Minimising scarring after glaucoma surgery

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Clinical Issues: Minimising scarring after glaucoma surgery

1) Current Approaches

The trabeculectomy procedure is the most commonly performed glaucoma filtration surgery (GFS) and scarring is the most important reason for failure.1 Simple but significant modifications to the original techniques have reduced the complications of surgery with anti-metabolites. These include wider surgical area of treatment, and much better aqueous flow control, embodied in a system known as the Moorfields Safer Surgery System.1 Current agents used in both the clinic and the operating theatre to minimise scarring include steroids and anti-metabolites (5-FU and MMC). However, these treatments still carry increased risks of significant complications including corneal epithelial damage, wound leak, shallow anterior chamber and cataract.2 Various strategies can be used to prevent scarring in order to improve outcomes; these are summarised in Table 1. However, it is important to develop even better treatments with increased efficacy and a higher safety profile.

2) Future Trends

Wound healing is a complex process consisting of a series of overlapping events with different cell types influencing each other’s behaviours through different interactions (Figure 1).3 Recent investigations into novel therapies include agents with direct effects on cells and cytoskeletal functions such as serum amyloid P (SAP), anti-inflammatory agents, anti-growth factor antibodies targeting vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP) inhibitors and TGF-β.

SAP is an acute phase protein found to regulate the activation of fibrocytes and phase II trials are underway to assess its use as an anti scarring agent by sub-conjunctival post-operative injection for GFS.2 While broad-spectrum anti-inflammatory drugs such as steroids are widely used post-operatively, better anti-inflammatory steroid-like molecules with potentially less side effects and improved drug delivery approaches are being investigated. Conjugation to dextrimers or association to cyclodextrins may allow for prolonged release and enhanced bioavailability, reducing the risk of scar formation.

Various protein growth factors have been shown to play a critical part in scarring. Much interest has focused on VEGF, partly because of its role in neo-vascularisation in wet macular degeneration. VEGF expression is increased in the Tenon’s tissue of patients with failed GFS compared with those with successful surgery or no glaucoma.4 Development of a combination of anti-VEGF agents with 5-FU or MMC is continuing.4 MMPs play a significant role throughout the entire wound healing process and results from studies of MMP inhibitors such as Ilomastat and Doxycycline have shown promise experimentally.5

Apart from antagonists to VEGF, TGF-β is a pro-fibrotic cytokine that is increased in glaucoma patients; it stimulates fibroblast migration, proliferation, collagen synthesis and myofibroblast differentiation. Therapeutic approaches to target TGF-β include antisense oligonucleotides and antibodies. The failure of a clinical trial of TGF-β2 antibody may have resulted from inadequate antibody levels (only 30 minute half life) and lack of TGF-β1 antagonist activity.

Improved antagonism of targets using other molecules such as short interfering RNA (siRNA) may offer much longer inhibition of TGF-β and other targets in the eye. Further development of new therapeutics includes modified antibodies, RNAi, gene therapy, nanoparticles and liposomes.6 Further developments in these areas will include combinations and optimal drug delivery approaches to minimise ocular toxicity; hopefully, this will improve prognosis in GFS.

3) Conclusions

While anti-metabolites have had a profound effect on the success of GFS, their associated complications have resulted in a search for suitable options with improved efficacy and therefore improved surgical success. There are already simple strategies that can improve outcome (Table 1) With novel targets, treatments and drug delivery methods being developed, soon we should have a number of tools to minimise scarring and ultimately to reduce the risk of...
glaucoma progression for our patients through more reliable intraocular pressure (IOP) control.

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Table 1: Strategies to minimise scarring during after glaucoma surgery

- Identify high-risk patients – consider appropriate actions including antimetabolite
- Reduce inflammation – non-preserved drops, minimize anti-glaucoma drops, short pre-operative course of steroids topically (preferably preservative-free) or systemically if extremely inflamed
- Hemostasis – apraclonidine or adrenaline to vasoconstrict. Cauterize leaking vessels
- In scarred eyes hydrodissect conjunctiva to reduce trauma and bleeding
- Use local anaesthetic in trabeculectomy area for their anti-scarring effects on fibroblasts and to stop pain – vascular leakage reflex
- Maintain blood aqueous barrier – prevent intra and post-operative hypotony, consider bevacizumab in hypervascular eyes to reduce protein leakage and stimulation.
- Use anti-metabolite and apply over wide surface area to encourage diffuse non-cystic blebs
- Use steroids for at least 3 months after surgery
- Ensure early aqueous flow to prevent contact scarring/flattening of forming bleb
- If maximum grading of redness/inflammation on Moorfields bleb scale (www.blebs.net, 2-6 times risk of failure depending on time after surgery) and/or rising IOP consider sub-conjunctival (s/c) antimetabolites + steroid + local anaesthetic (for pain relief and anti-scarring). If persistent consider s/c bevacizumab, topical and oral non-steroidal anti-inflammatory drugs and steroids.
- If needling required and significant scarring present, consider pre-operative s/c MMC (up to 0.2mg/ml) with great care

References