Comparison of the effects of intraocular irrigating solutions on the corneal endothelium in intraocular lens implantation

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Abstract

We conducted a randomised prospective controlled study to determine the effects of a glucose glutathione bicarbonate solution (BSS Plus) and a citrate acetate bicarbonate solution (S-MA₂) on the corneal endothelium in patients undergoing extracapsular cataract extraction with posterior chamber lens implantation. One eye of each patient was randomly assigned to receive BSS Plus, and the other eye to receive S-MA₂. BSS Plus caused significantly less corneal swelling on the first postoperative day than did S-MA₂. There was no difference between the two solutions in their effect on corneal thickness one week and one month postoperatively. Computer assisted morphometric analysis of wide-field specular microscopic photographs demonstrated minimal changes in endothelial morphological characteristics in the eyes irrigated with BSS Plus. By comparison S-MA₂ caused a significant loss of endothelial cells and a marked reduction in the figure coefficient. These results indicated that BSS Plus has a clinical advantage over S-MA₂ with respect to the corneal endothelium.

With the development of sophisticated intraocular surgical techniques, there is an increasing need for commercially available intraocular irrigating solutions that can maintain the integrity of the corneal endothelium and other intraocular tissues even when used in a large volume and for a long time period. Previous in-vitro perfusion studies have shown that normal saline, Plasma-lyte 148, lactated Ringer's solution, and balanced salt solution (BSS) are toxic to the corneal endothelium.^{1,2} These studies have also shown that maintenance of endothelial integrity can best be obtained by use of glutathione bicarbonate Ringer's solution (GBR), which is similar in chemical composition to that of aqueous humour.^{1,4} However, GBR is not suitable for clinical use, since it is chemically unstable once made up.

Two intraocular irrigating solutions have recently become commercially available (Table 1). They are BSS Plus,⁵ a glucose glutathione bicarbonate solution, and S-MA₂,^{6,7} a citrate acetate bicarbonate solution. BSS Plus is similar to GBR except for lacking adenosine and having an addition of oxidised glutathione instead of reduced glutathione. S-MA₂ is also similar to GBR except that citrate and acetate are added, and glutathione and adenosine are lacking from the medium. Previous experimental studies⁵⁻⁸ and clinical trials⁹⁻¹² have demonstrated that both

solutions are more effective in preventing corneal swelling and maintaining the structure of the corneal endothelium than either lactated Ringer's solution or BSS.

Which irrigating solution, BSS Plus or S-MA₂, is better for the corneal endothelium is of great importance. Recent experimental studies on rabbit, cat, and human donor corneas have consistently shown that S-MA₂ may be more harmful to the endothelium than BSS Plus.^{13,14} Consequently this randomised prospective controlled study was undertaken to determine whether there is a difference between BSS Plus and S-MA₂ concerning the effects on the corneal endothelium in patients undergoing posterior chamber lens implantation.

Materials and methods

We studied 21 patients with senile cataract scheduled for extracapsular cataract extraction with posterior chamber lens implantation. The age of the patients ranged from 58 to 88 years (mean, 74 years). Informed written consent was obtained from each patient. Both eyes of each patient were operated on by one surgeon with the same technique and medications. The operations were performed at one-week intervals. One eye of each patient was randomly assigned to receive BSS Plus and the other eye to receive S-MA₂.

A complete ocular examination was performed on all patients. We excluded patients with a history of ocular trauma, surgery, or contact lens wear. Patients with systemic disease, such as diabetes and cystic fibrosis, or ocular conditions that might affect the corneal endothelium, such as uveitis, pseudoexfoliation syndrome, and glaucoma, were also excluded, as were patients with low cell densities or morphological abnormalities of the endothelium preoperatively. Only

Table 1 Chemical composition of GBR, BSS Plus, and S-MA₂

Constituent	GBR	BSS Plus	S-MA ₂
Sodium chloride	111.6	122.2	112.9
Potassium chloride	4.8	5.08	4.8
Calcium chloride	1.1	1.05	1.2
Magnesium chloride	0.78	0.98	—
Magnesium sulphate	—	—	1.2
Sodium acetate	—	—	4.4
Sodium citrate	—	—	3.4
Sodium acid phosphate	0.86	—	—
Disodium phosphate	—	3.0	—
Sodium bicarbonate	29.2	25.0	25.0
Dextrose	5.01	5.11	8.3
Glutathione (reduced)	0.30	—	—
Glutathione (oxidised)	—	0.30	—
Adenosine	0.50	—	—
pH	7.4	7.4	7.3
Osmolarity (mOsm)	274	305	290

All concentrations expressed in mmol/l of solution.

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patients with neither surgical nor postoperative complications were included in the study.

A standard surgical technique was used on all patients. We made a fornix-based conjunctival flap and limbal incision of a 10 mm arc length and filled the anterior chamber with 1% sodium hyaluronate. After anterior capsulotomy with a bent 23 gauge needle the lens nucleus was expressed by a two-point compression without collapse of the corneal dome. We then performed a cortical clean-up with an aspiration-irrigation instrument, followed by expansion of the capsular bag with 1% sodium hyaluronate, insertion of posterior chamber lens in the capsular bag, and aspiration of the viscoelastic substance. The wound was closed with five to seven interrupted 10-0 nylon sutures. No epinephrine was added to the irrigating solutions or injected into the anterior chamber. At the end of surgery 0.1 to 0.6 ml of acetylcholine chloride was injected into the anterior chamber. Postoperative medications, including topical antibiotics and corticosteroids, were given in the same fashion to all patients.

Central corneal thickness was measured preoperatively and at one day, one week, and one month after surgery. A Haag-Streit slit-lamp with a pachymeter fitted with central fixation lights, according to Mishima and Hedbys,¹⁵ is used for these measurements. The use of these fixation lights is essential in order to obtain consistent measurements of central thickness. Each time the average of three consecutive readings was recorded. The endothelium of the central cornea (3 to 4 mm in diameter) was also photographed with a wide-field specular microscope preoperatively and at one week and one month after the operation. Specular microscopy during the first postoperative week was not performed in order to keep the eyes as sterile as possible.

Approximately 10 to 15 photographs were taken of each cornea. Adequate photographs were obtained from each eye of the 21 patients at all examinations. The photographs with good resolution were used for analysis. A total of 100 adjacent cells were analysed with a computerised digitiser, as previously described.^{16,17} Corneal pachymetry, endothelial photography, and morphological evaluation were performed by independent examiners who were unaware of which irrigating solution was used for any eye until the entire study was completed.

Endothelial cell density (cells/mm²) was calculated by dividing 10⁶ by the mean cell area. Cell loss was expressed as a percentage of the preoperative cell density. The coefficient of variation in cell size (SD expressed as a ratio to the mean cell area) was used as a quantitative measurement of cell size variability (poly-megethism). Cell shape was defined by the number of apices of each cell. The percentage of hexagonal cells was used to describe cell shape variability (pleomorphism). The figure coefficient was also calculated by the formula of $4\pi A/P^2$, where A is the cell area and P is the total perimeter. This factor is a dimensionless index describing the degree to which a cell approximates to a circle. The value of this index is 1.0 for a perfect circle and 0.907 for a perfect hexagon.

Table 2 Clinical data and preoperative endothelial morphology: mean (SEM)

	BSS Plus group (n=21)	S-MA ₂ group (n=21: paired eyes)
Irrigation time (min)	8.9 (1.0)	10.0 (1.7)
Infusion volume (ml)	97.1 (12.8)	97.4 (12.1)
Corneal thickness (mm)	0.53 (0.008)	0.53 (0.008)
Endothelial morphology		
Cell density (cells/mm ²)	2900 (89)	2961 (125)
Coefficient of variation*	0.330: 0.298, 0.390	0.314: 0.276, 0.348
Hexagonal cells (%)	58.3 (1.7)	61.0 (1.7)
Figure coefficient	0.850 (0.002)	0.852 (0.002)

*Median: quartile.

The figure coefficient was used to quantify the degree to which the endothelial monolayer deviates from its normal hexagonal patterns.

Differences were considered statistically significant if parametric (two-tailed paired *t* test) and non-parametric (two-tailed Wilcoxon one-sample test) tests yielded a *p* value of less than 0.05.

Results

There were no significant differences in amount of irrigating solution or irrigation time between the eyes receiving BSS Plus and those receiving S-MA₂ (Table 2). These two groups were also equivalent with respect to all the baseline variables, including corneal thickness, endothelial cell density, coefficient of variation in cell size, percentage of hexagonal cells, and figure coefficient.

In both the BSS Plus and S-MA₂ groups the corneal thickness increased significantly over the baseline values one day after surgery and steadily decreased with time (Fig 1). The corneal thickness on day 1 was significantly greater in the S-MA₂ group than in the BSS Plus group. There was no significant difference in corneal thickness between the two groups one week and one month after surgery. One month postoperatively, the corneal thickness returned to the baseline values in the BSS Plus group, while it was significantly increased from the preoperative value in the S-MA₂ group.

The eyes receiving S-MA₂ had a significant endothelial cell loss from the baseline one week and one month after surgery, whereas those with BSS Plus did not (Fig 2). The mean cell losses were higher for the S-MA₂ group than for the BSS Plus group at any point in time, though this difference was statistically insignificant. The coefficient of variation in cell size and percentage of hexagonal cells remained unchanged from the baseline values in both groups. The S-MA₂ group demonstrated a significant decrease in the figure coefficient compared with the baseline value and with the BSS Plus group one month after surgery. No change in the figure coefficient was noted in the BSS Plus group.

Discussion

The results of this randomised prospective controlled study demonstrated that BSS Plus offers a significant clinical advantage over S-MA₂ with respect to the corneal endothelium in

Figure 1 Central corneal thickness in the eyes receiving BSS Plus or S-MA₂. Each point represents the mean; bars represent SEM. *Significantly different ($p < 0.05$) from the baseline value. #Significantly different ($p < 0.05$) compared with the BSS Plus group.

patients undergoing extracapsular cataract extraction with posterior chamber lens implantation. The eyes receiving BSS Plus had less corneal swelling and fewer endothelial morphological changes than the paired eyes receiving S-MA₂.

Araie¹³ recently showed that S-MA₂ perfusion substantially increased the permeability of carboxyfluorescein to the rabbit corneal endothelium, while BSS Plus did not. In an in-

vitro perfusion of human donor corneas Edelhauser¹⁴ has also noted that S-MA₂ caused more corneal swelling than BSS Plus and a marked breakdown of the endothelial cell junctions, which is similar to what occurs in calcium-free medium,^{12 18 19} whereas BSS Plus maintained the functional and structural integrity of the endothelium. These observations suggest that a significantly greater corneal thickness noted in our patients with S-MA₂ one day after surgery may be due at least in part to compromised endothelial barrier function.

In our study none of the morphological parameters changed significantly from the baseline values in the eyes receiving BSS Plus. By comparison a significant cell loss from the baseline was noted in the paired eyes receiving S-MA₂. The S-MA₂ group also showed a marked decrease in the figure coefficient one month after surgery, indicating a loss of the normal hexagonal pattern. However, no significant change was noted in the coefficient of variation in cell size (polymegethism) or percentage of hexagonal cells (pleomorphism). A recent study has also demonstrated that in-vivo irrigation of the anterior chamber in cats with S-MA₂ caused marked endothelial morphological changes (polymegethism and pleomorphism), while BSS Plus did not.¹⁴ These endothelial changes were found to be present during the early postoperative period and to resolve within one week after the irrigation. Since we took the first endothelial photographs one week after surgery, significant increases in polymegethism and pleomorphism caused by S-MA₂ might not have been detectable.

The normal corneal endothelium is a densely packed monolayer with a regular hexagonal pattern. A regular hexagonal shape (given a

Figure 2 Endothelial cell loss (top left), coefficient of variation in cell size (top right), percentage of hexagonal cells (bottom left) and figure coefficient (bottom right) in the eyes receiving BSS Plus or S-MA₂. *Significantly different ($p < 0.05$) from the baseline value. #Significantly different ($p < 0.05$) compared with the BSS Plus group.

constant area) is the most geometrically or thermodynamically stable configuration to cover a plane,²⁰⁻²² because this shape will keep the total perimeter at a minimum, and thus produce the minimum surface tension energy. Therefore it can be proposed that a marked disruption of regular hexagonal pattern noted after S-MA₂ irrigation represents an endothelium in a physically unstable state,^{16,23} which may be more susceptible to additional trauma. Moreover, a loss of regular hexagonal pattern may reflect cell loss, causing adjacent cells to assume irregular hexagonal or elongated shapes (given a constant area) to cover the cell free area.^{16,23}

The difference between BSS Plus and S-MA₂ is that S-MA₂ lacks glutathione and contains sodium acetate and citrate. Oxidised or reduced glutathione, which are present in the aqueous humour²⁴ and corneal endothelium,²⁵ have been shown to be important for the maintenance of endothelial cell junctions and barrier function.^{13,4,26-28} Since acetate and citrate are unnatural buffers to the intraocular tissues, they may have some adverse effects on the endothelium.^{13,14} In addition there is a possibility^{13,14} that citrate may chelate calcium in the solution and decrease an amount of free Ca²⁺, which is essential for maintaining endothelial junctional complexes and barrier function.^{12,18,19} Therefore the lack of glutathione, presence of acetate and citrate, and possible loss of free Ca²⁺ in S-MA₂ may all be responsible for the endothelial alterations observed in both previous experimental investigations^{13,14} and the present clinical study.

Our results indicated that BSS Plus is more effective in protecting the functional and structural integrity of the corneal endothelium than S-MA₂ in patients undergoing posterior chamber lens implantation. The ability of BSS Plus to maintain endothelial integrity can be attributed to its chemical similarity to aqueous humour. Patients with low cell densities or morphological abnormalities of the endothelium have been shown to be more susceptible to surgical trauma and to a variety of stresses.^{16,29-33} The use of BSS Plus may be preferable and safer in this group of high-risk patients.

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