—Review—

Free Radical Development in Phacoemulsification Cataract Surgery

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Abstract

Phacoemulsification and aspiration (PEA) has become the most popular cataract surgery, due to the establishment of safe surgical techniques and development of associated instruments. However, corneal endothelial damage still represents a serious complication, as excessive damage can lead to irreversible bullous keratopathy. In addition to causes such as mechanical or heat injuries, free radical formation due to ultrasound has been posited as another cause of corneal endothelium damage in PEA. Ultrasound in aqueous solution induces cavitation, directly causing water molecule disintegration and resulting in the formation of hydroxylradicals, the most potent of the reactive oxygen species. Considering the oxidative insult to endothelial cells caused by free radicals, their presence in the anterior chamber may represent one of the most harmful factors during these procedures. Indeed, some researchers have recently started to evaluate PEA from the perspective of oxidative stress. Conversely, the major ingredient in ophthalmic viscosurgical devices (OVDs), which are indispensable for maintaining the anterior chamber in PEA surgery, is sodium hyaluronate, a known free radical scavenger. OVDs can thus be expected to provide some anti-free radical effect during PEA procedures. In addition, since commercially available OVDs display different properties regarding retention in the anterior chamber during PEA, the anti-free radical effect of OVDs is likely to depend on behavior during irrigation and aspiration. The present study followed standard PEA procedures in an eye model and measured hydroxylradicals in the anterior chamber using electron spin resonance. The kinetics of free radical intensity and effects of several OVDs during clinical PEA were also demonstrated. These studies may be of significance in re-evaluating OVDs as a chemical protectant for corneal endothelium, since the OVD has thus far only been regarded as a physical barrier. In addition, many reports about corneal endothelium damage during PEA have been published, but objective evaluation of various damaging factors has been difficult. The present assay of free radicals in a simulation of clinical PEA offers the first method to quantitatively assess stress on the corneal endothelium.

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Key words: phacoemulsification, cataract surgery, free radical, ophthalmic viscosurgical device

Introduction

Recently, most cataract surgeries have been performed using phacoemulsification and aspiration (PEA), a technique that utilizes high-intensity ultrasound energy for the fragmentation and emulsification of the cataractous lens. Owing to

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progress in surgical devices and the development of techniques, safety and efficacy of PEA have improved markedly, and PEA represents one of the most sophisticated eye surgeries today. However, as PEA is a typical closed-eye surgery, meaning that the crystalline lens is totally emulsified and aspirated in the anterior chamber, injuries can arise in the front or posterior tissues of the lens. Corneal endothelial injury may occur in the front, and lens capsule rupture in the posterior. Regarding rupture of the posterior capsule of the lens, incidence has decreased considerably with improvements in stability of the space in the anterior chamber using surgical devices. In addition, appropriate intraoperative manipulation rarely results in serious sequelae. However, corneal endothelial damage can induce long-term impairment of vision quality. Since human corneal endothelial cells lack a regenerative potential, excessive damage causes significant decreases in endothelial cell density. Corneal endothelium maintains hydration of the corneal tissues by acting as a barrier and a draining pump against the aqueous humor, so decreases in endothelial cell density can induce irreversible corneal edema (bullous keratopathy), in turn causing permanent blurred vision and pain. Once bullous keratopathy develops, penetrating keratoplasty represents the only effective therapeutic approach. Unfortunately, the number of cases of bullous keratopathy after PEA has not been decreasing. One reason is that the volume of PEA has itself been increasing. Another reason is that PEA has become the first choice intervention for cataract surgery, even in cases with hard lens nucleus or where functional reservoirs of corneal endothelium are poor. In any event, protection of corneal endothelium from extensive damage represents a crucial task for surgeons performing PEA.

Corneal endothelium damage in PEA is reportedly attributable to several factors, including excessive duration of phacoemulsification[1–3], localized temperature increase[4], contact or collision of lens nucleus fragments following turbulent flow of irrigating solution[5,6] or air bubbles[7,8], not to mention surgical skill. These factors can roughly be divided into 2 categories: factors accompanying utilization of ultrasound energy; and factors associated with irrigation. Localized temperature increase causes thermal damage to corneal tissue and belongs to the first group, and improvements in surgical devices such as cooling functions for ultrasound probes have been used to counteract this effect. Collision of lens fragments by turbulent flow causes physical breakdown of corneal endothelium and belongs to the second group, and can be controlled to some extent by setting lower irrigation and aspiration flow rates. However, another harmful factor that accompanies the use of ultrasound is the development of free radicals, i.e. oxidative stress. This has not been widely recognized as a harmful factor in PEA. Considering the oxidative insult to endothelial cells caused by free radicals, their presence in the anterior chamber may represent one of the most damaging factors during these procedures.

Effects on Tissues of Ultrasound Medical Instruments

Ultrasound medical instruments can be divided into 2 categories-diagnostic and surgical. Another kind of medical instrument aims for blood flow improvement using ultrasound, but will not be dealt with in this review. As both methods apply ultrasound to the human body, consideration of potential tissue injury from ultrasound is necessary. From the perspective of the medical device market, diagnostic devices are much more common than surgical devices. In internal medicine or obstetrics, diagnostic devices are widely used for tomography or distance measurement, using ultrasound energy in the high-frequency (MHz) range at low intensity. Various studies have investigated tissue injury from diagnostic ultrasound, and no evidence of injurious influence has yet been identified[9–13]. However, surgical ultrasound devices are used in neurosurgery, resection of the liver and other soft tissues, ultrasonic assisted lipoplasty and other operations, by applying ultrasound energy in the low-frequency range of 20～60 kHz with a high-intensity range of 15 to ＞ 1,000 W/cm^2. PEA devices also operate at the 20- to 50-kHz frequency

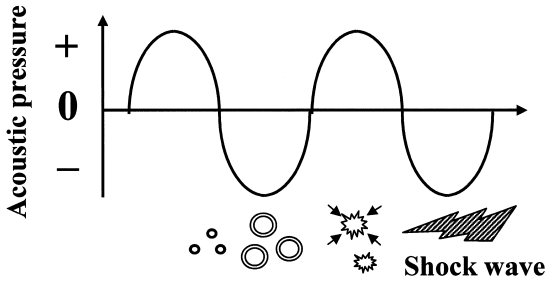

Fig. 1 Acoustic cavitation
In aqueous solution, high intensity ultrasound causes sound pressure fluctuation which induces acoustic cavitaion. Gas bubbles develop and grow at negative pressure. At positive pressure, the bubbles are compressed and collapse which generates shock wave.

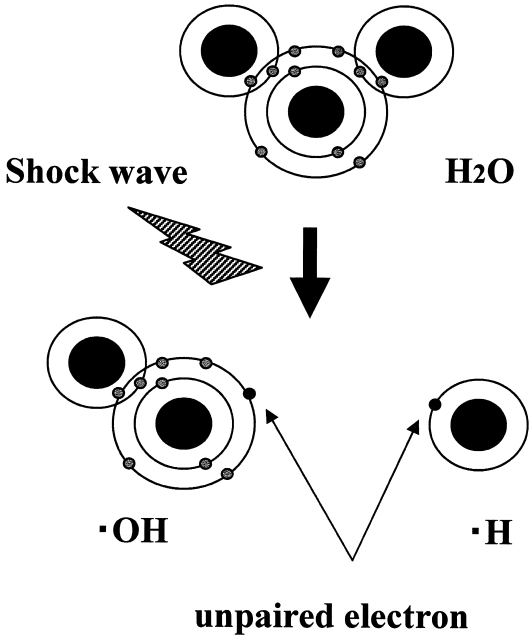

Fig. 2 Sonolysis
A water molecule is directly disintegrated into a hydroxylradical and a hydrogen atom radical in localized high pressures of over 600-atmosphere and temperature of over 5,000°K induced by energy of shock wave.

range and utilize high power intensity; in the maximal upper range of 1,000 W/cm^2. Ultrasound exerts 2 kinds of influence on tissues: thermal effects; and non-thermal effects[14]. Thermal effects are caused by the conversion of ultrasonic energy into thermal energy. In PEA, this corresponds to thermal burn of the cornea. Meanwhile, non-thermal effects represents acoustic cavitation and the resultant shock waves, and formation of free radicals. Although the ultrasound used in surgical devices is by its very nature much more harmful than that in diagnostic devices, few reports have investigated associated tissue injuries. In this respect, the factor most in need of consideration seems to be development of free radicals. The mechanisms of development for free radicals are described in the following section.

Ultrasound and Free Radicals

In the fields of physics and engineering, high intensity ultrasound oscillated in aqueous solution is well known to induce free radicals[15]. The cause is acoustic cavitation, a phenomenon whereby gas bubbles develop due to ebullism or evaporation and grow under negative pressure, then collapse under positive pressure as a result of pressure fluctuations caused by ultrasound (**Fig. 1**). When bubbles collapse, they generate shock waves that induce localized high pressures of > 600 atmospheres and temperature elevations of > 5,000 K. Instrument such as ultrasound washers employ this phenomenon of shock waves. The energy created extends to neighboring water molecules, causing direct disintegration (**Fig. 2**). This phenomenon ($H_2O \rightarrow \cdot OH + \cdot H$) is called sonolysis, and the ·OH, i.e. hydroxylradical, is the most reactive of the various reactive oxygen species, including superoxide anion, singlet-dioxygen and hydrogen peroxide. Under physiological conditions, hydroxylradicals are primarily formed in biological systems through Fenton or Fenton-like reactions. In sonolysis, however, direct generation of hydroxylradicals occurs, and Fenton reactions are bypassed, eliminating the need for dioxygen, hydrogen peroxide and transition metals for the generation of hydroxylradicals. A similar phenomenon occurs in ionizing radiation (radiolysis), which represents one of the most dangerous factors associated with exposure to radiation. In this respect, ultrasonic surgical devices are analogous to ionizing radiation. PEA utilizes a piezoelectric transducer that vibrates a metal tip with cycles of 40～50 kHz to emulsify the lens nucleus. The PEA

probe should thus be recognized as a high-frequency oscillating blade that utilizes the mechanisms of ultrasound, rather than equipment to induce ultrasound. In other words, ultrasound is essential to PEA as the mechanism while concomitant to the purpose. However, the phenomena described above associated with ultrasound oscillation in water remain an inevitable consequence of the process[16].

Clinical PEA and Free Radicals

Several studies in the early 1990's demonstrated ophthalmic PEA device-related free radical formation. Shimmura et al. first described free radical formation in vitro[17], and Holst et al. demonstrated this phenomenon in vivo[18]. Both studies, however, employed chemiluminescence techniques that, while suitable for detecting superoxides, do not detect hydroxylradicals, the most potent of the free radical species. Cameron et al. recently reported on the ability to detect hydroxylradical formation using electron spin resonance (ESR)[19]. However, they applied ultrasound in a test chamber with a closed circulation loop in which the same solution was recirculated, resulting in conditions quite different to those in clinical PEA.

At least 2 factors must be considered in studying free radical formation under clinical conditions. One is the exchange of aqueous humor by constant irrigation and aspiration. In clinical PEA, irrigation and aspiration of the medium occurs at various rates. The aqueous humor is thus continuously replaced by irrigating solution. Consequently, actual free radical concentrations in the anterior chamber are determined by the ratio of production to subsequent clearance. Another factor is the use of ophthalmic viscosurgical devices (OVDs-a new term recommended by the International Organization for Standardization for viscoelastic materials)[20]. In clinical PEA, the OVD is injected into the anterior chamber before application of ultrasound. Originally, OVDs were used for space maintenance of the anterior chamber and lens capsule dilation for intraocular lens insertion. With regards to protecting the corneal endothelium from mechanical injuries, the effectiveness of OVD is well known[21,22]. In addition, the major ingredient of OVD is sodium hyaluronate (HA), which is a known free radical scavenger. Several studies have revealed that HA plays important roles in protecting against oxidative damage in arthritis[23]. HA injection therapy into the joint cavity was introduced with the expectation of providing an anti-free radical effect[24]. Other ophthalmic studies have also reported the protective properties of HA against oxidative stress in the corneal endothelium[25,26]. OVDs can thus be expected to provide some anti-free radical effect during PEA procedures. Actually, OVDs reportedly reduce free radical concentrations caused by ultrasound when added to test solutions both in vitro and in vivo[18]. Furthermore, various OVDs are available commercially, with each displaying unique molecular weights and composition, resulting in different properties regarding retention in the anterior chamber during PEA. Some materials flow out immediately, while some are retained for a longer period in the anterior chamber, even with irrigation and aspiration. A representative material of the former is Healon (Pharmacia, Uppsala, Sweden), which is known as a cohesive agent, while an example of the latter is Viscoat (Alcon Laboratories, Fort Worth, TX), a known dispersive agent. Healon contains only 1% HA, while Viscoat comprises 3% HA and 4% chondroitin sulfate, another free radical scavenger. Several studies have examined retention time for these 2 agents during PEA. Assia et al. experimentally compared removal time for several OVDs from the anterior chamber due to irrigation and aspiration, and found that removal time was 20～25 s for Healon and 3.5 min for Viscoat[27]. Poyer et al. quantitatively measured vacuum levels when bolus removal of materials occurred, and showed that such phenomena were commonly observed with cohesive agents including Healon, but not with Viscoat[28]. Viscoat has also been shown to provide a thicker coating over endothelial cells than any other agents after PEA procedures[29]. The individual behaviors of each agent during PEA may thus alter the net result that occurs. Assuming that free radical concentrations will be affected by continuous irrigation and aspiration and the behavior of OVDs thus appears reasonable.

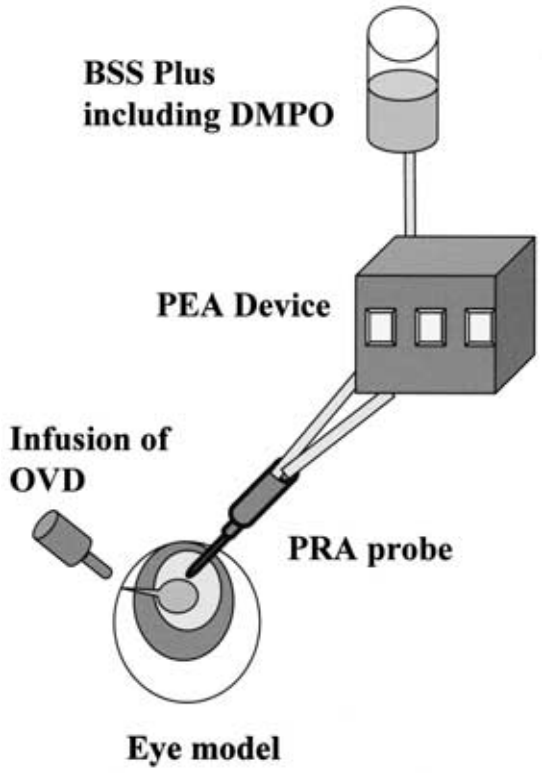

Fig. 3 PEA simulation
The PEA probe was inserted through a 3.2 mm incision and the tip was fixed at the center and on the iris plane of the model eye. Healon, or Viscoat (0.3 m*l*) was injected into the anterior chamber before ultrasound applied. PEA was performed either for 10, 20, or 30 seconds with a 100% US power level. After PEA, 300 μ*l* of the solutions were collected from the anterior chambers and free radical intensity was determined via ESR.

Given these factors, we sought to simulate clinical PEA procedures using a Series 10,000 phacoemulsifier (Alcon Laboratories) with irrigation and aspiration at a rate of 20 m*l*/min and a vacuum pressure of 150 mmHg in an eye model (Marty System; Iatrotech, Menlo Park, CA) for 10～30 s. Presence of free radicals was detected using ESR (**Fig. 3**)[30]. As electron transfer occurs immediately after generation, free radicals including hydroxylradical are highly reactive and short-lived. Measurements are therefore achieved using radical trap agents and the detection of these radical adducts by ESR. This is called the electron spin trap method. For hydroxylradicals, 5,5-dimethyl-1-pyrroline N-oxide (DMPO) is usually used as a trapping agent. We mixed 1% DMPO with irrigating solution, BSS Plus (Alcon Laboratories) in advance, and performed PEA in an eye model. Immediately after PEA, aqueous humor was collected and signals from the spin adduct DMPO-OH were measured using a JES-RE3X ESR spectrometer (JEOL, Tokyo, Japan). The results clearly demonstrated the spin adduct signal with a characteristic quartet pattern, which is specific for the hydroxylradical (**Fig. 4**). The hyperfine coupling constants for the spin adduct were consistent with those for the hydroxylradical according to a previous report[31]. Superoxide-related signals were not detected. In the control experiment, in which neither irrigation and aspiration nor OVD was used, signals increased and plateaued at 20 s. Interestingly, in the BSS group in which no OVD was used, signals were enhanced in a time-dependent fashion, but intensity at 30 s was not significantly different from that at 20 s, indicating that free radicals may reach a stable concentration due to constant production and clearance by irrigation and aspiration. This is the first ESR evidence that hydroxylradicals exist in the anterior chamber during PEA, even with irrigation and aspiration. To examine the influence of OVDs on free radical development, Healon or Viscoat was injected into the anterior chamber before ultrasound application. The results confirmed that both types of OVD inhibited development of free radicals, suggesting that the OVD, itself a radical scavenger, functions as an alternate reactant for the radicals and consequently reduces free radical concentrations in the aqueous solution. In addition, while Healon suppressed the for signal 10～20 s, Viscoat significantly suppressed signals throughout the entire course of ultrasound application confirming the results from previous studies concerning retention of OVDs during PEA (**Fig. 5**)[27–29].

Next, we performed additional PEA simulations to examine in more detail the influence of irrigation and aspiration conditions and various OVDs on free radical formation. The influence of irrigation and aspiration was examined by comparing high (35 m*l*/min with 250 mmHg vacuum) and low (15 m*l*/min with 60 mmHg vacuum) flow rates. To examine the influence of OVDs, we chose additional OVDs that

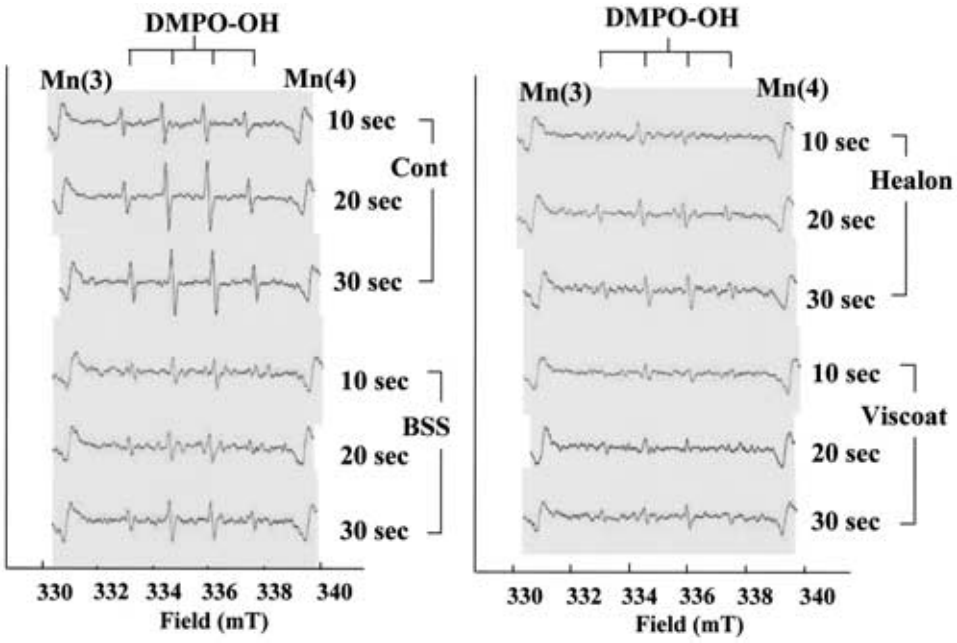

Fig. 4 DMPO-OH signals in PEA simulation
Representative signals in Control, BSS, Healon, and Viscoat group. (1) Control: Irrigation and aspiration (I/A) (−), OVD (−). (2) BSS: I/A (25 m*l*/min), OVD (−). (3) Healon and (4) Viscoat: I/A (25 m*l*/min), injection of 0.3 m*l* of Healon, or Viscoat into the anterior chamber before US. Mn (3) and Mn (4), the third and forth signals, respectively, of the manganese in the ESR spectra. Spectrometer settings were as follows: modulation frequency, 100 kHz; microwave frequency, 9.4 GHz; microwave power, 10 mW; scan time, 120 seconds; time constant, 0.3 seconds; receiver gain, 2,500.

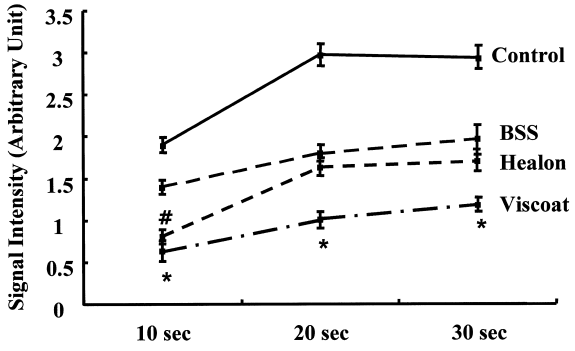

Fig. 5 Signal intensities shown with arbitrary unit in PEA simulation
In the control, signals increased and reach a plateau at 20 seconds. In the BSS group, signals were enhanced in a time-dependent fashion, but the intensity at 30 seconds was not significantly different from that at 20 seconds. Both of Healon and Viscoat inhibited the signal for 10 seconds, however, the inhibition by Healon was significant only at 10 seconds (#: $p < 0.05$; Healon vs BSS) while Viscoat's suppression was significant even at 30 seconds (*: $p < 0.05$; Viscoat vs BSS).

are currently in common use in Japan, namely Opegan (Santen Pharmaceutical, Osaka, Japan) and Healon V (Pharmacia), in addition to Healon and Viscoat. The major ingredient of Opegan is 1% HA, but molecular weight (1,200 kD) is much smaller than that of Healon (4,000 kD). Consequently, Opegan exhibits lower viscosity and longer retention compared to Healon[32,33]. Healon V is the newest OVD to contain HA as a major ingredient. HA concentration is 2.3%, and the agent shows a unique behavior in the anterior chamber. When irrigation and aspiration flow is high, Healon V flows out immediately like Healon, but at a low rate, the agent remains in the anterior chamber for a longer time, like Viscoat. Healon V is thus defined as a visco-adaptive agent[34–36]. This investigation yielded the following results: with a low flow rate, all OVDs can inhibit development of free radicals. Suppression at 30 s was better in Opegan, Healon V and Viscoat than in Healon. However, with high flow, suppression at 10 s was already poor with Healon and Opegan, and at 30 s, no notable inhibition was

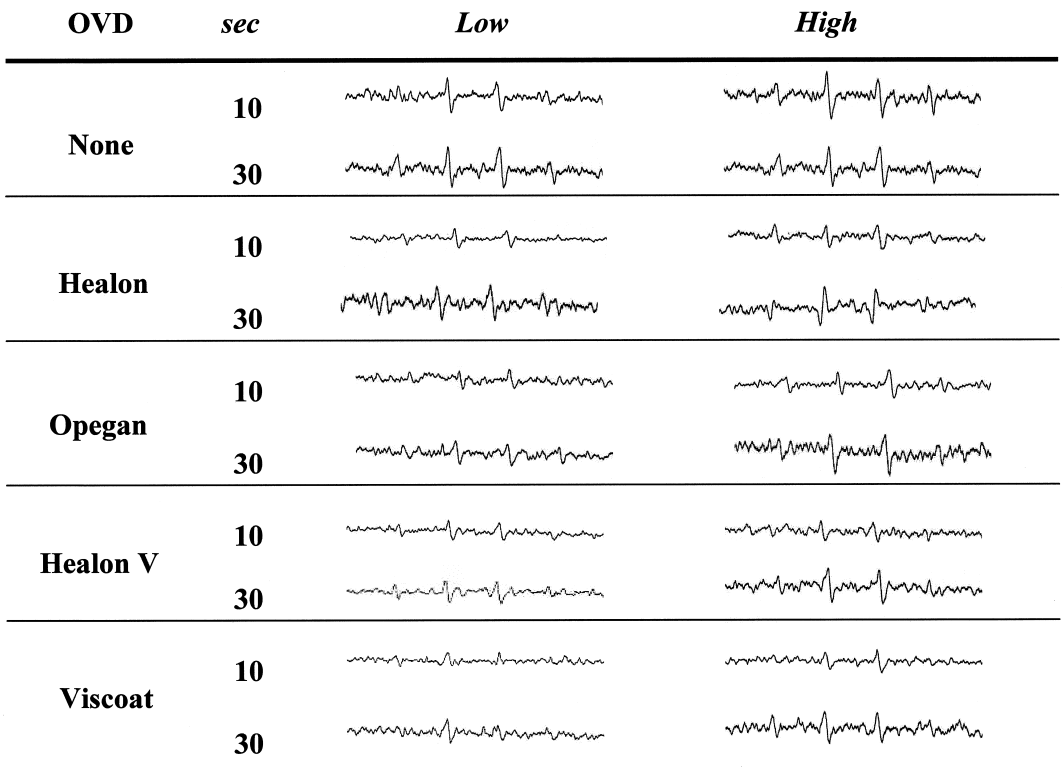

Fig. 6 DMPO-OH signals in additional PEA simulations
The DMPO-OH signals were confirmed in all settings examined. The signals, however, varied depending on the combination of the flow settings and the kinds of OVD used. *Low* represents the low flow setting with 15 m*l*/min aspiration with 60 mmHg vacuum, and *High* represents the high flow setting with 35 m*l*/min aspiration with 250 mmHg vacuum.

send for any OVD. In summary, inhibition of free radicals was observed with Viscoat, Healon V, Opegan and Healon, in order of effectiveness (**Figs. 6, 7**). This result presents a guideline by which free radical development and subsequent oxidative stress on the corneal endothelium can be reduced. To reduce oxidative stress, OVDs with high retention in the anterior chamber should be used with a low flow rate for irrigation and aspiration. The present studies may be useful in reevaluating OVDs as a chemical protectant for corneal endothelium, since OVDs have previously been regarded as a physical barrier only. In addition, although many reports have described damage to the corneal endothelium by PEA, objective evaluation of various factors contributing to damage has been difficult. The present assay of free radicals in a simulation of clinical PEA offers the first method to quantitatively assess stress on the corneal endothelium.

Oxidative Stress: a New Perspective on PEA-associated Tissue Damage

Some researchers have started to evaluate PEA from the viewpoint of oxidative stress. Rubowitz et al. showed the effectiveness of ascorbic acid as an irrigating solution in PEA due to free-radical-scavenging properties. Ascorbic acid in irrigating solution significantly reduced cell loss and damage to the corneal endothelium in rabbits[37]. Augustin et al. performed PEA in 130 patients and measured lipid peroxide concentrations in the aqueous humor using the thiobarbituric acid method[38]. Lipid peroxides were used as a marker of oxidative tissue damage. Patients were divided into three groups depending on duration of phacoemulsification: $<$20 s; 20$\sim$40 s; and $>$40 s. The results clearly demonstrated that lipid peroxide levels correlated well with duration of phacoemulsification. In addition, they showed that oxidative stress was reduced using OVDs. That

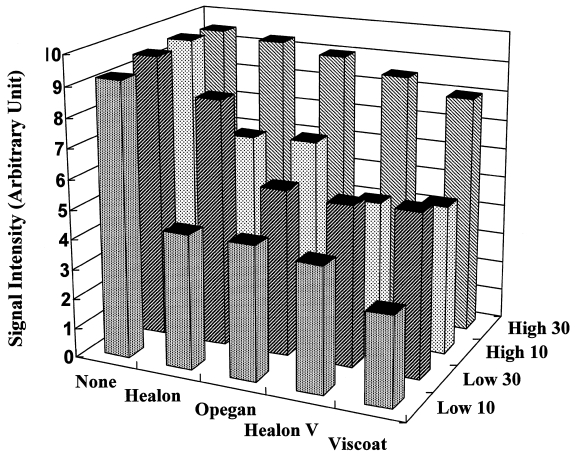

Fig. 7 Signal intensities shown with arbitrary unit in additional PEA simulations
With the low flow, all OVDs can inhibit the development of free radicals. The suppression at 30 seconds was better in Opegan, Healon V, and Viscoat than in Healon. However, with the high flow, the suppression at 10 seconds was already poor with Healon and Opegan, and at 30 seconds, inhibition with all OVDs was not remarkable. In summary, the performance of inhibition was observed with Viscoat, Healon V, Opegan, and Healon in order of effectiveness.

study presented the first evidence of oxidative stress in clinical PEA. Direct evidence of PEA-associated oxidative stress in corneal endothelium, however, has not yet been documented. Biochemical or pathological studies using a marker of oxidative stress are thus needed.

Achieving Safer PEA

Several million PEA procedures are performed around the world every year, and this intervention represents the most influential surgery for quality of vision in senior citizens So far, factors associated with damage to the corneal endothelium during PEA have been discussed empirically rather than with a scientific stance. As discussed in this review, scientific analysis such as oxidative stress evaluation has just started to be used. Investigations with more substantial approaches should be continued.

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