THE EFFECTS OF SODIUM HYALURONATE, CHONDROITIN SULFATE, AND METHYLCELLULOSE ON THE CORNEAL ENDOTHELIUM AND INTRAOCULAR PRESSURE

SCOTT M. MAC RAE, M.D., HENRY F. EDELHAUSER, PH.D., ROBERT A. HYNDIUK, M.D., EILEEN M. BURD, B.S., AND RICHARD O. SCHULTZ, M.D.

Milwaukee, Wisconsin

Sodium hyaluronate (Healon), chondroitin sulfate, and methylcellulose have been used to protect the corneal endothelium from intraocular lens trauma. A study of the efficacy and toxicity of these compounds showed that 1% sodium hyaluronate, 0.4% methylcellulose, and 20% chondroitin sulfate were nontoxic to the corneal endothelium, but that 20% chondroitin sulfate caused a marked decrease in corneal thickness because of its hypertonicity. Anterior chamber injection of these viscous substances resulted in an increase in intraocular pressure. Within one to four hours the maximum intraocular pressure with 1% sodium hyaluronate was 67 ± 4.1 mm Hg and that with 20% chondroitin sulfate was 55 ± 3.5 mm Hg. The intraocular pressure did not increase to these high levels with 10% chondroitin sulfate or 0.4% methylcellulose or when the test substances were washed out of the anterior chamber. The corneal endothelium was protected from injury with 1% sodium hyaluronate and 20% chondroitin sulfate, but 10% chondroitin sulfate and 0.4% methylcellulose provided only minimal protection.

Even momentary contact between a polymethylmethacrylate intraocular lens and the corneal endothelium results in a tearing of the endothelial cell membrane.[1,2] Several methods of minimizing endothelial cell damage have been proposed, including coating the implant with high-viscosity substances.[3,4]

In 1980 sodium hyaluronate (Healon) was introduced as a viscoelastic aqueous substitute to prevent endothelial cell loss during intraocular lens implantation. Corneal pachymetry,[5,6] specular microscopy,[5] and scanning and transmission electron microscopy[5,6] have demonstrated that sodium hyaluronate is not toxic to the endothelium and provides endothelial protection. To the best of our knowledge, however, no reports based on direct endothelial perfusion have been published.

Several investigators have noted that sodium hyaluronate causes a transient increase in intraocular pressure in humans when measured the day after cataract surgery.[7-9] Passo and Ernest[10] also reported transient increases in intraocular pressure seven and 16 hours after surgery. During the course of our experiments with sodium hyaluronate and

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From the Departments of Physiology (Drs. Mac Rae and Edelhauser) and Ophthalmology (Drs. Mac Rae, Edelhauser, and Schultz and Ms. Burd), Medical College of Wisconsin, and the Research Service, Woods Veterans Administration Center (Dr. Edelhauser), Milwaukee, Wisconsin. This study was supported by training grant EY07016 and research grant EY00933 from the National Eye Institute, and by grant P30-EY01931 from the Ophthalmic Research Center. Dr. Edelhauser is an Olga K. Wiess Research Scholar of Research to Prevent Blindness, Inc. (1982).

Reprint requests to Henry F. Edelhauser, Ph.D., Department of Physiology, Medical College of Wisconsin, P.O. Box 26509, Milwaukee, WI 53226.

chondroitin sulfate, we found striking increases in intraocular pressure that occurred even earlier after instillation into the anterior chamber than previously documented. We therefore injected sodium hyaluronate or other viscous aqueous substitutes into the anterior chamber and measured intraocular pressure hourly to establish an intraocular pressure peak for each substance.

Another proteoglycan, chondroitin sulfate, is one of the three major mucopolysaccharides of the cornea. Soll and associates[4] reported that this compound protected the corneal endothelium against intraocular lens trauma. Chondroitin sulfate washes out of the anterior chamber in 24 to 30 hours, compared to the seven to 14 days sometimes needed for clearance of sodium hyaluronate.[11] Soll and Harrison[12] found no significant increases in intraocular pressure in experimental animals by Schiøtz tonometry, although the measurements were done 24 hours after the injections.

Methylcellulose has also been proposed as a viscous mechanical endothelial buffer. It is relatively inexpensive and readily available. Fechner[13] noted an increase in intraocular pressure (45 mm Hg) on the first postoperative day in patients who underwent intraocular lens implantations in which methylcellulose was used but observed no other clinical toxicity.

Our purpose was to compare the efficacy and toxicity of intraocularly administered sodium hyaluronate, methylcellulose, and chondroitin sulfate.

The study was divided into three parts: (1) in vitro corneal endothelial perfusion with each of the test substances; (2) anterior chamber injection of each of the test substances with sequential intraocular pressure determinations (particularly during the first four hours after injection); and (3) an evaluation of the degree of corneal endothelial protection each test substance provided when we abraded the endothelium with an intraocular lens in vitro.

Material and Methods

Corneal perfusion—Because of its high viscosity (Table 1), we could not perfuse 1% sodium hyaluronate to the endothelium. Therefore, we diluted the 1% sodium hyaluronate for these studies (one part sodium hyaluronate to two parts BSS solution).

A 20% solution of high-grade purified shark chondroitin sulfate, type C, had

TABLE 1

Composition, osmolality, pH, and viscosity of the test solutions

Test Solution	Osmolality (mOsm)	pH	Viscosity (centistokes)
BSS	310	7.4	1 to 1.1
Sodium hyaluronate (undiluted)*	—	7.4	72,000
1 part 1% sodium hyaluronate: 2 parts BSS	316	7.2	—
0.4% methylcellulose in BSS	320	7.6	12-30
10% chondroitin sulfate in BSS without sodium chloride	375	7.3	26
20% chondroitin sulfate in BSS without sodium chloride	656	7.3	120
20% chondroitin sulfate in BSS with sodium chloride	1,051	7.2	—

*We were unable to measure the osmolality of undiluted 1% sodium hyaluronate because of its viscosity.

an osmolality of 1,041 mOsm when diluted with BSS. To decrease this osmolality, we prepared BSS without sodium chloride. This vehicle had an osmolality of 105 mOsm. When we added the 20% chondroitin sulfate to this vehicle, the final osmolality was 656 mOsm. A 10% solution of chondroitin sulfate in the BSS vehicle without sodium chloride had an osmolality of 352 to 392 mOsm.

A solution of 0.4% methylcellulose, also prepared with BSS, had a pH of 7.6 and an osmolality of 320 mOsm. We used a 0.4% methylcellulose solution because its viscosity was similar to that of the 1% methylcellulose described by Fechner.[13]

Corneal perfusion experiments were done in the manner described by Edelhauser and associates.[14] We killed New Zealand albino rabbits, weighing approximately 2 to 3 kg each, enucleated their eyes, and mounted the corneas in a dual-chamber perfusion specular microscope.[15] One cornea of each animal was perfused with sodium hyaluronate, methylcellulose, or chondroitin sulfate for 60 to 90 minutes. The other cornea served as a control and was simultaneously perfused with BSS. Control and test corneas were perfused with glutathione bicarbonate Ringer's solution before and after perfusion with the test substance. At the end of the endothelial perfusion the cornea was fixed for scanning and transmission electron microscopy.

Intraocular pressure—Before and after anterior chamber injection of each of the test substances, 16 New Zealand albino rabbits (both sexes) were given two drops of 0.5% proparacaine HCl and their intraocular pressures were measured with a pneumotonograph. The animals were anesthetized with intramuscular injections of 0.8 to 1 ml of 1:1 ketamine HCl (30 mg/kg of body weight) and xylazine (6 mg/kg of body weight). Both eyes of each rabbit were studied.

A 30-gauge needle was passed into the cornea in a lamellar plane for approximately 2 mm before it entered the anterior chamber. We then aspirated 0.12 to 0.15 ml of aqueous, being careful not to collapse the anterior chamber. One of the following substances was then injected through the same site: 1% sodium hyaluronate (undiluted), 10% chondroitin sulfate, 20% chondroitin sulfate, 0.4% methylcellulose, BSS (control), or reinjected aqueous (control). We injected equal amounts of each substance.

Intraocular pressure determinations were performed by a masked observer 15 minutes after the injections, hourly thereafter for the first ten hours, and every two hours for the next 24 hours. The determinations were repeated at 48 hours and at one week. The rabbits were then killed and their corneas fixed for scanning and transmission electron microscopy.

We repeated this experiment with ten cynomolgus monkeys (both sexes) weighing 2 to 3 kg each. The animals were anesthetized with ketamine HCl (11 mg/kg of body weight), acepromazine (0.55 mg/kg of body weight), and atropine (11 mg/kg of body weight). One eye of each animal was studied. Because the number of animals was limited, the test was limited to four injections of 20% chondroitin sulfate, four of 1% sodium hyaluronate, and two of BSS (control).

Two eyes (one injected with 20% chondroitin sulfate and the other with 1% sodium hyaluronate) were aspirated and irrigated (volume, 0.12 to 0.15 ml). We then made a 4-mm corneal incision into the anterior chamber with a Weck blade. The test substance was washed out with 0.15 cc of BSS and a 23-gauge needle. The wound was then tightly closed with 9-0 nylon sutures.

Intraocular pressures were measured just before the injection, immediately after the injection, and after 1½, 3½, six, 24, and 48 hours by a masked examiner.

Endothelial protection—We assessed the endothelial protection provided by the test substances by placing the test substance on the endothelial surface of fresh 7-mm corneal buttons from rabbits and sliding a Leisky intraocular lens held with a forceps across the endothelium in four different directions. BSS was placed on the control corneas, which were not abraded. BSS was applied to another group of corneal buttons before the implant was passed over their endothelial surfaces. After each procedure, the corneas were stained for two minutes with trypan blue and viewed with a light microscope. We graded the amount of endothelial cell damage from 0 to 100%, using a damage index similar to that described by Knight and Link.[16]

RESULTS

Corneal perfusion—Corneal endothelial perfusion studies in rabbit eyes showed that 1:2 diluted 1% sodium hyaluronate, 0.4% methylcellulose, and 10% chondroitin sulfate did not significantly change corneal thickness (Fig. 1). The endothelial cell pattern, observed with a specular microscope, was maintained through the perfusion period, and the ultrastructural appearance of the endothelial cells was also normal with these test substances.

When the 20% chondroitin sulfate in BSS without sodium chloride (osmolality, 656 mOsm) was perfused to the corneal endothelium, there was a sharp decrease in corneal thickness compared to the BSS controls (Fig. 1). When the chondroitin sulfate perfusion solution was removed, the corneal thickness rebounded above the control corneal thickness and stabilized. The 20% chondroitin sulfate mixed with BSS (osmolality, 1,052 mOsm) caused a greater reduction in corneal thickness. After the solution was removed from the corneal endothelium, a rebound in corneal thickness also occurred; again, this stabilized without any indications of toxicity.

Scanning and transmission electron microscopy of the corneas perfused with BSS or 20% chondroitin sulfate in BSS with sodium chloride showed the endothelial cells to be intact. However, the corneas perfused with 20% chondroitin sulfate with BSS lost some surface microvilli and the cell junctions were loose (Fig. 2). Transmission electron microscopy disclosed some endothelial cell edema in the corneas perfused with 20% chondroitin sulfate; all other organelles were normal (Fig. 3). By comparison, the BSS control corneas had normal endothelial cells on both scanning (Fig. 4) and transmission (Fig. 5) electron microscopy.

Intraocular pressure—Intraocular pressure in the rabbit corneas injected with 20% chondroitin sulfate increased to a mean (± S.E.) peak of 50 ± 3.4 mm Hg two hours after injection (Fig. 6). Those injected with 1% sodium hyaluronate had a mean intraocular pressure peak of 48 ± 4.4 mm Hg at three hours. Those injected with 10% chondroitin sulfate (37 ± 4.6 mm Hg) and 0.4% methylcellulose (36 ± 3.7 mm Hg) also showed moderate peak increases one and two hours after injection respectively. In the control groups, mild peak increases in intraocular pressure occurred in the eyes injected with BSS (21 ± 2.8 mm Hg) and reinjected aqueous humor (27 ± 2.8 mm Hg) at three and four hours respectively. The intraocular pressure decreased in all groups during the next 14 hours and had stabilized in the normal range by 24 hours after injection.

The cynomolgus monkey experiments also disclosed a substantial increase in intraocular pressure with the 1% sodium hyaluronate (67 ± 4.1 mm Hg) and 20% chondroitin sulfate (55 ± 3.5 mm Hg) 90 minutes after injection (Fig. 7). The intraocular pressures gradually decreased to the preinjection level during the next

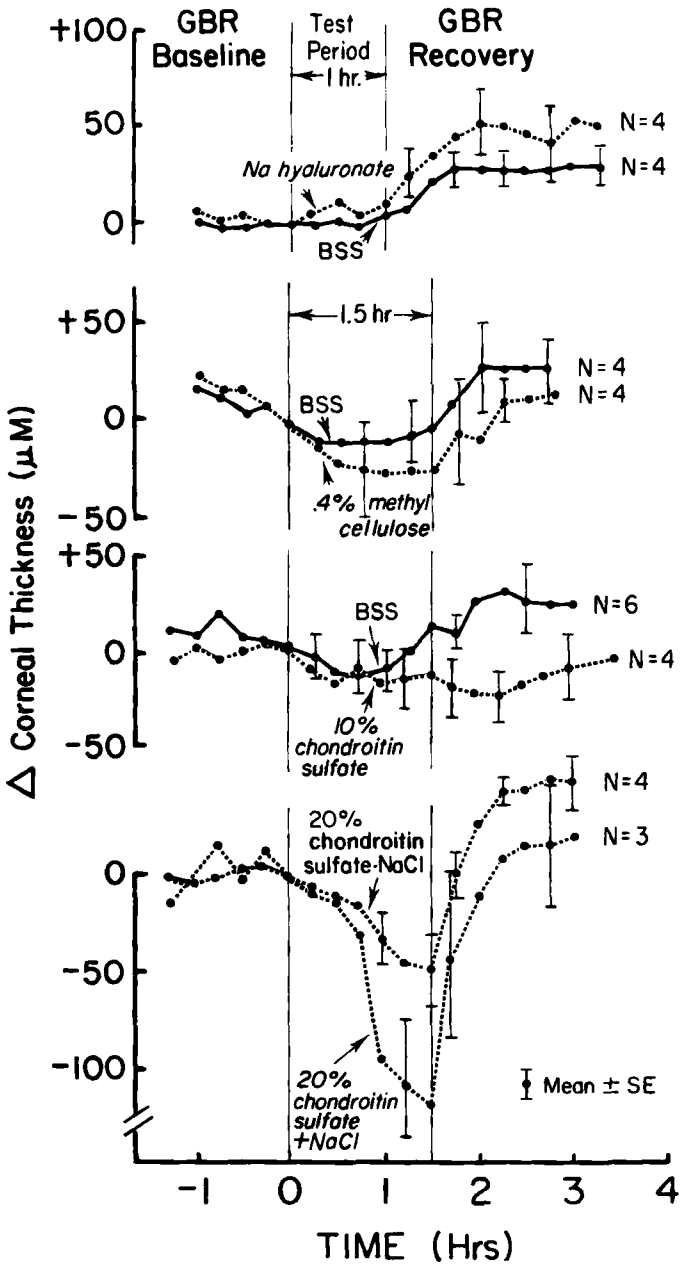

Fig. 1 (Mac Rae and associates). Corneal thickness during the first four hours after perfusion with the various test substances. GBR, glutathione bicarbonate Ringer's solution.

24 to 48 hours. The eyes treated with sodium hyaluronate and chondroitin sulfate and then washed out had intraocular pressures of 40 mm Hg and 30 mm Hg respectively at 90 minutes, but the intraocular pressures returned to normal earlier than they did in the eyes in which the test substances were not washed out. Slit-lamp examinations three months after the anterior chamber injections disclosed mild anterior subcapsular vesicles in three of the four monkeys who received 20% chondroitin sulfate (656 mOsm), including the animal whose

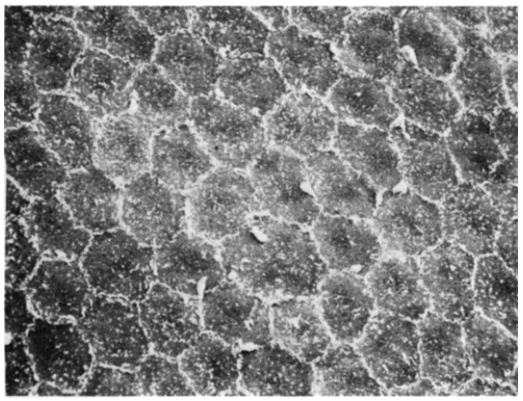

Fig. 2 (Mac Rae and associates). Endothelium of a rabbit cornea perfused with 20% chondroitin sulfate (osmolality, 1,051 mOsm) during 90-minute test period shows slight loss of the surface microvilli and some loosening of the cell junctions (SEM, ×835).

eye was washed out. The lenses in the eyes treated with sodium hyaluronate, methylcellulose, and BSS were normal.

Endothelial protection—The endothelial abrasion tests with an intraocular lens proved that both 1% sodium hyaluronate and 20% chondroitin sulfate provide excellent endothelial protection from polymethylmethacrylate intraocular lens surfaces (Table 2). The 10% chondroitin sulfate and 0.4% methylcellulose provided less endothelial protection, but these

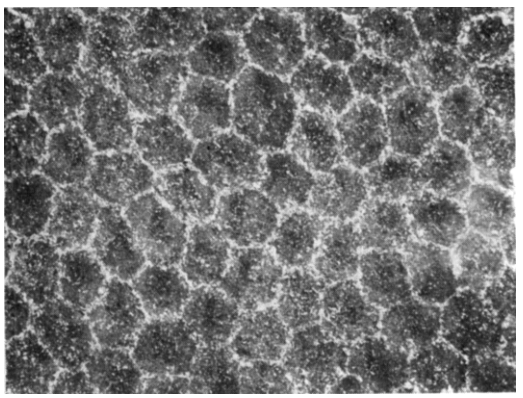

Fig. 4 (Mac Rae and associates). Endothelium of a control rabbit cornea perfused with BSS during the test period. The endothelial mosaic appears to be normal (SEM, ×835).

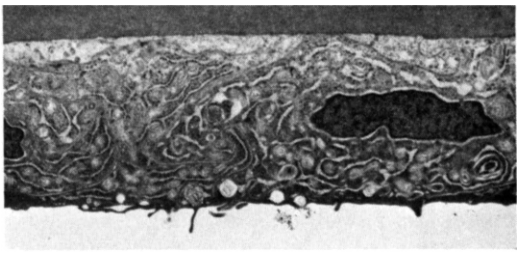

Fig. 3 (Mac Rae and associates). Another view of the cornea shown in Figure 2 discloses some basal endothelial cell edema. All other organelles are normal (TEM, ×6,000).

corneas had less damage than did those treated with BSS.

Discussion

Our results showed that minimal damage occurred to the corneal endothelium from direct exposure to 1% sodium hyaluronate. These results agreed with the findings of Graue, Polack, and Balazs.[5] Stanifer and Kretzer[6] also reported that 1% sodium hyaluronate caused no endothelial toxicity by corneal pachymetry and electron microscopy after anterior segment surgery in rabbits. Similarly, no toxicity results from endothelial perfusion with 0.4% methylcellulose or 10% chondroitin sulfate.

The corneal thinning that occurred with 20% chondroitin sulfate was similar to the corneal response observed by Edelhauser and associates[14] in their study on the osmotic tolerance of the endothelium. The ultrastructure of the rabbit corneas perfused with 20% chondroitin sul-

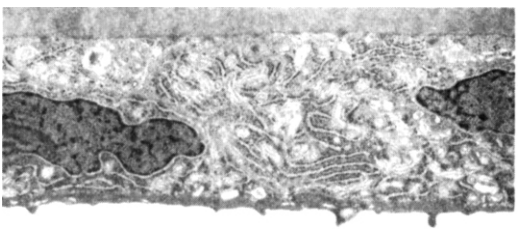

Fig. 5 (Mac Rae and associates). Another view of the cornea shown in Figure 4 shows a normal cell ultrastructure (TEM, ×6,000).

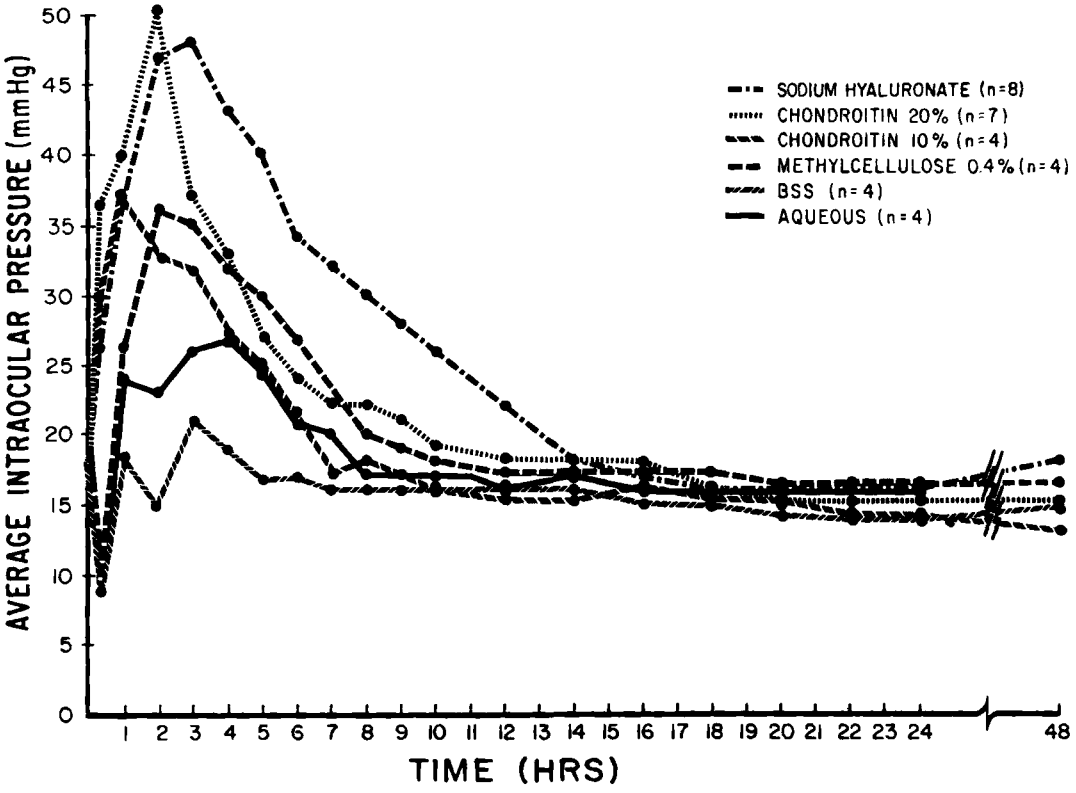

Fig. 6 (Mac Rae and associates). Average intraocular pressure in rabbits after injection with each of the test substances.

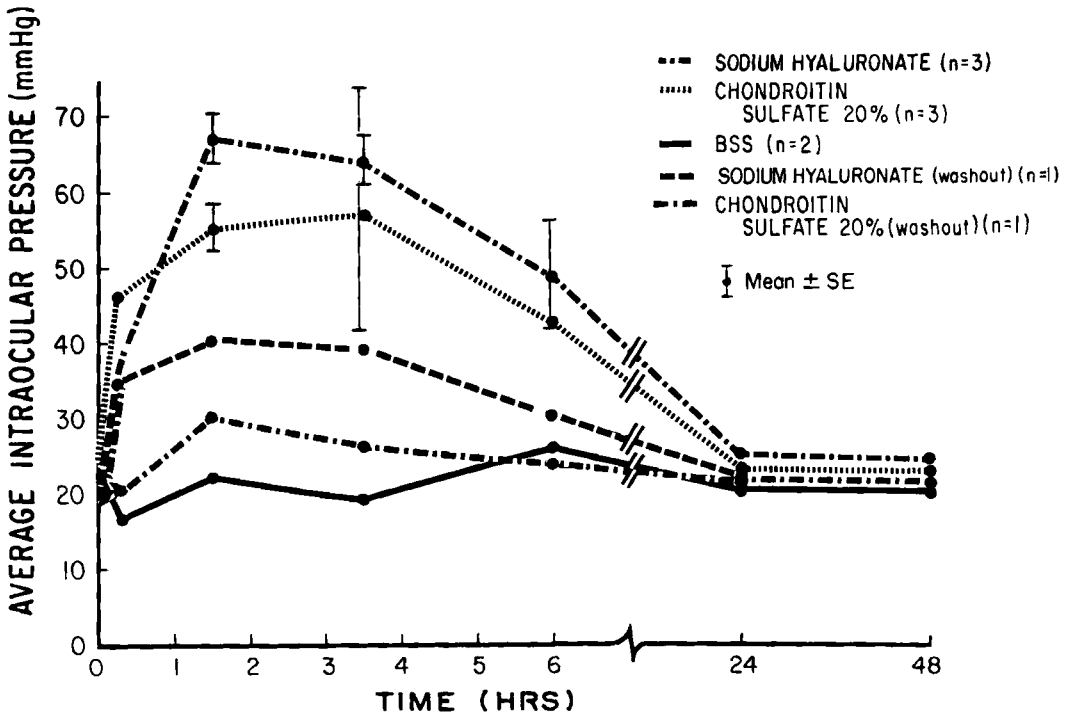

Fig. 7 (Mac Rae and associates). Average intraocular pressure in monkeys after injection with each of the test substances.

TABLE 2

ENDOTHELIAL ABRASION TEST

Treatment Group	No. of Corneas	Endothelial Damage (% ± S.E.)
Unabraded control (BSS)	13	12.6 ± 1.7
Abraded (BSS)	10	48.1 ± 4.8
1% sodium hyaluronate	13	10.1 ± 1.7
20% chondroitin sulfate	20	9.5 ± 1.5
10% chondroitin sulfate	4	23.2 ± 6.7
0.4% methylcellulose	7	34.0 ± 7.2

fate did show some swelling of the basal layer of endothelium, a finding similar to that reported for corneal perfusion with a hyperosmolar solution.[14] The minimal morphologic changes, however, apparently did not cause irreversible damage to the corneal endothelium because the corneal thickness stabilized during the recovery phase of the perfusion experiment. The small anterior subcapsular lens vesicles noted three months after anterior chamber injection of 20% chondroitin sulfate in monkeys were also probably caused by the hypertonicity of the 20% chondroitin sulfate. Transient cataracts have been induced in rabbits with intracameral injections of Miochol, a substance which is also hyperosmotic.[17] Our study showed that a 20% solution of chondroitin sulfate prepared in BSS increased the osmolality of the solution above the osmotic tolerance established for the endothelium (200 to 450 mOsm); therefore, before chondroitin sulfate can be used intraocularly, a more appropriate vehicle for the material may have to be developed. (In Cilco's original investigational study, 20% chondroitin sulfate and 50% chondroitin sulfate had osmolalities of 636 and 1,666 mOsm respectively; the viscosity of the 20% solution was 150 centistokes and that of the 50% chondroitin sulfate was 3,100 centistokes.)

The increases in intraocular pressure that occurred after anterior chamber injection were greatest with 1% sodium hyaluronate and 20% chondroitin sulfate during the first four hours after injection. The intraocular pressure then decreased during the next 20 hours. Several investigators have failed to find a significant increase in intraocular pressure 24 hours or more after using sodium hyaluronate in the anterior segment.[3,8,18] Using a protocol similar to ours, Graue, Polack, and Balazs[5] reported mildly increased intraocular pressures (18.8 mm Hg in treated eyes vs 14 mm Hg in controls) six hours after intracameral injections of sodium hyaluronate, but this difference was not significant.

Passo and Ernest[10] performed a prospective randomized clinical trial on patients undergoing intracapsular cataract extractions. They compared intraocular pressures after re-forming the anterior chamber with either 1% sodium hyaluronate or air. The treated patients had a significant increase in intraocular pressure (32.1 mm Hg) compared with the control group (10.1 mm Hg) six to seven hours after surgery. If their values are compared to our intraocular pressure curves, the 90-minute to four-hour peaks observed with 1% sodium hyaluronate and 20% chondroitin sulfate may have been 15 to 18 mm Hg higher than those noted at six to seven hours. Thus, a high intraocular pressure peak may easily go undetected, particularly in an early postoperative clinical setting where applanation may be difficult.

Pape[19] reported increased intraocular pressures in several patients who received 1% sodium hyaluronate (in three patients the intraocular pressure was more than 50 mm Hg). This increase persisted for one to four days postoperatively. He also demonstrated that washing the 1% sodium hyaluronate out of the anterior chamber with BSS prevented the increases in intraocular pressure noted after extracapsular cataract surgery, and

stated that the viscosity-dependent ocular hypertension is dilution-dependent. Several of our findings confirmed this dilution-dependent mechanism of ocular hypertension. The 20% chondroitin sulfate produced larger increases in intraocular pressure than did the 10% chondroitin sulfate. Additionally, we found that an anterior chamber washout prevents the increases. The dilution dependence and rapidity of onset of the ocular hypertension suggest that these viscous solutions mechanically restrict outflow. This theory gained support from a recent study by Berson, Epstein, and Patterson[20] who filled the anterior chamber of enucleated human eyes with 1% sodium hyaluronate and found a 62% reduction in outflow. An anterior chamber washout minimized this reduction. Pape[19] suggested a viscosity-dependent mechanism for the increase in intraocular pressure caused by 1% sodium hyaluronate and Hoffer[18] proposed the term Healon-block glaucoma. Because high intraocular pressures occur with viscous 20% chondroitin sulfate as well as 1% sodium hyaluronate, it may be more appropriate to call this entity viscosity-induced ocular hypertension. Moreover, it is important to note that an anterior chamber washout after using viscous aqueous substitutes makes these early increases in intraocular pressure less likely.

The endothelial abrasion test showed that 1% sodium hyaluronate and 20% chondroitin sulfate provided equivalent endothelial protection. Soll and associates[4] found that 20% chondroitin sulfate provided better endothelial protection than did 12% hyaluronic acid, but they did not use 1% sodium hyaluronate. Both 10% chondroitin sulfate and 0.4% methylcellulose provided less protection than the more viscous 1% sodium hyaluronate and 20% chondroitin sulfate. BSS provided the least protection to the corneal endothelium.

We noted several differences in physical properties between 1% sodium hyaluronate and 20% chondroitin sulfate during the course of the experiment. We needed extremely high pressures to irrigate 20% chondroitin sulfate through a 30-gauge needle. One rabbit eye was excluded from the study after a needle broke off the syringe and traumatized the lens. However, 1% sodium hyaluronate, 10% chondroitin sulfate, and 0.4% methylcellulose could be irrigated through a 30-gauge needle without excessive pressure. A Luer-Lok syringe or larger-bore needle should be used with 20% chondroitin sulfate solution.

We also observed that 1% sodium hyaluronate does not adhere to the intraocular lens surface,[21] whereas chondroitin sulfate[12] and methylcellulose do adhere to polymethylmethacrylate implants. This may have important clinical significance, because 1% sodium hyaluronate tends to bead, forming a high wetting angle on the implant surface, and does not cover the entire implant surface, particularly the implant edges. If a 1% sodium hyaluronate droplet does form on the implant, it has a tendency to slip off the implant, especially if the implant is turned in a vertical plane. Because of its tendency to bead and slide off of implants, it is not desirable to inject 1% sodium hyaluronate onto the surface of the intraocular lens before implantation. It is better to inject sodium hyaluronate directly into the anterior chamber before implantation; this provides a more continuous layer of sodium hyaluronate for endothelial protection. In contrast, if one dips the implant into chondroitin sulfate or methylcellulose, the substance adheres to the entire surface of the intraocular lens. Therefore, it may be unnecessary to inject chondroitin sulfate or methylcellulose into the anterior chamber to provide endothelial protection. Coating the implant with chondroitin sul-

fate or methylcellulose also minimizes the early postoperative increases in intraocular pressure because less of the substance is introduced into the anterior chamber.

The results of this study showed that both sodium hyaluronate and 20% chondroitin sulfate are nontoxic and protect the corneal endothelium, although 20% chondroitin sulfate is hyperosmolar, causing corneal thinning. Both substances may cause a sharp increase in intraocular pressure in the first one to four hours after intracameral injection, and, therefore, anterior chamber washout is indicated when a significant volume of either test substance is used. Neither 0.4% methylcellulose nor 10% chondroitin sulfate is toxic to the endothelium, but they do not adequately protect the corneal endothelium.

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