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Air and Gas Toxicity on the Corneal Endothelium

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Abstract

Air and gas injection into anterior chamber of the eye during intraocular surgeries have been occasionally used by the ophthalmologists. However, these substances, in particular air bubbles, during an intraocular surgery may inevitably occur and lead to corneal endothelium damage. Up to now, many researchers have tried solutions, such as viscoelastic materials to overcome this problem. On the other hand, recent studies demonstrated that the viscoelastic materials alone might not be sufficient to prevent corneal endothelial insult. This paper is an overview of the researches related to air and gas toxicity on corneal endothelial damage.

Keywords: Air and Gas Toxicity; Corneal Endothelium; Viscoelastic; Phacoemulsification; Intracameral

Abbreviations: HPMC: Hidroxypropylmethylcellulose; CAT: Catalase; SOD: Superoxide Dismutase; HO-1: Heme Oxygenase-1.

Introduction

Maintaining of the anterior chamber during intraocular surgeries is important to get rid of corneal endothelium damage. Due to lack of mitotic activity in vivo in corneal endothelium cells, it is critical to conserve them sufficiently that able to maintain endothelial pumping function. Air had largely been used for this purpose in intraocular surgeries for long years, despite their proven damaging effect on the corneal endothelium. Later, the viscoelastic solutions took over the role of air to maintain anterior chamber during intraocular surgeries due to their lubricating, lower flow rate and shock absorbing effects [1-5]. However, a number of researchers reported that the type of the viscoelastic agent is also important to prevent corneal endothelial damage [6-8]. Although the viscoelastic agents mostly overcome the toxic effect on corneal endothelium, introducing small and larger air bubbles into anterior chamber may be inevitable around an incision or through processing a phacoemulsification stage for a dense cataract or during vitreal fluid-air exchange in a pars plana vitrectomy procedure [5,9,10]. This article reviews the corneal endothelial damage by air bubbles and prevention ways of this problem during intraocular surgeries.

Air and Corneal Endothelium

Previously, air had been used to maintain anterior chamber and to prevent corneal endothelial damage during intraocular surgeries. The first experimental study related to air damage on the corneal endothelium in rabbits demonstrated that both air and sulfur

hexafluoride gases might cause degenerative changes on the endothelial layer called as 'peau d'orange' [1]. In another experimental study, Leibowitz et al. found that replacing anterior chamber with air in rabbit eye led to several events termed 'explosions' and 'non explosions' [2]. Explosions represented disturbed and losing of many cell membranes in number, while non explosions represented tiny, small tears in the cell membrane. Moreover, these events occurred within minutes after air injection. However, due to regenerative property of a rabbit endothelium, Olson pointed that it would be more valuable to investigate a cat endothelium, which does not have the regenerative capacity as in humans, about the air toxicity [11]. The author studied with 36 of the healthy cat eyes and compared the results between the two groups. First, in all eyes 0.7 mL of aqueous fluid was removed, then in 11 eyes 0.7 mL of balanced salt solution and in 25 eyes 0.7 mL air were injected to re-form of the anterior chamber. All of the eyes were examined daily by slit lamp microscopy to inspect the changes in the endothelium. Two months after injection, a random sampling of five areas over the cornea was performed for each eye. At the end of the study, mean endothelial cell density was 102% ± 7% in the eyes injected with BSS and 93% ± 11% in the eyes injected with air ($p<0.005$). In 1990, Craig et al. published a paper in which they demonstrated that air bubble endothelial damage during phacoemulsicifation in human eye bank eyes [5]. All eyes were in good physical condition. They categorized the eyes into 4 groups as negative control (viscoelastic alone), positive control (air alone), air plus Healon® and air plus Viscoat®.

They introduced a controlled amount of small air bubbles into anterior chamber during phaco surgery in same fashion for all eyes in the groups. The corneal endothelium was stained with 0.25% try pan blue for each eye, and then endothelial cell counting was performed with a light microscope using 400-x power. The numbers of damaged cells (blue-staining nuclei) and normal cells (pink staining nuclei) were compared to each other. Finally, endothelial cells were counted on scanning electron microscopy. As a result, percentage of the damaged cells was 4.5% in positive control group, 0.4% in negative control group, 4.9% in air plus Healon® group and 0.3 in air plus Viscoat® group (Statistical comparison of positive control and negative control: $p<0.001$; of positive control and air plus Viscoat®: $p<0.001$; of negative control and air plus Healon®: $p<0.02$; air plus Healon® and air plus Viscoat®: $p<0.02$). The results of this study indicated that not only air bubbles have toxicity on corneal endothelium, but also viscoelastic materials have a protective property on the endothelium.

In addition, the results revealed that dispersive viscoelastic agents are more protective to air toxicity on the endothelium. In their detailed study of air bubbles toxicity during phacoemulsification surgery, Kim et al. published the results of a series of experiments in white rabbit and human eyes [12]. The author grouped the experiments into four conditions: during phacoemulsification, intracameral air during irrigation in vivo, in vitro perfusion with BSS-plus and intracameral air in vivo. After all experiments, F-actin staining and electron microscopy were performed to examine the corneal endothelium cells. Consequently, the corneal endothelial cells in the eyes having phacoemulsification surgery with a 40% power setting had a normal distribution of F-actin filaments, and minimal disrupted cell membranes on scanning electron microscope.

In contrast, in the eyes having phacoemulsification surgery with a power setting of 90%, due to many small air bubbles during the surgery, there were many small circular areas that did not stain for F-actin and many cells with disrupted cell membranes. Interestingly, intracameral air bubbles during irrigation in vivo led to prominent ring shaped of cell damage around the periphery of the air bubble. In vitro perfusion experiments demonstrated that the eyes perfused with BSS-plus for 60 minutes without exposure to air bubble had a normal morphology whereas the eyes that was exposed to air bubble more than 10 seconds had a local and ring shaped damage on the endothelium. Intracameral air in vivo experiment revealed that the air injection into anterior chamber for up to 10 minutes without irrigation did not have toxicity on the endothelium. However, after 20 minutes of exposure, early changes were seen in the circular region corresponding to adjacent border of the air bubble. One of the interesting finding related the irrigation in vivo group was that endothelial damage could still occur without phacoemulsification too. Furthermore, the ring shaped damage did not occur without presence of the air bubbles. The author underlined the two critical observations for possible explanation of the ring shaped damage: the damage occurred on the adjacent border of air bubble and there was damage only the absence of the aqueous humor (or the presence of irrigation).

The author points out that the probable explanation for ring shaped damage is 'surface tension phenomenon' due to lack of aqueous humor in which proteins as surfactant. Another important finding was that there was no ring shaped damage in phacoemulsification group unlike the other groups. It was likely that air bubbles smaller than a

critical size would cause damage with an inner-ring diameter of 0 mm, thereby creating a circular damage. In a recent study, Landry et al. studied with the eyes of 16 healthy adult cats that were injected with 0.7 mL air into anterior chamber of one eye and sulfur hexafluoride (SF6) into anterior chamber of the fellow eye [13].

As a result, SF6 gas was found to have more toxic effect than air on corneal endothelium. The endothelial cell counts were significantly lower after injection in the SF6 group (mean air-SF6 difference before injection: -35±37, p=0.35 cells/m^2; after injection 128±41 cells/m^2, p=0.008). In addition, they found that endothelial cell loss was significantly greater in the superior cornea, and scanning electron microscopy examinations showed that there was greater damage on the endothelium, such as cell membrane disruption, missing cells in the SF6 group related to air group. Landry et al. list the possible mechanisms for endothelial toxicity: a mechanical interaction resulting from surface tension, an inflammatory reaction following the injection of air or SF6 and presence of changes in the anti-oxidant system of the aqueous humour after the injection [13]. In support of this, Doi et al. described more toxicity of intravitreal injection of air, SF6 and perfluoropropane (C3F8) in the superior retina (where gases were in contact more) compared to other quadrant of the retina [14].

Air toxicity on corneal endothelium has been investigated during posterior segment surgery besides anterior segment surgery: A recent study by Cekic, et al. discussed the effects of humidified and dry air on corneal endothelial cells during vitreal fluid-air exchange in aphakic-pigmented rabbits [15]. They examined the eyes with F-actin staining and measurement of intracellular permeability after 5, 10 and 20 minutes of fluid-air exchange with dry and humidified air, then compared the results with normal control rabbit eyes. The results demonstrated that the humidified air-exposed corneas showed a similar act in staining with the control corneas up to 20 minutes while the dry air-exposed corneas had highly disorganized act in staining even in 5 minutes after the vitreal fluid-air exchange. Likewise, the endothelial permeability was comparably preserved in humidified air-exposed corneas compared to dry air-exposed corneas (Transendothelial permeability values after 20 minutes, mean ± SEM: 5.22 ± 1.29 in humidified air group vs. 33.37 ± 7.33 in dry air group, p<0.001). This comprehensive study confirms the importance of F-actin that acts as a scaffold and supports the cell membrane. Their results suggested that humidified air maintains the F-actin structure and cellular junctions more stable. With regard to F-act in structure and endothelial cell membrane stabilization, these results are consistent with those of Kim and co-workers' study [12]. Cekic, et al. asserts that the humidified air, clusters of millions of water molecules are distributed to the air system, forms a more physiologic environment similar to aqueous state of endothelial cells better than the dry air [15].

How to Protect Corneal Endothelium from Air and Gas Toxicity?

Numerous studies suggested that viscoelastic materials were more useful and protective than air against to corneal endothelium toxicity due to their slower flow rate, cushioning and lubricating effects [5-7]. Alpar showed that the endothelial cell loss during the corneal transplant surgery was at lower rate in the eyes used Healon® than in the eyes used air/BSS. In his randomized clincal trial, Muir et al. reported that 2% hidroxypropyl methylcellulose (HPMC) and 1% sodium hyaluronate (NA) were found to be less toxic compared to air on the corneal endothelium [9,16,17]. However, the author noted that there was no significantly difference of the degrees of cell loss between the eyes having surgery with BSS/air and NA (cell loss percentage: 24.4% in BSS/air group vs. 14.3% in NA group). Nevertheless, these researches did not take into account the type of viscoelastic solutions on the effect of protection for corneal endothelium. In terms of the efficacy of type of viscoelastic material in protecting endothelium, as discussed previous section, Craig and co-authors concluded that Viscoat® (consists of 4% chondroitin sulfate-CS and 3% NA) is more protective on the corneal endothelium. Similarly, Kim and co-workers investigated role of the type of viscoelastic solutions in protecting the endothelium for white rabbits and human eyes [5,10].

In this controlled study, they sought for protective effect of different type of viscoelastics during phacoemulsification and irrigation/aspiration (I/A) experiments. The results were comparable of those Craig and McDermott's studies, and they indicated that F-actin staining showed noticable patchy injury to endothelial cells and areas with denuded cells in control group (without viscoelastic material) and NA group [5,18]. In contrast, none of the corneas in Viscoat® group showed endothelial damage during phacoemulsification. In addition, after the I/A experiment, they found that mucinous layer thickness was significantly thinner in Viscoat® group than of those control and NA groups. The author underlined that the possible explanation for this result may be more adherent feature of Viscoat®

compared to NA on transient the mucinous layer. In fact, this evidence indicated that Viscoat® has more interaction with the corneal endothelium, in other words, has more protective effects on the endothelium. In another study, Cekic et al. questioned whether two viscoelastic agents (1% NA and 3% NA + 4% CS) have additional protection on the corneal endothelium under humidified and dry air conditions during fluid-air exchange in aphakic rabbits or not [19].

They examined all the corneas using F-actin staining, scanning electron microscope and in vitro corneal permeability. This study revealed that corneas exposed to dry air exhibited greater irregularity of cell shapes and borders, and intercellular junctions were loose and separated in structure. Humidified air exposed cells had relatively irregular and less interdigitated. On the other hand, HA humidified and CS+HA humidified corneas were similar to the structure of normal corneas with slightly irregular borders. Humidified air corneas had a superiority in preserving microvilli contrast to HA dry air and HA+CS dry air corneas. F-actin staining proved that the double band act in staining was still present in HA and HA+ CS used corneas 20 minutes after both dry and humidified air infusion. In viscoelastic used corneas, there was better double band act in staining in humidified corneas than dry corneas. Likewise, the paracellular permeability was significantly preserved in viscoelastic used dry air infused corneas, and the difference viscoelastic used humidified air infused corneas and dry air infused only corneas was more prominent. Cekic and co-authors suggested that humidified air infusion has an additional protection on corneal endothelial permeability of viscoelastic-coated corneas.

Recently, an experimental study proved that hydrogen (H_2) is very useful to prevent corneal endothelial damage in phacoemulsification surgery. It was known that collapsing air bubbles during phacoemulsicifaction induce the created energy to trigger of adjacent water molecules. This causes 'sonolysis' phenomenon (H_2O--->OH^- + H^+) [20]. The presence of OH- radicals in the anterior chamber during ultrasound oscillating leads to insult to endothelial cells. In their study, Igarashi and co-workers evaluated the effects of H_2 in rabbits with a control group [21]. Regarding the effect of H_2 against to OH^- radicals, the author argued that H_2 dissolved in ocular irrigating solution should work as a free radical scavenger in the anterior chamber. They performed image analysis of corneal edema, real time polimerase chain reaction analysis of antioxidative enzymes, such as catalase (CAT), superoxide dismutase (SOD), heme oxygenase-1 (HO-1) mRNAs, and immunohistologic examination of two oxidative stress markers, 4-HNE and 8- OhdG.

In their study, intensity of the opaque lesions (i.e. corneal edema) was less apparent in the H_2 group than the control group. US exposure increased the expressions of HO-1, SOD and CAT mRNA after 5 hours of exposure, and then increased expressions of these anti-oxidative enzymes were significantly suppressed in the H_2 group than the control group. Moreover, the number of 4-HNE (4-hydroxy-2-nonenal) and 8-OhdG (8-hydroxy-2-deoxyguanosine) positive cells was significantly less in the H_2 group than the control group. Prior studies noted the importance of protective effect of free-radical scavengers on corneal endothelial insult in phacoemulsification surgery. In addition, Igarashi and co-workers underlined that their results demonstrated that more corneal endothelial damage in the control group than in the H_2 group despite the presence of glutathione, as a anti-oxidative agent, in the ocular irrigation solution of the control group [21-24]. Similarly, the protective effect of ascorbic acid, as an anti-oxidative agent, was reported in vivo and in vitro models. Hence, the findings observed in this study mirror those of previous studies that examined the effect of free-radical scavengers in protecting corneal endothelium [22,23].

Conclusion

Intraocular surgeries, such as cataract, refractive and vitrectomy have been performed very routinely by the ophthalmologists in many clinics. Many surgeons may occasionally encounter with corneal endothelium insult due to air bubbles or gas toxicity in their daily practices. Consequently, it is very important to cope with this issue during the intraocular surgeries. To date, the findings from several experimental and clinical studies related to air and gas toxicity on corneal endothelium enhance our understanding of that this toxicity can be preventable with some methods, such as using of proper viscoelastic during anterior segment surgery or infusion of humidified air during fluid-air exchange in vitrectomy. Although the results of these studies are promising, further researches in this field would be great help in discovering the methods for protection corneal endothelium during the intraocular surgeries.

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