patients 3 and 5). In contrast, one patient in the Healonid® group had a reduction from 18 to 6 mmHg (Patient 16), and one patient in the "OPHTHALIN" group had a reduction from 20 to 12 mmHg (Patient 28). Average rises in intraocular pressure on the first postoperative day were 6.1 mmHg and by the second postoperative day these had fallen to 3.0 mmHg. However, Patient 28 in "OPHTHALIN" group, whose intraocular pressure had fallen on the first postoperative day, had a pressure of 50 mmHg on the second postoperative day.

By the time of the two-week and three-month follow-ups, intraocular pressures had fallen to 1.7 mmHg and 2.5 mmHg, respectively, below baseline levels. At no time during the study did the differences between the formulations reach the 20% level of significance.

Change in Corneal Thickness

At two weeks there was no appreciable change in corneal thickness. At 3 months there was a slight overall decrease in mean thickness (-0.014 mm in the "OPHTHALIN" group and - 0.025 mm in the Healonid® group). There was no statistically significant difference between the treatment groups (Table 3).

Change in Corneal Endothelial Cell Counts

Some patients had cell counts which were slightly larger postoperatively than preoperatively. As this must have been due to errors in the counting procedures, such results were taken to indicate no change when percentage changes after surgery were calculated. The mean percentage reduction was 22% at two weeks postoperatively and 26% at three months postoperatively, with no suggestion of differences between the treatment groups (Table 4). However, some large changes were seen:

- the count for Patient 28 fell from 2715 cells.mm^{-2} preoperatively to 366 cells.mm^{-2} at two weeks;

- the count for Patient 5 (Healonid®) fell from 2105 cells/mm^2 to 925 cells/mm^2;
- patients 3 and 13 ("OPHTHALIN") had counts of less than 1000 cells.mm^{-2} at three months post-surgery.

Sodium Hyaluronate performance

On the first post-operative day, the performance of the sodium hyaluronate was assessed as "very good" for all patients. At 3 months post-operatively performance was assessed as "very good" for 26 patients in the "OPHTHALIN" group (2 patients not assessed) and 14 in the Healonid® group.

Patient Recovery

This was assessed on a five-point scale for all patients on the second post-operative day, at two weeks and after 3 months. Eighty eight percent of patients were rated as "good" or "very good" throughout. At two weeks, one patient was assessed as "average" in the "OPHTHALIN" group. There were no statistically significant differences between the treatment groups (Table 5).

TABLE 2 - INTRAOCULAR PRESSURES (mmHg) BY VISIT AND TREATMENT GROUP

	Fermentech Formulation			Pharmacia Formulation			p*	95% CI for difference (Pharmacia-Fermentech)
	N	Mean	S.D.	N	Mean	S.D.		
Baseline	28	17.5	2.6	14	16.2	3.0		
First postoperative day	28	24.4	7.0	14	20.6	7.5		
Difference from baseline		7.0	6.5		4.4	7.8	0.27	-7.2, 2.1
Second postoperative day	28	21.1	7.9	14	17.9	7.8		
Difference from baseline		3.5	7.6		1.7	7.6	0.43	-6.9, 3.0
Two-week follow-up	27	15.3	2.0	14	15.2	3.7		
Difference from baseline		-2.1	3.0		-1.0	3.3	0.27	-0.9, 3.2
Three-month follow-up	27	14.6	3.1	13	13.8	3.1		
Difference from baseline		-2.7	3.1		-2.2	2.9	0.62	-1.6, 2.6
Maximum postoperative value	28	-26.1	8.1	14	22.4	6.7		
Difference from baseline		8.6	7.1	14	6.1	6.2	0.28	-8.8, 1.3

* p-value based on two-sample t-test

TABLE 3 - CORNEAL THICKNESS (mm) BY VISIT AND TREATMENT GROUP

	Fermentech Formulation			Pharmacia Formulation			p*	95% CI for difference (Pharmacia-Fermentech)
	N	Mean	S.D.	N	Mean	S.D.		
Baseline	28	0.570	0.035	14	0.567	0.035		
Two-week follow-up	27	0.583	0.052	14	0.564	0.035		
Difference from baseline		0.014	0.036		-0.004	0.022	0.10	-0.040, 0.004
Three-month follow-up	26	0.556	0.041	13	0.543	0.031		
Difference from baseline		-0.014	0.012		-0.025	0.023	0.08	-0.022, 0.001
Maximum postoperative value	28	0.584	0.052	14	0.564	0.036		
Difference from baseline		0.014	0.036		-0.003	0.021	0.11	-0.038, 0.004

* p-value based on two-sample t-test

TABLE 5 - PATIENT RECOVERY BY VISIT AND TREATMENT GROUP

	Second Postoperative Day		Two-Week Follow-up		Three-Month Follow-Up	
Recovery Assessment	Fermentech Formulation	Pharmacia Formulation	Fermentech Formulation	Pharmacia Formulation	Fermentech Formulation	Pharmacia Formulation
Poor	1	0	0	0	0	0
Average	1	1	1	0	0	0
Good	1	2	0	0	0	0
Very Good	25	11	26	13	27	13
Total	28	14	27	13	27	13
p*	1.00		1.00			

* Exact probability for the trend test in contingency tables (Mantel-Haenszel Test)

3.6 Safety Evaluation

No specific laboratory checks (*eg* haematology or clinical chemistry) were performed after surgery. The patients were monitored following normal in-patient practice for up to 3 days after admission. Patients were discharged from hospital on day 3 (assuming an uneventful postoperative period). Specific follow up procedures were the measurement and recording of IOP, endothelial cell counts and corneal thickness. If IOP was raised, then treatment with timolol or acetazolamide was initiated. Full details of the treatment were recorded and an Adverse Event Form completed. If the eye became inflamed then corticosteroid drops were administered until the inflammation had subsided and details recorded as above.

Adverse events are summarised in Table 6 below and a full data listing is provided in Appendix I. Due to the low numbers of adverse events recorded, no statistical analysis has been performed.

Table 6

ADVERSE EVENTS BY TREATMENT GROUP

AE Description	"OPHTHALIN"	Healonid®
	Number of patients (%)	Number of patients (%)
Sore eye	0 (0%)	1 (7%)
Raised IOP	1 (4%)	1 (7%)
Vomiting	0 (0%)	1 (7%)
Capsular tear	2 (7%)	3 (21%)
Corneal oedema	1 (4%)	2 (14%)
Death	1 (4%)	2 (14%)
Miscellaneous		
eg vitreous loss	0 (0%)	1 (7%)
lens caught in wound	1 (4%)	0 (0%)
Total number of patients with AE	4 (14%)	5 (36%)
Total number of patients	28	14

* Deaths were not related to treatment medication.

It should be noted that, due to the design of the Case Record Form and Adverse Event Form, there were several instances when adverse events were noted on the CRF but not recorded on an Adverse Event Form. However, these inconsistencies do not affect the conclusions that can be drawn from the data.

4. DISCUSSION

The purpose of this study was to demonstrate the safety and efficacy of sodium-hyaluronate produced by a novel bacterial method and to compare this with the currently available product produced from an animal source (combs of cockerels).

The study was small (28 patients treated with "OPHTHALIN" and 14 treated with Healonid®) and was undertaken at a single centre. However, the results indicate that the clinical usefulness of the new product is comparable to that of the currently licensed product. Also, the safety profile of the 2 products is similar with no new or unexpected adverse events being recorded with the new product.

5. REFERENCES

1. Comper, W. D., & Laurent, T. C., Physiological function of Connective Tissue polysaccharides. Physiology Review 1978; 58:255-315.

2. Balazs, E. A., & Armand, G. Glycosaminoglycans and Proteoglycans in Physiological and Pathological processes of Body System. 1982; Basel Karger.

3. Balazs, E. A., Muller, D & Stegmann, R. Viscosurgery and the use of Hyaluronate in intraocular lens implantation 1979. Paper presented at the International Congress and First Film Festival on Intraocular Implantation, Cannes France.

4. Lazenby, G. W., Sodium Hyaluronate. A guide to its use in Ophthalmic Surgery, 1983, (5); 69-77, John Wiley & Sons, New York.

5. Stegmann, R., & Miller, D. Extracapsular cataract extraction with hyaluronate sodium. Ann. Ophthamol 1982; 14:813-815.

6. Stegmann, R., & Miller, Sodium Hyaluronate. A guide to its use in Ophthalmic Surgery, 1983, (3); 45-57, John Wiley & Sons, New York.

7. Keeler-Konan, Clinical Manual for the Pocklington Specular Microscope Issue 001, Published by Keeler-Konan.

8. DBMS/COPY Plus, Version 3.0 Conceptual Software Inc. Published by SPSS Inc, 1991

9. Documenta Geigy Scientific Tables, 7th edition. Diem K, Lentner C (eds). Geigy Pharmaceuticals, 1970

10. StatXact User Manual, Version 2. CYTEL Software Corporation 1991. Section 4.7