Sodium Hyaluronate (Healon®) in Glaucoma Filtering Procedures

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ABSTRACT

Healon® (sodium hyaluronate) has been used in a prospective study designed to investigate its possible usefulness in promoting effective bleb formation and preventing cleft closure in trabeculectomy for glaucoma. One hundred fourteen patients with open-angle glaucoma were randomly assigned to one of two groups. In one group (55 patients), filtering surgery was performed without the use of Healon. In the remaining 59 patients, Healon was used to separate the iris from the cleft, the sclera from the sclera and the conjunctiva from the sclera. The surgical procedure used was the Stallard-Worst triangular modification of Cairns' method, combined with removal of the Tenon's capsule. The patients whose operations were performed with the aid of Healon had a higher success rate, as manifested by better and more permanent bleb formation and maintenance, more open clefts, less scarring, less peripheral anterior synechiae formation, and significantly lower long-term intraocular pressure. Moreover, the number of patients requiring supplemental postoperative timolol therapy was significantly smaller in the Healon group (5/59 patients: 8.5%) than in the control group (33/55 patients: 60%). There was a transient delay in the reduction of intraocular pressure following trabeculectomy in the Healon patients which was not observed in control patients. Apart from this, no adverse effects were associated with the use of Healon.

Microsurgical techniques have made the filtering procedure a safe operation for glaucoma treatment. At present, the main unsolved problems are the scarring down of the bleb and the closing of the cleft. Bleb and cleft failure often lead to a recurrence of dangerously high intraocular pressure which can cause progressive optic nerve damage and visual field changes leading to blindness. To prevent this, it is necessary in a significant number of cases to supplement the filtering surgery with a chronic postoperative regimen of hypotensive medication.

It would be desirable, once surgical therapy has become the necessary treatment for glaucoma, to secure normal levels of postoperative intraocular pressure entirely by means of trabeculectomy, without the need of supplemental medication. Pape and Balazs have demonstrated that the use of Healon in conjunction with trabeculectomy is an effective way to achieve this goal. In their study, they observed that effective filtering blebs formed in all 15 patients who underwent trabeculectomy for glaucoma, and that blebs were maintained in a functional state for the full 19 months of follow-up. As a result, intraocular pressure was well controlled in all patients without the use of postoperative hypotensive medication.

Healon (manufactured by Pharmacia, Inc., Uppsala, Sweden) is the high molecular weight viscoelastic, non-inflammatory preparation of 1% sodium hyaluronate extracted from rooster combs. Despite the fact that the preparation of Healon used in viscosurgery is 98% water, it has a viscosity of 400,000 times that of balanced salt solution. This unique combination of properties allows Healon to provide a rigid mechanical support for maintaining an open cleft while allowing free aqueous filtration.

The present study was designed to investigate the potential effectiveness of Healon in maintaining an open cleft and non-fibrosed bleb, which would result in an efficient aqueous filtration site to prevent postoperative increases of intraocular pressure.

MATERIALS AND METHODS

Patients: A total of 114 patients with open-angle glaucoma requiring surgery were included in the study. Seventy-one patients (62%) were female and 43 (38%) were male.
were male. Patients ranged in age from 50 to 68 years (mean age 58 years). Sixty-six patients (58%) were white and 48 (42%) were non-white. All patients were free of uncontrolled systemic diseases, and none of them had obvious tendencies to keloid formation.

Based on random selection using envelopes, patients were divided into two treatment groups: one group (Healon) consisted of 59 patients (52%) who underwent open-angle glaucoma surgery with the use of Healon; the other group (control) consisted of 55 patients (48%) who were operated on without the use of Healon. The surgical technique as well as preoperative and postoperative therapy were similar in both groups (with the exception of postoperative timolol treatment described below).

Preoperatively, all patients were on 4% pilocarpine every six hours, 0.5% timolol, and 0.1% dipivefrin hydrochloride every 12 hours for variable periods of time. Two days preoperatively, all patients were started on topical antibiotics and steroids every six hours.

Postoperatively, patients continued on topical antibiotic and steroid treatment every six hours for the first week, every eight hours for the second week, every 12 hours for the third week, every 24 hours for the fourth and fifth weeks, and every 48 hours for the four following weeks. The pupils were dilated with 1% tropicamide applied every 12 hours for three days postoperatively and at bedtime for the week following surgery. If postoperative, IOP increased above 20 mmHg, treatment with 0.5% timolol every 12 hours was begun in both Healon and non-Healon treated patients.

All patients were followed for two years after surgery. Informed consent had been obtained from each patient following a full explanation of the nature of the investigation.

**Surgical Procedure:** Filtering surgery was performed according to the Stallard-Worst triangular modification of the trabeculectomy procedure originally introduced by Cairns. In addition, the Tenon’s capsule overlying the surgical area was removed in all cases. In all patients, a paracentesis was performed at 6 o’clock, or at the temporal limbus, before the anterior chamber was penetrated. This incision was made for safety reasons and was not sutured.

The surgery was performed under local anesthesia using retrobulbar block with 2% lidocaine and 0.75% buricaine hydrochloride. First, a superior rectus halter suture was applied. Following this, a limbus-based triangular flap was made in the sclera in front of the superior rectus insertion, with the apex near the insertion of the superior rectus muscle and with a 5-mm base in front of the corneal side of the limbus. This flap was two-thirds of the scleral thickness. A smaller, fornix-based triangle with a 3-mm baseline and with the apex in the corneal side of the limbus was then fashioned. This fornix baseline was about 4-mm from the limbus and incorporated the full thickness of the remaining sclera: its apical area included the trabecular meshwork, so that reflection of this small triangle exposed the ciliary body. Thus, in effect, creating a cycloidalysis in that area.

Peripheral iridectomy was performed by first pulling the iris gently toward the nasal side and then pulling it toward the temporal side to make a second cut. Thus, the iris coloboma was away from the edges of the cleft.

The apexes were then anchored to the sclera in front of the insertion of the superior rectus with a single 50mu steel alloy suture. Two interrupted steel alloy sutures were placed on either side of the triangle, and the conjunctival flap was then resutured with continuous 8-0 Vicryl sutures.

In patients whose surgery was performed with the aid of Healon, the viscous preparation was applied after the peripheral iridectomy had been completed. At this time, 0.2 ml of Healon was placed in the anterior chamber over the iridectomy to keep the iris away from the incision. Another 0.1 ml of Healon was then placed over the exposed ciliary body and over the small triangle. Before suturing the conjunctival incision, 0.1 ml of Healon was injected between the sclera and the conjunctiva.

In the control patients, when the scleral flap was secured, a small amount of BSS was injected under the flap and into the anterior chamber to maintain it.

**Observations:** Intraocular pressure was measured with the Goldmann applanation tonometer, and values were recorded for all patients preoperatively and postoperatively at: 12 and 24 hours, 3 and 10 days, at one week, and at 3, 6, and 12 months. After 12 months, the pressure was checked at every visit, but for the purpose of this study, intraocular pressure is reported only at 24 months for the second-year follow-up segment.

The condition of the eye was also examined at these visits. The size of the bleb was measured and mapped on the chart, and photographic records and measurements were also made. The angle of the corneal cleft was measured gonioscopically prior to surgery, 10 days following surgery, and on all subsequent visits.

**Statistics:** The effect of Healon on bleb formation and preservation, and on maintenance of cleft opening was tested using the z-test, a non-parametric analog of the t-test. The z-test was also employed to compare the postoperative use of timolol between the Healon and control groups.

Mean postoperative intraocular pressures were compared with mean preoperative pressure using paired t-tests. Mean reduction in intraocular pressure with Healon vs. control was compared at the various postoperative time points using unpaired t-tests.

**RESULTS**

The protective effect of Healon in filtering surgery for glaucoma was evaluated in this study according to three major parameters: (1) filtering bleb formation and maintenance, (2) maintenance of cleft opening, and (3) intraocular pressure.

OPHTHALMIC SURGERY
### TABLE 1

**FILTRATION BLEB FORMATION FOLLOWING TRABECULECTOMY**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Postoperative Time</th>
<th>24 Hours</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td>Bleb</td>
<td>No Bleb</td>
<td>Bleb</td>
<td>No Bleb</td>
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<tr>
<td>Healon (n=59)</td>
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<td>59</td>
<td>0</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>No. of Patients</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Percent (%)</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Control (n=55)</td>
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<td>11</td>
<td>44</td>
<td>52</td>
<td>3</td>
<td>51</td>
<td>4</td>
</tr>
<tr>
<td>No. of Patients</td>
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<td>20</td>
<td>95</td>
<td>93</td>
<td>85</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>Percent (%)</td>
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<td>85</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.10</td>
<td>=0.002</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</table>

*P values refer to z-test of number of patients with blebs in Healon vs. Control group.*

### TABLE 2

**MAINTENANCE OF CLEFT OPENING FOLLOWING TRABECULECTOMY**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Postoperative Time</th>
<th>10 Days</th>
<th>1 Month</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Open</td>
<td>Closed</td>
</tr>
<tr>
<td>Healon (n=59)</td>
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<td>0</td>
</tr>
<tr>
<td>No. of Patients</td>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Percent (%)</td>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Control (n=55)</td>
<td></td>
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<td>3</td>
</tr>
<tr>
<td>No. of Patients</td>
<td></td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>Percent (%)</td>
<td></td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.10</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

*P values refer to z-test of number of patients with open clefts in Healon vs. Control group.*

**Bleb Formation and Maintenance:** The data on bleb formation and maintenance are presented in Table 1. Successful bleb formation was observed immediately after surgery and during the first 24 hours postoperatively in all 59 Healon treated patients. Blebs were maintained in 58 (98%) of these patients throughout the 24-month observation period. Bleb failure occurred in only one Healon treated patient. Failure in this case was first observed 12 months after surgery and persisted after 24 months.

In contrast, successful blebs formed in only 11 of 55 (20%) control patients during the first 24 hours postoperatively. One month after surgery, 52 of the 55 control patients (95%) had formed filtering blebs while three (5%) of them still showed no bleb formation. Bleb failure was subsequently observed in these 52 patients, however, beginning at three months and in a progressing number during the 24 months postoperative
period. By the end of the 24-month period, the number of control patients with successful blebs had been reduced to 37 (67%).

Cleft Opening (Gonioscopy): Maintenance of cleft opening is shown in Table 2. Gonioscopic monitoring of the filtration cleft showed that in 56 of 59 (95%) of the Healon treated patients, the cleft remained open for the entire 24-month period after surgery. Among the three Healon patients with cleft closure, a questionable closure was first observed in one patient six months following trabeculectomy: examination at 12 months indicated a definite cleft closure in this patient. The remaining two cases of cleft closure in this group were observed at about 24 months after surgery.

In 36 of 55 control patients (65%), the cleft remained open after two years following surgery. In this group, cleft closure was progressive: at ten days postopera-

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<tbody>
<tr>
<td>MEAN INTRAOCULAR PRESSURES (mmHg)</td>
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<tr>
<td>Treatment</td>
</tr>
<tr>
<td>P (n=55)</td>
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<td>Control vs. Healon P</td>
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</table>

P values refer to paired t-tests of the means.

<table>
<thead>
<tr>
<th>TABLE 4</th>
</tr>
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<tbody>
<tr>
<td>MEAN CHANGES IN INTRAOCULAR PRESSURE (mmHg)</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Control (n=55)</td>
</tr>
<tr>
<td>Control vs. Healon P</td>
</tr>
</tbody>
</table>

P values refer to unpaired t-tests of the means.

Intraocular Pressure (IOP): Mean intraocular pressures are listed in Table 3. Compared to preoperative levels, mean IOP after surgery was significantly reduced (P<0.001) in both groups. In the Healon treated patients, IOP was significantly lower than in
the control patients one month (P<0.001) through 24 months postoperatively (P=0.05). During the immediate 12 to 24 hours postoperatively, however, (in Healon treated patients), IOP was significantly higher (P<0.001) than in control patients.

Mean changes in IOP from preoperative to postoperative values at 12 and 24 hours, 1, 3, 6, 12, and 24 months are listed for both groups in Table 4. The Healon group showed significantly greater mean reduction in postoperative IOP from preoperative values from one month (P<0.001) to 24 months (P<0.05) after surgery. During the first 24 hours after surgery, the mean reduction in IOP in the Healon group was significantly less (P<0.001) than that in the control group. Postoperative timolol maleate therapy was started in all patients in whom application pressure, on at least four different occasions taken at different times on different days by examiners who did not know which patient had Healon during surgery and which did not, was above 20 mmHg.

The use of timolol for the supplemental control of elevated postoperative IOP is summarized for both Healon and control groups in Table 5. Only five of 59 patients (8%) in the Healon group required postoperative timolol therapy. Three (5%) of these patients were given 0.5% timolol every 12 hours beginning at six months, and an additional two patients were started on a timolol regimen at 12 months.

In the control group, 33 of 55 patients (60%) needed timolol treatment in addition to surgery in order to control their IOP effectively. Ten (18%) began taking 0.5% timolol every 12 hours at one month, another eight patients (15%) began at three months, nine (16%) more at six months, and the final six patients at 12 months, after surgery.

The overall difference in the number of patients requiring timolol therapy in the Healon (five patients) vs. the control group (33 patients) was significant (P<0.001). However, statistical analysis of the IOP data in which timolol treated patients in both groups was excluded did not produce significantly different results: the greater effectiveness of Healon in lowering IOP (after the immediate postoperative period) was slightly accentuated, but the probability levels did not change.

DISCUSSION

Since Cairns'4,5 first introduced trabeculectomy, the procedure has undergone several modifications, each designed to keep the iris from blocking the cleft, the cleft from closing, and the Tenon's capsule and conjunctiva from scarring.

In this study, we employed the Stallard-Worst triangular modification of Cairns' procedure. A number of advantages were gained by this approach. The triangular exposure allowed us to be sure that part of the trabecular meshwork had in fact been removed. In addition, it created a mechanical hump over the everted scleral triangle. By exposing part of the ciliary body, the triangular modification method made the operation of a combination of trabeculectomy and cycloclysis. Finally, by pulling the iris first in one direction and then in the other while performing the iridectomy, we ascertained that the base of the iris coloboma was well away from the created cleft.

The removal of Tenon's capsule has been recommended as a way to decrease scarring in non-white patients. In this study, the Tenon's capsule was removed in all patients in order to secure standardization of treatment.
According to Luntz,19 the expected drop in IOP with trabeculectomy is about 10 mmHg. For technical reasons, he has recommended the use of a fornix-based flap for filtering operations, a procedure we are now investigating in a small series of patients.

Despite the technical improvements in the trabeculectomy procedures, postoperative bleb and cleft failure leading to elevated IOPs has remained a significant problem. Because of this, it is still frequently necessary to augment surgical therapy with medication such as timolol in order to gain full control of a patient's glaucoma. The present study had demonstrated the great usefulness of Healon as a non-medical alternative to hypotensive drugs. In addition to providing a mechanical support to keep the filtering angle open following surgery, Healon maintains the conjunctiva in a succulent state, which greatly reduces the incidence of postoperative fibrosis and associated cleft failure. In this study, all patients were maintained at an IOP less than 20 mmHg. As standard medical practice, therefore, patients were started on a regimen of timolol (0.5%) every 12 hours when their postoperative IOP rose to 20 mmHg or greater. While all patients were then maintained at clinically safe postoperative IOP levels, the majority of control patients required timolol therapy to keep their IOPs within the normal range whereas the majority of Healon patients did not. During the 24-hour postoperative observations, only 22 of 55 control patients (40%) treated with trabeculectomy alone achieved adequate control of IOP without supplemental timolol treatment. In contrast, 54 of 59 Healon patients (91.5%), had complete control of their glaucoma during this period. Only five of 59 Healon patients (8.5%) required timolol therapy to control elevated IOPs.

The mean IOP among Healon treated patients was statistically significantly higher than the control group mean IOP in the immediate 24 postoperative hours. However, Healon mean IOPs fell rapidly to levels which were statistically significantly lower than control mean IOPs and, with the exception of the five patients mentioned above, remained significantly lower for the duration of the study.

A transient elevation of IOP in the immediate postoperative period has also been reported in a number of studies20-30 with the use of Healon in cataract surgery (for which there is much more extensive literature than is the case for the use of Healon in glaucoma surgery to date). In these reports, the IOP elevation with Healon is always transient, and there are no studies showing a long-term increase of IOP associated with the use of Healon.31 Furthermore, several other cataract studies have reported no IOP elevation with Healon.32 37

It has been suggested38 that while a number of factors may contribute to the postoperative rise in IOP following the use of Healon, a major one may be the amount of Healon injected into the anterior chamber. Pape and Balazs9 and Holmberg et al.39 have suggested that no more than 0.2 ml of Healon should be left in the anterior chamber at the end of surgery. Accordingly, in this study, care was taken not to overfill the anterior chamber, and the 0.2 ml placed there to help form the filtering bleb was accurately measured. The subject of Healon and intraocular pressure has been reviewed recently by Kusman, et al.39

The successful control of IOP in Healon treated patients in this study was accomplished due to the ability of Healon to maintain functional, non-scarring filtering blebs in these patients. As clearly shown in Table 1, blebs were formed in 100% of the Healon treated patients immediately after trabeculectomy and were maintained over the entire 24-month period of the study. By the end of this period, 98% (58 of 59 patients) still had successful filtering blebs.

In contrast, bleb formation among control patients displayed a parabolic course. Only 20% (11 of 55 patients) of them formed blebs immediately after surgery. After one month, 95% (52 of 55 patients) of the control patients had filtering blebs, but they were not stable and showed a high tendency for failure: 24 months after surgery, 67% (37 of 55 patients) of the control group patients maintained functional filtering blebs. We feel that the question whether the Healon maintained the cyclodialysis deliberately created by the surgical technique or maintained the trabeculectomy cleft is not important since the same technique was employed in both the Healon and non-Healon group.

The maintenance of open clefts in the two groups of patients followed a similar pattern. Healon treated patients showed a constant level of open cleft maintenance over the entire 24-month period of the study: all 59 Healon patients had open clefts immediately following surgery and 95% (56 of 59 patients) of them maintained open clefts 24 months later. In contrast, the number of open clefts among control patients, ranged from 95% (52 of 55 patients) immediately following surgery to 65% (36 of 55 patients) 24 months later.

In addition to being effective, Healon was also well tolerated. No pupillary block glaucoma was observed as a result of Healon application. There were no differences in the behavior of visual acuity between the two groups of patients. Almost since its introduction we have been filling existing filtering blebs during cataract surgery with Healon. Wolter,39 in 1984, published his technique and good results in a case.

In summary, this study had demonstrated that patients whose glaucoma filtering operations were performed with the aid of Healon had a higher success rate, as manifested by more effective and sustained bleb formation, less bleb and conjunctival scarring, greater maintenance of cleft openings, lower incidence of peripheral anterior synechiae formation, and better control of postoperative IOP. Significantly fewer patients who had Healon during surgery needed additional medical therapy to maintain low intraocular pressure after the surgery than those in the control group.
group who did not have Healon employed during the operation. These findings, which are in agreement with the results of previously published work, support the view that the use of Healon can significantly improve the therapeutic efficacy of microsurgical filtering techniques in the treatment of glaucoma.

REFERENCES