WOUND HEALING AFTER GLAUCOMA SURGERY: HOW TO MANAGE IT?

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ABSTRACT

Agents such as the antimetabolites 5-fluorouracil (5FU) and mitomycin-C (MMC) have revolutionised glaucoma surgery in patients with a high risk of surgical failure. However, vision threatening complications can be associated with the use of these agents. Changes in antimetabolites application during and after the surgery can increase the safety and reduce the complications while maintaining effectiveness.

RÉSUMÉ

Les antimétabolites tels que le 5 fluorouracil (5-FU) et la Mitomycine-C (MMC) ont révolutionné la chirurgie du glaucome, surtout chez les patients à haut risque d'échec chirurgical. Cependant, la vision peut être compromise par l'utilisation de ces produits cytostatiques. Ainsi afin de limiter leurs complications tout en maintenant leur efficacité, l'application des antimitotiques se réalise pendant et après la chirurgie selon différentes modalités, dont les détails seront discutés dans ce papier.

KEY WORDS

Wound healing, management, glaucoma, surgery.

MOTS-CLÉS

Cicatrisation, traitement, glaucome, chirurgie.

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INTRODUCTION

Recent research (3) has suggested that glaucomatous progression can be stopped in the majority of patients over a decade or more if pressure can be controlled in the 10-15 mmHg range. This can sometimes only be achieved with glaucoma surgery and adjunctive agents to prevent scarring, which is the most important determinant of long-term intraocular pressure control. However, this often leads to hypotony, blebitis, endophthalmitis, cystic uncomfortable blebs and paradoxically failure in the long-term due to scarring.

In this presentation I will outline the improvements in glaucoma surgery and wound healing modulation which will help us to achieve better long-term results with less complications, particularly from the patient's point of view.

PATHOPHYSIOLOGY AND PHASES OF WOUND HEALING

During the first four days (inflammatory phase) tissue trauma resulting from glaucoma filtering surgery leads to a constriction of blood vessels and to a shift of plasma proteins and blood cells from the intracellular to the extracellular space. Tissue factors such as histamine, serotonin, prostaglandins, leucotrienes, and complement factors are secreted. Vascular permeability results in an accumulation of fibrinogens, fibronectin, and platelets. Fibrinogen is transformed to fibrin. Platelets attach to the fibrin network and to vascular endothelial cells. A clot of fibrin, fibronectin, platelets, and trapped blood cells is formed.

During the next 5-14 days (proliferative phase) the macrophages from the surrounding tissue release factors that stimulate fibroblast migration and proliferation. Most fibroblasts secrete procollagen, which in turn is transformed into collagen stabilized by mucopolysaccharides. Angiogenesis and fibroblast proliferation result in granulation tissue. The last phase of wound healing (remodelling phase) begins during the fibroblastic phase (day 5) and can last for more than 1 year. During this period collagen matures and the number of fibroblasts and blood vessels decreases. A dense collagenous subconjunctival scar results.
A number of mechanisms may change the fibroblast phenotype, leading to activation of fibrosis. Khaw and co-authors have confirmed an increased number of preoperative conjunctival cells (''prestimulated fibroblasts'' for the proliferative phase) in patients with higher IOP after surgery (4). Of special interest, the use of multiple medications can increase the number of these preactivated conjunctival cells (macrophages, lymphocytes, mast cells and fibroblasts), thereby increasing the risk of bleb fibrosis (1). Hence, pretreatment with topical steroids can be recommended if intensive glaucoma medication has been administered for longer periods (4).

CLINICAL BLEB CLASSIFICATION

The development of the filtering bleb after trabeculectomy is essential for the long-term success of filtering surgery. Meticulous slit-lamp examination and bleb histopathology are equally important in recognizing the signs of unfavourable bleb development. This will allow for earlier decision making with regard to the necessity, modality and timing of further treatment (i.e. increase of local steroids or use of antimetabolites).
The two main morphological classifications are *Indiana bleb appearance classification (IBAGS) and Grehn classification*. Based on serial pictures, the IBAGS classification grade the height of the bleb from H0-H3, the extent from E0-E3, the vascularity from V0-V4 and the presence or absence of the Seidel signs (2). Grehn classification is based on favourable (microcysts of conjunctiva, paucity of vessels, diffuse bleb, moderate elevation of the bleb) and unfavourable (''cork-screw'' vessels, excessive conjunctival inflammation, high-domed appearance, encapsulation of the bleb) bleb development signs (6).
With a careful slit lamp exam of the bleb, the clinician may have a good idea at each postoperative visit if impending failure will appear so that a proper antiscarring agent can be applied quickly before wound healing has sealed the scleral flap.

ANTIPROLIFERATIVE AGENTS

Without inflammation, wound healing does not take place. Hence, preoperative and postoperative inflammation should be minimized by treatment with an anti-inflammatory agent, such as a corticosteroid.
Topical corticosteroid treatment after trabeculectomy is associated with a significant reduction in final IOP (4). The role of nonsteroidal anti-inflammatory drugs (NSAIDs) is still uncertain. Newer agents inhibiting some aspects of the inflammation pathway (e.g. cyclooxygenase-2) may also be useful. Another agent modulating inflammatory cell activity is cyclosporine, which may have a role in preventing scarring (4).
TGF-β2 is assumed to play an important role in glaucoma and glaucoma surgery. This factor's highest concentration in the body is seen in the aqueous humour, with generally higher concentrations in glaucoma subgroups than in controls.
TGFb2 is a cytokine that stimulates extracellular matrix formation, inhibits proteolytic enzymes, and mediates immunosuppression. TGF-ß may even neutralize the effect of MMC *in vivo* (4).
CAT-152, a human monoclonal antibody that neutralises transforming growth factor b2 (TGFβ2), seems a promising future alternative to antimetabolites now in use to prevent bleb failure. CAT-152 (Cambridge Antibody Technology, Melbourn, UK) is a fully human monoclonal antibody specific to the active form of human TGF-β2, which is the predominant form in the eye.

Unlike to the more widespread effects of antimetabolites such as 5-FU and mitomycin-C that are used for modulation of filtration surgical wound healing, anti TGF-b2 antibodies are very specific. They selectively inhibit inflammatory factors that are released when the ocular tissues are damaged during surgery.

The inhibitory effect of the CAT-152 antibody on scar formation following trabeculectomy is the subject of the European CAT-152 (Cambridge Antibody Technology) Study in Trabeculectomy Trial, a multicentre, double-masked, randomised, placebo-controlled study investigating the efficacy, safety, and tolerability of the substance.

The Phase III study enrolled 344 patients at 38 centres in six countries (Belgium, France, Germany, the Netherlands, Sweden, and the UK). The results of this study are not yet available, as the follow-up of the patients is still ongoing.

In a previous pilot study involving 24 patients from the UK, glaucoma surgery lowered IOP in both the CAT-152 and placebo groups. However, there was a statistically significant superior IOP reduction 12-months postoperatively for CAT-152 recipients and fewer medications were necessary to achieve target IOP. The results showed good efficacy and excellent local tolerance of CAT-152. There was no sign of increased inflammation in the anterior chamber (7).

GUIDELINES FOR MANAGEMENT OF WOUND HEALING

1. During the surgery: safe surgery system

The antimetabolites 5-FU and MMC continue to be the backbone of antiscarring treatments. Although subjonjunctival 5-FU was the first widespread antimetabolite regimen used, intraoperative regimens of MMC or 5-FU have gained favour because of the convenience, supplemented by postoperative 5-FU injections. Their respective indications are based on the patients'risk of surgical failure (table 1) (4).
Strategies to minimize the incidence of complications associated with antimetabolite use in glaucoma filtration surgery include increasing the surface area of application, fornix based conjunctival incisions and scleral flap size. Furthermore, without touching the edges of the fornix based conjunctival incision, 5-FU should be applied intraoperatively during 3 minutes because the tissue uptake rises sharply and then peaks at about 3 minutes, with only a small rise thereafter (8). These strategies have led to a dramatic reduction in cystic blebs and long term complications such as endophthalmitis (4).
Future approaches to wound healing modulation will use TGFß2 antibodies, which have

Table 1: *Moorfields Eye Hospital intraoperative antiscarring regimen.*

Low- risk patients (nothing or intra-operative 5-FU 50mg/ml)
No risk factors
Topical medications (βblockers/pilocarpine)
Afro-Caribbeans (elderly)
Youth <40 years without other risk factors
Intermediate risk patients (intraoperative 5-FU 50mg/ml or MMC 0.2 mg/ml)
Topical medication (adrenaline)
Previous cataract surgery without conjunctival incision
Several low-risk factors
Combined glaucoma filtration surgery/cataract extraction
Previous conjunctival surgery (*eg*. squint surgery/detachment surgery/trabeculectomy)
High-risk patients (intraoperative MMC 0.5 mg/ml)
Neovascular glaucoma
Chronic persistent uveitis
Previous failed trabeculectomy/tubes
Chronic conjunctival inflammation
Multiple risk factors
Aphakic glaucoma (a tube may be more appropriate in this case)

fewer side effects and may more effectively control postoperative wound healing.

2. After the surgery: Intensified Postoperative Care

Based on the morphological classification of filtering blebs (6), Intensified Postoperative Care (IPC) used a rigorous regimen of 5-FU injections or needling if excessive wound healing occurred (5).

So when corkscrew vessels (dilated conjunctival vessels) were present, the steroid application was first increasing up to eight times a day and then, if insufficient, 5-FU injections were started. When early signs of scarring (fixed conjunctiva on the scleral flap) appeared, 5-FU injections were applied. The 5-FU injection requires a single dose of 5.0 mg 5-FU per day the first week and then per week for six weeks if needed (5). Needling was performed if an encapsulated bleb developped, followed by a series of 5-FU injections. Marquardt et al. compared first trabeculectomy operations between an IPC group and a 'normal' postoperative group over a four-year follow-up period. Of the 177 trabeculectomies, 73 had intensified follow-up and 104 had conventional follow-up. The target IOP success rate at four years was recorded with or without medication. Some 64 % of IPC patients reached target IOP without medication, compared with 39 % of non-IPC patients (5).

Following that regimen (5), maximum administration of 5-FU usually was 13 injections which is, in a clinical practise, time-consuming and for the patients, frightening.

Since the advent of intraoperative 5-FU application and the use of subconjunctival viscoelastic prior the postoperative 5-FU injections, the number of 5-FU injections should doubtless decrease. After the lid speculum is inserted, the eye is anesthetised and washed with Isobetadine®. A 30 Gauge needle mounted on the viscoelastic is inserted subconjunctivally between 40 degrees to 90 degrees from the bleb depending of the exposure. The viscoelastic is injected first. The needle should be left in place and used to inject the 5-FU beyond the viscoelastic. This new technique of postoperative 5-FU injections offers considerably less corneal complications and more confort for the patients (9).

CONCLUSION

The success rate of glaucoma surgery can be increased by following recommendations developed into a "Safer surgery system" and into a "Intensified Postoperative Care":

1) The judicious use of antimetabolites at the time of and after surgery, including 5-fluorouracil and mitomycin-C.

2) The method of applying antimetabolite intraoperatively has been improved. Increased surface of application, fornix based conjunctival incisions and larger scleral flaps have led to a dramatic reduction in cystic blebs and long term complications such as endophthalmitis. The time of 5-FU application should be 3 minutes, followed by BBS wash.

3) Better methods of applying postoperative anti-scarring agents including the use of viscoelastics.

4) The use of newer antiscarring techniques, including "smart" agents such as human monoclonal antibody to transforming growth factor beta-2 (TrabioR) which has a much better safety profile and is now in a multicentre trial around the world.

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