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Review

Cataract: Advances in surgery and whether surgery remains the only treatment in future

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ABSTRACT

Background: Cataract is the world's leading eye disease that causes blindness. The prevalence of cataract aged 40 years and older is approximately 11.8%–18.8%. Currently, surgery is the only way to treat cataracts.

Main Text: From early intracapsular cataract extraction to extracapsular cataract extraction, to current phacoemulsification cataract surgery, the incision ranges from 12 to 3 mm, and sometimes to even 1.8 mm or less, and the revolution in cataract surgery is ongoing. Cataract surgery has transformed from vision recovery to refractive surgery, leading to the era of refractive cataract surgery, and premium intraocular lenses (IOLs) such as toric IOLs, multifocal IOLs, and extended depth-of-focus IOLs are being increasingly used to meet the individual needs of patients. With its advantages of providing better visual acuity and causing fewer complications, phacoemulsification is currently the mainstream cataract surgery technique worldwide. However, patient expectations for the safety and accuracy of the operation are continually increasing. Femtosecond laser-assisted cataract surgery (FLACS) has entered the public's field of vision. FLACS is a combination of new laser technology and artificial intelligence to replace fine manual clear corneal incision, capsulorhexis, and nuclear pre-fragmentation, providing new alternative technologies for patients and ophthalmologists. As FLACS matures, it is being increasingly applied in complex cases; however, some think it is not cost-effective. Although more than 26 million cataract surgeries are performed each year, there is still a gap in the prevalence of cataracts, especially in developing countries. Although cataract surgery is a nearly ideal procedure and complications are manageable, both patients and doctors dream of using drugs to cure cataracts. Is surgery really the only way to treat cataracts in the future? It has been verified by animal experiments that lanosterol therapy in rabbits and dogs could make cataract severity alleviated and lens transparency partially recovered. Although there is still much to learn about cataract reversal, this groundbreaking work provided a new strategy for the prevention and treatment of cataracts.

Conclusions: Although cataract surgery is nearly ideal, it is still insufficient, we expect the prospects for cataract drugs to be bright.

1. Overview of cataract surgery

According to the World Health Organization, cataract is the world's leading eye disease causing blindness, affecting approximately 65.2 million people.[1] Approximately 51% of blindness is related to cataract, which is also a major factor in poor vision in both developed and developing countries.[2] Among all eye diseases, the blindness rate caused by cataract was 5% in developed countries, while 50% or more in poor and/or remote regions. Nearly 18 million people in the world suffered from bilaterally blind due to cataracts, and cataracts have caused moderate to severe vision loss in 52.6 million individuals.[1] The prevalence of cataract in the population aged 40 years and older is approximately 11.8%–18.8%.[2] At present, there are no effective methods for cataract prevention or drug treatment; however, surgical removal of the opaque lens and implantation of an intraocular lens (IOL) can restore vision in patients with cataracts. Cataract surgery is the most common ophthalmic surgery performed worldwide.[3] More than 26 million cataract surgeries are performed annually. Driven by demographic changes and access to more medical services, procedure volume is growing at a compound annual rate of 3.1%.

Standards for cataract surgery are developing worldwide. The revolution of cataract surgery has never stopped and has been going on, from early intracapsular cataract extraction (ICCE) to extracapsular cataract extraction (ECCE), even to current phacoemulsification (PCS). In

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developed countries, PCS is the mainstream method of cataract surgery. However, due to the high cost of operation, the shortage of well-trained surgeons and the poor maintenance of advanced equipment, the large-scale promotion of PCS in developing countries is facing certain challenges at this stage. Hence, small incision cataract surgery (SICS), an improved ECCE method, may be a more suitable alternative to PCS in developing countries due to its lower cost and less technical requirements.

2. Premium intraocular lenses (IOLs)

With the unceasing improvement in surgical equipment and techniques, cataract surgery has proven to be one of the safest and most successful operations around the world. With increases in standards of living, new technologies, including microincision cataract surgery and premium IOLs, have emerged one after another, while the impetus for cataract surgery has evolved from vision rehabilitation to vision improvement. It has converted from vision recovery to refractive surgery, leading to the era of refractive cataract surgery (RCS), and the application of premium IOLs is becoming more and more extensive in order to satisfy the personalized demands of patients. Multifocal IOLs showed superiority to monofocal IOLs in uncorrected distance visual acuity, the distant spectacles-independent rate is over 90% in patients with multifocal IOLs implantation, while only 52.4%–85% in monofoal IOLs patients. Among the patients with multifocal IOLs implantation, 81.8%–84.9% of them gained both distant and near spectacles-independence, while 7.5%–12% in patients with monofocal IOLs.[4] For patients with a requirement to correct corneal astigmatism, Toric IOLs creates a new possibility to meet their personal requirements during cataract surgery process, and spectacles-independence could be achieved in over 70% patients can see far without glasses.[5,6] Despite extensive positive experiences with multifocal IOLs, some patients showed dissatisfied symptoms postoperatively. Residual refractive error is the leading cause of poor vision after multifocal IOLs implantation**,** which causes nearly 64% of patients suffering from this.[7] However, among all IOLs, the multifocal IOLs accounts for 6–31%, and the main source is optical aberrations, for example, glare, halo, and so on.[8] Meanwhile, a new type of IOLs, the extended depth-of -focus (EDOF) IOLs, appears in the public field of vision. It can make up for the gap between the monofocal IOLs and the multifocal IOLs, by improving intermediate distance visual acuity and providing better contrast sensitivity.[9–12] (See Table .1).

3. Surgery technology innovation

In addition to intraocular lens calculation and intraocular lens design, the improvement of operation technology may also play a decisive role in further improving the visual effect after operation.[13] The advantages of providing better visual acuity and fewer complications, along with the suitability of premium IOLs presently, make phacoemulsification the predominant cataract surgical technique applied worldwide. Nevertheless, is phacoemulsification the culmination of cataract surgery innovation.

Table 1
Comparison between trifocal IOLs and EDOF IOLs.

	Trifocal IOLs	EDOF IOLs
UDVA/CDVA[12,95,96]	No significant difference	
UIVA/DCIVA[12,95,96]	No significant difference	
UNVA/DCNVA[12,97–99]	Superior	Inferior
Defocus curve[95,96,98,99]	Perform better from -4D to -2D	Perform better from -1.5D to -1D
Contrast sensitivity[96–98,100]	No significant difference in both photopic and scotopic conditions	
Spectacle independence[98,99,101,102]	90%–100% at far distance; 90%–100% at intermediate distance; 85%–95% at near distance (significantly better)	85%–100% at far distance; 85%–100% at intermediate distance; 60%–90% at near distance (significantly worse)
Photic disturbance[96,100,101]	More halo and glare	Less

The major complications of modern cataract extraction combined with IOL implantation include postoperative inflammatory response, surgically induced astigmatism, and posterior capsule opacification, which are also refractory to poor vision recovery in patients after cataract surgery. Surgical astigmatism is proportional to the longitude of the surgical incision. Postoperative inflammatory response and post-operative cataract are particularly associated with surgical trauma. Therefore, the focal point of cataract surgery innovation in the past two decades has been to decrease the size of the surgical incision and establish a set of surgical techniques to reduce surgical trauma and complications. In recent decades, the cataract surgical incision was reduced from 11 mm (ECCE) to 1.8 mm or less (PCS),[14] and surgical techniques have been established that effectively reduced surgical trauma, surgical astigmatism, the postoperative inflammatory response, and the occurrence of posterior capsule opacification. The standard procedure for 1.8 mm micro-incision surgery effectively reduced astigmatism from 0.88 D to 0.44 D.[14,15] However, a decrease in incision size alone does not satisfy the requirement, studies showed that converting from 3.0 to 2.0 to 1.8 mm incision will not lengthen the duration of the surgery or reduce the efficiency of the surgery, suggesting that SICS and MICS are equally efficient and safe.[14]

4. Femtosecond laser-assisted cataract surgery

Although great progress has been made in modern cataract surgery, many patients still suffer significant complications after surgery, such as corneal edema, macular edema, and inflammation, which may cause severe visual impairment and require continuous review. Meanwhile, the expectations of patients regarding the security and accuracy of surgery are constantly increasing. Hence, cataract surgery innovation is better to turn to a new creative way. Femtosecond laser-assisted cataract surgery (FLACS) has come into public view as an alternative technology for patients and ophthalmologists. By 2020, 972 SCI records of FLACS had been found, of which 712 were full-text articles. Outcomes (20.36%), cornea influence (17.13%), and complications (16.01%) were the most concerning areasarea. Learning curve, education, and equipment design have also gained extensive attention in the past two years. In 2009 and 2013, there were two inflection points; 98% of the articles were published after 2009, and from 2014, at least 100 articles have been published annually.

Femtosecond laser can assist in performing lens fragmentation, anterior capsulotomy, and self-sealing corneal incisions, and astigmatism correction[16,17] in cataract surgery. Femtosecond laser assistance enables precise implementation of each step, which optimizes the position of the IOL and the refractive state of the eye, remarkably promoting accuracy, effectiveness, and safety of cataract extraction surgery and opening up new alternatives to patients and ophthalmologists.[18]

Although some ophthalmologists still hold a doubt attitude towards the advantages of FLACS, several meta-analyses and random clinical trials (RCTs) have shown that, compared to PCS, FLACS achieves better visual and refractive outcomes, and gets effective reduction in endothelial cell loss and postoperative corneal edema.[18–28] A study focusing on endothelial analysis[29] showed that low-energy FLACS has advantages in endothelial cell loss, size, and shape variations in certain cataract grades. FLACS was showed to have the ability to preserve endothelial cells better and is more precise than PCS. FLACS is safe and does not cause a significant increase in macular thickness.[30] Some studies[31,32] have reported that, although macular central subfield thickness, cube volume, and cube average thickness increased postoperatively, while the values were similar between the FLACS and PCS throughout the whole 6-month follow-up, and no significant differences were found in central corneal thickness (CCT). Inflammatory flare values in FLACS were lower than those in PCS at 6 months. Hence, both FLACS achieved similar safety and efficacy outcomes as PCS.[33] (See Table .2).

With accumulating clinical experience, femtosecond cataract surgery has reached a relatively mature state. The accuracy, effectiveness, and safety of FLACS are greatly improved by optimizing the IOL position[34] and the eye refractive state, which increases our confidence in applying FLACS in complex situations. There is a high proportion of intraoperative endothelial cell loss in PCS for hard nuclear cataracts. Compared to PCS, FLACS for hard nuclear cataract surgery has been shown to reduce corneal endothelial damage, reduce corneal endothelial loss from 19.96% to 7.85%, and reduce vision recovery time from 3 months to 1 month.[35–37] Similarly, a mature white cataract may have increased capsular tear due to liquefaction of the cortex, although another study showed that compared to PCS, FLACS decreased the incidence of anterior capsular tears (0/66 vs. 8/66) and irregularity and decentration of capsulorhexis in white cataract, therefore implanting premium IOLs, including toric IOL, can be considered.[38,39] The safety of FLACS in myopia cases was confirmed in another study[40] showing that FLACS did not cause macular thickness increasing significantly. Yamazaki et al.[41] found that patients with atopic cataract can also get FLACS safely despite anterior subcapsular fibrosis and/or intumescent white cataract (IWC). Recent studies[42–44] on cataract patients with Fuchs endothelial corneal dystrophy indicated that FLACS may perform better than conventional phacoemulsification in the reduction of corneal endothelial cell loss and CCT changes. This trial of FLACS was expanded to more complex cases such as Marfan syndrome, subluxated lens,[45,46] Alport syndrome,[47] and shallow anterior chamber.[48,49]

The high cost of FLACS, requiring a much higher burden of scientific evidence and justification, makes it difficult to accept FLACS widely, as patients have to bear the cost themselves. Nevertheless, some others think that costs could decrease with more entrants in the market, which will lead to the procedure being more financially efficient with widespread adoption, which in turn will lead to further development. Although excellent ophthalmologists may control complications and visual outcomes in PCS to reach a level similar to that of FLACS, it should be emphasized that FLACS may help less experienced and skilled surgeons. Thus, it is controversial whether FLACS is an ideal or excessive surgical method. As the technology has been designed to promote safety and efficacy, should it be incorporated into our practice in the same way that phacoemulsification supplanted ECCE in the treatment of cataracts? Is it valuable to make an ongoing effort to guide the way forward in this new approach to cataract surgery? We believe that these questions may be answered in the future.

5. Current situation

In addition to technological innovation, we also need to focus on an issue of vital importance: whether surgery is the only way to cure cataracts. Is surgery sufficient for cataracts so that there is no need to develop other treatments?

Table 2
Comparison between FLACS and PCS.

	FLACS	PCS
Visual and refractive outcomes	Better in early stage in FLACS,[19,24] no significant difference in the long term[19,21,24]	
Surgical induced astigmatism[24]	No significant difference	
IOL decentration and tilt[21]	More horizontally centered in FLACS than in PCS	
Endothelial cell loss[19,21,24]	Less in FLACS than in PCS, especially in Fuchs endothelial corneal dystrophy and hard nuclear cataract[35,42]	
Macular thickness[19,24,31]	No significant increase	
Dry eye symptom[61]	Worse in FLACS than in PCS	
Overall incidence of complication[21]	No significant difference	
Price	High	Low

If conditions permit, one ophthalmologist has the ability to complete more than 2000 cataract surgeries a year, such as having sufficient support personnel, perfect infrastructure and patients who can afford and are willing to pay for them.[50] Cataract surgery rate (CSR) is the number of cataract operations per million people per year, which is an important indicator of cataract services availability. However, only when the calculation of CSR includes all cataract surgeries in a country/region with a specific population size, CSR can be used as a quantitative index of cataract surgery services. The median of global CSR is 1406, and the interquartile range is 633–2450. However, the median CSR in some African regions is 488, which is only one third of the global average, and even one tenth of that in high-income countries. Even considering the age distribution and the difference of blindness rate in different regions, there is still a big gap between the CSR of less than 1000 and the number of cataract surgeries needed to prevent avoidable cataract blindness, even less than 500. Among 102 countries that can monitor CSR, 19 countries had a CSR of less than 500, and 23 countries had that between 501 and 1000.[51] Therefore, as the only way to treat cataract, surgery is in short supply. Should we further seek other routes?

6. Complications

In addition, there is a certain risk of complications in any surgery, including cataract surgery. The prevalence of posterior capsule rupture is about 0.5%–5.2%, which is the most common intraoperative complication in cataract surgery.[52,53] And meantime, posterior capsule rupture leads to the increasing risk of endophthalmitis (4.22–9.49 times)[54] and retinal detachment surgery (15–18 times).[55] The prevalence of endophthalmitis, the most serious postoperative complication, ranges 0.03%–0.4%.[56,57] Clinical cystoid macular edema without any other complications or risk factors, had a reported prevalence of 1.2%–11.0%.[58] As the most common postoperative complication, the incidence of posterior capsule opacification is approximately 11.8% at 1 year, 20.7% at 3 years, and 28.4% at 5 years.[59] Both FLACS and PCS may aggravate dry eye, FLACS may increase the risk of postoperative fluorescein staining and dry eye symptoms.[60–62] Therefore, we need to pay more attention to dry eye patients undergoing FLACS through postoperative earlier evaluation and treatment.

7. Artificial intelligence and drugs in cataract treatment

In recent years, artificial intelligence (AI) research in ophthalmology has progressed rapidly, especially in the field of machine learning and deep learning. This may trigger a revolution that may completely subvert ophthalmic practice. AI systems have been partly used in glaucoma[63] and retinal disorders.[64] Different testing modalities, including optic nerve images, optical coherence tomography, and visual fields in automated glaucoma detection, relying on deep learning, has been promoted[65,66] AI based on fundus photos could also show advantages in screening and diagnosis of retinal disorders, including age-related macular degeneration (AMD) and diabetic retinopathy[67,68] The application of AI for cataracts is growing, and the research showed that compared with professional graders, deep learning is superior to other published automatic cataract grading methods in grading nuclear cataract from cross-sectional slit lamp images on Wisconsin grading system.[69–71] However, as research on AI for cataract has been limited to providing assistance for diagnosis, the question remains as to whether it is possible to expand its use to surgical applications. Therefore, as a new tool, AI may become a part of daily surgical care in the near future while bringing benefits to both patients and clinicians.

Inadequate cataract surgery increases the economic burden, and the emergence of postoperative complications has prompted profound consideration of screening drugs for cataract treatment. Oxidative stress is essential in the initiation and development of cataracts. Antioxidants or reactive oxygen species scavengers, such as GSH, vitamin E/C, zeaxanthin, lutein, carotenoids, and L-cystine, have been shown to protect lens lipid peroxidation and have a positive effect on slowing down the process of cataract formation.[72–76] Vita-iodurol (France) and Quinax (USA) are commercially available antioxidative drops that have also been applied to cataracts.[77] Quinone is also a critical factor in the pathogenesis of cataracts. Quinones at low concentrations can react with lentic proteins and show a damaging effect. In 1958, pirenoxine was introduced as a commercial eye drop to slow down the development of cataracts.[78] Pirenoxine could block the sulfhydryl combination with lentic proteins and slows down the development of cataracts.[79] Although numerous compounds have the potential to prevent development, the process of cataract formation cannot be reversed.

Currently, two groundbreaking studies have been conducted. In one, Makley et al.[80] found that the molecular 5-cholesten-3β,25-diol could reverse α-crystallin mutations related cataracts by upregulating the activity of the α-crystallin chaperone. Compared with treatment that is efficacious only for α-crystallin mutation-related cataracts, another more inspired work showed that lanosterol is a universal compound for reversing the formation of cataracts. The latter study found two lanosterol synthase (LSS) gene mutations related to congenital cataracts in two families. Moreover, LSS and lanosterol could delay and reverse the lentic protein aggregation, which has been evidenced in animals.[81] These groundbreaking studies bring a novel strategy for the cataracts treatment and have been highly remarked as "A new dawn for cataracts" in *Science*[82] and "Cataracts dissolved" in *Nature*.[83]

Recently, increasingly studies have focused on the drug-likeness mechanism of lanosterol. Kang et al. showed, via molecular dynamics simulations, that lanosterol can disrupt γD-crystallin aggregation by docking to the hydrophobic domain.[84] Meanwhile, experimental evidence has shown that lanosterol could prevent the aggregation caused by βB1/2 crystallin aggregation.[85,86] Although some conversely pointed out that lanosterol unable to reverse protein aggregation, further mechanistic studies have shown that lanosterol could remit and reverse universal aggregation probably by activating the proteasome and ubiquitin system.[87–90] However, lanosterol has limitations as a potential candidate from the perspective of drug-likeness properties. First, lanosterol would transform into other steroids uncontrollably, which may greatly influence its half-life in-vivo.[91] Second, the efficacy of lanosterol is relatively low. Furthermore, a study showed that the efficacy of lanosterol is strongly dependent on cataract severity in qualitative and quantitative ex vivo assays.[92] Therefore, it is worthwhile to continue studying new and potent synthetic molecules.

With the development of high-throughput techniques, appropriate compounds can be identified out of millions of candidates. A high-throughput platform in which human lens particles were removed from patients during routine cataract surgery and treated with candidate compounds has been established.[93] Based on the most recent one, 34 new synthetic lanosterol analogs were synthesized and evaluated, and lanosterol derivatives were demonstrated to reverse the lentic protein aggregation with better potency and efficacy.[94] Further evaluation of the lanosterol derivatives in lentoid bodies (LBs) and animal models, as well as detailed mechanistic studies, are in progress. We found that cataractous LBs became transparent when treated with a specific kind of lanosterol derivative. This unsubmitted result supports the anti-aggregation effect of lanosterol derivatives in human cataracts and shows the possible prospect of pharmaceutics.

Although ophthalmologists have been anticipating drug treatment for cataracts, research on medications for cataract prevention and treatment has also progressed. However, until now, there have been no rigorous controlled clinical studies, and drug research is still in progress. Consequently, surgery remains the only effective method for treating cataracts. There is still much to learn about cataract reversal, despite the many relevant meaningful previous results. These anti-aggregation compounds provide the possibility of cataract medication. We expect the prospects for cataract drugs to be bright.

Study Approval

Not applicable.

Author Contributions

Ke Yao conceived, designed, and supervised the review. Xinyi Chen and Jingjie Xu wrote the initial draft. Xiangjun Chen provided further editing. All authors have read and approved the final version of the manuscript. All authors attest that they meet the current ICMJE criteria for authorship.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Editorship Disclosure

Given his role as Editor-in-Chief, Ke Yao had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Andrzej Grzybowski.

Abbreviations

IOL	intraocular lenses
FLACS	femtosecond laser-assisted cataract surgery
ICC	intracapsular cataract extraction
ECCE	extracapsular cataract extraction
PCS	phacoemulsification
SICS	small incision cataract surgery
RCS	refractive cataract surgery
EDOF	extended depth-of -focus
RCTs	random clinical trials
CCT	central corneal thickness
CSR	cataract surgery rate
AI	artificial intelligence
AMD	age-related macular degeneration
GSH	Glutathione
LSS	lanosterol synthase

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