

# To analyze the factors and intervention measures of corneal endothelial cell injury in patients with age-related cataract during phacoemulsification

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**Abstract** Age-related cataract (ARC) is the most common type of cataract, which is more common in middle-aged and elderly people over 50 years old. With the aging of the global population, the incidence of ARC and the number of patients are rising, becoming the world's first blinding eye disease. Its pathogenesis is related to nutrition, metabolism, environment, genetics and other factors, which is the result of the combined action of various factors in vivo and in vitro. At present, phacoemulsification (PEA) combined with intraocular lens implantation is an important method for the treatment of ARC. Compared with small incision extracapsular extraction, PEA has the advantages of small incision, less damage to intraocular tissue, good recovery of visual function, and higher safety. However, with the wide application of PEA in clinical practice, how to reduce the loss of corneal endothelial cells has become the focus of many doctors. This paper reviews the factors analysis and intervention measures of corneal endothelial cell injury in ARC patients undergoing PEA.

**Keywords:** Age-related cataract, Phacoemulsification surgery, Corneal endothelial cells

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## Introduction

Age-related cataract (ARC), the most common type of cataract, predominantly affects individuals over 50 years old. Its pathogenesis involves nutritional, metabolic, environmental, and genetic factors. Advances in molecular biology have revealed associations with oxidative lens damage, apoptosis, and crystallin protein denaturation [1]. Phacoemulsification aspiration (PEA) has replaced traditional extracapsular cataract extraction due to its small incision, minimal intraocular trauma, and rapid visual recovery [2]. However, corneal endothelial cell (CEC) injury remains a serious complication [3], influenced by surgical incision, ultrasonic energy control, and operative techniques. This review analyzes these factors and protective measures.

## 1. Factors Contributing to Corneal Endothelial Cell Injury

### 1.1 Anterior Chamber Depth

Adequate anterior chamber depth (ACD) is critical for safe phacoemulsification. Shallow ACD (<2.8 mm) restricts instrument maneuverability, increasing direct contact between the phaco tip/chopper and corneal endothelium [4]. Heat accumulation in confined spaces exacerbates thermal damage [4, 5]. Patients with shallow ACD and high LOCS II-grade cataracts exhibit higher postoperative CEC loss rates [6]. Conversely, deeper ACD ( $\geq 2.8$  mm) reduces ultrasonic energy exposure and CEC loss [7, 8].

### 1.2 Anterior Chamber Stability

Intraoperative chamber instability elevates complication

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risks. Inadequate irrigation flow (due to low bottle height or tubing compression) causes anterior chamber collapse [9]. Excessive irrigation pressure or prolonged surgery (>45 minutes) increases endothelial apoptosis [10]. Turbulent fluid dynamics from phaco tip vibrations may induce surge, risking posterior capsule rupture [11–13]. Balanced infusion-aspiration and surge-control systems are essential.

### *1.3 Viscoelastic Agents*

During the phacoemulsification surgery, the superpapilla continuously releases energy and heat, and may even directly contact the corneal endothelium. Injecting viscoelastic agents into the anterior chamber can well fill the anterior chamber and form a stable surgical space. Due to the differences in their composition and rheological properties (such as viscosity, pseudoplasticity, and coating ability), different types of viscoelastic agents have varying protective effects on intraoperative irrigation fluid scouring, mechanical damage, ultrasonic energy, and lens debris. According to the two prominent physical properties of viscoelastic agents, namely "zero shear rate viscosity" and "cohesion or dispersion", viscoelastic agents can be classified into two major categories: dispersive viscoelastic agents and cohesive viscoelastic agents [14]. Diffuse viscoelastic agents (such as those containing hyaluronic acid or hydroxypropyl methylcellulose) have low viscosity and strong tissue adhesion. They can better cover the surface of the corneal endothelium, form a physical barrier, and reduce the direct damage to the endothelium caused by ultrasound energy and lens fragments [15, 16]. Cohesive viscoelastic agents (such as high-concentration hyaluronic acid preparations) can better maintain the stability of the anterior chamber space due to their high cohesion. However, during the phacoemulsification process, they

may lose their barrier effect due to rapid aspiration, increasing the risk of corneal endothelial cells being exposed to mechanical or ultrasonic damage [16]. Studies have pointed out that when cohesive viscoelastic agents are used alone, the decrease in corneal endothelial cell density 3 days after cataract surgery is greater than that of the dispersed type [17]. At present, there are mainly 12 popular viscoelastic types in the US market, including 7 sodium hyaluronate derivatives, 22% hydroxypropyl methylcellulose derivatives, and 3 combinations of chondroitin sulfate and sodium hyaluronate. However, none of the materials covers all the required physical properties [18]. Surgeons must select the appropriate viscoelastic agent based on the surgical conditions and the needs of the patients. Studies have found that the use of the compound viscoelastic agent (chondroitin sulfate - hyaluronic acid complex) during the operation has a better corneal endothelial protective effect compared with sodium hyaluronate alone. The loss rate of corneal endothelial cells is lower 3 months after the operation, and the change in central corneal thickness after the operation is smaller [19, 20].

### *1.4 Incision Location and Size*

The correct selection of the surgical incision location plays an important role in protecting corneal endothelial cells. The upper approach incision may cause more turbulence due to gravity, increasing the exposure of endothelial cells to mechanical stress [21]. The temporal incision is more in line with the surgeon's operating habits. The operating Angle is more in line with the natural movement trajectory of the phacoemulsification instrument. Moreover, the corneal incision is far from the center of the cornea, which can reduce the direct contact of the instrument with the endothelial cells in the central cornea [21]. Secondly, the

size of the surgical incision can directly affect the stability of the fluid flow during the operation. Larger surgical incisions can lead to rapid loss of perfusion fluid and increase anterior chamber instability. The smaller damaged incision can reduce the fluid dynamic disturbance in the anterior chamber during the operation, lower the direct impact of mechanical damage and ultrasound energy on the corneal endothelium, and thereby reduce the loss of endothelial cells [22]. Studies have shown that smaller incisions (such as 2.2-2.8 mm) can reduce the turbulence and fluctuation of the anterior chamber fluid during surgery, thereby reducing mechanical damage to the corneal endothelium [5]. However, some scholars believe that overly small incisions may lead to restricted operation of surgical instruments, increase the usage time of ultrasound energy, and indirectly aggravate endothelial cell injury [23].

### *1.5 Nucleus Fragmentation Techniques*

In phacoemulsification for cataract, an effective nuclear splitting method can reduce the use of intraoperative ultrasound energy and lower the postoperative loss rate of corneal endothelial cells [24]. Direct-chop refers to the Direct splitting of the lens nucleus without the need for pre-grooving, reducing the usage time of ultrasonic energy and the actual superemulsion time, thereby reducing the damage to endothelial cells caused by thermal effects and mechanical stress. Aprajita Sinha et al. found by comparing three different phacoemulsification techniques that the direct nucleation technique uses less ultrasonic energy compared with the traditional Stop-and-chop technique [24]. pre-chopping nucleofragmentation is a technique that pre-splits the lens nucleus into smaller fragments through mechanical segmentation. Its core feature is that it completely does not use phaco energy, thereby reducing the

loss of corneal endothelial cells [25]. Studies have found that in grade three nuclear cataracts, the loss rate of corneal endothelial cell density after pre-splitting technology is only 5.8%, while it is 15.2% in the traditional phacoemulsification group [26]. The X-shaped nuclear splitting method (cross nuclear splitting) is developed on the basis of traditional nuclear splitting techniques (such as interception nuclear splitting and pre-splitting techniques). Its characteristic is that the nucleus is divided into four quadrants (similar to the shape of the letter X) through two vertical cross splits. Its advantage lies in that the fragments formed by cross nuclear splitting are smaller and more regular in volume, reducing the disorderly rotation of nuclear fragments within the capsule. Thereby reducing the use of ultrasound energy and lowering the risk of posterior capsule rupture [27]. With the advancement of science and technology, future development directions include the research and development of intelligent nuclear splitting devices (such as laser-assisted pre-splitting) and the selection of personalized nuclear splitting methods, further reducing the risk of surgical complications. During the clinical application process, surgeons need to flexibly select the nuclear splitting strategy in combination with nuclear hardness, capsule state and the surgeon's experience.

### *1.6 Ultrasonic Energy Control*

During the phacoemulsification process, the phacoemulsifier generates high-frequency ultrasonic waves (typically 40-80 kHz) through piezoelectric crystals inside the handle, converting electrical energy into mechanical vibration energy, which is then transmitted to the lens core via the metal phacoemulsification needle [28]. During vibration, the metal emulsion needle exerts a mechanical effect on the lens core, and microbubbles are formed in

front of the emulsion needle at the same time, creating cavitation and fragmentation effects. During this process, liquid and particulate matter continuously form liquid waves, and finally, a thermal effect is also brought about [29]. Therefore, the reasonable setting of phacoemulsification energy (continuous, pulsed, and burst modes) can prevent excessive heat generation and reduce thermal damage to corneal endothelial cells. Cumulative Dissipated Energy (CDE) is a key indicator reflecting the total amount of ultrasound energy used. The higher the CDE, the greater the total amount of ultrasound energy released during the operation, and the greater the risk of mechanical damage to corneal endothelial cells due to cavitation effect or thermal effect [29, 30]. Some literature indicates that for every 1% second increase in CDE, the postoperative corneal endothelial cell density may decrease by approximately 0.5% to 1% [31]. Reducing CDE is the core strategy for reducing corneal endothelial cell damage. Optimizing nuclear processing techniques (such as splitting nuclei instead of block excision) and fluid control systems, choosing appropriate viscoelastic agents for protection and personalized energy parameter Settings can protect corneal endothelial function to the greatest extent.

### 1.7 Core hardness of the lens

The higher the hardness of the lens nucleus is, the longer the phacoemulsification time and the total operation time will be required. This may increase the repeated movement of instruments in the anterior chamber and the fluctuation of perfusion pressure, and also increase the contact probability of endothelial cells with the ultrasonic needle or lens fragments, causing physical abrasions [32]. Kazuo Ichikawa et al. 's study on 342 eyes with different nuclear hardness (grades II-IV) found that the ultrasound energy parameters (such as effective ultrasound time and average

power) in the hard nucleus group (grade IV) were significantly higher than those in the soft nucleus group, resulting in a higher postoperative loss rate of corneal endothelial cells. Hardcore surgery not only leads to a reduction in the number of cells, but also causes morphological abnormalities. Francesco Saverio Sorrentino monitored 50 patients with nuclear hardness grade IV after phacoemulsification and found that the mean endothelial cell area (AVG) increased by 16% and the proportion of hexagonal cells (HEX) decreased by 12%, suggesting compensatory cell dilation and structural disorder [33]. The nuclear hardness was accurately evaluated by Emery nuclear hardness grading or LOCS III system before the operation. For patients with sclerotinia, giving priority to femtosecond laser pre-splitting of the nucleus, low-temperature perfusion fluid and low-flow mode can effectively reduce the damage to corneal endothelial cells.

## 2. Protective and Therapeutic Measures

### 2.1 Intraoperative Protection

Corneal endothelial cell injury after phacoemulsification for cataract is a common phenomenon, usually manifested as decreased corneal endothelial cell density, abnormal cell morphology, intercellular junction rupture and compensatory volume increase. Bjorn Lundberg followed up 20 patients after phacoemulsification for cataract for 7 years and found that the corneal endothelial cell density of the patients was consistently lower than the preoperative level, suggesting that endothelial cell damage was irreversible [34]. Postoperative impairment of corneal endothelial cell function can lead to a decline in endothelial cell pump function, imbalance in water metabolism, and cause corneal stromal edema. Severe endothelial injury (endothelial cell density < 1000 cells/mm<sup>2</sup>) may lead to

persistent corneal edema and progress to bullous keratopathy [35]. Abnormal morphology of corneal endothelial cells (such as a decrease in the proportion of hexagonal cells) and corneal edema can lead to opacity of refractive media and affect postoperative visual recovery [30].

Before the operation, a comprehensive assessment of the patient should be conducted. It is necessary to inquire in detail whether there is a history of systemic diseases (such as diabetes, hyperuricemia, etc.), ocular history (such as glaucoma, Fuchs corneal endothelial dystrophy, uveitis, etc.), and ocular surgery history (such as anti-glaucoma surgery, vitrectomy, etc.) [36]. Preoperatively, the morphology of the lens can be evaluated by ultrasound biological microscopy (UBM) or optical coherence tomography (OCT), and the optimal emulsification strategy (such as nuclear splitting depth and energy gradient) can be selected [37]. During the operation, it is necessary to pay attention to controlling the size of the surgical incision. A larger surgical incision is prone to cause the loss of perfusion fluid and increase the instability of the anterior chamber. Too small incisions will limit the operation of ultrasound equipment, increase the usage time of ultrasound energy, and the friction between the equipment and the edge of the incision will also increase the damage to corneal endothelial cells. For high-risk populations (such as diabetes, Fuchs endothelial dystrophy, and after penetrating corneal transplantation), low-temperature, low-perfusion techniques (such as torsional ultrasound) can be adopted, with priority given to low-energy techniques. The use of cryogenic perfusion fluid (4°C) during the operation can reduce metabolic activity, decrease the expression of endothelial cell apoptosis-related proteins (such as Bax, Caspase-3), and simultaneously inhibit the

release of inflammatory factors [38]. Viscoelastic agents can buffer mechanical shock and maintain anterior chamber stability. Compared with sodium hyaluronate alone, the compound viscoelastic agent has a better corneal endothelial protective effect. For hard-core or high-risk cases, pre-splitting technology or femtosecond laser-assisted cataract surgery can be adopted. The use of femtosecond laser to pre-cut the lens nucleus reduces the demand for ultrasound energy, resulting in less loss of corneal endothelial cells and postoperative inflammatory responses [39]. With the continuous advancement of science and technology, new assistive devices or more optimized phacoemulsification systems are gradually being put into clinical use. Seonghwan Kim used corneal contact protectors (such as senofilcon A mechanical protectors) on the rabbit eye model, which could physically isolate the direct damage of ultrasonic energy to the endothelium during phacoemulsification [40].

## *2.2 Postoperative intervention measures for corneal endothelial cell injury*

For patients with impaired corneal endothelial cell function after phacoemulsification for cataract, the adoption of certain intervention measures after the operation can reduce the impact of corneal endothelial cell injury. Studies have found that the local use of Rho kinase inhibitor (such as Ripasudil) eye drops after cataract surgery helps maintain the integrity of corneal endothelial cells, reduces endothelial cell apoptosis, and promotes cell migration and repair [41]. The release of oxidative stress factors and inflammatory factors is an important factor for corneal endothelial cell injury after phacoemulsification. After the operation, non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid eye drops are used in a standardized manner to control the inflammatory response and avoid

further damage to endothelial cells by inflammatory factors. Patients with corneal edema can effectively alleviate corneal edema by using hypertonic agents such as 5% sodium chloride (NaCl) or 10% mannitol locally. Hypertonic agents promote corneal dehydration and improve transparency through osmotic pressure [42]. Ocular nebulization therapy with glucocorticoids mixed with oxygen (oxygen supply through goggles) can accelerate the resolution of edema. For severe or persistent corneal edema (such as endothelial cell density lower than the critical value), posterior elastic layer endothelial keratoplasty is an effective treatment option, especially suitable for severe corneal endothelial decompensation that cannot be restored after cataract surgery, especially for patients with Fuchs corneal endothelial dystrophy [43].

### 3. Summary

To sum up, corneal endothelial cell injury after phacoemulsification in patients with age-related cataract is the result of the combined effect of multiple factors. Due to the individual differences among patients and the variations in specific intraoperative conditions, phacoemulsification does not have a fixed and unchanging pattern. Surgeons need to take into account the patient's own factors, preoperative corneal condition, and the hardness grade of the lens core, and conduct comprehensive management through preoperative risk assessment, intraoperative technical optimization (such as FLACS, low-energy mode), and postoperative monitoring. Corneal endothelial cell injury is irreversible. However, with the continuous advancement of medical technology, cell therapy techniques (such as in vitro expanded HCECs, corneal endothelial stem cells and in vivo regeneration technology) are gradually being applied in clinical practice. The

application of new ultrasound equipment, operating instruments and femtosecond laser-assisted technology can effectively reduce the damage of corneal endothelial cells during the operation. In the future, individualized surgical parameter prediction models need to be established to promote the development of precision medicine.

### Conflict of Interests

None.

### Conflict of funding statement

None.

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