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Hypothermic Perfusion Effects on Corneal Endothelial after Phacoemulsification

Afia Nuzila Fadhlina[1]
[1]Fakultas Kedokteran dan Kesehatan, Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia

Corresponding Author: afia.nuzila@its.ac.id

Abstract — Phacoemulsification is the most common cataract surgery performed as an efficient and safe cataract surgery technique compared to other cataract surgery techniques. Indeed, phacoemulsification uses high-intensity ultrasound energy to fragment and emulsify the lens, which can cause trauma to the cornea, especially the endothelial layer. Surgical trauma to the CEC can have severe complications on functional outcomes such as decompensation, leading to corneal edema with visual impairment and irreversible bullous keratopathy. The application of hypothermia is known to have a protective effect on various cells and tissues, so hypothermia perfusion is considered to protect the corneal endothelium during phacoemulsification procedures. Hypothermic perfusion suppresses ROS production, so can be used to reduce corneal endothelial cell damage during phacoemulsification procedures.

Keywords — *phacoemulsification; hypothermic perfusion; corneal endothelial cell*

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INTRODUCTION

Cataract is one of the leading causes of blindness around the world and primary ophthalmological public health issues in both industrialized and developing nations. It can drastically lower patient's quality of life [1,2]. Studies reported that 36 million people are blind globally, with cataracts accounting for more than 12 million of those cases [3]. Cataracts are nearly always treatable and cataract surgery is the only proven treatment for cataracts [1,4]. Cataract surgery has many improvements, including new techniques, devices, and viscoelastic uses. Nowadays, phacoemulsification is the most common cataract surgery performed as an efficient and safe cataract surgery technique compared to other cataract surgery techniques [5,6]. Phacoemulsification can be performed at any stage of cataract development [7]. Indeed, phacoemulsification uses high-intensity ultrasound energy to fragment and emulsify the lens, which can cause trauma to the cornea, especially the endothelial layer [8]. The assessment of risk factors for corneal endothelial cells (CEC) preoperative, intraoperative, and postoperative are important information for the cataract surgeon. Preoperative factors include advanced age and hard nucleus density [9]. Intraoperative factors known to cause CEC damage include ultrasonic power fluctuation, the jackhammering effect of phaco, implosion of air bubbles in the anterior chamber, collision of lens nucleus fragments, irrigation pressure, temperature rise, and free radicals production [5,7,8]. Surgical trauma to the CEC can have severe complications such as decompensation, leading to corneal edema with visual impairment and irreversible bullous keratopathy [10,11].

CEC count decreases by 0.6% each year throughout life [5]. Park *et al.* reported a decrease in CEC of 5.2%-9.1% two months after phacoemulsification and continued to decline for up to a year [12]. Even with advanced modern techniques, phacoemulsification procedures can cause in 4.2-16.7% CEC loss [13]. Other studies report that the CEC loss approximately 8.0% and 16.7% after phacoemulsification procedures [14]. Some studies found that 16.67% CEC loss is associated with trauma during phacoemulsification, 4-15% CEC loss after phacoemulsification by experienced surgeons and 6.4% after the same procedure by senior residents [15]. Bullous keratopathy is a late complication of phacoemulsification and occurs in

approximately 1%-2% of patients after cataract surgery [11]. A national survey of bullous keratopathy in Japan showed that cataract surgery was the most common cause of penetrating keratoplasty (24.2%), and a recent study in United Kingdom reported that among the indications for endothelial keratoplasty, cataract surgery ranked second after Fuchs Endothelial Dystrophy [8,16].

Studies have shown that hypothermia is widely used in the medical field to protect organs or tissue from ischemia and hypoxia, such as to treat heart damage and brain damage [17]. Hypothermia also can be used in the ophthalmology field, for example preservation of corneal tissue in the eye bank, protect the retina from acute ischemic damage, and relief of eye symptoms. Hypothermic techniques have important applications in ophthalmic surgery, such as vitrectomy surgery, cryotherapy for end-stage glaucoma, corneal refractive surgery, and adjunctive therapy to reduce CEC damage due to phacoemulsification [11,18]. Many studies reported that hypothermia has a protective effect on CEC during phacoemulsification surgery.

Corneal Endothelial Cells

The cornea is an important part of the optical system. The cornea is an avascular and transparent, dome-shaped structure that covers one-sixth of the surface of the eyeball and plays a role in protecting the structure within the intraocular. The human cornea consists of 5 layers, the epithelium, the Bowman's layer, the stroma, the Descemet's membrane, and the endothelial cells layer [19-21].

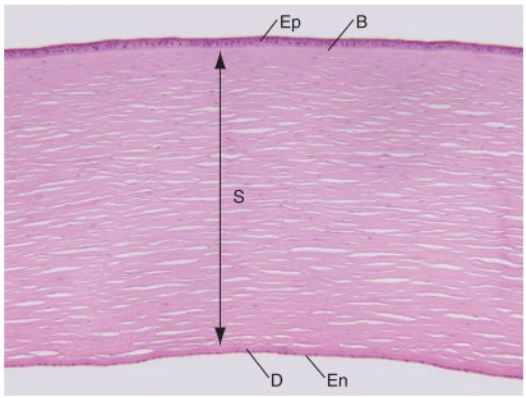

Fig. 1. Histology of the Corneal Layers [20]

The corneal endothelial cells layer is a single layer with a thickness of 4-6 μm and a surface area of approximately 130 mm^2. The corneal endothelial is derived from the neural crest, and neuroectodermal in origin. The endothelial development occurs around the fourth week of embryonic endometrial development and endothelial progenitor cells are produced by mesenchymal cells of the mesoderm. During corneal formation, cell migration occurs from the nerve endings which then produce a hexagonal shape in the endothelial [19,20].

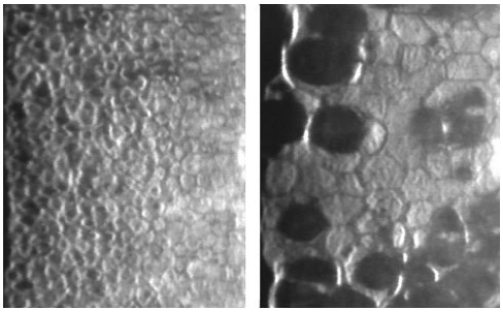

Fig. 2. Specular microscopy of the corneal endothelial cells [20]

The primary function of the CEC is to maintain stromal dehydration, which maximizes the quality of light entering the cornea. This gradient of hydration and transport protein is maintained by endothelial cell tight junctions as well as pump activity linked to bicarbonate-dependent Mg^{2+}-ATPase and NA^{+}/K^{+}-ATPase [22]. Na+/K+ATPase pump removes water and ions from the stroma into aqueous humor through osmosis, which helps maintain corneal thickness and transparency. It was found that approximately three million Na+/K+ATPase reside in the lateral membrane of CEC [19,22].

CEC play an important role because they are responsible for regulating of fluid and soluble flow through a barrier function and a pump-leak mechanism between the aqueous humor and the layers of the corneal stroma [19,21,22]. The barrier function of the CEC depends on a sufficient number of CEC to cover the posterior surface of the cornea and having integrity of CEC tight junctions, which are present in the intercellular spaces between CEC. This barrier prevents the bulk flow of fluid from aqueous humor to the corneal stroma, but does allow moderate diffusion of nutrients, water, and other metabolites to cross into the stroma through the 2-4 nm wide extracellular spaces [23]. In turn, endothelial failure is characterized by corneal edema, which is a net inflow of aqueous fluid into the cornea at a higher rate than the amount pumped out during a given period time [22].

The density of central CEC at birth is approximately 5000 cells/mm^2 and changes from the second to the eighth decade of life. CEC density decreases to around 3500 cells/mm^2 at the age of 5 years and to 3000 cells/mm^2 at the age of 14-20 years (20). The decrease in central CEC density occurs around 0.3-0.6% per year, so that the cell density in late adulthood is around 2500 cells/mm^2 [19,24]. Differences in race, geography, and environmental factors can influence the rate of decrease in endothelial cell density [20]. At the same time, the cell hexagonality ratio also decreased from 75%-80% to 60%. Corneal dysfunction is possible in a number of cells less than 500/mm^2 [21,23].

CEC do not demonstrate mitosis in vivo. Replacement of CEC damage occurs not through cell division but migration. Migration is the process of replacing endothelial cell function from damage and cell death [22]. A focal loss of CEC centrally, therefore results in centripetal migration of adjacent CEC, subsequent formation of tight junctions and restoration of pump function, causing gradual remodeling of CEC structure from enlarged, irregularly shaped CEC to a more hexagonal pattern. [19]. Cell density is a good indicator of functionality, which can be supplemented by other parameters such as size variation (polymegatism) and cell morphology (pleomorphism) [20,21,23]. A study of endothelial cell density in the central, peripheral, and paracentral regions of normal eyes and eye bank corneas showed that the endothelial cell density in the peripheral and paracentral zones was 10% and 5% greater than in the central cornea [22]. The current study reported that CEC undergo proliferation at a very low rate to replace dead cells, and this process mainly occurs in the peripheral area of the cornea adjacent to the Schwalbe line [19,22].

Phacoemulsification Effect on Corneal Endothelial Cells

Cataract is the opacity of the crystalline lens and one of the most common ocular pathologies, particularly age-related cataracts [7]. Treatment of cataracts consists of the surgical removal of the opaque crystalline lens and replacement by an intraocular lens. Cataract surgery should be a painless, quick, safety, and highly effective procedure [4,7]. Phacoemulsification is currently one of the safest and most effective procedures used at any stage of cataract development [25,26]. The main advantages of this technique is small incision, which effectively shortens the recovery period. Phacoemulsification uses high-intensity ultrasound energy for the fragmentation and emulsification of the cataractous lens [8,16,25]. In order to emulsify the lens nucleus, the phacoemulsification probe vibrates the metal tip of the phacoemulsification needle by converting electrical energy into mechanical energy [27].

Phacoemulsification is a common closed-eye surgery in which the crystalline lens is completely emulsified and aspirated in the anterior chamber, damage may occur to the lens's anterior or posterior structures [25]. Trauma to the corneal endothelial and rupture of the posterior capsule of the lens are the most common complications during phacoemulsification [27]. Factors leading to CEC damage during phacoemulsification include the jackhammering effect of phaco cutting, implosions of air bubbles, a localized rise in temperature, fluctuation of ultrasonic power, irrigating pressure, the elevated temperature of the aqueous humor, collision between lens nuclear fragments and the endothelial, fluid turbulence, excessive ultrasonic energy, and production of free radicals [5,16,26]. CEC damage is mediated by prostaglandins which lead to significant inflammation and corneal swelling and increased thickness [5].

Trauma of the CEC in the phacoemulsification procedure caused by mechanical trauma and thermal trauma. Mechanical trauma is caused by high-intensity ultrasonic wave oscillations that occur in the aqueous humor, which induces acoustic cavitation [28]. Acoustic cavitation is a phenomenon of the formation of gas bubbles due to evaporation that occurs under negative pressure. It emits the gas and then collapses under positive pressure due to ultrasonic pressure. When the gas bubbles collapse, it triggers a shock wave that induces a local pressure increase of >600 atmospheres and a temperature increase of >5000 K. The energy formed then extends to the surrounding air molecules, causing direct disintegration of the air molecules. This reaction is called a sonolysis reaction, produces hydroxyl radicals (OH^-), which are free radicals. The Fenton reaction produces hydroxyl radicals in physiological settings. However, the sonolysis reaction produces hydroxyl radicals directly, by passing the Fenton reaction. CEC damage is the outcome of oxidative stress on the corneal endothelial brought on by the production hydroxyl radicals [16,25].

Thermal trauma is caused by the generation of heat from both the frequency and stroke length of the ultrasonic power which causes damage to the corneal endothelial [29]. The phacoemulsification process is linked to two heat-generating sources. First, heat produced from the process of converting ultrasonic energy into mechanical energy. Most phacoemulsification machines have a maximum power level of 40 watts (100% power), but more than 10% of the ultrasonic energy (4 watts) lost as unused heat. Second, heat generation due to vibration of the phacoemulsification probe tip which is in direct contact with the probe's sleeve [27]. Suzuki *et al.* reported that setting US power over 50% causes temperature rises that can exceed 40^0C. This show that continuous mode with high US power should not be used even for a few seconds [30]. From the Finite Element Method (FEM) it is known that the rate of heat generation in the phacotip is 0.0004 cal/s/mm^2. The maximum temperature that the corneal endothelial can accept is between 41.57-52.67^{0}C for 60 seconds. Other studies evaluated intraoperative factors that increase the risk of thermal trauma during phacoemulsification. The temperature differences that occur are influenced by many factors, namely the distance from the probe tip, the duration of phacoemulsification, the use of irrigation fluid during phacoemulsification, the vacuum setting which affects the aspiration flow, and continuous irrigation. Factors causing thermal trauma must be controlled to reduce damage to surrounding tissues, especially the endothelial [26,27].

Thermal trauma on the cornea causes different effects on each layer of the cornea. Thermal trauma to the epithelium induces a healing process with the proliferation and mitotic activity of epithelial cells, so that it does not cause long-term complications. Thermal trauma to the stroma would affect the collagen fibers, where the regularity of the arrangement of the collagen fibers plays a role in the transparency of the cornea, even though the structure is thicker. Thermal trauma on keratocytes is that keratocytes become motile and undergo mitosis which develop actin cytoskeletal fibers. Activated cells then produce a fibrotic extracellular matrix with proteoglycans and altered glycosaminoglycans that contribute to scar tissue opacification [27,31].

Trauma of the CEC due to phacoemulsification is clinically and functionally more significant than damage to other layers of the cornea [27,31]. Loss of endothelial function due to damage to endothelial cells causes increased corneal thickness

and reduced corneal transparency as well as increased stromal hydration due to impaired pump function. Central corneal thickness increased significantly on the first postoperative day, followed by a gradual decrease in central corneal thickness but did not reach preoperative thickness values [9,32].

CEC trauma can be identified by evaluating cell density. The decrease in endothelial cell density after surgery will continue until the third month after surgery, but the decrease in density occurs greater on the first day after surgery [5,33]. Kim *et al.* reported a significant decrease in endothelial cell density and an increase in endothelial cell area (ECA) in the paracentral temporal area, related to injury to the corneal incision due to the movement of surgical instruments in and out of the incision [32].

Exposure to high-intensity ultrasonic energy during phacoemulsification produces heat that causes damage to endothelial cells [34]. Excessive heat exposure increases aerobic metabolic activity in the mitochondria of endothelial cells, resulting in mitochondrial dysfunction [35]. Mitochondrial dysfunction causes disruption in the respiratory chain so that it cannot control ROS production. Excessive ROS accumulation in the cornea will affect signal transduction, cell proliferation, and cause cell death [36]. Xanthine oxidase is an enzyme that produces ROS, found in the epithelium and endothelium of the human cornea. The cornea is equipped with an antioxidant defense system consisting of some molecules that can ward off free radicals [36,37]. An imbalance between the production of free radicals and antioxidants triggers oxidative stress. Oxidative stress then induces reaction pathways in the resulting CEC apoptosis [37].

In the intrinsic pathway, apoptosis that occurs in mitochondria is regulated by the Bcl-2 protein. The presence of oxidative stress will reduce the activity of the Bcl-2 protein, then stimulate the release of cytochrome C from mitochondria and activate the destruction pathway through the caspase cascade. The release of cytochrome C induces pro-caspase 9 to become active caspase 9. Caspase 9 then induces pro-caspase to become caspase 3 which triggers apoptosis and cell death [14,38].

CEC has limited regeneration ability. If damage occurs, the remaining CEC will compensate by changing the shape and size of the cells [32]. Migration and enlargement of cell size is carried out to cover surrounding cells that are damaged. An increase in cell size is called polymegatism, while a change in cells from hexagonal to polygonal shape is called pleomorphism [39]. Changes in CEC morphology can be evaluated using a specular microscope by looking at the increase in the Coefficient of Variation (CV) and hexagonality of the CEC. After phacoemulsification, the maximum increase in CV occurs in the early postoperative period, and the maximum decrease in the percentage of CEC hexagonality occurs on the first postoperative day [38,40].

Hypothermic Therapy in The Ophthalmology

The application of hypothermic therapy has been widely used in the medical field, for example stroke, brain trauma, and neonatal ischemic-hypoxic encephalopathy. Hypothermia therapy is potentially important in reducing metabolism so as to prolong tissue survival [17,18]. Many studies in the field of ophthalmology apply hypothermia therapy, both in trauma and postoperative cases. Rey-Funes *et al*. reported that hypothermia therapy in mice can prevent retinal damage caused by optic nerve trauma [41]. Other studies suggest that hypothermia can protect the retina from acute ischemic trauma after vitrectomy surgery, for preserving corneal and sclera tissue in eye banks, cryotherapy in intracapsular cataract extraction surgery, and cyclocryotherapy in glaucoma surgery [17]. Hypothermia can reduce the volume of intraocular bleeding, reduce fibrin production and postoperative inflammation. The use of cold patches on the eyes after photorefractive keratectomy is effective in reducing pain and inflammation, thereby reducing the use of pain relievers [18,41].

Hypothermia's protective impact during ocular anterior segment surgery is influenced by a number of factors. Hypothermia can stimulate conditions that are effective against ischemic trauma or hypoxia because a decrease in temperature

causes a decrease in the metabolic rate of the tissue cells involved. Exposure to a hypothermic environment will affect the expression of several proteins or cytokines that regulate metabolism [17]. Studies reported that hypothermia can affect cellular metabolism in the mitochondria. Mitochondria are the site of oxidative metabolism and synthesize ATP to produce the energy needed by cells. Normal mitochondrial function requires the activity of various enzymes, but these enzyme activities will decrease under hypothermic conditions. Hypothermia can maintain ATP levels, slow cellular processes, and reduce metabolic demands [18].

Hypothermic Perfusion Mechanism on Phacoemulsification

Many methods have been used to minimize complications caused by thermal trauma after phacoemulsification, namely the use of divide and conquer (D&C) and chop techniques to clean the nucleus, shorten the duration of surgery and reduce the power used, use viscoelastic, and irrigation fluid during phacoemulsification [42]. Thermal trauma can lead to hyperthermia, then cause mitochondrial dysfunction and an increase in ROS. This is typically worsened by decreased SOD activity. SODs are an endogenous antioxidant that plays a vital role in preventing disorders caused by oxidative stress. SOD plays a role in oxidative signaling as the first response to increased reactive oxygen species (ROS) and functions as an anti-inflammatory [11].

CEC damage from thermal trauma can be prevented by intraocular perfusion, which prevents phaco tip friction with the corneal endothelial and cooling the anterior chamber [17]. Initially, Ringer's Lactate (RL) was used as a substitute for aqueous humor. The ion composition of RL is different from that of aqueous humor, causing the complication rate after phacoemulsification to remain high [43]. Currently, intraocular perfusion fluid is being replaced with Balanced Salt Solution (BSS), which has an ionic composition similar to aqueous to minimize postoperative complications. However, CEC damage after phacoemulsification is still found [11]. The rate of intraocular perfusion during surgery must also be considered [44]. Generally, intraocular perfusion is given at a rate of 20-30 mL/minute. Intraocular perfusion must be carried out continuously during the phacoemulsification process to prevent heat buildup in the phacotip. Apart from reducing heat due to phacoemulsification, intraocular perfusion also functions to form anterior chamber, thereby preventing friction between the phacotip and the endothelial layer [27,28]. Hypothermia is shown to inhibit hyperthermia. It is also inhibit the decrease in SOD, thus potentially reducing ROS accumulation, then lessening oxidative stress, preserving mitochondrial function, and ultimately reducing apoptosis and endothelial cell loss.

BSS perfusion at room temperature can reduce post-phacoemulsification complications such as inflammation of the BMD, corneal edema, and endothelial damage [45]. However, the demand for optimal surgical results and maximum postoperative visual acuity requires additional methods during phacoemulsification. One way is by administering hypothermic perfusion fluid during phacoemulsification [30]. The application of hypothermia is known to have a protective effect on various cells and tissues, so hypothermic perfusion is considered to protect the corneal endothelium during cataract extraction procedures, especially phacoemulsification [29,30,46]. The heat energy generated during phacoemulsification needs to be cooled by the irrigation fluid around the phaco tip [17,29,45]. If perfusion with a hypothermic solution is performed, the temperature within the anterior chamber quickly decreases to the level of the irrigating solution [44]. Reduced or stopped fluid flow will cause the phacotip's thermal energy to come into direct contact with the corneal layers, particularly the endothelial [27,28].

Several studies have determined the effectiveness of providing hypothermic intraocular perfusion during phacoemulsification procedures. Joussen *et al*. evaluated the effect of irrigation temperature on corneal function. The corneal temperature is below normal temperature, and progressively decreases from the endothelial layer to the outer surface. The central corneal temperature is around 30.7^0C–35.0^0C. The cornea is an avascular tissue, so temperature is transmitted from the vascularized anterior uvea via aqueous humor. The optimal temperature for irrigation fluid during intraocular surgery is still

debated, but an increase in temperature due to obstruction of irrigation flow causes endothelial damage. Endothelial cell loss can reach 10% after increasing the aqueous temperature from 29.1^{0}C–33.4^{0}C. If hypothermic perfusion is used, the temperature in the anterior chamber will decrease rapidly following the temperature of the irrigation fluid. However, the BMD temperature will reach normal temperature after a few minutes of hypothermic perfusion being stopped [44].

Zhang *et al.* compared the condition of the corneal endothelium after surgery using cold-temperature irrigation fluid (12^{0}C) and room temperature (25^{0}C). It was found that cryoirrigation during phacoemulsification can relieve postoperative corneal edema without side effects. Uthaisang *et al.* examined the use of BSS at temperatures of 8^{0}C, 25^{0}C, and 37^{0}C during phacoemulsification and found that BSS at low temperatures (8^{0}C) could reduce the loss of endothelial cells compared to normal temperatures (37^{0}C). At cold-temperature BSS there is almost no cell death, so it is recommended to use cooled perfusion fluid to prevent thermal damage during phacoemulsification [29,42].

Wan *et al.* studied the effect of administering hypothermic BSS (temperature 4^{0}C) in rabbits and patients during the phacoemulsification procedure and then evaluated the postoperative endothelial condition. Hypothermic perfusion at 4^{0}C is easy to perform and safe to use during phacoemulsification procedures. Hypothermia can protect the corneal endothelium and reduce corneal edema in the early postoperative stages. Corneal edema decreased significantly on the first postoperative day compared to the 24^{0}C BSS group. The decrease in endothelial cell density was milder in the 4^{0}C BSS group. Histological examination of experimental animals exposed to phacoemulsification for 20 seconds showed that the corneal stromal fibers were more regular and the CCT was thinner in the hypothermia perfusion group compared to the room temperature group. The inflammatory reaction in postoperative BMD was milder in the hypothermic perfusion group compared with the room temperature perfusion group [17].

Meduri *et al.* evaluated differences in the number of endothelial cells after phacoemulsification using BSS at room temperature (20^{0}C) and cold temperature (2.7^{0}C). In the first stage, we use an artificial eye model to evaluate temperature variations with different phacotype distances and conditions. This stage is to ensure there is no potential risk to the patient. In the second stage, evaluating the effect of temperature differences during phacoemulsification performed on cataract patients. The use of hypothermic perfusion at 2.7^{0}C during phacoemulsification can reduce corneal endothelial cell damage by 50% compared to perfusion at 20^{0}C. This proves that the use of irrigation fluid at room temperature can still cause damage to the corneal endothelium [10].

CONCLUSION

In summary, it is important to prevent an increase in the anterior chamber temperature in order to achieve phacoemulsification that is safer for the corneal tissue, especially corneal endothelial cells (CEC). Hypothermic perfusion was a protective intervention to decrease corneal edema, endothelial lesions, and ocular anterior segmental inflammation caused by thermal damage. By using hypothermic perfusion, heat would be more effectively transferred from the area around the phaco tip, preventing the anterior chamber's temperature from rising too high above that of the irrigating solution. The hypothermic perfusion should provide some protection to the local tissue. Further research is needed to determine the effect of hypothermic perfusion on oxidative stress caused by phacoemulsification.

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