Etiology, pathogenesis, and management of acute intraocular lens opacification: a systematic review

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Abstract

● Millions of cataract surgeries with intraocular lens (IOL) implantation are performed worldwide. Although cataract surgery brings many benefits to the patients, the risk of various complications is still a concern. One of the infrequent adverse events but potentially affecting on patients’ visual acuity and contrast sensitivity is losing the transparency of IOL. IOL opacification may lead to IOL removal or exchange, which is unpleasant to both the patient and the surgeon. A significant proportion of explanted IOLs in an eye center in the United States was secondary to optic opacification or discoloration. Several reports of acute IOL clouding are available in the literature describing various etiologies of this phenomenon, however, the exact mechanism remained unclear in some cases. Herein, we aimed to review the causes and outcomes of intraoperative and early postoperative IOL opacification and provide a discussion on prevention from unnecessary IOL explantation in selected individuals.

 MATERIALS AND METHODS

The required information was gathered by reviewing various databases including PubMed/Medline, Google Scholar, and Cochrane library, up to September 2021. We systematically searched the literature using the following keywords: (“intraocular lens opacification” OR “intraocular lens clouding” OR “intraocular lens fogging” OR “intraocular lens discoloration”) AND (“acute” OR “transient” OR “early” OR “reversible” OR “temporary” OR “intraoperative”). No limitations on publication status or study design were imposed. The most relevant papers to IOL discoloration until one month after implantation were collected. The reference list of eligible articles was also explored for additional resources. Finally, all of the selected studies were reviewed.

RESULTS

Intraoperative Intraocular Lens Opacification

Intraoperative IOL opacification is defined as when the surgeon noticed the opacity during the operation. It is responsible for the majority
of acute IOL clouding cases in the literature. Different etiologic categories are discussed in the following sections.

**Temperature fluctuation** Reports of acute IOL clouding immediately after implantation of the IOL into the anterior chamber have been discussed, probably related to the storage condition. Transferring of the IOL from the outside temperature below freezing to the theater shortly before surgery is the common point of these studies. Sudden IOL implantation into the eye with a temperature of 37°C is the hypothesized mechanism of this kind of opacification. The haziness was described in the optic plate’s body without surface deposits and tended to be milky white. Both hydrophilic and hydrophobic acrylic IOLs were affected. The opacity was transient and lasted for less than 24h with spontaneous resolution\(^{[12]}\).

Adherence to the manufacture’s guidelines regarding the storage temperature of the IOL is recommended to avoid abrupt changes in the temperature and subsequent aforementioned intraoperative IOL clouding. The underlying mechanism is not well known. A previous case report of IOL clouding in an acrylic hydrophilic IOL suggested that the imbibitions of water following a rapid temperature fluctuation is the causal factor\(^{[13]}\). Zheng et al\(^{[14]}\) explained a possible cause in which increasing temperature may lead to microbubble production by releasing the air inside the IOL. This causes light refraction, which appears as IOL clouding\(^{[15-16]}\). They also hypothesized that the equilibrium in the air dissolution in the IOL and water would lead to resolution of the clouding after a while. Intraoperative opacification of a hydrophilic acrylic with hydrophobic surface IOL following storage in low temperature was described in a case report. The authors performed an in vitro experiment by placing a CT Spheris 504 IOL in a 37°C balanced salt solution (BSS) after staying at 4°C for 24h. The same IOL clouding occurred. They mentioned that consolidation of water vapor on the IOL surface deposits. The authors performed an in vitro experiment by placing a CT Spheris 504 IOL in a 37°C balanced salt solution (BSS) after staying at 4°C for 24h. The same IOL clouding occurred. They mentioned that consolidation of water vapor on the IOL surface deposits. The authors performed an in vitro experiment by placing a CT Spheris 504 IOL in a 37°C balanced salt solution (BSS) after staying at 4°C for 24h. The same IOL clouding occurred. They mentioned that consolidation of water vapor on the IOL surface deposits. The authors performed an in vitro experiment by placing a CT Spheris 504 IOL in a 37°C balanced salt solution (BSS) after staying at 4°C for 24h. The same IOL clouding occurred. 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IOL opacification

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (y), sex</th>
<th>Type of IOL</th>
<th>Features of discoloration</th>
<th>IOL storage condition</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyagi et al[25]</td>
<td>52, male</td>
<td>Hydrophilic acrylic IOL (PhysIOL)</td>
<td>Immediate clouding</td>
<td>Transfer at a temperature below 0°C, 10min before surgery</td>
<td>Clearing started at the periphery of the optic after 45min. The IOL was completely transparent 3h postoperatively.</td>
</tr>
<tr>
<td>Helvacı[29]</td>
<td>70, male; 45, female; 58, female</td>
<td>Acrylic hydrophobic IOL (Acira UD613, VSY, Istanbul, Turkey)</td>
<td>Immediate whitening</td>
<td>Storage at cold temperature immediately before use</td>
<td>All three IOLs were entirely cleared on the first postoperative day.</td>
</tr>
<tr>
<td>Gutierrez[27]</td>
<td>80, female</td>
<td>Hydrophilic acrylic IOL with a hydrophobic surface (CT Spheris 204; Carl Zeiss Meditec)</td>
<td>Immediate homogenous and complete opacification</td>
<td>Storage at a cold place for 12h</td>
<td>The IOL was completely cleared 24h postoperatively.</td>
</tr>
<tr>
<td>Sonbolestan and Abtahi[20]</td>
<td>61, male</td>
<td>Foldable, 13 mm, one-piece, square edge, and 25% hydrophilic acrylic IOL (Cristal®, Cristalens, France)</td>
<td>Immediate milky white discoloration that changed to dense white after seconds</td>
<td>Storage at temperature -10°C immediately before surgery</td>
<td>The IOL was completely cleared one day after surgery.</td>
</tr>
<tr>
<td>Liu et al[27]</td>
<td>79, female</td>
<td>Trifocal IOL (AT LISA tri 839MP, Carl Zeiss)</td>
<td>Immediate clouding</td>
<td>Transfer at a temperature of -3°C, 10min before surgery</td>
<td>After one hour, the IOL was removed and exchanged with another same type of IOL. The second IOL opacified too and replaced with a ZCB00 (Allergan) after 8min. The removed IOL became transparent after 5min in vitro.</td>
</tr>
<tr>
<td>Zhang et al[14]</td>
<td>25, male</td>
<td>Trifocal IOL (AT LISA tri 839MP, Carl Zeiss)</td>
<td>Immediate clouding</td>
<td>Transfer at a temperature of -7°C, 30min before surgery</td>
<td>The IOL turned completely transparent 3h postoperatively.</td>
</tr>
<tr>
<td>Danese et al[27]</td>
<td>83, female</td>
<td>Sutureless scleral fixed hydrophilic acrylic IOL</td>
<td>Milky white discoloration of central optic immediately after removing from its package before folding which changed to dense white opacity</td>
<td>Delivery at -1°C for 90min and storage at 35°C for 15min before implantation</td>
<td>The IOL turned transparent on the first postoperative day.</td>
</tr>
<tr>
<td>Lee and Han[28]</td>
<td>N/A</td>
<td>Hydrophilic IOL (Claré, Cristalens Industries)</td>
<td>Total IOL clouding during implantation</td>
<td>Storage at temperature -8°C and exposure to room temperature (26°C) 1h before implantation</td>
<td>The diameter of the opacity decreased to 3 mm after 4h and less than 1 mm after 8h. The IOL was cleared 24h after the operation.</td>
</tr>
<tr>
<td>McKibbin et al[14]</td>
<td>78, female</td>
<td>AcrySof lens (Model MA30BA)</td>
<td>Semi-opacity of the IOL optic after unfolding in the bag</td>
<td>Warming the lens in a heating cupboard at 47°C before folding</td>
<td>The IOL was exchanged with a rigid PMMA lens after 5min. The explanted IOL was placed dry at room temperature in its packaging and cleared spontaneously after 3h.</td>
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IOL: Intraocular lens; PMMA: Polymethyl methacrylate.

of single-piece hydrophobic acrylic IOLs immediately after injection into the eye (loaded with Viscoats and Healon GVs, respectively). IOLs were removed and analyzed. They did not find calcium on the surface of lenses and liquid chromatography/mass spectroscopy showed albumin and hemoglobin, which are typically found in aqueous. They hypothesized that crystallization and drying out of OVDs could occur during IOL loading in the cartridge. Various gross appearances could be seen based on the type of viscoelastic used[28]. Plastic exfoliations from the cartridge may result in intraoperative deposits between the IOL and posterior capsule when the hydrophilic acrylic lens is implanted without viscoelastic[29].

Early Postoperative Intraocular Lens Opacification We assessed cases of IOL clouding up to one month after surgery. Here the classifications are provided based on the presumed etiologies. Some of the mentioned underlying pathologies occurred before the IOL implantation but we put them in the postoperative category because no opacity was noted during the surgery. There are different explanations for it. First, elapsing of time is required for interactions to cause visible haziness. Second, there is a possibility of preexisting opacity, which is missed by the surgeon due to poor visualization through a surgical microscope.

Intraocular lens contamination, manufacturing defects, and changing hydrophilicity The manufacturing process, IOL design, and material are essential features for evaluating the causes of decreasing in IOL transparency. Surgeons and scrub nurses may miss the preexisting haziness of the IOL because of viewing through the surgical microscope with
lower magnification and higher illumination in comparison to postoperative slit-lamp examination\(^\text{[30]}\). The quality control of all production steps will help to avoid IOL opacification and additional surgery for IOL removal.

Opacification of the silicone optic of an Allergan Medical Optics SI118NB lens was noted seven days after surgery. A nucleus-shaped brown discoloration in the central area was attributed to a material defect and low molecular weight silicone fractions not cross-linked during the manufacturing process. Light scattering from water vapor that diffused into the silicone material in the anterior chamber caused a brown haze. This finding was stable in follow-up visits and did not affect the patient’s visual acuity\(^\text{[31]}\). Others stated that the interaction with some intracameral medications, inadequate filtering, or instability of silicone material could lead to discoloration of silicone IOLs\(^\text{[32]}\).

Hilgert et al\(^\text{[33]}\) published a case series of four patients who developed silicone IOL opacification on the first postoperative day. The optic was homogeneously affected by non-progressive milky gray/yellow opacity resulting in lens explantation in three patients. Analysis of an explanted IOL revealed that the clouding was only observed in a hydrated state and no deposits were found. They explained the theory of IOL contamination after the manufacturing process because the affected lenses were from different lots. Exogenous molecule contaminants (terpenes and ketones) could change the hydrophilicity of the hydrophobic silicone IOL giving rise to the influx of water and early opacification of silicone lenses\(^\text{[33]}\).

Another similar event observed with the same IOL, SI-40NB IOL (Allergan) showed a brown haziness the day after surgery. Incubation of the explanted lens in saline at room temperature did not change the opacity after two months. Microscopic examination exhibited numerous abnormal spheroid structures in the central area far from the surface. They hypothesized that it could be related to the chemical compositions of the Allergan silicone IOL or the sterilization process with ethylene oxide gas exposure. The incorporation of water into silicone IOL may be the responsible pathologic phenomenon. Adequate resolution of this type of clouding is unlikely over time, and IOL exchange is often necessary to improve visual function\(^\text{[34]}\). However, a case report in 2011 described a diffuse translucent milky white haziness throughout the substance of an AMO Z9002 silicone lens one day after uncomplicated cataract surgery. Clearing of the lens periphery was observed eight days after surgery. The central haze disappeared as well on postoperative day 14. Contamination with industrial chemicals is possible during the manufacturing, sterilization, or packaging process. The mechanism used to explain the initial clearing of the lens periphery was the entrapment of gas or liquid molecules in the lens material and releasing them into the anterior chamber based on the law of diffusion. The peripheral part of the IOL is thinner than the central area. So, less time is required for the diffusion of the contaminants. Besides that, the lens epithelial cells in the capsular bag may have some role in the rapid resolution of opacity in the periphery. A similar pattern of clearing in the same IOL design should be closely visited due to the possibility of spontaneous resolution with excellent visual gain\(^\text{[30]}\).

Werner et al\(^\text{[35]}\) published data from an analysis of 6 explanted 3-piece silicone lenses due to optic opacification a few hours following implantation. Gross and microscopic studies showed that the IOLs became clear at dry state but whitened during hydration. Gas chromatography/mass spectrometry (GC-MS) analysis was performed. Suspect exogenous chemicals (general classes: terpenes and ketones) were found. These compounds are used in industrial cleaning agents and fumigants. Most IOL packages are semi-permeable for the sterilization process. The introduction of contaminants and chemicals through these packages is possible via aerosolizing solutions during the disinfection of the storage rooms. This could result in changes in the material toward hydrophilicity and allowing water entrance after implantation in the eye. Further evaluation revealed that all 6 IOLs were kept in the a same place in Brazil preoperatively\(^\text{[35]}\).

Gray white to faint brown discoloration of an Array SA40N silicone multifocal IOL 1wk after implantation was reported to be related to lens hydration. After 3mo, the patient presented with a blurry vision, which finally led to IOL removal. Light microscopic analysis of the explanted lens was negative for any deposits on or within the IOL material. A chromatographic peak for lidocaine was also noted. Keeping the lens in a dry state resulted in gradual clearing from the peripheral area toward the center. Permeability of the lens material to water and increasing hydrophilicity was attributed to processing defects\(^\text{[36]}\).

Another study mentioned transient homogenous central opacification of a MemoryLens IOL (model CV232, Ioltech) on the first postoperative day, which cleared after a week. Although the exact cause was unknown, the contamination during manufacturing was postulated to be a possible mechanism\(^\text{[37]}\).

**Intraocular lens discoloration secondary to intracameral dye** The use of capsular dyes in cataract surgery helps better visualization of the anterior capsule during capsulorhexis in advanced cataracts. Evaluation of interaction between different IOLs (PMMA, silicone, three-piece hydrophobic acrylic, single-piece hydrophobic acrylic, and single-piece hydrophilic acrylic) and trypan blue 0.1%, fluorescein sodium 2%, and indocyanine green (ICG) 0.5% revealed that only the hydrophilic acrylic...
Intraocular lens discoloration by povidone iodine  Early hydrophobic silicone IOL opacification by povidone-iodine has been demonstrated in an experimental setting. The IOL staining was seen to be concentration-dependent. The duration of exposure was also determined. The most significant risk is when the povidone-iodine is instilled at the end of surgery. Inadvertent leakage could lead to the entrance of the toxic chemical into the anterior chamber. Complete wound closure is strongly advocated to prevent IOL and corneal endothelial damage by povidone-iodine[42].

Breakdown of ocular-blood barrier  One bilateral reversible IOL opacification case has been reported in a woman with a history of diabetic retinopathy and chronic myelogenous leukemia. The patient underwent bilateral phacoemulsification and hydrophilic acrylic IOL (Akreos MI-60) implantation one month before notifying the significant IOL cloudiness on the anterior surface of both lenses. Bilateral intravitreal injection of bevacizumab was done for treating severe cystoid macular edema in the first postoperative month. One week later, clearing the opacity started with nearly complete resolution after two months. Alterations in the ocular blood barrier and increasing vascular permeability secondary to surgery and the underlying diseases (diabetes and leukemia) could affect aqueous humor composition. The pattern of central clearing is compatible with the role of aqueous in dissolving the deposits based on the concentration gradient. In this case, anti-vascular endothelial growth factor injection reversed the haziness[43].

Postoperative inflammation  Kim et al[44] introduced a 72 years old female for whom a hydrophobic acrylic IOL (Tecnis ZCB00) was implanted during cataract surgery. She presented with significant IOL opacification over the entire anterior surface of the lens, sparing the central region two weeks after surgery. Slit-lamp examination showed mild anterior chamber reaction as well. The frequency of topical corticosteroid eye drop increased. The concentric opacity wholly resolved after four weeks. Two main reasons were discussed. The first is the possibility of temporary growth of lens epithelial cells because of the beginning of opacification from the peripheral optic. Another hypothesis is the presence of an atypical and delayed form of TASS. The accompanying anterior chamber reaction and resolution of clouding after frequent steroid prescription favor inflammatory origin[44]. Similarly, there is a report in a 68-year-old woman who experienced temporary IOL opacification[45].

Miscellaneous  A study by Mehta[46] described seven to nine thin elongated oval-shaped markings on the posterior surface of Aquafold IOL (model CB F32 UVA, Omni Lens Pvt. Ltd.). The lines were 3-7 mm long parallel to each other and perpendicular to the direction of the lens folding in the cartridge and eventually disappeared after four months. These
unusual lines were not compatible with folding marks and they were also uncommon for being inflammatory in origin due to linear configuration and late complete resolution. It has been mentioned that mild secondary calcification of some residual viscoelastic/ethylene oxide as a nidus could be the underlying reason.[46]

Another published report of early postoperative opacification discussed a patient with cataract and dense vitreous hemorrhage who underwent a triple pars plana vitrectomy, phacoemulsification, and IOL implantation. On the third postoperative day, many small brown corpuscles with the appearance of a dusty haze were seen on the lens surface. The IOL was a single-piece AcrySof acrylic (SA60AT, Alcon, USA). The surgeons explanted and exchanged it with another same type of lens which remained clear. After analysis, proteinaceous material (particularly fragments consisting of 17 aminoacids) was identified on the IOL surface but there was no triamcinolone or calcium. A probable theory is the adherence of the hemocyte element of the residual vitreous hemorrhage to the adhesive AcrySof surface[47].

Parkin and Pitts-Crick[48] discussed a milky opacification throughout the whole body of an AMO PhacoFlex IOL (Model S130NB, Allergan) on the first day following cataract extraction in a 69-year-old man. After four days, the affected IOL was replaced with a PMMA lens due to its adverse effect on visual acuity. Heating at 50°C cleared the opacity of the explanted lens. No specific cause was identified regarding the manufacturing process[48].

**DISCUSSION**

IOL opacification may have severe adverse effects on visual function and contrast sensitivity[49-51]. Several pathologic processes have been proposed for the loss of transparency of the implanted IOLs[52]. Although no direct cause and effect relationship was demonstrated, knowledge of these different mechanisms and patterns of IOL clouding is essential for cataract surgeons. It could guide them to make the best decision for their patients.

IOL opacification may be detected during implantation. The most common presumed cause in intraoperative IOL clouding is rapid temperature change. Almost all of these IOLs transferred shortly before implantation into the operating room in subzero temperature. Sudden temperature rise after introduction into the anterior chamber may cause the incorporation of water into the IOL material. Microbubble formation, water vapor consolidation on a cold surface, and subsequent light refraction are also described. The IOL will be clear after several minutes to hours following dehydration. Delayed IOL exchange is recommended in the setting of storage in cold temperature because of the high rate of spontaneous resolution. Taking precautions to IOL storage conditions to prevent from rapid temperature fluctuations is important. It is suggested to store the IOL at room temperature and consider the manufacturer’s guidelines.

In contrast, crystallization of the IOL surface due to the reaction between calcium in the irrigating solutions with the phosphate of the OVD is unlikely to clear spontaneously. Drying out of OVD is another possible cause. It is particularly visually significant with silicone lenses. The surgeons could load IOLs shortly before implantation by using an appropriate injector and irrigate the viscoelastic carefully to avoid this complication. It is advisable to remove the lens if such complications during surgery is encountered. Capsulotomy may also be beneficial in some patients.

Several factors could be involved when a surgeon detects IOL clouding in postoperative visits. We reviewed these cases up to the first month following surgery. It should be mentioned that no definite rule and definition is available regarding the duration of acute IOL opacification. The preoperative manufacturing process is critical. Careful monitoring is required particularly during IOL packaging, disinfection, and storage procedures. Accidental introduction of volatile chemicals such as disinfectants and insecticides into the IOL through vapor-permeable packaging is a likely event that may change the hydrophilicity of the lens material. As a result, IOL hydration could occur and IOL clearance would be affected. It is mainly seen with silicone lenses, which will demonstrate gray-white or brown haze. A pattern of peripheral clearing is described. However, this type of opacity often requires IOL exchange due to its persistence and reduction of vision.

Permanent IOL blue discoloration was reported due to residual amounts of intraocular trypan blue dye. The most vulnerable lenses were hydrophilic acrylic IOLs. Careful irrigation of intracameral dyes is important to avoid IOL staining. Complete wound closure is also essential for preventing from the entrance of povidone-iodine or prescribed ophthalmic ointments into the eye. These are other probable causes of IOL discoloration.

Postoperative inflammation and TASS were implicated in a few cases. The opacity is potentially reversible. Corticosteroids have a leading role in the management.

Regardless to the shape, productive company, material properties, and surface technology of materials, acute IOL discoloration can be occurred in almost all types of IOLs such as hydrophilic acrylic IOL, acrylic hydrophobic IOL, hydrophilic acrylic IOL with a hydrophobic surface, trifocal IOL, silicone IOL, and PMMA IOL[14-18,20-24,53-57]. However, some types of discoloration are more common is some particular types of IOLs. This fact shows that acute IOL discoloration whether intraoperative or early postoperative is relatively unpredictable and should not change the surgery plan.
or IOL selection. On the other hand, incidence of this event is extremely remarkable compared to the number of performed cataract surgeries. Also, the role of underlying diseases such as diabetes mellitus and uveitis in acute IOL discoloration is unclear. However, we think unlike late IOL opacifications, this role is not significant since the number of reported cases of acute discoloration with underlying conditions like diabetes mellitus is extremely low.

Almost all of these mechanisms are theoretical and ophthalmologists may encounter patients with no definable origin for loss of lens clarity. Several variables are involved in decision making for IOL explantation, including the severity and pattern of the opacification, the level of visual dysfunction, patient’s visual demands, other ocular and systemic comorbidities, and observation of any sign of clearance in follow-up visits.

In conclusion, most of the acute IOL opacifications could be avoided by taking precautions in manufacturing and storage conditions. Keeping the IOL dry and clean away from rapid temperature fluctuations is advisable. The role of standard surgical procedures and choosing of proper surgical materials should also be considered. Conservative management before IOL explantation is a reasonable approach in many patients.

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