Adjunctive Therapy in Trabeculectomy and Tube Shunts: MMC / 5FU and Other Perioperative Injections

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Wound Healing

• The most common cause of failure on glaucoma filtering surgery.

• Increased fibroblast activity with associated production of collagen and glycosaminoglycans.

• Incision into any tissue leads to a complex process to heal the wound.

Allingham, RR. et al. Shields’ Textbook of Glaucoma
Wound Healing After Glaucoma Surgery

- Main determinant of long-term IOP after glaucoma filtration.
- Control Fibroblast Activity: MMC and 5-FU

Wound Healing After Glaucoma Surgery

- Is just like the Goldilocks Story
- It’s a process of trial and error in healing
- Until you get it “just right”

Wound Healing After Glaucoma Surgery

- Optimize the Effects of Antimetabolites by titration against risk factors.

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Characteristics</th>
<th>Regimen</th>
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</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>No risk factors</td>
<td>Nothing or Intraoperative 5-FU for 5 min</td>
</tr>
<tr>
<td></td>
<td>Topical Meds (ββ, Pilo)</td>
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<td></td>
<td>African and elderly</td>
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<tr>
<td>Mid Risk</td>
<td>Topical Meds (others)</td>
<td>Intraoperative 5-FU 50mg/ml for 5 min or MMC 0.2mg/ml for 3 min</td>
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<tr>
<td></td>
<td>Previous Cataract Surgery</td>
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<tr>
<td></td>
<td>Combined Glaucoma Cataract Surgery</td>
<td></td>
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<tr>
<td></td>
<td>Previous Conjunctival Surgery</td>
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<tr>
<td>High Risk</td>
<td>Neovascular Glaucoma</td>
<td>MMC 0.5mg/ml for 3 min (+/- Tube)</td>
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<tr>
<td></td>
<td>Chronic Persistent Uveitis</td>
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<td></td>
<td>Previous Failed Trab/Tube</td>
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<tr>
<td></td>
<td>Chronic Conjunctival Inflammation</td>
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<tr>
<td></td>
<td>Multiple Risk Factors</td>
<td></td>
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</tbody>
</table>

Khaw PT et al. Glaucoma Today; July/August 2004, pp 12-19
Wound Healing After Glaucoma Surgery

Size of Antimetabolite Treatment Area:
– Employ a large treatment area – avoid “ring of steel”

Application Technique:
– Apply under conjunctiva and scleral flap prior to entering the anterior chamber.

Khaw PT et al. Glaucoma Today; July/August 2004, pp 12-19

5 Fluorouracil

Pyrimidine analogue blocking DNA synthesis (thymidylate synthesis) in the S phase of the cell cycle

First drug to be studied after corticosteroids to control wound healing following a trabeculectomy.

Intraoperative 50mg/ml on a surgical sponge similar to MMC.

Post operatively may be injected 5mg in 0.1-0.5ml

Total dose can be monitored for healing response and toxicity.

Allingham, RR. et al. Shields’ Textbook of Glaucoma
The Fluorouracil Filtering Surgery Study Group

- Multicenter, randomized clinical trial of 213 patients with glaucoma.

- Demonstrated improved success rate of filtering surgery in high risk cases.

- Protocol: 5mg 5 FU Sub conjunctiva injections BID for 7 days, then once daily for 7 more days.

Allingham, RR. et al. Shields’ Textbook of Glaucoma
Gupta, AK. et al. Handbook of Clinical Trials in Ophthalmology

Mitomycin C

- A naturally occurring antineoplastic agent derived from Streptomyces caespitiosus.

- Alkylating agent resulting in DNA crosslinking and prevents replication.

- Suppresses fibrosis and vascular ingrowth

- Toxic to fibroblasts in all stages of the cell cycle

- MMC was reported by Chen to enhance IOP lowering efficacy of trab when applied to eyes at high risk for failure.

Mitomycin C

- Several clinical trials have demonstrated MMC as an adjunct to the trabeculectomy.

- In comparing 5 FU to MMC intraoperative, MMC has been shown to be superior to lowering IOP over 5 FU.

- Major complications: Hypotony maculopathy due to excessive filtration (ciliary body hyposecretion), leaks, endophthalmitis.

Allingham, RR. et al. Shields’ Textbook of Glaucoma
Gupta, AK. et al. Handbook of Clinical Trials in Ophthalmology
Mitomycin C

Concentrations in current usage MMC 0.1-0.5 mg/ml applied to sub conjunctival tissues, 1-5 min.
– Exposure time can be varied based on the patient risk factors for excessive fibrosis.
– Other studies suggest 0.02% MMC applied for 2 min.
– Several Delivery systems:
  • Subconjunctival depot pre op
  • Merocel sponges, Weck Cell
  • Mitosol™ delivery system

5 FU vs. MMC

• Randomized clinical trials comparing 5 FU and MMC have reported better efficacy with MMC in terms of IOP control.
  – Skuta GL et al. compared MMC vs. 5 FU in high-risk glaucoma filtering surgery
  – Katz GJ et al. compared in follow up
• Palanca-Capistrano in a prospective randomized control trial.
  – No difference between MMC & 5 FU in reducing IOP after primary trab.
  – Both had significant bleb leakage.
• De Fendi et. al. in a meta analysis of 5 clinical trials revealed that Trab with MMC were associated with significantly lower IOP than 5 FU group.
  – There were significantly lower incidence of epithelial defects with MMC as compared to 5 FU

University of York Centre for Reviews and Dissemination, 2014.
Allingham, RR. et al. Shields’ Textbook of Glaucoma

VEGF

• Vascular Endothelial Growth Factor
• Cytokine, with angiogenic and mitogenic actions.
• Selective action on vascular endothelial cells and secondary action on microphage migration.
• Histological evidence suggesting VEGF induces fibroblast proliferation.
• Found in aqueous humor of glaucoma patients and Tendons’ capsule of eyes post glaucoma surgery


Bevacizumab

• Avastin (Genetech)
• Humanized, nonselective monoclonal antibody against VEGF
• Developed for colon cancer, used in ophthalmology for different retinal diseases.
• Few studies regarding the efficacy in trabeculectomy.

Use of Bevacizumab in Glaucoma Surgery

• Few Studies:
  – Chua et al. - Trab with 5 FU/bevacizumab exhibited central bleb avascularity compared with 5FU Trabs.

  – Nilforushan et al. Trabs with MMC (0.02%) vs. Bevacizumab injection (2.5mg/0.1ml) both control IOP, MMC more so.

  – Kahook reported that intravitreal Lucentis and topical MMC at the time of Trab resulted in a more diffuse bleb with less vascularity compared to MMC alone.


Glaucoma Drainage Devices - Tubes

• Ahmed, Baerveldt, Krupin, Molteno, Schocket
• Undergo two phases in the healing process
  – Hypotensive (Early) and Hypertensive Phase (Late)

• Hypertensive phase 1-3 months later
  – Fibrous capsule forms around implant
  – Major source of resistance of flow of aqueous from anterior chamber to the reservoir

Anti fibrotic and Tubes

• Early studies with Krupin Implant and MMC showed promise with lower IOP
  - Less pronounced hypertensive phase
  - More complications

• Other studies showed no clear benefit
The Story of Goldilocks and the Three Bears

Is the same as finding the right parameters for wound healing in glaucoma surgery!

Any Questions?