Official Title: A Prospective Randomized Clinical Trial Comparing Three Delivery Methods of Mitomycin-C for Trabeculectomy Surgery: Preoperative Subconjunctival Injection, Intraoperative Subconjunctival Injection, and Topical Application (Conventional Use) During Trabeculectomy Surgery

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Mitomycin-C Injection for Trabeculectomy: Pilot study

Title

Comparison of three delivery methods of Mitomycin C for trabeculectomy surgery: Preoperative subconjunctival injection, intraoperative subconjunctival injection and topical application during trabeculectomy surgery: A pilot study

Purpose:

To obtain estimates of the effect on intraocular pressure and side effects of three delivery methods of Mitomycin C (MMC) compared among each other: preoperative subconjunctival injection of 0.1 mL MMC 0.002%, subconjunctival injection of 0.1 mL MMC 0.01% intraoperatively and conventional sponge applied MMC (0.02%) during trabeculectomy surgery in patients with Primary Open Angle Glaucoma who did not have any filtering surgeries before.

Objective:

To obtain estimates for intraocular pressure reduction among three delivery methods of MMC compared among each other: preoperative subconjunctival injection, intraoperative subconjunctival injection and intraoperative topical use during trabeculectomy surgery and to report any associated adverse effects.

Null hypothesis:

There is no use of hypothesis testing in this pilot study

Alternative hypothesis:

There is no use of hypothesis testing in this pilot study

BRIEF SUMMARY

In this Pilot explorative study, we are going to estimate and compare the outcomes of three different delivery methods of MMC for Trabeculectomy: a subconjunctival injection of MMC 0.002% at the site of future Trabeculectomy two to four weeks before the surgery, a subconjunctival injection of MMC 0.01% intraoperatively and topical sponge applied MMC 0.02% intraoperatively (typical use) in patients with Primary Open Angle Glaucoma who did not have any filtering surgeries before.

After obtaining informed consent from the patients, the patients are randomly divided into three groups via a block randomization method: Group A receives 0.1 mL MMC 0.002 % (0.1mL MMC 0.02mg/mL) subconjunctival injection preoperatively in superior conjunctiva at the site of future Trabeculectomy surgery. Group B receives 0.1mL MMC 0.01% subconjunctival injection intraoperatively at the site of Trabeculectomy and Group C receives conventional sponge delivery of MMC 0.02% intraoperatively. To avoid observer bias during postoperative evaluation of results, IOP staff obtaining measurements of IOP will be masked to the randomization allocation.

All groups undergo conventional Trabeculectomy surgery (fornix-based) as scheduled, and the same routine follow up and post-op regimen will be scheduled for all three groups. Patients are routinely visited in the clinic at first day postoperatively, one week (+/-2 days), one month (+/-1 week), three months (+/-2 weeks), six months (+/-3 weeks) and finally at one year (+/-(4 weeks)). In each of these visits we will be assessing: Visual acuity, intraocular pressure, number and type of glaucoma medication, slit lamp examination of the anterior segment and fundus examination.

BACKGROUND INFORMATION

The effect and safety of MMC subconjunctival injection either preoperatively or intraoperatively has been previously investigated in Pterygium surgery (Khakshoor H, Razavi ME, Daneshvar R, Shakeri MT, Ghate MF, Ghooshkhanehi H. Am J Ophthalmol. 2010 Aug;150(2):193-8. Preoperative subpterygeal injection vs intraoperative mitomycin C for pterygium removal: comparison of results and complications).

Previous studies comparing effectiveness of subconjunctival injection of MMC vs sponge-applied MMC have shown inconsistent results. In one retrospective study, Mitomycin-C applied by injection resulted in significantly lower IOP, and the need for fewer glaucoma medications, however description of methods is incomplete. (Lim MC. A comparison of trabeculectomy surgery outcomes with mitomycin-C applied by intra-Tenon injection versus sponge method. American Glaucoma Society 23rd Annual Meeting; 2013, San Francisco, CA). One retrospective study showed similar efficacy and safety of intraoperative MMC injection compare to sponge application in trabeculectomy surgery with overall lower IOP in the injection group and main advantages being a large surface area of exposure and a predictable dose of deliver when the injection was performed. No difference in postoperative complications between groups was observed. A small sample size (30) in each group might prevent finding statistical significant results. (Khouri AS, Huang G, Huang LY. Intraoperative Injection vs Sponge-applied Mitomycin C during Trabeculectomy: One-year Study. J Curr Glaucoma Pract 2017;11(3):101-106). A previous case report on preoperative administration of MMC for Trabeculectomy showed reduction of IOP with short follow-up (6 months) Hung PT, Lin LL, Hsieh JW, Wang TH. Preoperative mitomycin-C subconjunctival injection and glaucoma filtering surgery. *J Ocul Pharmacol Ther.* 1995;11(3):233-241.
One RCT with a follow-up of 3 years compared outcomes of intraoperative injection versus sponge-applied MMC and no significant difference in IOP was found however a more favorable bleb morphology was found in the injection group which is correlated with better function and long-term success of Trabeculectomy (Esfandiari, Hamed et al. Treatment Outcomes of Mitomycin C-Augmented Trabeculectomy, Sub-Tenon Injection versus Soaked Sponges, after 3 Years of Follow-up (Ophthalmology Glaucoma , Volume 1 , Issue 1 , 66 – 74)

In this study the comparison will be the timing and route of delivery of MMC in all three groups, having found inconsistent reports in the literature and very scarce data on the effect of preoperative subconjunctival MMC we like to further explore in this pilot study the effect of subconjunctival injection on IOP reduction for trabeculectomy at preoperative and intraoperative phases. Since there is no group receiving placebo, the inclusion of a sham injection will not affect the outcomes compared to GROUP C and could increase preoperative risks to patients. The same methodology has been applied in two previous randomized controlled trials. (Pakravan M, Esfandiari H, Yazdani S, et al. Mitomycin C-augmented trabeculectomy: subtenon injection versus soaked sponges: a randomized clinical trial Br J Ophthalmol 2017;101:1275–1280 and Khan F, Niazi S, Awais M et all. Effectiveness of Preoperative Subconjunctival Injection of Mitomycin-C in Primary Pterygium Surgery Journal of the College of Physicians and Surgeons Pakistan 2017, Vol. 27 (2): 88-91)

Glaucoma patients who need glaucoma surgery, such as trabeculectomy, have ongoing damages that cannot be managed only with medication such as drops, and pressure reduction is absolutely crucial in preserving visual function in these patients, hence any possible action that can add to this reduction is valuable.

On the other hand, there are several risks associated with the topical applied MMC usage at the time of surgery mainly due to the inability to precisely quantify the amount of MMC delivered by the sponge application which was shown to be far less with the injection of MMC by delivering a predicted volume either at surgery or before the surgery which are mentioned in the first two paper references.
The selected concentrations for the MMC injection are based on pharmacological studies performed on ocular tissue in which the concentration achieved after subconjunctival injection was established

STUDY DESIGN

This is a multicenter randomized controlled pilot study with a main objective of obtaining estimates of differences in IOP reduction among three methods of delivery of mitomycin C for use in trabeculectomy surgery.
The injectors and patients are unmasked in this study while the evaluators are masked.

Inclusion Criteria

1. Age: 20-85 years
2. Willingness to participate in the study by signing informed consent
3. Primary open angle glaucoma (including pigmentary glaucoma and pseudoexfoliation glaucoma) indicated with open angles upon previous gonioscopy and demonstrative optic nerve and visual field damage
4. Trabeculectomy needed as treatment as determined by the care provider

Exclusion criteria

1. Patient unwilling or unable to give informed consent, unwilling to accept randomization, or unable to return for scheduled study visits throughout the duration of the study (1 year)
2. Any secondary cause of glaucoma, or angle closure shown on gonioscopy
3. Any ocular or neurological problems with optic nerve or visual field defect (ie. retinal disease, post trauma, corneal scar) that may confound the interpretation of glaucoma such as visual field or optic nerve interpretation
4. Pregnant women, nursing women, and/or anyone with a history of allergy to MMC
5. Previous glaucoma surgery or ocular surgery that included manipulation of the conjunctiva.

METHODS

Patients who met inclusion criteria and had signed an informed consent will then be randomized into three groups as follows:

- Group A: Patients will receive a subconjunctival injection of 0.1mL MMC 0.02mg/mL which corresponds to 0.002% (a tenth of the concentration of conventional topical MMC use) at the site of future trabeculectomy surgery two to four weeks in advance. A follow-up phone call 1 week after the MMC injection will assess any side effects of the procedure. If side effects are reported by the patient an appointment will be schedule for a follow up in-office visit and appropriate treatment will be delivered. On the day of conventional trabeculectomy no MMC will be injected. Follow-up will be scheduled for one year.

- Group B: On the day of conventional trabeculectomy patients will receive a subconjunctival injection intraoperatively of 0.1 mL MMC 0.1mg/mL which corresponds to 0.01% (half the

concentration of conventional topical MMC use) at the site of trabeculectomy. Surgeon will irrigate the surface of the eye after MMC injection to remove any MMC that might have leaked out. Follow-up will be scheduled for one year.

- Group C: On the day of conventional trabeculectomy patients will receive MMC by applying a sponge soaked in 1mL of MMC 0.2 mg/mL (0.02%) for 1 minute to the site of trabeculectomy surgery followed by irrigation. MMC is standard of care for trabeculectomy surgery at UCLA. This differs from the proposed research because the MMC will be administered as an injection either two to four weeks before the surgery in Group A or intraoperatively in Group B rather than the usual topical administration on the day of surgery (Group C). Follow-up will be scheduled for one year.

The concentration of MMC in each group were chosen according to the delivery method and the timing of exposition of the tissue to the MMC in order to prevent complications from overdose. Based on experimental studies on ocular tissues that evaluated the final amount of MMC delivered to scleral tissue and finding a similar result when using subconjunctival injection of 0.02% with immediate irrigation and 0.002% without irrigation, we chose the latter for group A. Few studies evaluated MMC subconjunctival injection one month before pterygium surgery using 0.02% and 0.015% with a follow-up of 3 years establishing safety of this approach. For group B we chose a similar methodology of a previous RCT comparing subconjunctival injection versus topical administration of MMC for trabeculectomy that used a reduced concentration of 0.01%.

Data collection will be as follows: At preoperative visit, first day postoperatively, one week (+/- 2 days), one month (+/- 1 week), three months (+/- 2 weeks), six months (+/- 3 weeks) and one year (+/- (4 weeks)). The data will be recorded trough the Redcap (Research Electronic Data Capture) software which has free access and allows for easy recording and uploading of imaging (VF, Optic nerve OCT, AS-OCT and bleb photography) for future analysis.

In each of these visits the following data will be collected: Visual acuity, intraocular pressure, number and type of glaucoma medication, slit lamp examination of the anterior segment, fundus examination and adverse events if present. Visual field and optic nerve OCT will also be included in the preoperative evaluation and at 12 months postoperatively.
For better assessment of the bleb morphology we will include a clinical grade system, slitlamp photography and AS-OCT (Anterior segment module of Spectralis OCT device (Heidelberg Engineering, Inc., Heidelberg, Germany) of the bleb.
For the clinical description of the bleb and a more standardized comparison of the morphological changes over time we included at every postoperative visit the description of the bleb using the Moorfields Bleb Grading System (MBGS) which captures more morphological features and regional vascularity compared to other systems. (*Wells AP, Ashraff N, HalL RC et all Comparison of Two Clinical Bleb Grading Systems Ophthalmology 2006;113:77–83).*
The bleb photography will be included at the 3 and 12 months postoperatively and AS-OCT at 1,3,6 and 12 months follow-ups. The inclusion of AS-OCT allows for evaluation of the internal structure of the bleb that has been shown to have prognostic implications for outcomes of surgery. *Kokubun T, Tsuda S, Kunikata H et all. Anterior-Segment Optical Coherence Tomography for Predicting Postoperative Outcomes After Trabeculectomy, Current Eye Research, DOI: 10.1080/02713683.2018.1446535*

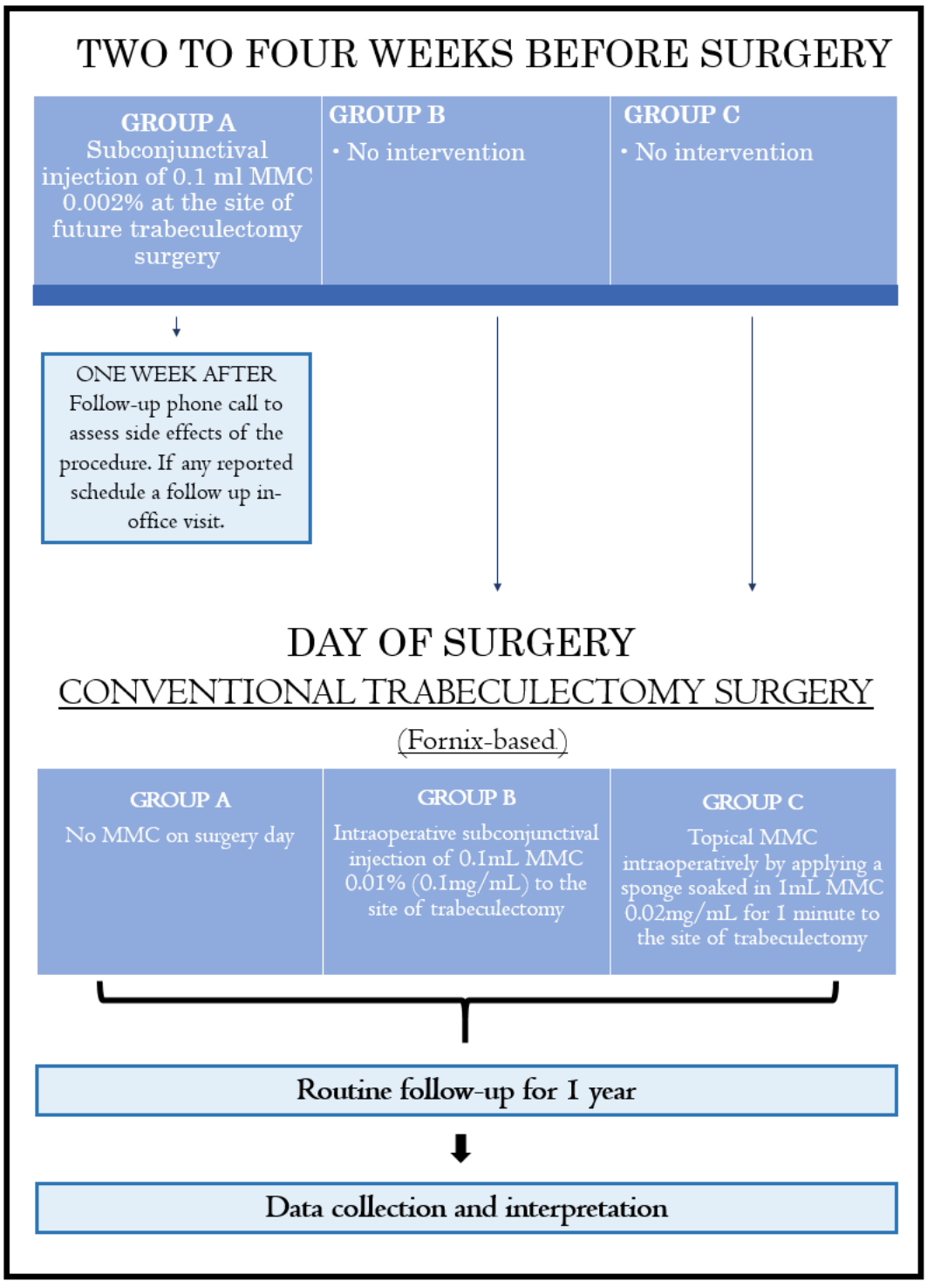
Block randomization:

To ensure the balance of sample size between three treatment groups, block randomization is used for treatment assignment. Specifically, each block consists of 6 patients, including 2 patients in each of three treatment groups, and all possible permutations of a sequence of treatment assignment for these 6 patients are generated, such as AABBCC, ABCABC, etc. A random number is then generated to select a block of treatment assignment for 6 patients among all possible blocks, and a sequence of such random blocks will form the sequence of treatment assignment for all patients after their enrollment.

Statistical analysis

Since the literature on the effect of preoperative subconjunctival injection and intraoperative subconjunctival injections for trabeculectomy shows inconsistent results and there are no estimates available for the IOP reduction among all three methods, the primary objective is to obtain such estimates in this pilot study. Hence, we want to perform pairwise comparisons among three groups and obtain the mean IOP estimates at each time point up to 1 year. The sample size for each randomized will be 50 patients (total 150 patients) taking in consideration the patient flow and recruitment for trabeculectomy surgery at the Glaucoma Division.

SCHEDULE	VA	IOP	Glaucoma medications	Ant. segment exam	Fundus exam	Bleb photo	AS-OCT	Optic nerve -OCT	Visual field
Preoperative exam	✓	✓	✓	✓	✓			✓	✓
Postoperative exam day 1	✓	✓	✓	✓					
Postoperative exam week 1	✓	✓	✓	✓					
Postoperative exam month 1	✓	✓	✓	✓			✓		
Postoperative exam month 3	✓	✓	✓	✓		✓	✓		
Postoperative exam month 6	✓	✓	✓	✓			✓		✓
Postoperative exam month 12	✓	✓	✓	✓	✓	✓	✓	✓	✓


TWO TO FOUR WEEKS BEFORE SURGERY
GROUP A
Subconjunctival injection of 0.1 ml MMC 0.002% at the site of future trabeculectomy surgery
GROUP B
• No intervention
GROUP C
• No intervention
ONE WEEK AFTER
Follow-up phone call to assess side effects of the procedure. If any reported schedule a follow up in-office visit.
DAY OF SURGERY
CONVENTIONAL TRABECULECTOMY SURGERY
(Fornix-based)
GROUP A
No MMC on surgery day
GROUP B
Intraoperative subconjunctival injection of 0.1mL MMC 0.01% (0.1mg/mL) to the site of trabeculectomy
GROUP C
Topical MMC intraoperatively by applying a sponge soaked in 1mL MMC 0.02mg/mL for 1 minute to the site of trabeculectomy
Routine follow-up for 1 year
Data collection and interpretation