MITOMYCIN C AS AN ADJUNCT TO TRABECULECTOMY (THE DOUBLE EDGED SWORD)

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Pharmacological modulation of wound healing has been our biggest problem.

During the 1st half of the 20th century, the glaucoma procedures were all full thickness, sclerectomies, trephinations and the like, and some of us who can remember those days, remember there were a lot of complications, associated with full thickness procedures not the least of which were

- Hypotony
- Flat anterior chamber

Full Thickness Filtration History		
Sclerectomy	LaGrange	1906
	Holth	1909
Trephination	Elliot	1909
	Fergus	1909
Thermal Sclerostomy	Preziosis	1924
	Scheie	1958

- Choroidal detachment
- Thin blebs with bleb leaks

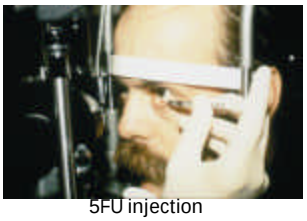
Guarded Filtration- History		
Guarded Thermal Scerostomy	Shaffer et al	1971
Scleral Shell Tamponade	Simmons et al	1979
Trabeculectomy	Sugar	1961
	Cairns	1968

- Endophthalmitis

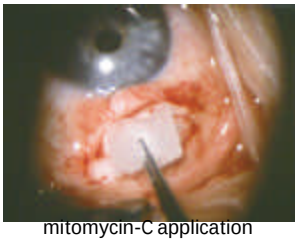
When the concept of the guarded filter came along there were several attempts at creating a guarded filter, like putting internal sutures across the fistula, before the trabeculectomy was developed. The Simmon's shell which today we use to treat excessive filtration and leaks was originally designed to flatten out the filter to prevent excessive flow early on. But it was the work in the early 60s by Saul Sugar and then by John Cairns in the UK which really popularized the operation of trabeculectomy, which although it wasn't designed originally for that purpose, eventually became a guarded filtering procedure. With this major change there were fewer major complications of the type seen earlier in the 1st half of the 20th century with the full thickness procedures, but as time went along we began to look at the long term results of the guarded filters versus the full thickness ones and realize that the guarded filters were not getting as low a pressure in the long term as were the full thickness procedures and some of us went back and did full thickness procedures when we needed very low pressures and guarded procedures when we needed pressures not quite as low. Now we had the position where we had a safer operation but one that wasn't really providing the low pressures that we needed for a lot of our patients.
It was known for some time predominantly through the work of Ed Maumenee, that the major cause of failure in glaucoma filtering surgery was excessive fibrosis which could be due to a variety of factors:

- Aqueous humour factors
- Patient characteristics
- Chronic medications or other surgery.

So it was logical considering that fibrosis was the major cause of failure that we should try to find agents that would minimize postoperative fibrosis. The first of these of course were the corticosteroids. George Spaeth and some of his colleagues did work that confirmed that corticosteroids do in fact increase the success rate of filtering procedures. But we all know that they do not do so in a profound significant way in many patients and that in many patients the filters fail in spite of the steroids. So there was clearly a need for more potent anti-fibrotic agents and the first major one that was studied was 5-fluorouracil. This is a pyrimidine analogue anti-metabolite and blocks DNA synthesis, thereby inhibiting fibroblast proliferation.
The problem with 5 FU is that you have to give numerous postoperative injections.
The original trials by Parish and Heuer called for 2 injections a day for the 1st week and then 1 injection a day for the next week. Since this was not really practicable, most clinicians modified the protocol to 1 injection a day for 7-14 days. On top of this difficulty was the incidence of major complications like wound leakage and corneal epithelial defects. So we felt there was a need for a better

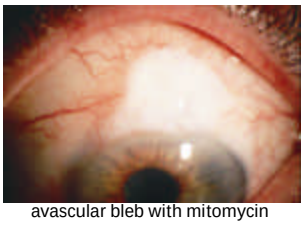

5FU injection

operation. The medicine that came along next was mitomycin-C, which is somewhat similar to 5 FU in that it is an anti-metabolite. In addition to affecting DNA it also affects RNA and protein synthesis. It thereby inhibits fibroblast proliferation and is toxic to endothelial cells.

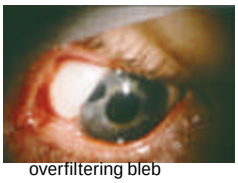

mitomycin-C application

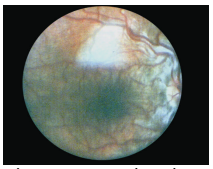
Mitomycin also has a more profound effect than 5 FU in inhibiting fibroblast proliferation and hence it can be given intra-operatively rather than postoperatively.

The effect of vascular endothelial toxicity may or may not be an advantage, but what is definite is that it gives lower pressures than 5FU.Though it does not have the disadvantages that 5 FU has it introduces new complications of its own most notably hypotony maculopathy. Hypotony maculopathy is the clinical situation where due to hypotony you get fine radiating striae at the macula and choroidal folds and disc edema which can cause very significant reduction in vision.


avascular bleb with mitomycin

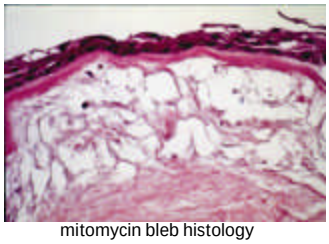
The hypotony that causes hypotony maculopathy in most cases is due to excessive filtration from a bleb that is too thin and leaky. However sometimes with mitomycin hypotony there may be a bleb that is not too large or avascular or even there may be no bleb at all, and in these cases it appears that hypotony is due to decreased production, and there have been studies that show that mitomycin can affect aqueous production.


overfiltering bleb


hypotony maculopathy

Not every one of the persons who has hypotony will get maculopathy. The maculopathy is more commonly associated with young persons and myopic persons, which is unfortunate because it is precisely these younger patients who are more likely to have failure of the bleb because of a strong fibroblastic response. Uveitis also may be a problem, especially because in cases with uveitis aqueous production may already be decreased leading to an increase in the hypotony.

In my first 7 cases where I used the original protocol of 0.4 mg/ml for 5 minutes, I really got burnt on it because 2 developed hypotony maculopathy. The bleb histology in one of these cases where the bleb had to be excised showed a thin, avascular, irregular conjunctiva with irregular thick conjunctival epithelium, dyskeratosis and focal keratinization, an acellular band beneath thick basement membrane, and loose largely acellular subepithelium.


mitomycin bleb histology

We had done a study in rabbits to look at the effect of mitomycin on vascular endothelium. In 36 rabbits both eyes had a posterior lip sclerectomy done; one eye of each rabbit had mitomycin used in the normal way and the other eye had saline vehicle only. The animals were then looked at histologically from 0-72 hrs and it was found that the mitomycin blebs remained avascular throughout while the saline blebs quickly revascularized. The mitomycin blebs also showed a thinner conjunctiva, with decreased goblet cells, an acellular subepithelium, but the most striking finding was almost complete occlusion of blood vessels.


rabbit eye:mitomycin


rabbit eye:saline

On transmission electron microscopy what we saw

was endothelial cell toxicity of the bleb vessels. There were cytoplasmic vacuoles in the epithelium, necrotic epithelial cells, and pyknotic nuclei with swelling of the perinuclear cistern. The vessels were obstructed by blood cells and platelets and this is what many of us notice clinically in that there is a box car appearance or sludging of the red cells as they move slowly through the vessels and if you look a few days later, the blood vessel may be gone. This endothelial cell toxicity is one of the major differences between the effects of 5 FU and mitomycin.

So what we need to do is to find ways to prevent the hypotony and to maximize the benefits of mitomycin.

There are basically 3 ways to minimize the occurrence of hypotony and these are:

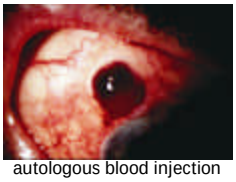
1. Cautious use of mitomycin
2. Tight wound closure. I would rather have a higher pressure for the 1st few days than to have hypotony as the higher pressure can be dealt with by releasing a suture or by laser suturolysis. It is therefore important to have a thick scleral flap with tight suturing.
3. Patient selection: in terms of selecting the patient these are the risk factors for patients who are likely to develop excessive fibrosis and would therefore be good candidates for the use of mitomycin:

- Young age
- Black race
- Active anterior uveitis
- Rubeosis iridis
- Prior failed filter
- Previous surgery or chronic drops use

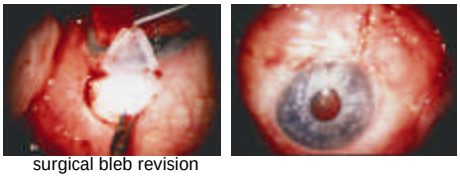
In terms of titrating the protocol we can titrate

- Concentration of mitomycin
- Duration of exposure
- Delivery vehicle
- Patient selection

It seems to me that of all these factors patient selection is what decides most often whether we get hypotony, a successful bleb or failure of the bleb due to fibrosis despite the use of mitomycin. So what we have done is to take the patient risk factors and assign relative scores to each of these factors. Before we take a patient up for surgery we look at all the risk factors the patient has using this arbitrary scoring system, and based on the score we select an appropriate concentration and duration of exposure of mitomycin.


autologous blood injection

Despite our best efforts however we still get hypotony and the question is: what do we do about it. Some things that don't work in this situation are: Pressure patching, scleral shells or contact lenses, trichloroacetic acid and cryotherapy. Some things that might work in this situation are: autologous blood injection, laser applications and mattress sutures, but surgical bleb revision is what is more often than not required when we get hypotony maculopathy.


surgical bleb revision

In conclusion we can say that mitomycin is a really effective way of lowering the intraocular pressure***, but it is clearly a double edged sword***, because it also has many serious complications. To maximize the benefit of mitomycin we must consider

Patient selection
Protocol titration
Surgical technique.

SCORING FOR MMC TITRATION			
1 point	2 points	3 points	4 points
Less than 40 yrs	Less than 25 yrs	Less than 10 yrs	Prior filter with MMC
Black race	PCIOL/conj scar	Prior filter with 5 FU	Prior filter x 2
PCIOL/virgin conj	AC IOL/no AC vitreous	AC IOL with vitreous in AC	Active uveitis
	Inactive uveitis	Aphakia	Rubeosis

MMC Titration Protocol		
Selecting Protocol From Score		
Score	Conc(mg/ml)	Time (min)
0-1	0.2	0.5-1
1-2	0.2	2-3
2-3	0.3	2-3
3-4	0.3	4-5
4-5	0.4	3-4
>5	0.4	5-6