



INTRAOPERATIVE MITOMYCIN C AND 5 FLUOROURACIL APPLICATION DURING PRIMARY TRABECULECTOMY : A COMPARATIVE STUDY

Ophthalmology

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ABSTRACT

Aim: To compare the outcome variables of these 2 commonly used anti-metabolites 5-Fluorouracil and Mitomycin-C in trabeculectomy surgeries in primary glaucoma.

Material & methods: The present study was conducted on 50 eyes of 39 patients of primary glaucoma who underwent trabeculectomy over a period from January 2019 to August 2020 at Darbhanga Medical College & Hospital, Laheriasarai, Darbhanga. The patients were randomly categorized into 2 groups of 25 each. One group received 5-Fluorouracil in the dose of 50 mg/ml for duration of 4 to 5 minutes intraoperatively. The other group received intraoperative Mitomycin-C in the dose of 0.4 mg/ml applied over duration of 2 to 3 minutes.

Result: Maximum complications were seen during early postoperative period in which maximum number were seen with POAG (9 cases) followed by PACG (5 cases). Late postoperative complications were seen in POAG and PACG (2 in each).

Conclusion: Long-term complications may only become apparent many years later. Since our study had average period follow up of about 42 weeks, we are not able to comment on the long-term complications following the use of these drugs. In this study both 5-Fluorouracil and Mitomycin-C were found to be equally safe.

KEYWORDS

Primary glaucoma, trabeculectomy, Long-term complications.

INTRODUCTION

Glaucoma is the second most cause of blindness worldwide. WHO has estimated that 4.5 million people are blind due to glaucoma. In India, glaucoma is the leading cause of irreversible blindness with at least 12 million people affected and nearly 1.2 million people blind from the disease. More than 90 percent of cases of glaucoma remain undiagnosed in the community. Glaucoma prevalence increases with age.

Trabeculectomy acts by facilitating the drainage of aqueous through the new drainage channel or fistulous tract created through the transcleral route to the subconjunctival space mainly as well as by the normal drainage channel. Maintaining adequate long-term filtration with acceptable intraocular pressure control remains a difficult problem. However external scarring at the level of conjunctiva Tenon's fascia and episcleral interface is the major cause for failure in glaucoma filtration surgery¹.

Modern wound modulators / cytotoxic drugs are available to prevent wound scarring (fibrosis) by inhibiting proliferation of fibroblast at the filtering site. These drugs thus help to maintain the functioning of the bleb. Steroids, Mitomycin-C, 5-Fluorouracil, Daunorubicin are used for this purpose. Nowadays Mitomycin-C and 5-Fluorouracil are the drugs which are used worldwide to maintain the filtering bleb. Chen first used intraoperative Mitomycin-C clinically in 1981. Since the late 1980 its use has increased worldwide because of the ease of application and the dramatic effects. The anti-metabolite 5-Fluorouracil best known as an anti-proliferative agent in colonic and breast cancer palliation was first described to improve bleb formation after filtering surgery in an owl monkey model in 1984. Subsequent pilot studies have suggested a beneficial effect on lowering intraocular pressure after filtering surgery in human eyes in high-risk cases of glaucoma.

So, in this study we have made a humble attempt to answer these questions and have tried to compare the outcome variables by using these two anti-metabolites.

This study was undertaken to compare the outcome variables of these 2 commonly used anti-metabolites 5-Fluorouracil and Mitomycin-C in trabeculectomy surgeries in primary glaucoma.

The parameters compared Were:

1. Complications intraoperative and postoperative and their management following the use of these drugs.
2. Intraocular pressures over a period of time.

3. Maintenance of bleb over a period of time.
4. Finally, with all these parameters to conclude the efficacy, safety and superiority between these 2 drugs.

MATERIAL & METHODS

The present study was conducted on 50 eyes of 39 patients of primary glaucoma who underwent trabeculectomy over a period from January 2019 to August 2020 at Darbhanga Medical College & Hospital, Laheriasarai, Darbhanga.

The patients were randomly categorized into 2 groups of 25 each. One group received 5-Fluorouracil in the dose of 50 mg/ml for duration of 4 to 5 minutes intraoperatively. The other group received intraoperative Mitomycin-C in the dose of 0.4 mg/ml applied over duration of 2 to 3 minutes.

INCLUSION CRITERIA

All the patients of primary open angle glaucoma and primary closed angle glaucoma where anterior synechiae has blocked more than 1/3rd of the angle of anterior chamber were included in this study.

RESULT AND DISCUSSION

In this study, success of uhu is defined as lowering of intraocular pressure less than or equal to 18mm Hg without any adjuvant anti-glaucoma therapy. Watson defined glaucoma control as an intraocular pressure less than 21 mm Hg on three successive readings with no further visual field loss. Since we have not defined the target pressure for each case, it is very difficult whether trabeculectomy is effective in reducing the intraocular pressure to a level that we can ensure the preservation of vision in that particular case this makes it also difficult to compare the success rates of various studies.

Grant and Burke have stressed the importance of lowering the intraocular pressure to less than 17 mm Hg in patients with advanced glaucoma with optic atrophy on visual field effects that encroach upon fixation, they stress the facts that the people with pressures in the mid teens continue to become blind².

Now in our study, we had a mean intraocular pressure of 41.52 mm Hg in 5-Fluorouracil group and 39.6 mm Hg in Mitomycin-C group at the time of presentation. The final outcome of intraocular pressure following a mean follow up period of 41.4 weeks, the two groups gave a pressure of 14.84 mm Hg in 5-Fluorouracil group and 14.52 mm Hg in Mitomycin-C group. Thus, we are able to conclude these 2 drugs, 5-Fluorouracil and Mitomycin-C used intraoperatively can equally reduce the pressure to mid teens.

"Result of intraoperative 5-Fluorouracil in undergoing trabeculectomy" study conducted by L. Vijaya et al (1996)³ concluded that intraoperative 5-Fluorouracil use achieves a success rate of 92.3% cases whereas in our study a success rate of 84% was achieved in this group.

A study conducted by **Dastur, Dasgupta et al (1994)**⁴ on the role of initial 5-FU trabeculectomy in primary glaucoma also showed significant lowering of IOP after its use which is similar to our study.

Rahman et al (2001)⁵ concluded that intraoperative use of Mitomycin-C is very effective in trabeculectomy surgery (IOP < 21 mm Hg in 80.9% of cases after 3 years). Bleb failure was seen in 20% cases and 1 case developed hypotony maculopathy. In our study we achieved a success rate of 88% in Mitomycin-C patient group and bleb failure was seen in 12% of cases only. 1 case in our also developed hypotony maculopathy.

Fereshtekhou et al in (2007)⁶ reported that high dose MMC is safe effective for high risk patients with a glaucoma who undergo trabeculectomy and it leads to significant control of IOP (mean postoperative IOP 12.6 ± 2.93 mm HG)- In 25% cases wound leak was observed. In our study we achieved a mean IOP of 14.52 mm HG while using Mitomycin-C.

Singh K et al (1997)⁷ had concluded in their study that the adjunctive use of Mitomycin-C with trabeculectomy is equally safe and more efficacious compared to 5-Fluorouracil in West African population. Their reported use of Mitomycin-C in their study was not associated with a statistically significant greater proportion of patients achieving low intraocular pressure (less than 15 mm Hg) compared to 5-Fluorouracil. Their mean postoperative intraocular pressure was 13.7 mm Hg in Mitomycin-C group and 16.3 mm Hg in 5-Fluorouracil group. While in our study mean postoperative intraocular pressure of 14.52 mm Hg was seen in Mitomycin-C group and 14.84 mm Hg in 5-Fluorouracil group was recorded.

Their success rate was 93.2% cases in Mitomycin-C group and 73% cases in 5-Fluorouracil group whereas in our study 88% cases of Mitomycin-C and 84% cases of 5-Fluorouracil group achieved a reduction in intraocular pressure.

Singh K et al (2000)⁸ study showing trabeculectomy with intraoperative Mitomycin-C versus 5-Fluorouracil found that both drugs are equally safe. In our study we found that rate of complication was a little more in Mitomycin-C group than 5-Fluorouracil group.

A trial of 5-Fluorouracil versus Mitomycin-C done by **WuDunn et al (2002)**⁹ also showed that there is no statistically significant difference in efficacy or side effects in the two groups which is similar to our study.

Katz GJ et al¹⁰ in their comparative study between Mitomycin-C versus 5-Fluorouracil in high risk glaucoma had reported that the eyes treated with Mitomycin-C had lower intraocular pressure on fewer medication than the eyes treated with 5-Fluorouracil.

Costa V. Patel¹¹ in their study on loss of visual acuity after trabeculectomy had 83% of the cases with visual loss (2 or more Snellen lines) due to cataract, hypotony maculopathy or "wipeout of central field" or wipeout was more common among older patients with advanced visual field defects or macular splitting preoperatively and extreme hypotony of less than 21 mm Hg on the postoperative day.

Due to shorter follow up, inability to obtain a stabilized visual field, avoiding learning curve changes, patient non-compliance to undergo visual field analysis, this study could not use visual field as a definitive indicator of success, which could have been more convincing.

We had two intra-operative complications in Mitomycin-C group. One case developed flat anterior chamber with increase in intraocular pressure, a differential diagnosis of choroidal haemorrhage and malignant glaucoma was made. To confirm this diagnosis on-table indirect ophthalmoscopy was done which did not reveal any choroidal effusion. On-table needle aspiration of fluid vitreous was done using a 26 G needle at about 5 mm from the limbus and the anterior chamber was formed using oculose. For the second case we had difficulty forming the anterior chamber for which oculose was used to form the anterior chamber.

In 5-Fluorouracil group 2 case developed intraoperative complication which was kept on observation, and conjunctival button hole which was sutured with 10-0 nylon.

The frequent postoperative complications of trabeculectomy are shallow anterior chamber or flat anterior chamber and choroidal detachment.

The incidence of shallow or flat anterior chamber in different reports ranged from 4.8% to as high as 70%^{12,13}.

In this study 32% had shallow anterior chamber and flat anterior chamber in Mitomycin-C group. 36% had shallow anterior chamber and flat anterior chamber was noted in 5-Fluorouracil (Spaeth GL working system for grading of shallow anterior chambers). So based upon this complication we could derive shallow anterior chamber is more common with 5-Fluorouracil group.

Yamashita et al¹⁴ proposed the use of sodium hyaluronate intracamerally at the end of surgery to prevent the complication of the shallow anterior chamber. Gehring JR39 described pressure patching and over the filtration on area to Prevent excess run off of aqueous and patients are kept on observation. We followed this method in all our cases of shallow anterior chamber and successfully formed the chamber depth within a week, requiring no surgery. A special type of contact lens called as Simmon's shell is also used commonly in treatment and so is the symblepharon ring. These shell tamponade methods were not employed in any of our cases.

Hyphaema was reported 4% in 5 fluorouracil group and in 12% eyes in mitomycin c group in this study, which required no surgical intervention and resolved spontaneously within one week postoperatively.

Hypotony maculopathy as described by Gass was responsible for 14.3% of all cases of early postoperative visual loss. In our study 2 cases developed hypotony maculopathy (one in each group). Hyung SM et al¹⁵ used a 3 step approach to manage this condition first intrableb autologous blood injection, second surgical exploration and additional suturing of the scleral flap; third excision of the cystic bleb and advancement of conjunctival flap. In our study we did pressure patching with topical steroids cycloplegic and observation was done, by this technique hypotonic maculopathy resolved over a span of time.

The progression of cataract after glaucoma surgery ranges from 2 to 53 percent in various reports. The rate of cataract formation may increase due to topical corticosteroids. There is also a strong correlation with flat anterior chamber³⁶. Progressive cataract development is more common in patients with pre-existing cataract. Robin AL et al¹⁶ had reported that progressive lens opacification was the most frequent complication when Mitomycin-C was used for a longer exposure time. In this study we noted two cataractous changes one in each group. A longer follow up of other cases may reveal a higher incidence.

Tenon's cyst developed in 5 cases (20%) in 5-Fluorouracil group. No such complications were seen in the Mitomycin-C group. However, Katz GJ¹⁰ et al had reported increased incidence of Tenon's cyst formation as a late complication seen after 3 months in patients treated with Mitomycin-C compared to none in patients treated with 5-Fluorouracil. Van Buskirk¹⁷ advocate rigorous medical therapy, which included topical corticosteroids, anti-glaucoma drugs and digital massage. But they observed that surgical intervention is occasionally necessary. In our none required surgical intervention. In contrast, Peder and Smith¹⁸ reported encouraging results with acceptable intraocular pressure control after surgical needling or total bleb excision. In this study needling of the Tenon's cyst to break open the loculations was done In 4 out of 5 eyes according to Van Buskirk's technique. With the above management intraocular pressure was controlled and stabilized in all cases.

Yamashita et al¹⁴ reported an incidence of 27.7% of choroidal detachment in their long-term follow up study. We encountered one case of choroidal detachment in the Mitomycin-C group and 1 case of choroidal detachment in 5-Fluorouracil group. These cases were managed conservatively and resolved over a span of two weeks. Though Mattox-C45 had reported a higher incidence of corneal toxicity in 5-Fluorouracil treated eyes compared to Mitomycin-C group, we encountered 1 case 1 in each group, which resolved gradually by patching over a period of one week.

David A Belyea et al¹⁹ had reported late onset of sequential multifocal bleb leaks after glaucoma filtration surgery with 5-Fluorouracil and Mitomycin-C associated with epithelial breakdown, hypocellularity and stromal collagen necrosis in the filtration bleb. In our study we encountered 1 early wound leaks consequent to conjunctival recession in fornix based conjunctival flap, which were managed by patching. To rule out late bleb leaks a longer time of follow up is required.

Benjamin F- Boyd et al²⁰ had reported Mitomycin-C to be associated with avascular thin cystic blebs and a higher incidence of endophthalmitis whereas SamraWaheed et al²¹ reputed an increased rate of recurrent bleb related infections in patients receiving adjunctive 5-Fluorouracil compared to Mitomycin-C and they attributed this finding due to a longer follow up of 5-Fluorouracil. Mochizuki et al²² reported a similar incidence of delayed onset, bleb related infection after trabeculectomy with and without adjunctive antiproliferatives.

In our study we encountered 2 cases of thin polycystic blebs as a late complication in each group with none of the cases developing any infection of the bleb or endophthalmitis. Apart from other minor complications 2 cases in 5-Fluorouracil treated eyes and 3 cases in the Mitomycin-C treated eyes had a transient increase in intraocular pressure in the immediate postoperative period which was managed by oral acetazolamide given in the dose of 250 mg twice a day for 1 week along with topical anti-glaucoma medication.

CONCLUSION

Unfortunately, we are confronted daily with Patients whose glaucoma remains recalcitrant to standard medical and surgical therapy. Our overwhelming desire is to affect a speedy and permanent cure. In practice this means decreasing intraocular pressure to a non-damaging level.

In our desire to achieve this goal 5-Fluorouracil and Mitomycin-C were used intraoperatively in trabeculectomy in our study, and they proved extremely effective in prevention of fibrosis and they are equally potent in reducing the intraocular pressure to mid teens.

Though we did not find any serious complications, the complications of clinical significance did occur in the 2 groups. The incidence and severity of the complications in both the groups were statistically equal. Long-term complications may only become apparent many years later. Since our study had average period follow up of about 42 weeks, we are not able to comment on the long-term complications following the use of these drugs. In this study both 5-Fluorouracil and Mitomycin-C were found to be equally safe.

Statistical studies comparing the results of the two patient groups in our study did not reveal any significant differences between the two groups. The two drugs 5-Fluorouracil and Mitomycin-C proved to be equally effective in reducing the intraocular pressure. The difference in the incidence of complications between the two groups was not found to be significant.

The advantage of greater surgical success with lower intraocular pressure puts anti-metabolites into the armamentarium of every surgeon who performs glaucoma procedures, but we are cautioned to temper our enthusiasm for employing new therapies by the time honored dictum of medical care "Primum non nocere" i.e. first do not harm. So a key area for the future here is a better understanding of the cellular and molecular process involved in the healing process and the exact effects of the various agents used to modulate this process.

SURGICAL COMPLICATIONS OBSERVED IN THE PATIENT GROUP THAT RECEIVED MITOMYCIN-C

Type of Glaucoma	Complications				
	Intra-operative	Early postoperative	Late postoperative	Early / late	Nil
POAG	1	9	2	2	0
PACG	1	5	2	2	1
Total	2	14	4	4	1

INCIDENCE OF POSTOPERATIVE COMPLICATIONS IN THE MITOMYCIN-C GROUP

Complication	POAG	PACG
Shallow anterior chamber (SAC)	4	0
Flat anterior chamber (FAC)	1	3

Hyphema (Hyph)	2	1
Choroidal detachment (CD)	0	1
Tenon's cyst (TC)	0	0
Hypotony (Hypo)	0	1
Hypotonic maculopathy (HM)	0	1
PAS at fistula site	1	0
Iris tuck at fistula site (IT)	1	1
Superior Retinal haemorrhage (RH)	0	0
Sub-conjunctival haemorrhage (SCH)	0	1
Wound leak (WL)	0	0
TIOP	2	1
Epithelial stria (ES)	1	0
PB	1	1
Bleb scar	1	0

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