



Comprehensive Analysis of the Effects of Surgery on the Other Eyes of Patients with Bilateral Cataracts after Surgery on One Eye

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Abstract: Cataracts often affect both eyes, requiring bilateral surgery. The outcome of the first-eye surgery can significantly impact the surgical timing, intraocular lens power selection, and pain sensitivity of the second-eye surgery, though a unified consensus is lacking. This article reviews recent research on these effects, providing insights to help clinicians optimize treatment plans for bilateral cataract patients.

Keywords: cataract; aqueous humor; inflammatory factors; cytokines; IOL; ISBCS; second eye

1. Introduction

Cataracts are the leading cause of blindness, accounting for approximately 56.7% of cases[1]. Sequential phacoemulsification with intraocular lens (IOL) implantation is the most common and effective treatment[2]. Cataracts typically affect both eyes, leading to disparities in visual acuity and refractive status after the first surgery, which can impair stereoscopic vision[3] and reduce quality of life[4]. Consequently, most patients require second-eye cataract surgery shortly afterward.

The degree of pain during the operation directly determines the degree of cooperation[5][6]. Clinical observations indicate that patients undergoing second-eye cataract surgery shortly after the first often experience more intense intraoperative pain[6][7][8][9], reducing their cooperation[5], and increasing surgical risk, which can negatively impact the overall experience. However, this phenomenon remains unexplained.

With the increasing precision and expectations of cataract surgery[10], many ophthalmologists face challenges such as adjusting IOL selection for the second eye based on the refractive state of the first and determining the optimal timing for the second surgery. Currently, there is no consensus on these issues. This review aims to explore and analyze these concerns, providing guidance for clinical practice.

2. Is second-eye surgery more painful than first-eye surgery?

2.1 Research on the subjective psychological level

This issue has been widely discussed, but most research has focused on the subjective psychological aspect, resulting in inconsistent conclusions. Some studies reported a slight increase in pain during the second eye surgery in bilateral sequential cataract patients, linked to reduced preoperative anxiety [7][11][12][13]. Patients are generally more relaxed during second-eye surgery[14], but reduced anxiety may heighten intraoperative awareness, leading to increased pain sensitivity and a less favorable surgical experience. A recent questionnaire study confirmed that patients undergoing second-eye surgery within 2 weeks experienced more pronounced pain, with factors such as age, gender, and education level playing a role[15]. In contrast, some studies found no significant difference in pain perception and cooperation during bilateral cataract surgery. This may be because patients have a diminished memory of the first-eye pain, leading to an illusion of increased pain sensitivity in the second eye[16].

2.2 Research on cytokine level

XiangJia Zhu's team found a significant increase in monocyte chemoattractant protein-1 (MCP-1) levels in the aqueous humor (AH) before second-eye surgery in bilateral cataract patients. This inflammatory trend, linked to pain and inflammatory response, suggests sympathetic uveitis in the contralateral eye after first-eye surgery, explaining the increased pain during second-eye phacoemulsification[17]. This provides physiological and biochemical basis for exploring this clinical issue. Subsequently, more teams confirmed that MCP-1 in patients who underwent second eye surgery within a short period of time

was significantly higher than that of the first eye [11][12][15][19].

In the study of this issue, more teams subsequently found increases in different biological factors in the eyes, such as granulocyte colony stimulating factor (CSF3) [13], transforming growth factor β 2 (TGF- β 2)[18], TNF- α , IL-1 β [19], granulocyte-macrophage colony stimulating factor (GM-CSF), IL-2, IL-13[29], substance P (SP) [21], etc. The biological factors discussed in the relevant literature currently retrieved can be found in the attached table 1.

The discussions regarding biological factors can be summarized as follows: after surgery on one eye, various reasons—such as disruption of the blood-aqueous barrier and subclinical sympathetic uveitis—can lead to a breakdown of immune homeostasis. This immune response mobilizes various biological factors, which may either inhibit or stimulate inflammation, further closely linking inflammation and pain[22][23]. This provides a reasonable explanation for the issue. Furthermore, Zheng Fan and colleagues visually validated this phenomenon in a rat model through trigeminal nerve electrophysiology and corneal sensitivity experiments [13].

Interestingly, different teams employ varied detection methods, or even the same method, yet the detected cytokines often differ. Other teams also utilized the Bio-Plex suspension array system but did not observe elevated MCP-1 levels in the second eye[18][20]. Additionally, when comparing the AH of both eyes in patients with congenital cataracts, the detected biological factors show considerable variability[24][25]. What factors contribute to this inconsistency in results? We summarize the reasons as follows:

(1) Technical differences.

Detection methods: The Bio-Plex suspension array system, Luminex system, multiplex bead immunoassay, ELISA, and other methods exhibit differences in sensitivity, specificity, and operational procedures.

Environmental factors: laboratory conditions, reagent batches, operator's technical level, etc. can also affect the test results[26].

Sample processing and storage: sample storage temperature, storage time, number of freezing and thawing, etc. can affect the stability and concentration of biological factors[27].

Surgical operation: surgical time, ultrasonic emulsification parameter settings, light intensity[28], etc. may stimulate patients' different physiological and biochemical reactions to surgery.

(2) Biological differences.

Individual differences: living environment[29], eating habits, stress level, sleep quality, age, disease status[20], and even the expression of biological factors in the AH of patients in different regions may be different. For example, Compared with patients with simple cataracts from other groups[21], there is a possibility that the cytokine expression of AH may be different in cataract patients with diabetes[11][30]. It must be emphasized that hyperglycemia is a risk factor for oxidative stress[31]. Studies have found that hyperglycemia significantly increases the expression of MCP-1[32].

Differences in the immune system: Different individuals, or even different tissues within the same individual, can elicit varying immune responses to the same stimulus. These differences in immune response intensity are likely influenced by both genetic and environmental factors[33].

(3) Cytokine interactions.

The immune response results from the combined action of multiple cytokines and signaling molecules, with interactions varying among individuals. Some factors may be upregulated in one individual while downregulated in another, leading to distinct inflammatory response patterns, typically reflected in changes in cytokine levels from different cell populations. These cytokines interact in a highly dependent manner to regulate inflammation[34]. We speculate that if subclinical uveitis exists in unoperated eyes, cytokine interactions may help achieve a personalized immune balance, leading to individual variations in cytokine expression.

(4) Dynamic changes of cytokines.

Many studies have shown that the concentrations of the same cytokines vary at different times, indicating that dynamic changes occur in the cytokines in the AH of the other eye after surgery on one eye. As a result, different research teams choose different time points after surgery on one eye to test the AH of the other eye, leading to the detection of different cytokines[12][13][19][35].

2.3 Neurological research

Additionally, earlier studies have demonstrated that peripheral nerve damage can impact contralateral intact structures, exhibiting effects similar to those on the ipsilateral side, albeit typically less intense and shorter in duration[36]. Increasing evidence suggests that molecular mechanisms involving cytokines may be the primary cause of mirror pain (MP)[37]. The high symmetry between both eyes and the invasive nature of cataract surgery on corneal nerves provide a strong foundation for investigating pain in the second eye. Recognizing this neural interdependence, the Giannaccare team quantitatively

assessed the bilateral subbasal corneal nerve plexus (SNP) in unilateral cataract surgery patients. They found that unilateral surgery led to a reduction in SNP in both eyes, confirming its sympathetic impact on contralateral corneal nerve damage[38]. Significant changes in SNPs were also observed in the fellow eye of patients with unilateral neurotrophic keratitis (NK) secondary to central nervous system (CNS) disease[39]. It is known that corneal nerve endings have sensors that monitor tear film thickness and integrity [40], which play an important role in the blink reflex, wound healing, and tear secretion. Therefore, when the corneal nerve is damaged, the corneal sensitivity decreases, resulting in a decrease in blink and tear film reflexes, which affects the stability of the tear film [41]. This may explain why some patients experience dryness and light sensitivity in the untreated eye after unilateral cataract surgery, potentially leading to greater discomfort during surgery on the second eye. Interestingly, research also indicates that corneal nerve fiber status affects anesthetic efficacy in fibromyalgia, with abnormal corneal nerves resulting in a poorer analgesic response[42]. Both changes in the ocular surface due to interference with the contralateral corneal nerves and the reduced efficacy of local anesthetics may explain the increased pain during second-eye surgery. However, further research is needed to validate these findings.

2.4 Conclusion

So, does increased pain in the second eye truly occur after surgery on the first? Clinically, this phenomenon appears genuine, with numerous studies supporting it[7]. While many biochemical and physiological studies link this to changes in cytokine levels, the conclusions remain inconsistent. This raises the question of whether alternative research methods or more rigorous, standardized study criteria might provide a clearer explanation.

3. How does first-eye surgery impact the IOL power selection for the second eye?

Modern cataract surgery has become much safer and more accurate, with advanced measurement tools and IOL prediction formulas reducing selection errors[43]. Clinically, the refractive status and visual quality of the first eye post-surgery often guide IOL selection for the second eye to optimize binocular vision. However, a few patients do not achieve the desired refractive target after first-eye surgery, making it challenging to select the refractive power for the second eye[43][44]. Comprehensive evaluation of the postoperative optical results of the first eye and re-evaluation of the choice of IOL before surgery on the second eye are still particularly important steps in clinical practice[43][45]. The high optical symmetry between both eyes serves as an important theoretical basis for guiding IOL power adjustments in the second eye when there is a significant refractive error (PE) after the first-eye surgery[46]. Studies have shown that in cases of symmetrical eyes with minimal error sources, the surgical outcome of the first eye can be used to adjust the prediction for the second eye, increasing the proportion of patients achieving a postoperative refractive target within ± 0.50 D[45] and reducing the predicted PE of the two eyes after surgery[47].

To address this issue, various teams have employed different methods for accurately selecting the IOL for the second eye. Olsen et al. used the anterior chamber depth (ACD) one month post-surgery to reduce prediction errors for the second eye[48]. Nicole Mechleb's team attempted to reverse-calculate the optimal intraocular lens position based on the first eye's surgery to enhance formula accuracy for the second eye[49]. The National Institute for Health and Care Excellence in the UK proposed a straightforward guideline: apply a 50% correction factor to the second eye when a refractive error occurs in the first eye[50][51]. Further research showed that when the first eye's PE exceeds 0.50 D (stable subjective refraction for at least 4 weeks), adjustment coefficients of 0.30 for the Barrett Universal II formula and 0.50 for the Hoffer Q, Holladay I, and SRK/T formulas can be reliably applied. The adjusted prediction formula for the second eye is: predicted postoperative refraction value (PPOR) + (adjustment coefficient \times PE of the first eye)[45]. Additionally, Mechleb's team found that the optimal correction coefficient should be 60%[49].

Finally, it is emphasized that the above adjustment consensus is based on the symmetry of the two eyes. If the axial AL difference between the two eyes exceeds 0.5 mm, or the corneal curvature difference exceeds 0.75D, complications such as implantation errors (e.g., incorrect IOL placement, biometric errors) and IOL positioning abnormalities (e.g., eccentricity, tilt, astigmatic rotation, retention of ophthalmic viscoelastic device, capsular ectasia syndrome, choroidal effusion) may arise. In such cases, the correction formula may not improve the accuracy of the second eye's IOL and could even be detrimental[45][49].

4. Is it feasible to perform immediate simultaneous bilateral cataract surgery (ISBCS)?

The main concern in the debate over ISBCS is the risk of endophthalmitis, which could lead to simultaneous vision loss in both eyes[52][53]. Another key concern is the inability to adjust the IOL power for the second eye based on the refractive

outcome of the first eye surgery[54].

However, we cannot completely deny the advantages of ISBCS, especially compared with the decrease in quality of life caused by anisometropia caused by delayed sequential cataract surgery (DSBCS)[55]. Secondly, reducing the number of visits lowers the financial and caregiving burden on patients and their families, offering clear benefits[56]. In addition, the ISBCS strategy can reduce hospital costs and the burden on medical insurance, thereby benefiting medical insurance finances [57][58]. It is undeniable that in recent years, the acceptance of ISBCS among patients and clinicians worldwide is gradually increasing[59][60]. As early as 2015, a systematic review and meta-analysis on ISBCS and DSBCS showed that there was no significant difference in the improvement of patients' quality of life, best-corrected visual acuity, and visual function [61]. Many recent studies comparing the surgical efficacy, safety, and complication rates of the two have shown that DSBCS has no advantage over ISBCS [62][63], and even the probability of endophthalmitis after ISBCS is lower[64][65]. Furthermore, studies from numerous countries have shown no statistically significant differences in refractive outcomes and BCVA between ISBCS and DSBCS patients[52][66][67].

Ultimately, the author believes the primary consideration in choosing between the two surgical strategies should be the option that best benefits the patient's health, followed by cost, convenience of healthcare services, and third-party profit margins. From the patient's perspective, the key points are: (1)The catastrophic risks of ISBCS, like simultaneous bilateral endophthalmitis and toxic anterior segment syndrome leading to blindness, are harder to manage, while DSBCS can help mitigate these risks. (2) In clinical practice, ISBCS complications may be underestimated, as serious postoperative issues are often underreported to avoid negative repercussions, leading to statistical bias. A recent study found that literature published after 2007 on both surgical options showed low-quality evidence on visual quality, safety, and cost reduction, indicating potential lack of objectivity in previous findings[68]. (3)With the ISBCS approach, the refractive power of the second-eye IOL cannot be adjusted based on the postoperative refractive state of the first eye. While optically adjustable IOLs[69]offer a solution, they remain unsuitable for most patients currently. (4)After IOL implantation, patients may experience pseudophakic visual impairment or poor optical quality, leading to dissatisfaction with otherwise successful cataract surgery[70]. Bilateral cataract surgery risks vision impairment in both eyes, whereas the DSBCS approach allows assessment of optical side effects, enabling adjustments for the second eye, such as IOL replacement or alternative surgical methods. (5)Compared to the quality of life issues from anisometropia caused by DSBCS, shortening the waiting period for surgery on both eyes may effectively address this problem. (6)A more realistic concern is that the implementation of ISBCS may affect the income of ophthalmologists and hospitals due to the current distribution of medical policy revenues[69]. (7)This review has pointed out that physiological and biochemical changes occur in the contralateral eye after surgery on one eye, and simultaneous surgery may exacerbate these changes, enhancing adverse immune responses and potentially introducing unknown risks.

Considering all factors, promoting the ISBCS surgical strategy widely does not seem feasible solely from the perspective of patient health benefits. However, for patients who must travel long distances, children, or those requiring general anesthesia for other reasons, ISBCS may offer significant advantages. It is crucial to emphasize that if surgery is performed on both eyes on the same day, the second eye must be treated as an independent procedure, requiring separate instruments, medications, and drapes, with the surgeon re-sterilizing before the second surgery [52][71].

5. When is the optimal timing for second-eye surgery after the first?

For patients with bilateral cataracts, if surgery cannot be performed at the same time, the necessity and interval of surgery on both eyes need to be discussed. First, patients with cataracts and different visual acuity in both eyes will show binocular suppression, that is, binocular sensitivity is lower than that of one eye[4]. For patients with bilateral cataracts, if surgery is performed on one eye, the binocular refractive difference caused by surgery will seriously affect the patient's visual experience and quality of life[72]. On the contrary, patients who undergo surgery on both eyes experience greater improvements in visual sensitivity, stereoscopic vision, horizontal visual field, functional status, fall rate, and overall quality of life[73]. This improved visual experience can reduce the incidence of complaints and even lawsuits related to vision impairment in clinical practice[73]. All the information indicates that performing surgery on both eyes is necessary. So, When should the second-eye surgery be performed after the first?

Many countries' clinical guidelines do not specify the timing for the second ophthalmic surgery[52][73]. This indicates that the timing of second eye surgery is complex and depends on several factors: (1) the patient's visual needs and preferences; (2) the visual acuity and function of the second eye; (3) the refractive stability of the first eye and binocular refractive anisometropia; (4) the patient's intraoperative experience.

First, an important conclusion regarding refractive stability is that cataract surgery on the first and second eyes should be at least 4 weeks apart to ensure stable refractive outcomes[45].

From the perspective of cytokine expression, cytokines such as MCP-1, CSF3, TNF- α , and IL-1 β peaked one week after surgery, aligning with the observation that patients undergoing second eye surgery reported the most eye pain at that time [13][19]. A intuitive questionnaire survey reconfirmed that patients undergoing bilateral surgery within 2 weeks experienced more pain during the second eye surgery, with this pain differing based on the patient's age, gender, and education level[15]. From this perspective, it seems that avoiding surgery within two weeks will give patients a better experience during the operation. Additionally, to avoid damage caused by the aforementioned MP, it seems more reasonable to postpone the surgery for at least one month[74].

Considering only the above factors is not comprehensive, as anisometropia-related quality of life issues during the waiting period remain important. Therefore, if visual quality is not significantly affected and anisometropia does not cause serious problems, a 4-week interval may be an optimal time for the second surgery.

6. Conclusion

For patients with bilateral cataracts, in-depth thinking about the second eye surgery strategy after the first surgery is still an issue that needs further standardization and refinement in clinical practice. Although there is currently insufficient theoretical evidence that the second eye surgery is more painful than the first eye surgery, the impact on the second eye after the first surgery is not uncommon in clinical observations. In addition, the choice of IOL before the second eye surgery should be adjusted accordingly based on the stable refractive state and refractive error after the first eye surgery. For conventional patients with bilateral cataracts, ISBCS is not a better option at present. Taking into account the individual differences of patients, postoperative recovery, and quality of life, waiting one month after the first eye surgery before the second eye cataract surgery may be a more prudent and reasonable choice. This individualized treatment arrangement helps to optimize the surgical effect, reduce the patient's pain, and improve overall treatment satisfaction.

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