Malaysian Journal of Ophthalmology

© Malaysian Journal of Ophthalmology 2023; 5:1-16
Review article
https://doi.org/10.35119/myjo.v5i1.277

Antiscarring agents in glaucoma surgery: a literature review

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Abstract

Glaucoma filtering surgery has been gaining popularity as an early surgical intervention in glaucoma management. A thorough review of the literature revealed that the incidence of failure in glaucoma filtering surgery may be reduced with the use of antiscarring agents. Based on the published research, we hereby discuss the available types of antiscarring agents, their regimes, and their complications. Among the drugs used, mitomycin C and 5-fluorouracil are the most prominent. We discuss the indications for their use, mode of action, dosage, techniques, and duration of usage as well as complications. Although these agents have proven efficacy, they also increase the risk of complications. While newer agents have shown promising results, the long-term complications of these drugs are still inconclusive. We also explain the new agents and methods under investigation to control wound healing after filtration surgery. This is a crucial area to explore, as most of these agents are not tissue-selective and therefore their benefits must be weighed against their possible risks.

Keywords: 5-fluorouracil, antiscarring agents, glaucoma, glaucoma filtering surgery, mitomycin c

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Agen anti parut dalam pembedahan glaukoma: tinjauan literatur

Abstrak

Pembedahan filtrasi glaukoma semakin mendapat tempat sebagai mod intervasi awal penyakit glaukoma. Berdasarkan peninjauan literatur yang meluas kegagalan pembedahan ini dapat dikurangkan dengan mengguna agen anti parut. Objektif utama tinjauan kami adalah untuk membincangkan tentang kebaikan dan komplikasi agen anti parut yang sedang dan boleh digunakan dalam pembedahan filtrasi glaukoma. Mitomycin C dan 5- Fluorouracil merupakan dua agen anti parut yang kerap digunakan. Di sini indikasi bagi penggunaan agen ini, cara tindakan, dos, teknik dan jangka masa penggunaan serta komplikasi turut dibincangkan. Walaupun agen ini telah membuktikan efikasi mereka, namun risiko komplikasi agen ini masih tidak boleh diabaikan. Agen anti parut yang baru telah menunjukkan potensi yang bagus dari segi efikasi, namun komplikasi agen ini untuk jangka masa yang panjang masih tidak diketahui dan perlu ditinjau dengan lebih lanjut. Pengetahuan tenatang agen baru ini dari segi mod tindakan bagi mengawal penyembuhan parut yang masih dikaji turut diterangkan. Ini merupakan isu yang penting untuk diperhalusi disebabkan kebanyakkan agen ini tidak bersifat selektif, maka keberkesanannya perlu ditimbalbalas dengan kemungkinan risiko komplikasi.

Kata kunci: 5-flurouracil, agen anti parut, glaukoma, mitomycin C, pembedahan penapisan glaukoma

Introduction

Glaucoma is one of the leading causes of blindness and impaired vision worldwide after cataract.[1] This eye disease can result in progressive apoptosis of retinal ganglion cells and gradual loss of visual field. While there are many known risk factors for glaucoma progression, intraocular pressure (IOP) is the only modifiable risk factor. Therefore, most glaucoma treatment is catered toward lowering the IOP.[2] The goal of glaucoma treatment is to forestall any vision loss by controlling IOP in the same way blood pressure is optimised to reduce the risk of developing ischaemic heart disease or stroke.

The mainstay of glaucoma treatment has always been medical therapy, primarily in the form of eye drops. However, local and systemic side effects from either the active ingredient or preservatives in these eye drops limits their use.[3] Laser treatment is an intermediate option prior to surgical intervention. Selective laser trabeculoplasty

(SLT) and argon laser trabeculoplasty (ALT) are among the laser treatment options to increase conventional aqueous outflow through the trabecular meshwork in open-angle glaucoma. Being an office procedure and well tolerated with few side effects, SLT has become the preferred laser option. These laser treatments reduce the dependency on antiglaucoma eye drops, hence improving quality of life. However, most laser treatments have a failure rate of approximately 50% in 2 years.[4] In addition to being an intermediate option prior to surgery, laser treatment can also be used for glaucoma when traditional filtering surgeries are not suitable or have failed. Laser treatments include trans-scleral cyclophotocoagulation (TCP), micropulse cyclophotocoagulation (MPCP), and ultrasound cycloplasty (UCP). These procedures aim to reduce IOP by targeting the ciliary body, which produces aqueous humour. TCP involves using a laser to deliver controlled thermal energy to the ciliary body through the sclera without penetrating the eye. The laser energy is absorbed by the ciliary body, reducing its ability to produce aqueous humour and thus lowering IOP.[5] TCP is typically performed as an outpatient procedure and can be repeated if necessary. MPCP is a modified form of cyclophotocoagulation that uses a laser to deliver repetitive short pulses of energy to the ciliary body. Unlike continuous-wave cyclophotocoagulation, MPCP allows for rest periods between pulses, reducing the risk of thermal damage to surrounding tissues. By targeting the ciliary body, MPCP reduces aqueous humour production and lowers IOP. MPCP is considered a less invasive alternative to TCP, with potentially fewer side effects and complications.[6] UCP utilizes focused ultrasound energy to thermally coagulate the ciliary processes, reducing their ability to produce aqueous humour. The procedure involves the placement of an ultrasound device on the eye's surface, which emits focused ultrasound waves. The ultrasound energy is targeted to the ciliary processes, leading to their ablation and subsequent IOP reduction. UCP is a relatively new procedure and is still being evaluated. One study that evaluated the 3-year efficacy and safety of UCP in patients with refractory glaucoma reported that UCP significantly reduced IOP and demonstrated good long-term outcomes with a favourable safety profile.[7] These alternative laser treatments, including TCP, MPCP, and UCP, are considered when conventional filtering surgeries such as trabeculectomy or glaucoma drainage devices may not be suitable or have not provided sufficient IOP control.

Surgical intervention is the next step of treatment for inadequate IOP control with medical therapy and with or without laser treatment. With the advent of micro-invasive glaucoma surgery (MIGS), the options for surgical intervention in glaucoma have widened, catering to different levels of IOP control. Nevertheless, glaucoma filtration surgery has stood against the test of time and still remains the preferred option and the fall-back procedure should other surgical options fail.[8] These procedures include MIGS devices such as the XEN Gel Stent (Allergan Inc., Dublin, Ireland), Hydrus (Alcon, Fort Worth, TX, USA) iStent (Glaukos, San Clemente, CA, USA), Trabectome (NeoMedix Corporation, Tustin, CA, USA), and PreserFlo (Santen,

Inc., Emeryville, CA, USA),[9] as well as the conventional filtering surgeries such as trabeculectomy and glaucoma drainage device implantation.

One of the crucial factors in ensuring the success of surgical procedures that depend on subconjunctival bleb drainage is controlling scar tissue formation. Fibroblast proliferation and remodelling are key processes in wound healing in the context of glaucoma surgery. Fibroblasts play a crucial role in synthesizing extracellular matrix components and promoting tissue repair.[10] The duration of fibroblast proliferation and remodelling can vary depending on the specific wound and individual patient factors. In general, the proliferative phase of wound healing, which involves fibroblast activity, can last for several weeks to months. During this phase, fibroblasts migrate to the wound site, proliferate, and synthesize collagen, fibronectin, glycosaminoglycans, and other extracellular matrix components forming young fibrovascular connective tissue, also known as granulation tissue. Blood vessels are reabsorbed over time and fibroblasts largely disappear as the tissue is remodelled to form a dense collagenous subconjunctival scar. Fibroblasts proliferate between the conjunctiva/Tenon's capsule and the sclera at the surgical site, eventually leading to aqueous flow obstruction and failure of the filtering bleb.[10]

Ocular fibrosis following glaucoma filtration surgery is a complex process influenced by various factors. Here, we discuss some of the known causes of ocular fibrosis besides fibroblasts. Transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) are key cytokines involved in scarring. Park *et al.* reported that VEGF induces TGF-β1 to rise in the subconjunctival scar tissue after trabeculectomy and suggested that increased VEGF can stimulate the TGF-β1/Smad/Snail signalling pathway leading to myofibroblast transformation.[11] Inflammation plays a significant role in the development of ocular fibrosis. Inflammatory cells and cytokines released during the wound healing process can promote fibrotic tissue remodelling. Studies have shown that interleukin-6 (IL-6) and interleukin-1β (IL-1β) are involved in the fibrotic response following glaucoma filtration surgery. Finally, various biochemical and molecular mechanisms also contribute to ocular fibrosis. These include the upregulation of profibrotic factors, such as connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). Studies have shown increased expression of these factors in fibrotic tissues after glaucoma filtration surgery.[12]

The use of antiscarring agents has revolutionised filtering surgery. The introduction of 5-fluorouracil (5-FU) and subsequently mitomycin C (MMC) in the early 1990s revolutionised trabeculectomy and tremendously increased its success rate. These drugs are used to inhibit fibroblast proliferation and reduce excessive scarring. Its use has now widened to any procedure requiring a subconjunctival bleb as the route of drainage. However, they are not tissue-specific and give rise to many complications. Newer antiscarring drugs have been developed to prevent bleb scarring with minimal complications.

A literature search was undertaken on PubMed and Google Scholar on the topic of antiscarring agents in glaucoma surgery. This review examines the literature on the old and new antiscarring agents to discuss their efficacy, safety, and success in glaucoma surgery.

5-Fluorouracil

5-FU is a commonly used antiscarring agent in glaucoma surgery. It is a pyrimidine analogue that inhibits DNA synthesis, selectively inhibiting only the S and G2 phase of cell proliferation causing inhibition of fibroblast proliferation and enhancing bleb formation and function.[13] A systematic review conducted on postoperative use of 5-FU in glaucoma surgery showed that the inhibitory property of this antimetabolite agent reduced the probability of surgical failure in trabeculectomy, both in eyes at high risk of failure and those undergoing surgery for the first time.[14] 5-FU soaked in a sponge is usually administered to the sclera for 2 to 5 minutes before or after the half-thickness scleral flap incision is made. The technique used to deliver 5-FU varies. Postoperative 5-FU is administered in subconjunctival injections, the dose and regimen also varying widely.

Studies on postoperative subconjunctival 5-FU injections came about in the early 1990s to establish its efficacy and safety in trabeculectomy. The dose and concentration of 5-FU differed across the studies. The Fluorouracil Filtering Surgery Study was a randomised controlled trial aimed to evaluate the efficacy and safety of postoperative subconjunctival 5-FU injections after trabeculectomy in patients with poor prognoses. The regimen of 5-FU used was twice daily on postoperative days 1 through 7, and once daily on postoperative days 8 through 14. The investigators found failure rates of 51% with 5-FU (5.0 mg/0.5 ml) compared to 74% with placebo ($p < .001$).[15] In another randomized, controlled study, Ophir *et al.* administered 4 to 6 subconjunctival 5-FU injections (5 mg/0.5 ml of saline) in primary open-angle glaucoma (POAG) and chronic angle-closure glaucoma patients. After 17 months of follow-up, 96% of eyes in the treatment group maintained IOP of less than 20 mmHg, compared with 76% in the control group.[16] Goldenfeld *et al.* found significantly lower IOP (12.0 versus 16.8) with significantly fewer medications (0.2 versus 0.8) compared with controls at 20 months in another multicentre, prospective, randomized trial of 5-FU injections in primary trabeculectomy.[17] They used 5 injections of 5-FU (5 mg/0.1 ml) given over 2 weeks, with a total dose of 25 mg.

Intraoperative use of 5-FU (50 mg/ml for 5 min) in primary trabeculectomy has also been studied. Mora *et al.* performed augmented trabeculectomy using intraoperative sponge soaked with 50 mg/ml of 5-FU.[18] After a mean follow-up of 6 months, the mean postoperative IOP was 12.5 ± 5.7 mmHg with a mean IOP reduction of 52%. The mean number of glaucoma medications dropped from 2.5 to 0.3 postoperatively, with nearly 90% of patients not requiring antiglaucoma medications. While

there was no significant difference in the final IOP or success rate between low- and high-risk eyes, high-risk eyes seemed to require more postoperative supplementary 5-FU. The first masked randomised prospective controlled trial among East Asian patients, however, found that while intraoperative 5-FU (50 mg/mL) applied during trabeculectomy managed to significantly lower IOP after 3 years, there was no significant difference in optic disc and visual field progression.[19] Cunliffe et. al. studied eyes at high risk of surgical failure undergoing trabeculectomy with intraoperative surgical sponge soaked in 25 mg/ml of 5-FU directly on the sclera for 5 minutes.[20] They found the mean IOP reduction at final follow-up was 43.1%, with less postoperative complications compared to intraoperative subconjunctival injection of 5-FU, with less clinic visits and discomfort from repeated injections.

The XEN Gel Stent is a new approach to manage glaucoma. It provides an ab interno approach, thereby minimizing trauma to the conjunctiva and Tenon's as well as reducing excessive wound healing with the hope of improving bleb survival. Although this procedure appears less invasive, it can still cause bleb fibrosis as high as 45%, leading to high IOP.[21] To restore filtration in those failing blebs, postoperative needling revision is performed using 5-FU for lysis. One of the key predictors for 5-FU needling revision is postoperative day 1 IOP: the probability of requiring needling increases by 80% if postoperative day 1 IOP is greater than 20 mmHg and reduces to 35% if IOP is less than 10 mmHg.[22] One group published a result of 5-FU (5 mg/0.1 ml) subconjunctival injections as part of the postoperative management of bleb failure after XEN implantation. They found that mean IOP decreased from 23 mmHg to 13 mmHg and the number of medications decreased from 3 to 0.[23] Arnljots *et al.* conducted a study to analyse the efficacy and safety of needling with 5-FU following implantation of XEN Gel Stent with adjunctive MMC. This study found that needling revision resulted in good IOP-lowering effect without increasing the number of antiglaucoma medications, worsening in visual acuity, nor any major complications.[24] Hence, postoperative management with 5-FU is a safe, effective, and viable alternative to other methods.

Many of the complications of 5-FU use is attributed to corneal toxicity, which includes punctate keratopathy, corneal epithelial defects, and conjunctival erythema. In addition, there is also increased risk of hypotony, conjunctival bleb leak, and late-onset endophthalmitis.[25] Reducing the risk of 5-FU toxicity in glaucoma surgery is crucial to ensure patient safety. Some strategies have been suggested to minimize the risk of 5-FU toxicity, such as precise and adequate dosing and concentration during glaucoma surgery.[26] Adhering to proper surgical technique during glaucoma surgery is crucial in minimizing the risk of 5-FU toxicity. This includes meticulous application of the drug and avoiding inadvertent exposure to non-targeted areas. Surgeons should ensure that 5-FU is applied to the intended site and take precautions to prevent leakage or diffusion to surrounding tissues. The use of controlled-release delivery systems, such as biodegradable implants, has been investigated as a way to minimize the risk of 5-FU toxicity. These systems allow

sustained release of 5-FU, reducing the need for frequent injections and potentially lowering the overall systemic exposure to the drug.[27,28]

Close postoperative monitoring and timely follow-up visits are essential to detect and manage any signs of 5-FU toxicity. Regular evaluation of IOP, bleb morphology, and signs of ocular surface toxicity can help identify any adverse effects early on and allow for appropriate intervention.[29]

Mitomycin C

MMC is one of the two main antiscarring agents used to date.[13] It is an antineoplastic agent with antibiotic properties isolated from the fermentation filtrate of *Streptomyces caespitosus*, which has been shown to suppress fibroblastic activity. It possesses antitumour properties and has a direct cytotoxic effect, acting by reducing fibroblast collagen synthesis through inhibition of DNA-dependent RNA synthesis.[6] It also interferes with other components of wound healing, including cell migration and extracellular matrix production. MMC has also been postulated to have antiangiogenic properties as well as harmful effects on the ciliary epithelium.[6] The efficacy of MMC has been shown in studies to be better than placebo in lowering failure rates at 1 year and having significantly greater IOP-lowering effect.[30] Beckers *et al.* showed that the use of MMC 0.02% as an adjunct in trabeculectomy decreased IOP to less than 15 mmHg for 5 years with a success rate of 83 %.[31] Unfortunately, its use is also associated with complications such as hypotony, cataract formation, blebitis, endophthalmitis, and wound leak.[30,31]

A major limitation in MMC use is the need for an ideal dose to achieve a balance between its antimetabolite properties and avoiding its serious complications. There are multiple factors contributing to the effectiveness of MMC, among which its concentration is a significant one.[32] Robin *et al.* studied 4 groups of patients receiving either placebo or MMC, either in 0.2 mg/mL concentration for 2 minutes, 0.2 mg/mL for 4 minutes, or 0.4 mg/mL for 2 minutes. They concluded that increasing the concentration and duration of application has a possible slight benefit in IOP reduction, although complications such as development of cataract tend to be more significant at higher doses.[33]

The overall surgical success rate also increased with increased concentration, with rates of 88.9% with 0.2 mg/ml and 91.5% with 0.4 mg/ml MMC. However, the use of 0.4 mg/ml MMC leads to more complications, which results in surgical failure.[34] A study in Korea evaluated 26 patients who underwent trabeculectomy with different MMC concentrations of 0.4 mg/mL, 0.2 mg/mL, and 0.1 mg/mL for 5 minutes. IOP reduction correlated with MMC concentration used, with a mean IOP of 10.1 mmHg for 0.4 mg/mL MMC, 16.1 mmHg for 0.2 mg/mL, and 16.5 mmHg for 0.1 mg/mL after 3 months. They concluded that MMC in a dosage of 0.2 mg/mL gave the best results in terms of postoperative IOP, bleb formation, and low risk of complications.[35] This

finding corroborated reports by Casson *et al.*, who found that low-dose MMC concentration (0.02%) inhibits fibroblast proliferation for a prolonged period and the effect was localized to the treated area.[36]

Laube *et al.* evaluated 0.1/mL, 0.2/mL, and 0.4 mg/mL of MMC for 2.5 minutes, and found that 0.2 mg/mL was the most effective dose.[37] When comparatively evaluating the 0.02 mg/mL and 0.2 mg/mL MMC dose, Kitazawa *et al.* found 63.6% and 100% success rates, respectively, in primary trabeculectomy, but the more concentrated MMC resulted in transient hypotony maculopathy (18%) and cataract progression (18%).[38] Filtering surgery performed on higher risk eyes was as effective using a lower dose (0.2 mg/cc) of MMC as a higher dose (0.4 mg/cc), with incidence of complications and treatment failures slightly higher with higher-dose MMC.[39] These studies demonstrated that while higher concentration of MMC is related with better IOP reduction, it is also associated with significant complications that may result in failure of trabeculectomy surgery. The 0.2 mg/mL concentration of MMC seems to be the most effective concentration while having the least risk of complications.

The next variable that influences the success rate of glaucoma surgery is the duration for which MMC is applied. Manners *et al.* concluded that identical success rates were achieved whether MMC 0.2 mg/ml was applied to the tissue for 5 minutes or 2 minutes.[40] This finding is also supported by Mégevand,[41] which showed that a 2-minute intraoperative application of 0.2 mg/ml MMC is as effective as a 5-minute exposure while maintaining unaltered rate of complications. Exposure time has not been shown to affect postoperative IOP.[13,30]

For many years, surgeons have been using soaked sponges to deliver MMC to the subconjunctival space followed by copious irrigation. Preoperative injection of MMC in the subconjunctival space has been performed to replace the soaked sponge technique in recent years. Maheshwari *et al.* found the complete success rate of MMC injection in trabeculectomy was 90.5% compared to 87% with sponge application, with all major complications occurring in the sponge group.[42] Khouri *et al.* also found the injection group to be superior, as it required fewer needling procedures, although complication rate and IOP control were similar between both methods.[43] In a prospective study, Pakravan *et al.* also demonstrated equal safety and IOP results for injection and sponge, but a more favourable bleb morphology was demonstrated with the injection.[44]

MIGS provides a safer and less invasive alternative for IOP reduction than traditional surgery while reducing medication dependency. MIGS devices utilising subconjunctival filtration, such as the XEN Gel Stent, require MMC injection and formation of a filtrating bleb to create a non-physiologic route for aqueous outflow, which is the basis of the traditional trabeculectomy and aqueous shunt glaucoma surgeries. Galal *et al.* conducted a study where 13 POAG patients underwent XEN Gel Stent implantation with MMC 0.01% injection prior to implant insertion without MMC washout. This resulted in a significant IOP reduction from 16 ± 4 mmHg to 12 ± 3 mmHg (29.4% IOP reduction) after 12 months.[45]

Unlike trabeculectomy, usage of antifibrotic agents in glaucoma drainage devices remains controversial. In a study which compared usage of MMC in Molteno (Nova Eye, Inc., Fremont, CA, USA) versus placebo, adjunct MMC did not demonstrate a significant difference in outcomes compared with placebo.[46] In a study where the efficacy and safety of intraoperative MMC in eyes undergoing Ahmed Glaucoma Valve (New World Medical, Rancho Cucamonga, CA, USA) implantation were studied, mean IOP did not significantly differ between MMC and control eyes. Furthermore, the mean number of postoperative antiglaucoma medications was similar in MMC-treated eyes and controls. There was no significant difference in the incidence of postoperative complications between both groups.[47] One retrospective study reported no benefit of intraoperative use of MMC 0.4 mg/ml or 5-FU 50 mg/ml with Baerveldt (Johnson and Johnson Surgical Vision, Inc., Irvine, CA, USA) implants.[48] As a result of these investigations, antifibrotic agents are not currently used with glaucoma drainage devices.

Newer generation antiscarring agents

Anti-vascular endothelial growth factor and monoclonal antibodies

Complications related to antifibrotic agents have channelled research into alternative methods of preventing tissue fibrosis by focusing on the inhibition of Tenon's capsule fibroblasts through the regulation of various growth factors. Scar formation after glaucoma filtration surgery may be reduced by inhibiting VEGF.[49] This is because VEGF, which stimulates fibroblast proliferation *in vitro*, is upregulated in the aqueous humour of glaucoma patients. Animal studies conducted using this drug revealed that the complications associated with MMC and 5-FU are avoidable, although its potency for IOP reduction remains unanswered.[49] A systematic review by Liu *et al.* found that the use of bevacizumab increased the success rate of trabeculectomy and reduced IOP and number of antiglaucoma medications when compared with placebo; however, it increased the risk of bleb leakage.[50] Bevacizumab also significantly increased the rate of encysted blebs compared with MMC. On the other hand, Zarei *et al.* used topical bevacizumab 4 mg/ml for 2 weeks post-augmented trabeculectomy instead of intraoperatively and concluded that bevacizumab did not significantly affect the IOP trend, but significantly decreased cystic bleb formation in short-term follow-up.[51]

The eyes of glaucoma patients have been shown to overexpress TGF-β, which is thought to cause scarring in and around the eye. Human anti-TGF-β2 monoclonal antibody (CAT-152; lerdelimumab) has been studied as a new antiscarring agent that neutralizes the cytokine TGF-β2.[52] Postoperative subconjunctival injections of this drug in rabbits have been shown to significantly improve surgical outcomes, reduce subconjunctival scarring, and minimise the risk of corneal side effects.[52] However, in a subsequent phase III study, no significant difference was found between subcon-

junctival application of CAT-152 and placebo in preventing failure of primary trabeculectomy in humans.[53]

Other antithrombotic and anti-inflammatory agents

Saratin is a 12 kD protein which was originally isolated from the saliva of the leech *Hirudo medicinalis.* It has both antifibrotic and antithrombotic properties. This agent has been shown to successfully prolong bleb elevation comparable to MMC without significant toxicity.[54]

Collagen matrix implants (Ologen, Aeon Astron Europe B.V., Leiden, The Netherlands) and amniotic membrane transplantation (AMT) are other means that have been found to be successful in preventing fibrosis and reorganizing subconjunctival scar formation during the wound healing process. They also reduce postoperative inflammation, incidence of bleb leakage, and conjunctival erosion.[10]

Ologen is a collagen matrix implant that is placed on top of a sclera flap during a trabeculectomy surgery before the conjunctiva is closed. This degradable implant influences aqueous flow by absorbing aqueous humour into its porous structure and acts as a scaffold in guiding fibroblasts to grow in a haphazard manner rather than in an organised way. This changes tissue remodelling in trabeculectomy, resulting in reduced scar formation and therefore improving trabeculectomy outcomes.[55] Perez *et al.* conducted a study on trabeculectomy with Ologen and concluded it has the same success rate as trabeculectomy with MMC for lowering IOP at the 2-year follow-up. Due to its non-teratogenic properties, it may be a good substitute for poor MMC candidates such as pregnant women or patients with previous blebitis.[56] Subsequent studies that compared the long-term outcomes of the Ologen implant in trabeculectomy concluded it is a safe and effective procedure for glaucoma patients, and is comparable to MMC in terms of long-term success rates and efficacy in lowering IOP.[57,58] Ologen has also showed positive results in association with XEN Gel Stent implantation, where postoperative mean IOP reduction with and without Ologen was 24.5% and 19.7%, respectively.[59]

The amniotic membrane is a tissue that can be used as a replacement for conjunctiva over the filtration surgery site. It has many beneficial features: it is transparent, immunologically inert, and has been shown to have anti-inflammatory, antifibrotic, antiangiogenic, and possibly antimicrobial properties. The amniotic membrane acts as a substrate for epithelium to grow on and downregulates TGF-β signalling to reduce fibroblast production and myofibroblast differentiation. This prevents scarring in the subconjunctival space and promotes bleb survival.[60] Glaucoma filtering surgeries using AMT had higher success rates, lower postoperative mean IOPs, and fewer complications.[61,62] A systematic review of 5 randomised controlled trials showed that mean IOP was lower and that complications, including a flat anterior chamber and hyphema, were decreased in trabeculectomy with AMT compared to trabeculectomy without AMT at 1 year postoperative. However, the evidence that these devices are as safe as trabeculectomy alone is unclear.[63]

There are many newer antiscarring agents in development. However, future clinical use of these agents is still being established, as their effects on glaucoma surgery still needs to be ascertained.

Conclusion

Glaucoma filtering surgery has been gaining popularity as an early surgical intervention in glaucoma management. A thorough review of the literature reveals that the incidence of failure in glaucoma filtering surgery can be reduced with the use of antiscarring agents. Among the agents mentioned above, MMC remains the most potent in terms of IOP reduction and failure rate.[49] Although newer agents have shown promising results, their long-term effects remain to be elucidated. This is a crucial area to consider, as most of these agents are not tissue-selective. The advent of subconjunctival MIGS further increases the need to identify tissue-selective antiscarring agents.

Although intraoperative MMC provides greater IOP reduction in trabeculectomy compared to intraoperative 5-FU, both agents are comparable in qualified and complete success rates. Even though these antimetabolites result in significant IOP reduction, both drugs are not selective and cause widespread cell apoptosis, leading to a significant side effect profile including hypotony, blebitis, endophthalmitis, bleb leakage, and vision loss.[52]

While the increase of glaucoma surgery has started to change the face of glaucoma management, subconjunctival fibrosis remains a challenge. Although antifibrotic drugs are effective in reducing fibrosis, their side effects may be of concern, hence the continuing quest to find toxic-free, inexpensive, and potent antiscarring agents with localised area of action.

Declarations

Ethics approval and consent to participate
Not required, as this is a literature review.

Competing interests
None to declare.

Funding
None to declare.

Acknowledgements
None to declare.

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