Effect of Solcoseryl in Corneal Alkali Burn Rat Model

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Background and Objectives

Ocular alkali burns cause severe damage to the ocular tissues and vision loss. Solcoseryl is a standardized calf blood extract that normalizes the metabolic disturbance and aids in maintaining the chemical and hormonal balance and has been used to treat burns in various tissues. This study examined the effects of Solcoseryl on a rat corneal alkali burn model.

Materials and Methods

Twenty rats were assigned randomly to four equal groups, including alkali burn, hyaluronic acid, Solcoseryl eyedrop, and Solcoseryl gel. A corneal alkali burn was induced by a NaOH-soaked paper disc. The treatments were given twice a day, every day. The wound area was measured after 24 and 48 hours, and the degree of neovascularization and corneal opacity were scored every week. The rats were sacrificed after three weeks for immunohistochemistry (IHC) to compare the level of inflammatory cytokines, IL-1 β , IL-6, and TNF- α . The thickness of the retinal layers was compared to observe any changes in the retina.

Results

The use of Solcoseryl on corneal alkali burn accelerated wound healing with less neovascularization, greater opacity, and less cataract. IHC showed that the inflammation of the cornea was controlled by both the hyaluronic acid and Solcoseryl treatments. On the other hand, the inflammation had spread to the retina. When the dosage forms were compared, eyedrops were more effective on corneal inflammation, while the gel-type had a greater effect on retinal inflammation.

Conclusion

Solcoseryl was effective in accelerating the wound healing rate on a corneal alkali burn but could not prevent the spread of inflammation from the cornea to the retina. Eyedrops were more effective on inflammation in the cornea, and the gel was more effective in the retina.

Key words

Corneal burn; Alkali burn; In vivo; Solcoseryl; Inflammation

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INTRODUCTION

Corneal blindness, being the fourth leading cause of blindness globally, is one of the major causes of visual deficiency after cataract, glaucoma, and macular degeneration.¹ Corneal blindness may be caused by diseases or injuries, while corneal injuries contribute to blindness with about 2 million new cases of unilateral blindness annually.²

Especially, ocular burns constitute true ocular emergencies and both thermal and chemical burns represent potentially blinding ocular injuries. Chemical burns are caused by either alkaline or acidic agents, and alkaline agents are known to cause more severe damage than acidic agents since they have both hydrophilic and lipophilic properties, which allow them to penetrate cell membranes and enter the anterior chamber. Acidic agents cause less damage because many corneal proteins bound to acid serve as a chemical buffer and coagulated tissues act as a barrier which blocks further penetration of acid.³

When corneal alkali burn occurs, it is graded based on injured area, penetrated depth, and the characteristics of chemical agent exposed. As a first aid, immediate wash out using water, saline, or balanced salt solution must be performed, then appropriate treatments follow depending on the grades. Although surgical means are required in case of severe corneal burns, drugs and topical agents may also be prescribed to accelerate epithelial growth and cellular proliferation, to minimize ulcer formation, or to control inflammation.

Solcoseryl® is a chemically and biologically standardized protein free non-antigenic and non-pyrogenic dialysate of blood from healthy veal calves, developed as a result of the search for humoral factors controlling growth. It contains a broad spectrum of low molecular organic and inorganic substances which help in wound healing by normalizing metabolic disturbance and tissue damage associated with stress injury and hypoxia. It was well known that use of Solcoseryl reduces scarring and inflammation and accelerates wound healing by balancing cellular and hormonal reactions in various tissues,⁴ and such balance is crucial in recovery from alkali burn.

In the current study, we aimed to observe and confirm the effect of two commercially available Solcoseryl types *in vivo* on the corneal alkali burn rat model.

MATERIALS AND METHODS

Animals

The study was approved by the Dankook University Medical School Research Institutional Animal Care and Use Committee (DKU-21-002), and conducted on 6-week old SD rats (OrientBio, Seongnam, Korea). Animals were housed and maintained at the Laboratory Animal Unit of the Dankook University. All animals were treated in accordance with the Association for Research in Vision and Ophthalmology (ARVO) statement for the use of animals in ophthalmic and vision research. A total of 20 rats were randomly assigned to four equal groups according to the treatment plans as follows: (1) control group with corneal alkali burn with no treatment; (2) corneal alkali burn with hyaluronic acid treatment, (3) corneal alkali burn with Solcoseryl eyedrop treatment; and (4) corneal alkali burn with Solcoseryl gel treatment.

Corneal alkali burn induction

Corneal alkali burn was induced in all the experimental groups, by placing a 3.5-mm paper disc soaked in 1N NaOH on the center of cornea for 30 seconds. Cornea was washed right after removing the paper disc with 10 mL phosphate buffered saline thoroughly.

Hyaluronic acid and Solcoseryl treatments

Hyaluronic acid (Kynex®; Alcon, Seoul, Korea) and Solcoseryl (Solcorin® eyedrop and ophthalmic gel; Hanlim Pharm. Co., Seoul, Korea) treatments were given to the rats twice a day for three weeks of experiment period. A single drop (approximately 40 µL) was given at a time.

Ocular sign assessment

Cataract scores, neovascularization and corneal opacity scores were measured every week. Neovascularization scores were given to each corneal quadrant between 0 to 3 based on the centripetal extent of the neovascular branches from the limbus. Scores of each quadrant were summed ranging 0 to 12 for each eye.⁵ Corneal opacity was graded on a numerical scale of 0 to 4—0, clear cornea; 1, mild stromal opacity; 2, moderate stromal opacity; 3, severe corneal opacity with visible iris; 4, opaque cornea with iris not visible.⁶ Cataract scores were not given to the eyes with corneal opacity scores of 4.

Tissue collection for histological analysis

Eye and eyelid tissues including the nasal, central and temporal portion of the eye and eyeball were excised after CO₂ euthanasia on day 21. The tissues were fixed with 4%

paraformaldehyde, embedded in OCT compound (Tissue-Tek®, Sakura, Japan), and vertically cut into 15- μ m-thick sections. The sections were stained with hematoxylin and eosin for light microscopic examination.

Immunohistochemistry

For immunohistochemistry, inflammatory cytokines interleukin-1 beta (IL-1 β ; ab9722; Abcam, Cambridge, MA, USA), interleukin-6 (IL-6; ab208113; Abcam) and tumor necrosis factor-alpha (TNF- α ; ab6671; Abcam) were used to assess the level of inflammation in the collected tissues⁷.

Statistical Analysis

The data were analyzed using GraphPad Prism (GraphPad, San Diego, CA, USA) and are expressed as the mean $\pm$ standard deviation of the mean. The differences between the groups were analyzed using one-way analysis of variance (ANOVA), and statistical significance was defined as $p < 0.05$ using Tukey's test.

RESULTS

Observations under brightfield and blue lights showed that corneal alkali burn was successfully induced in all the groups, with the center of cornea being melt in uniform sizes (Fig. 1). When the rates of wound healing were compared in all the groups, treatment groups had faster

healing rate compared to the control group. Solcoseryl gel treatment group showed the fastest healing rate in all groups, and followed by hyaluronic acid and Solcoseryl eyedrop treatment groups (Fig. 2).

Neovascularization and corneal opacity scores were given every week at day 8, 15, 22 (Fig. 3, 4). Neovascularization scores in Solcoseryl gel treatment group showed a tendency to be lower than the control group every week, while hyaluronic acid treatment group had higher scores than the control every week. Solcoseryl eyedrop treatment group had higher scores in week 1 and 2, then score lowered down in the third week (Fig. 3). Corneal opacity results appeared to be similar with neovascularization scores: Solcoseryl gel treatment group being the lowest, Solcoseryl eyedrop treatment group being higher in the first two weeks and lower in third week compared to the control, hyaluronic acid treatment group being higher than the control group in all weeks (Fig. 4).

Weekly cataract scores in all groups were compared in this study, and the results showed that percentages of opaque cornea with iris not visible (grade not applicable; N/A) in the control and hyaluronic acid treatment groups were higher than Solcoseryl eyedrop and gel treatment groups, while ratio of less severe cataract were higher in Solcoseryl treatment groups (Fig. 5).

Histological analysis showed that corneal structures were more stable in Solcoseryl treatment groups, while bodily fluid accumulated in stroma was observed in hyal-

Fig. 1. Microscopic observations on corneal alkali burn wound healing in rat in vivo model. Bright field observation (above) and blue light observation (below) show similar wound healing rate in all experimental groups. There are almost no signs of wound at 48-hour period after giving alkali burn wounds.

Fig. 2. Corneal alkali burn wound healing rate in rat *in vivo* model. Various treatments on corneal alkali burn showed that the differences were observed at 24-hour period after giving wounds. Solcoseryl gel had the highest healing rate among the other experimental groups, and hyaluronic acid treatment group had higher healing rate when compared to the Solcoseryl eyedrop group.

Fig. 3. Neovascularization scores of corneal alkali burn rat *in vivo* model. There were no significant differences in neovascularization scores among all the experiment groups but there still was a trend that Solcoseryl treatment lowered the degree of neovascularization when compared to the control and hyaluronic acid treatment groups.

uronic acid treatment group (Fig. 6). Also, the levels of inflammatory cytokines in cornea were lower in Solcoseryl treatment groups. However, no significant differences were observed among hyaluronic acid and Solcoseryl treatment groups.

Immunohistochemistry on retina confirmed that the inflammation caused on corneal tissue was spread to all the retinal layers (Fig. 7). When the number of inflammatory ganglion cells were count, the level of IL-1 β was lower in all the treatment groups compared to the control ($p < 0.001$ in hyaluronic acid and Solcoseryl eyedrop treat-

Fig. 4. Corneal opacity scores of corneal alkali burn rat *in vivo* model. There were no significant differences in corneal opacity scores among all the experiment groups but Solcoseryl treatment groups showed a tendency to have lower corneal opacity scores when compared to the control and hyaluronic acid treatment groups.

Fig. 5. Cataract gradings of corneal alkali burn rat *in vivo* model. Opaque corneas with iris not visible are labelled as "N/A". Solcoseryl treatment groups had lower grades compared to other experiment groups.

ment group; $p < 0.01$ in Solcoseryl gel treatment group), IL-6 and TNF- α were lower in hyaluronic acid ($p < 0.05$) and Solcoseryl gel ($p < 0.01$) treatment groups. Solcoseryl eyedrop treatment group showed similar IL-6 and TNF- α levels when compared to the control.

To observe any changes caused by corneal alkali burn on retinal tissues, the thickness of retina and each retinal layer were measured and compared (Fig. 8). The thickness of entire retina was $232.8 \pm 5.53 \mu\text{m}$ in control group,

Fig. 6. Immunohistochemistry of cornea in corneal alkali burn rat model. IHC showed that corneal structures were stable in Solcoseryl treatment groups and the level of inflammatory cytokines were also lower in Solcoseryl treatment groups. However, there was no significant differences between hyaluronic acid treatment group.

while $216.3 \pm 2.99 \mu\text{m}$ in hyaluronic acid treatment group, $239.5 \pm 4.43 \mu\text{m}$ in Solcoseryl eyedrop treatment group, and $253.2 \pm 10.19 \mu\text{m}$ in Solcoseryl gel treatment group, showing no significant differences in all groups. The thickness of inner limiting membrane (ILM) and ganglion cell layer (GCL) was $21.98 \pm 1.67 \mu\text{m}$ in control, $25.05 \pm 0.92 \mu\text{m}$ in hyaluronic acid treatment group, $25.96 \pm 1.35 \mu\text{m}$ in Solcoseryl eyedrop treatment group, and $28.56 \pm 2.07 \mu\text{m}$ in Solcoseryl gel treatment group, Solcoseryl gel treatment group being significantly higher than the

control ($p < 0.05$). The thickness of inner plexiform layer (IPL) was $57.19 \pm 1.99 \mu\text{m}$ in control group, $74.97 \pm 2.27 \mu\text{m}$ in hyaluronic acid treatment group, $67.94 \pm 2.19 \mu\text{m}$ in Solcoseryl eyedrop treatment group, and $28.56 \pm 2.07 \mu\text{m}$ in Solcoseryl gel treatment group, hyaluronic acid and Solcoseryl gel treatment groups being significantly higher than the control ($p < 0.01$). The thickness of inner nuclear layer (INL) was $33.57 \pm 1.04 \mu\text{m}$ in control group, $34.66 \pm 0.81 \mu\text{m}$ in hyaluronic acid treatment group, $43.99 \pm 1.32 \mu\text{m}$ in Solcoseryl eyedrop treatment group, and $42.71 \pm$

Fig. 7. Immunohistochemistry of retina in corneal alkali burn rat model. IHC showed that the inflammation caused in cornea were spread to retina. Hyaluronic acid and Solcoseryl treatments did not alleviate retinal inflammation.

2.47 μm in Solcoseryl gel treatment group, Solcoseryl gel treatment group being significantly higher than the control ($p < 0.01$). The thickness of outer plexiform layer (OPL) was $13.34 \pm 0.56 \mu\text{m}$ in control group, $9.92 \pm 0.69 \mu\text{m}$ in hyaluronic acid treatment group, $11.58 \pm 0.57 \mu\text{m}$ in Solcoseryl eyedrop treatment group, and $12.51 \pm 0.73 \mu\text{m}$ in Solcoseryl gel treatment group, hyaluronic acid treatment group being significantly lower than the control ($p < 0.01$). The thickness of outer nuclear layer (ONL) was $73.41 \pm 2.64 \mu\text{m}$ in control group, $51.94 \pm 1.74 \mu\text{m}$ in hyaluronic acid treatment group, $57.26 \pm 0.99 \mu\text{m}$ in Solcoseryl eyedrop treatment group, and $64.83 \pm 4.38 \mu\text{m}$ in Solcoseryl gel treatment group, hyaluronic acid ($p < 0.001$) and Solcoseryl eyedrop ($p < 0.01$) treatment groups being

significantly higher than the control.

DISCUSSION

Solcoseryl is being used in treating burns in various models including horse,⁸ dog,⁹ rat,^{10,11} pig,¹² and guinea-pig¹³ both in vitro and in vivo, based on the previously reported studies regarding wound healing with minimal scarring⁴ and acceleration of healing burns and ulcers in human tissues.^{14,15}

The current study revealed that applying Solcoseryl on corneal alkali burn not only accelerates wound healing rates in cornea but also prevents neovascularization and maintains corneal opacity.

Fig. 8. Retinal layer thickness in corneal alkali burn rat model. Due to retinal inflammation the thickness of each retinal layer varied in the experimental groups.

Table 1. Comparison between the results of current study and previously reported studies

	HA	SE	SG	Disease
Retina	↓	↑	↑	↑ (Acute anterior uveitis) ²¹
ILM/GCL	↑	↑	↑*	↓ (Glaucoma/vision loss) ²²
IPL	↑**	↑	↑**	↓ (Glaucoma/vision loss) ²²
INL	↑	↑***	↑**	↓ (Acute macular neuroretinopathy) ²⁵
OPL	↓**	↓	↓	↑ (Retinal degeneration / photoreceptor loss) ²³
ONL	↓***	↓**	↓	↑ (Acute macular neuroretinopathy) ²⁵
				↓ (Acute macular neuroretinopathy/retinal degeneration) ^{23, 25}

ILM, inner limiting membrane; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer.

According to the in vitro studies on corneal epithelial cells, Solcoseryl aids wound healing in stimulating the secretion of various mucin proteins MUC1, MUC5AC, MUC7

and MUC16, and enhanced the activity of signaling factors Akt, FAK, ERK, and Src to regulate cellular migration, adhesion and proliferation.¹⁶ MUC1, MUC5AC secreted from

corneal epithelial cells and conjunctival cells and MUC7 secreted from lacrimal gland contribute to tear film formation and prevent infections,¹⁷ while MUC16 produces barrier on corneal surface to block adhesion of foreign matter.¹⁸ Such enhancement in tear film may aid washing out of the excess alkaline agent after alkali burn.

Immunohistochemistry results also confirmed the effect of Solcoseryl in controlling inflammatory cytokines IL-1b, IL-6, and TNF-a in all treatment groups. When comparing the two types of Solcoseryl, eyedrop was more effective in cornea, while gel was more effective in retina. This difference is thought to be caused by the physical traits of dosage forms. With the same ingredient and concentrations, the dosage form may also be a deciding factor in effective wound healing. Residence time on the ocular surface may be longer when applied as a gel compared to the eyedrop type. Some studies reported that topical ophthalmic drops dissipate almost completely after drop administration, and must also be applied frequently.^{19,20}

However, applying Solcoseryl on corneal alkali burn did not prevent the spread of inflammation from cornea to retina. The results of current study showed that the thickness of retina was affected by corneal alkali burn and the treatments. Based on the previous studies reporting about the correlation between various retinal conditions and retinal layer thickness, the current study compared the thickness of each retinal layer (Table 1).

The thickness of entire retina was similar in all the groups, with a decrease in hyaluronic acid treatment group and increase in Solcoseryl gel treatment group. It was reported that the thickness of entire retina gets thickened with acute anterior uveitis, which implies the hyaluronic acid treatment reduced the degree of inflammation in retina while Solcoseryl treatment did not affect on retinal inflammation.²¹

When the thickness of each layer was compared, the thickness of GCL and ILM was increased in all treatment groups compared to the control, with significant difference in Solcoseryl gel treatment group ($p < 0.05$). Also, IPL thickness was increased in all treatment groups, with significant difference in hyaluronic acid and Solcoseryl gel treatment groups ($p < 0.01$). The GCL and IPL thickness is known to be affected by glaucoma and vision loss to be decreased.²² The results of current study did not show any of the reported symptoms and the inflammation caused by corneal alkali burn was alleviated by hyaluronic acid and Solcoseryl treatments.

The thickness of INL had a tendency to be thickened in all treatment groups compared to the control, with sig-

nificant increase in Solcoseryl treatment groups. It has been known that macular degeneration and loss of photoreceptors occur with INL thickening,²³ and the results of current study suggest that photoreceptors could have been affected by retinal inflammation and the hypertrophy of Muller glial cells increased the layer thickness.²⁴

The thickness of OPL tended to decrease in all treatment groups, with significant difference in hyaluronic acid treatment group ($p < 0.01$). It has been reported that OPL thickness increases when acute macular neuroretinopathy occurs.²³ Also, acute macular neuroretinopathy may affect the OPL thickness, causing thrombosis to disrupt deep capillary network and giving ischemic damage to the retina.²⁵

The thickness of ONL decreased in all treatment groups with significant differences in hyaluronic acid treatment group ($p < 0.001$) and Solcoseryl gel treatment group ($p < 0.01$). It is known that the ONL thickness is affected by acute macular neuroretinopathy or macular degeneration to be decreased.^{23,25}

In conclusion, this study revealed that there are advantages and disadvantages in applying hyaluronic acid and Solcoseryl on corneal alkali burn. Hyaluronic acid treatment may control the inflammatory reactions in cornea and retina, but also cause instability in corneal tissue. Solcoseryl treatment accelerates wound healing rate while maintaining tissue stability, but cannot prevent the spread of inflammation from cornea to retina. The effectiveness of eyedrop in cornea and gel in retina seem to be caused by the residual time in the tissues.

CONFLICT OF INTEREST

Kyong Jin Cho is an editorial board member of the journal but was not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

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