• Review Article •

Pain perception enhancement in consecutive second-eye phacoemulsification cataract surgeries under topical anesthesia

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Abstract

● Cataract is the main cause of visual impairment and blindness worldwide while the only effective cure for cataract is still surgery. Consecutive phacoemulsification under topical anesthesia has been the routine procedure for cataract surgery. However, patients often grumbled that they felt more painful during the second-eye surgery compared to the first-eye surgery. The intraoperative pain experience has negative influence on satisfaction and willingness for second-eye cataract surgery of patients with bilateral cataracts. Intraoperative ocular pain is a complicated process induced by the nociceptors activation in the peripheral nervous system. Immunological, neuropsychological, and pharmacological factors work together in the enhancement of intraoperative pain. Accumulating published literatures have focused on the pain enhancement during the second-eye phacoemulsification surgeries. In this review, we searched PubMed database for articles associated with pain perception differences between consecutive cataract surgeries published up to Feb. 1, 2024. We summarized the recent research progress in mechanisms and interventions for pain perception enhancement in consecutive second-eye phacoemulsification cataract surgeries. This review aimed to provide novel insights into strategies for improving patients' intraoperative experience in second-eye cataract surgeries.

● **KEYWORDS:** ocular pain; cataract surgery; topical anesthesia; intraoperative experience; second-eye phacoemulsification

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INTRODUCTION

Cataract is the main cause of global visual impairment and blindness, while the only effective cure for cataract is still surgical removal[1]. At present, phacoemulsification under topical anesthesia is a widely applied methodology for routine cataract surgery[2]. Although phacoemulsification under topical anesthesia has been relatively safe and mature after decades of improvement, challenges still remain.

Patients with bilateral cataracts need twice surgeries. However, there was a debate in the choice of surgery timing (simultaneous surgery or consecutive surgery)[3]. Simultaneous surgery showed similar outcomes with consecutive surgery for patients with bilateral cataracts[4]. However, due to the higher risk of simultaneous bilateral complications, especially endophthalmitis[5-6], consecutive surgery is still a mainstream mode in cataract surgery.

Intraoperative pain perception is a crucial factor influencing the satisfaction and willingness for re-operation of patients with bilateral cataracts. In clinical practice, patients generally grumbled that pain experience was enhanced during the second-eye surgery compared to the first-eye surgery[7]. A growing number of studies focusing on this phenomenon have been conducted. We searched PubMed database for papers associated with pain perception differences between consecutive cataract surgeries published up to Feb. 1, 2024. This review summarized the possible mechanism and intervention measures of pain enhancement in second-eye cataract surgery. We hope to provide novel insight into strategy of improving the intraoperative experience of patients in second-eye cataract surgery.

ANATOMY AND PHYSIOLOGY FOR PAIN FORMATION IN CATARACT SURGERY

Physiological pain is a complicated process associated with the activation of nociceptors in the peripheral nervous system[8-9]. Peripheral ocular neurons are commonly evoked by two pathogenesis: 1) inflammation; 2) direct peripheral or central neuronal injury. Inflammation activates or sensitizes polymodal nociceptor fibers (inflammatory pain) while peripheral neuronal injury causes abnormal ectopic ongoing activities of nociceptor fibers (neuropathic pain)[10]. Although the lens is a transparent structure without nerves[11], there is a rich nerve innervation in surrounding tissues[12-13]. Thus, the intraoperative pain during cataract surgery should be mediated by surrounding sensory neuroreceptor, including corneal nerves, conjunctival nerves, *etc*. These ophthalmic sensory neurons are heterogeneous in functions and membrane properties[14-15].

Among ocular structures, cornea has the richest nociceptors[16-17]. Myelinated corneal nerves lose their myelin sheaths at about 1 mm from the limbus. Then, they penetrate into the cornea stroma radially from the periphery (mainly at 9 and 3 o'clock) and form the compact sub-basal nerve plexus in the anterior corneal stroma. Afterwards, the corneal nerve endings travel into corneal epithelium near the eye surface[18]. The corneal sensory nerve endings are highly sensitive to exogenous and endogenous stimulus. When mechanical stimulations applied to cornea, the corneal sensory nerves (as a part of the ophthalmic branch of trigeminal nerve) will transmit nociceptive impulses to the trigeminal ganglion and nucleus[19]. Sequentially, the nociceptive impulses transmitted by synapses in the thalamus (limbic) and ultimately reach the somatosensory cortex region of cerebrum[20-21] (Figure 1). The naked corneal nerve endings link to the medium or small neurons with myelinated Aδ type axons or unmyelinated C type axons, which also exist in the bulbar conjunctiva, uvea and sclera[12]. About 15% of the corneal nerve fibers are composed of Aδ type axons. Aδ type axon is the fastest conducting neuron in body which can adapt rapidly. Thus, the myelinated Aδ nerve fibers mainly transmit acute pain. The majority (about 70%) of corneal nerve fibers are polymodal. A minority of them are thin myelinated Aδ type axons, but most of polymodal nociceptors are composed of slow-conducting C type axons. The polymodal nociceptors can be activated by cold (<29°C), heat (>39°C), exogenous irritants or endogenous inflammatory cytokines. Therefore, this type of nociceptor can both perceive acute pain and chronic pain. Because neuropeptides can depolarize distant branches of the same neuron that is not directly activated by the original stimulations. The polymodal stimulation can spread not only centripetally but also peripherally. The polymodal nociceptors are also involved in tear reflex of cornea.

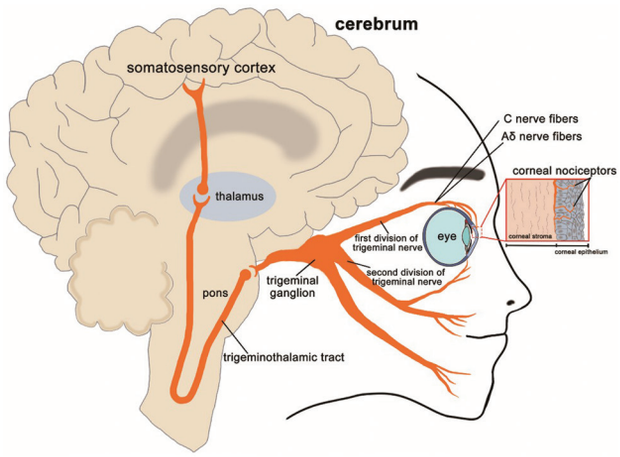

Figure 1 The pattern diagram of anatomical structure of ophthalmic sensory nerve and physiology for pain formation in cataract surgery.

The corneal/conjunctival sensory nerves are composed of Aδ type nerve fibers and C type nerve fibers. The surgery-related inflammatory, mechanical and chemical stimulations can activate corneal/conjunctival nerve endings and trigger impulses. The corneal sensory nerves are innervated from the first division of trigeminal nerve. The conjunctival nerve endings are innervated from first division and second division of trigeminal nerve. When a surgical stimulus occurs, the corneal/conjunctival sensory nerves transmit nociceptive impulses to the trigeminal ganglion and nucleus. Sequentially, the nociceptive impulses are transmitted by neurons synapse in thalamus, and finally reach the somatosensory cortex region of cerebrum.

Compared with corneal neurons, the density of conjunctival neurons is relatively low. The majority of conjunctival sensory neurons are innervated from the first division (ophthalmic branch) of the trigeminal nerve, while the minority of conjunctival sensory neurons are innervated from the second division (maxillary branch) of the trigeminal nerve (Figure 1). The receptive fields of polymodal nociceptor and mechano-nociceptor of corneal nerves, often extend into the perilimbal conjunctiva. Pure conjunctival polymodal nociceptors and mechano-nociceptors exist in the bulbar conjunctiva, which have similar features with corneal nociceptors[22-23]. Conjunctival sensory neurons are also composed of myelinated (Aδ type) and unmyelinated (C type) axons with peripheral endings (mostly unencapsulated). Conjunctival sensory neurons express markers of peptidergic sensory neurons, such as calcitonin gene-related peptide[24] and substance P[25]. The conjunctival peptidergic nerve endings commonly locate around the blood vessels in conjunctival stroma, and can also be found in conjunctival epithelium or around the acini of lymph follicles and meibomian glands.

MEASUREMENT OF PAIN PERCEPTION LEVEL IN CATARACT SURGERY

Accumulating researches focused on the pain perception

difference between twice cataract surgeries. In 2009, a research from Poland reported that preoperatively declared pain perception did not significantly correlated with the sequence of operation[26]. However, the time intervals and operators of the surgeries were not controlled same, which weakened the scientific of Omulecki *et al*'s[26] research.

In 2010, Mowatt *et al*[27] first reported that the pain perception of patients was higher in the 2nd cataract surgery. This research included 1835 patients and used the visual analogue pain scale (VAS), which ranged from 0 (no pain) to 10 (unbearable pain), to evaluate pain score[28]. Mowatt *et al*[27] found that average VAS was 0.85 for the second surgeries while mean VAS was 0.5 for the first surgeries, by topical anaesthesia. However, the deficiency of the research was that the two surgeries were operated by different ophthalmologists. The difference of the surgeons may affect the patients' pain perception.

Ursea *et al*[29] also revealed that pain perception slightly increased in the second-eye cataract surgery under topical anesthesia compared with the first-eye surgery. They additionally assessed the preoperative anxiety levels of patients using Amsterdam Preoperative Anxiety and Information Scale (APAIS) and State-Trait Anxiety Scale (STAI). Results showed that APAIS and STAI scores decreased before second surgery. The decreased preoperative anxiety appeared to contribute to the enhanced pain perception during second-eye surgery. In 2011, a research conducted by Bardocci *et al*[30] indicated that mean VAS pain score was slightly increased from 2.35 (first-eye surgery) to 2.89 (second-eye surgery) with no significance. It's worth noting that the sample size of Bardocci *et al*'s[30] research was relatively small (n=73).

In 2013, Aslan *et al*[31] reported that patients had worse cooperation and more pain during the second-eye phacoemulsification surgery. In 2015 Jiang *et al*[32] also compared VAS score and STAI between first-eye and second-eye cataract surgery. They reached similar conclusions with Ursea *et al*[29] that cataract patients were likely to perceive more pain during second-eye surgery, which had lower preoperative anxiety before second-eye surgery. In 2017, Akkaya *et al*[33] reported that patients had increased pain perception and worse cooperation during the second-eye phacoemulsification surgery under sub-Tenon's local anesthesia. From the above papers, the pain perception level seems to indeed increase in second-eye cataract surgery with specific time intervals.

MECHANISM OF PAIN DIVERSITY BETWEEN CONSECUTIVE FIRST-EYE AND SECOND-EYE CATARACT SURGERIES

Immune Microenvironment Change Mechanisms of pain perception enhancement in second-eye ophthalmic surgical procedure were discussed by El Rami *et al*[34]. They proposed that local inflammation induced sensitization of the contralateral eye corneal nociceptors and contributed to the pain enhancement during second-eye procedures[34]. Luna *et al*[35] also reported that inflammation or nerve lesion in the unilateral corneal sensory nerves would activate and sensitize the activity of contralateral eye nerves. Zhu *et al*[36] investigated the preoperative cytokines expression levels in aqueous humor from first-eye and second-eye surgeries. Results showed that the expression level of monocyte chemoattractant protein 1 (MCP-1), also known as C-C motif chemokine ligand 2 (CCL-2), was significantly up-regulated in aqueous humor in the second-eye after first-eye surgery. Chen *et al*[37] included self-controlled patients to investigate the change of inflammatory cytokines levels between two consecutive cataract surgeries. The findings of this study showed several discrepancies with Zhu *et al*'s[36] research. Although the expression level of MCP-1 was slightly higher in the second eye, the difference showed no significant. The differences in studies of Chen *et al*[37] and Zhu *et al*[36] may be attributed to discrepancies in subgroup design and time interval selection. Chen *et al*[37] and Yan *et al*[38] also found a higher level of preoperative transforming growth factor β2 (TGF-β2) expression in the second-eye aqueous humor two weeks after first-eye cataract surgery, especially in patients combined with high myopia.

Anterior chamber-associated immune deviation (ACAID) is an immuno-tolerance mechanism of eyes by suppressing antigen-specific delayed-type hypersensitivity[39-40]. TGF-β2 in aqueous humor was reported to play a key role in ACAID by promoting antigen-presenting cells (APCs) to induce development of Forkhead-box-p3 $(Foxp3)^+$ regulatory T cells (Tregs) in spleen[41-42]. The anti-inflammatory Tregs can secrete cytokines, including TGF-β, which inhibit APCs to activate naive T cells into Interferon-γ $(IFN\text{-}\gamma)^+$ effector T helper 1 cells (Th1)[43]. Intravitreal-injected TGF-β2 reduced inflammatory cell infiltration in the animal model of ocular inflammation[44]. The above-mentioned studies indicated a protective mechanism of TGF-β mitigating the sympathetic immune reaction triggered by unilateral cataract surgery[37-38].

As a pain-associated cytokine, expression of MCP-1 was reported to be significantly correlated to the pain perception level of patient with fibromyalgia[45]. Intrathecal injection of MCP-1 induced painful reactions and mechanical hypersensitivity on mice[46]. Zhang *et al*[47] found that MCP-1 level in aqueous humor significantly correlated with pain perception during cataract surgery. Another function of MCP-1 is recruiting leukocytes migrate to injured or inflammatory tissue, and furtherly triggering the inflammatory reaction cascade[48-49]. The secretion of inflammatory cytokines, such as MCP-1 and colony-stimulating factor 3 (CSF3), from residual lens epithelial cells (LECs) in capsule bag was significantly

enhanced after cataract surgery[50]. Elevated level of MCP-1 in aqueous humor from the contralateral eye after first-eye surgery pointed out a sympathetic eye condition. Sympathetic ophthalmia, which charactered as a type of bilateral diffuse granulomatous pan-uveitis, is one of the well-known sympathetic eye conditions. Sympathetic ophthalmia usually develops in bilateral eyes after penetrating injury to unilateral eye[51]. One of the molecular pathological mechanisms of sympathetic ophthalmia is T lymphocytes mediated delayed hypersensitivity (also known as type IV hypersensitivity)[52-54]. After recruited to injured ophthalmic tissue and activated by MCP-1 and interleukin (IL)-8, the infiltrating monocytes will release inflammatory mediators and present antigens (such as crystallin) to Th1 and Th17 lymphocytes. The Th lymphocytes differentiate into antigen-specific lymphocytes after stimulated by monocytes presented antigen and inflammatory cytokines. The activated Th1 and Th17 secrete proinflammatory cytokines (such as IFN-γ and IL-17) into the aqueous-blood circulation and furtherly amplify the inflammatory cascade. The activation of ocular anterior segment inflammation would induce iris vascular changes which manifested by the increase of vessel area density and vessel skeleton density[55-56]. Cui *et al*[57] reported that, for the second-eye surgery, patients' preoperative iris vessel area density significantly increased and was correlated with the perioperative pain. It indicated an upregulated anterior segment inflammatory state before second-eye cataract surgery compared to the first-eye surgery.

Serum immunoglobulins against crystallin proteins were also found in most cataract patients with active uveitis[58]. BetaB1-crystallin antigen was found in ciliary body tissue, which indicated a potential target for autoimmune reaction in anterior uveitis[59]. Crystallin proteins exposure and blood-aqueous barrier breakdown activating autoimmune reaction is a possible mechanism for the panuveitis after first-eye cataract surgery.

What is the origin of the up-regulated MCP-1 in aqueous humor after first-eye cataract surgery? Phacoemulsification induced oxidative stress of residual LECs in capsular bag[60-61]. Kawai *et al*[62] reported that the perioperative aqueous MCP-1 both increased in human and animal operated-eyes after phacoemulsification cataract surgery. *In situ* immunohistochemical staining showed MCP-1 expression significantly up-regulated in lens capsular (containing LECs) after cataract surgery. Expression of MCP-1 in LECs were significantly increased after TGF-β2 treatment *in vitro*. Therefore, proliferated LECs in capsule bag might be the main provenance of increased aqueous humor MCP-1 after phacoemulsification[62]. Similar results were reveals by Jiang *et al*[50] in their research that published in 2018. The data revealed that the up-regulated MCP-1 in anterior chamber may be secreted from the remnant LECs in capsular bag after phacoemulsification.

Recently, Fan *et al*[63] reported that CSF3 significantly increased in aqueous humor from second eye after the first eye surgery. In both patients and rabbit models, the expression level of CSF3 in second eye reached at maximum 1wk after the first-eye surgery. The up-regulated CSF3 in the second-eye aqueous humor could arouse nociception by directly interacting with neuroreceptor in the ciliary body and iris. Simultaneously, more neutrophils were recruited to the contralateral eye aqueous humor. Trigeminal ganglion electrophysiology pulse and corneal sensitivity of rat were significantly up regulated after one eye surgery. Superior cervical ganglionectomy could effectively suppress the trigeminal nerve pain and corneal high sensitivity. Results indicated that CSF3 regulated sympathetic activity alteration is a possible mechanism of pain-perception difference between twice consecutive cataract surgeries.

Tolerability to Anesthetic Drugs Ocular topical anesthesia is achieved using eye drop or jelly. Almost all eye drops have local tolerance problems, but the frequency is variable. After prolonged use of eye drops, local drug tolerance would induce pain on instillation, delay healing, allergic reactions and disturbances of lacrimal secretion[64]. Resistance to local anaesthetics was reported to occur even after correctly performed anaesthetics administration[65]. Ursea *et al*[29] suggested a pharmacological hypothesis that the previous exposure to anesthetic drugs during the first eye surgery leads to drug tolerance, so the reaction to the same drug is reduced during the second eye surgery. However, Akkaya *et al*[33] disagreed with this opinion for the following reasons: 1) The dosage of anesthetic drugs applied during the first operation was quite small; 2) The interval time between consecutive phacoemulsification surgeries was relatively long. In summary, the drug tolerance hypothesis lacks evidence support.

Neuropsychological Factors Mental and psychological factors (such as stress, depression, or anxiety) can greatly influence the perception of ocular pain[66-67]. Bardocci[68] considered that increased pain in second-eye cataract surgery should be attributed to the neuropathology of pain perception.

Short-term pain memory trace Pain perception is associated with patients' changed expectations and raised awareness[69]. The memory traces of pain also contribute to the pain experience enhancement. Pervious research investigated the memory traces of pain in the cerebral cortex[70]. Distinctive regions in brain cortex handle sensory discriminative and components of pain. The pain-related areas in cerebral cortex include primary somatosensory cortex/posterior parietal cortex, anterior insular cortex, and secondary somatosensory cortex. The anterior insular cortex activation is associated with the integration of sensory and cognitive (salience, memory, attention, and awareness) components of pain perception. Absence of memory-specific anterior cingulate

cortex activation is associated with pain-related suffering. It is noteworthy that the primary somatosensory cortex/posterior parietal cortex memory is involved in the short-term retention of intensity and spatial aspects of stimulation[70]. The short-term pain memory trace system is a potential explanation for the greater pain experienced in a second-eye phacoemulsification cataract surgery.

Preoperative anxiety Preoperative anxiety has debatable influences on intraoperative pain experience in phacoemulsification cataract surgery.

On the one hand, Ursea *et al*[29] reported that decreased preoperative anxiety scores were negatively correlated to the incremental pain perception in the second-eye cataract surgery. Similarly, data from Jiang *et al*[32] showed that cataract patients were more sensitive to pain during second-eye surgery than during first-eye surgery. The increased pain during second-eye surgery was negatively correlated with decreased preoperative anxiety level. Among patients who reported more pain in second-eye surgery, the VAS pain scores were positively correlated with the intraoperative monitoring parameters, including diastolic blood pressure, mean arterial pressure, and heart rate. Thus, the mean arterial pressure and heart rate during surgery are potential parameters for evaluating intraoperative pain risk[32].

On the other hand, some researches revealed that intraoperative pain experience during cataract surgery was positively correlated to preoperative anxiety level[71]. Socea *et al*[71] investigated anxiety of patients using visual analog scale for anxiety before cataract surgeries, simultaneously evaluated intraoperative pain perception using VAS. Results showed a significantly positive correlation between visual analog scale for anxiety and VAS. It indicated that the increased preoperative anxiety seems to contributed to the pain enhancement in second-eye surgery.

INTERVENTIONS ON PAIN PERCEPTION DURING CONSECUTIVE SECOND-EYE CATARACT SURGERY

Interventions on Inflammatory Cytokines Zhang *et al*[72] investigated the interventions on MCP-1 to control pain-increase in second cataract surgery. They found that the preoperative treatment of pranoprofen eye drops decreased the pain perception during second-eye cataract surgery, especially when the intervals time between the twice surgeries was 1-week or 6-week. The pain-relief mechanism of pranoprofen in second-eye surgery was associated with MCP-1 inhibition. In addition to non-specific anti-inflammatory drugs, MCP-1/CCL-2 specific inhibitors can precisely block the neuro-hypersensitivity and pain caused by MCP-1. Bindarit (a selective inhibitor of CCL2/CCL7/CCL8 protein family) effectively reduced neuropathic pain related behavior after peripheral nerve injury in mice model[46]. Besides that, blocking C-C chemokine receptor type 2 (the receptor of MCP-1) by specific antagonist (RS504393) can also effectively reduce pain-related behavior in neuropathic mice[73].

Fan *et al*[63] reported that superior cervical ganglionectomy could effectively suppress the secondary corneal sensitivity and trigeminal nerve pain of rats after one eye cataract surgery. Their results indicated that CSF3 and sympathetic activity were prospective targets on pain relief during ophthalmic surgeries. CSF3 monoclonal antibody and other specific inhibitors are worth further study.

Mental and Psychological Intervention Appropriate preoperative publicizing and education is important. Forewarning the patient of pain perception enhancement during second-eye cataract surgery may improve the intraoperative cooperation and experience of patients[68]. Ursea *et al*[29] suggested ophthalmologists to offer sufficient preoperative education for patients before second-eye cataract surgery by reminding patients to prepare for the possible pain increase.

Medical intervention on psychology can help relieve anxiety and decrease pain perception. Sane *et al*[74] reported that sublingual administration of 3 mg melatonin before cataract surgery under topical anesthesia reduced pain level, anxiety level, and intraocular pressure of patients during surgeries.

Several researches also explored the anxiolytic roles of perioperative music intervention on patients undergoing cataract surgery. Preoperative music intervention was reported to be an effective method to inhibit anxiety and pain experience during cataract surgery[75]. Binaural beat embedded music intervention during cataract surgery has been proved to reduce perceived pain, anxiety, heart rate and blood pressures of patients[76].

Individualized Anesthesia Strategy Singh *et al*[77] compared blood pressure of patients in phacoemulsification cataract surgery under topical and peribulbar anesthesia. The intraoperative blood pressure significant reduced in peribulbar anesthesia group versus topical anesthesia group. Conversely, topical anesthesia reported to cause less pain and discomfort than peribulbar anesthesia during phacoemulsification cataract surgery in a research performed by Maharjan *et al*[78].

Gombos *et al*[79] compared effectiveness of retrobulbar anesthesia and topical anesthesia in cataract phacoemulsification surgery. In the retrobulbar group, fewer patients experienced pain during surgery and fewer recalled any perioperative discomfort. With retrobulbar anesthesia the objective parameters were more stable than with topical anesthesia, and systolic blood pressure was significantly lower. The results suggested that retrobulbar anesthesia have better anesthetic effect than topical anesthesia during cataract surgeries.

Bardocci *et al*[30] explored pain perception between second eye cataract surgery and first eye cataract surgery under topical anesthesia using 2% lidocaine hydrochloride jelly, while

most of other researchers performed topical anesthesia by eye drops. The pain experienced and cooperation did not differ between first and second eye procedures in Bardocci *et al*'s[30] research. Another research from Bardocci *et al*[80] confirmed that lidocaine jelly gives significantly higher aqueous levels of lidocaine, better patient cooperation, better analgesia, and less need for intraoperative additional anesthesia than the same amount of lidocaine eye drops. The results indicated that lidocaine jelly may have better anesthetic effect than topical anesthesia eye drops.

Sharma *et al*[81] reported that there was no significant difference in levels of intraoperative pain perceptions between the first-eye and second-eye cataract surgeries under assisted topical anesthesia. Assisted topical anesthesia means topical anesthesia combined with sedative drugs (like midazolam, propofol, or fentanyl) intravenous infusion to help patients to achieve adequate relaxation. The results indicated that topical anesthesia combined with general sedation may be an effective strategy for reducing pain perception during second-eye cataract surgery.

Choosing Appropriate Timing for Surgery Rational selection of operation time is conducive to reduce pain experience in cataract surgery. Zhu *et al*[82] reported that patients underwent cataract surgery in the afternoon showed increased preoperative anxiety level which may upregulate the secretion of relevant stress hormones. The patient's stressful emotional state and hormone level acted together to enhance intraoperative pain perception in the afternoon.

Time intervals between bilateral consecutive surgeries were significantly correlated with pain scores in second-eye cataract surgery[57]. Another research from Zhang *et al*[72] showed that the VAS scores during second-eye surgery were significantly higher in 1-week interval and 6-week interval subgroups compared with the first-eye surgery. When the extended the interval between twice surgeries to more than 6wk, the MCP-1 level in the second-eye preoperative aqueous humor was relatively low. It suggested that extending the operation interval (>6wk) between two consecutive cataract surgeries may help to reduce the pain perception of patients during second-eye surgery.

However, the time-point of inflammation peak after first-eye cataract surgery is still in dispute. Liu *et al*[83] reported that patients who accepted the second-eye surgery two weeks after first-eye surgery perceived most pain than patients choosing other time-interval. Hence, the time-internal selection between bilateral consecutive cataract surgeries still needs further research.

Lubricating the Eyelid Speculum Eyelid speculum is also a trigger of conjunctival pain during ophthalmic surgery under topical anesthesia[84-85]. A research from Jha and Kurumkattil[86] indicated that previously lubricating the speculum by viscoelastic agents relieved conjunctival pain perceptions in first-eye and second-eye cataract surgeries under topical anesthesia. In dry-speculum group, 78.79% of patients felt that second-eye surgeries were more painful than first-eye surgeries. However, in lubricated-speculum group, only 12.5% of patients reported more pain in second-eye surgeries than first-eye surgeries[86]. Lubricating the speculum could reduce the friction and pressure on palpebral conjunctiva and reduce the pain perception in second-eye surgeries.

CONCLUSIONS

Pain perception enhancement during second-eye surgery of consecutive phacoemulsification under topical anesthesia is a tricky issue that has puzzled ophthalmologists for a long time. Second-eye surgical pain enhancement also greatly influenced satisfaction and willingness for re-operation of patients with bilateral cataracts. If patients hesitate to receive second-eye surgery, anisometropia induced by monocular cataract surgery may seriously reduce their visual function and quality of life[87-88]. Elucidating the pathology mechanisms of pain perception enhancement during second-eye cataract surgery is crucial for promotion of intervention.

According to present studies, individualized and comprehensive intervention strategy is essential to improve intraoperative experience and cooperation of patients underwent second-eye cataract surgery. Preventive measures should be considered on the following dimensions: 1) stabilizing inflammatory levels; 2) intensifying anesthesia protocols; 3) improving neuropsychological condition; 4) improving surgical procedures. For bilateral cataract patients, more precise examination and monitoring are needed before and during second-eye surgery. Preoperative serum and aqueous humor inflammatory cytokines levels detection is helpful in indicating the preoperative inflammation level of second-eye surgery. The preoperative inflammation level is related to the intraoperative perceived pain. Ophthalmologists should cooperate closely with anesthesiologists to improve intraoperative cooperation and pain experience of patients with high pain-risk. In addition, perioperative assessment of anxiety and pain scores helps ophthalmic nurses to adapt psychological care strategy. It is recommended to include perioperative anxiety and pain assessment into routine surgical examination.

Immunological, neuropsychological, and pharmacological factors work together in the enhancement of second-eye surgery intraoperative pain. Although some progress has been made focusing this issue, there are still numbers of questions remain to be answered. For example, why the inflammatory cytokines changed in the contralateral eye after first-eye surgery? How to explain the seemingly paradoxical relationship between ACAID and sympathetic ophthalmia? The mechanisms of pain strengthening in second-eye surgery

need further exploration. With the development of molecular biology, we will achieve better understand on the enhancement of pain perception in second-eye cataract surgery and promote more targeted clinical interventions in future.

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