Subconjunctival Versus Direct Mitomycin C in Trabeculectomy

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

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Version date: 9/30/2013

1. PROJECT TITLE

Subconjunctival versus direct scleral application of Mitomycin-C injection in trabeculectomy

2. PRINCIPAL INVESTIGATOR

Robert Weinreb MD, Jiun Do MD PhD

3. FACILITIES

Shiley Eye Institute, Secondary investigators: Brandon Wong MD, Benjamin Y. Xu MD, Andrew Camp MD, Philip Ngai MD, Derek Welsbie MD PhD

4. ESTIMATED DURATION OF THE STUDY

We estimate from the beginning of the study through the end of data analysis will take less than 18 months

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Trabeculectomy is routinely used as a surgical treatment for open angle glaucoma. Success of trabeculectomy is greatly augmented by the use of antimetabolites to inhibit wound healing, specifically Mitomycin C (MMC). MMC can be applied to the eye at various sites, concentrations, and times. This study aims to compare the two application routes that are commonly employed: subconjunctival pre-operative injection and intraoperative direct scleral application in terms of IOP lowering effect, bleb appearance and complications.

6. SPECIFIC AIMS

To describe differences in IOP lowering effect, bleb appearance and complications over a 6-month post-operative course between patients receiving subconjunctival MMC vs direct sclera application during trabeculectomy

7. BACKGROUND AND SIGNIFICANCE

Trabeculectomy is widely used as a surgical treatment of uncontrolled open glaucoma. Success of trabeculectomy at halting or slowing glaucoma progression primarily relies on the extent of conjunctival and sclera wound healing (1). The success rates of trabeculectomy increased dramatically with the introduction of anti-metabolites (2-4). For more than two decades mitomycin-c (MMC), a chemotherapeutic agent capable of decreasing fibroblast activity and modulating wound healing at the bleb, has been used with trabeculectomy. The complications of MMC are well known and several studies have described various methods of application based on exposure time, dose and surface area. Numerous retrospective and prospective studies have compared the efficacy of MMC applied beneath the conjunctival flap with soaked sponges versus intrascleral application (5-9). In 2008 Lee et al first described an alternative route of application: subconjunctival injection of MMC directly into the intra-Tenon area (11). Seventy-six eyes with primary and secondary open angle glaucoma underwent trabeculectomy with this approach and were followed for one year post-operatively. Eighty-six percent of eyes achieved an IOP <21 mm Hg and 57% an IOP<14 mm Hg at one year without adjunctive drops. Transient complications included hyphema, bleb leak and choroidal detachment. The advantages of injected MMC are primarily in controlling the exact dosage and area of application and reduced surgical time. Lim et al retrospectively reviewed the outcomes of trabeculectomy in 57 eyes using sponge application directly to the

sclera versus intra-tenon injection (10). IOP was significantly lower in the injection group at 1 month, 1, 2 and 3 years. Trabeculectomy success (IOP<21mm Hg or IOP >20% below baseline without medications or additional surgery) was greater in the injection group at 3 years. The sponge group experienced more encapsulated blebs and complication rates were similar in both groups. To date, there have been no prospective studies comparing the IOP-lowering efficacy and safety of intra-tenon injection versus direct sceral application of MMC.

8. PROGRESS REPORT

n/a

9. RESEARCH DESIGN AND METHODS

This study will be a prospective randomized study of eyes with medically uncontrolled open angle glaucoma in whom trabeculectomy is indicated (high intraocular pressure, worsening visual field, or optic nerve head changes). Evaluated preoperative data will include age, gender, IOP, best corrected visual acuity, and number of antiglaucoma medications. Patients with pathologic myopia (refractive error of >6 Diopters) will be excluded. To detect a minimum difference of 3mmHg in IOP between the two groups we will require 50 patients in each group. This assumes a standard deviation of measurements of 5mmHg which is in agreement with previous literature. The patients will be randomized using a random number generator found at http://www.graphpad.com/quickcalcs/randomize1/. The surgeons who perform the trabeculectomies and administer the MMC will not be masked. Masking of the surgeon would require injection of a vehicle (balanced salt solution) which would incur additional risks (subconjunctival hemorrhage). There will be masking during the follow-up post-operative appointments. An examiner who was not present during surgery and blind to the group assignments will be conduct all of the post-operative exams and perform this portion of data collection.

Patients will by random selection receive either 1) subconjunctival injection of MMC (0.15ml of 0.2mg/ml solutions) in the immediate pre-operative period or 2) direct scleral application for 1-2 minutes intraoperatively (0.4 mg/ml in cellulose sponges). The primary outcome in the study will be postoperative IOP measured at 1 day, 1 and 6 weeks, 3 months and 6 months; it is standard of care to examine patients on these post-operative dates. Surgical success will be defined as an IOP value of <21 mm Hg and at least a 30% reduction in IOP without IOP lowering drops. Secondary outcomes will include an IOP<21 mm Hg and 30% reduction with adjunctive antiglaucoma drops, appearance of the bleb using the Indiana Bleb Appearance Grading Scale (IBAGS) and complication rates. At each follow-up visit the bleb will graded during physical exam using the IBAGS based on height, extent, vascularity, and Seidel. A masked examiner blinded to the patient's group assignment will perform the post-operative examinations and collect the above data.

For statistical analysis, continuous variables will be reported as means and standard deviations or 95% confidence intervals; significance will be determined by paired t-test within groups, two-sample t-test between groups, or Mann-Whitney U-test. Categorical variables will be reported as counts and percentages; differences will be tested using Fisher's exact test. Analyses will be conducted using RStudio (RStudio Team, 2016, Boston, Massachusetts, Boston, ISA).

10. HUMAN SUBJECTS

Patients undergoing primary trabeculectomy will be recruited from the Shiley Eye Institute by Dr Weinreb, Dr Do, Dr Wong, and Dr Xu

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

None

12. INFORMED CONSENT

All patients will be consented for trabeculectomy with MMC- the route of application of which will be randomized. The patients will also be consented for participation in the study with explanation of the study's purpose.

13. ALTERNATIVES TO STUDY PARTICIPATION

Patients may opt to not have trabeculectomy, to undergo an alternative surgical glaucoma procedure, or to undergo trabeculectomy with MMC without randomization and without inclusion in the study.

14. POTENTIAL RISKS

Risks of trabeculectomy and MMC application include pain, infection, loss of eye, loss of vision, need for more surgery, hypotony, uncontrolled high IOP, retinal detachment, maculopathy, corneal edema, risk of loss of confidentiality. It is standard practice to deliver MMC during trabeculectomy by either route discussed above; all patients excluding high myopes receive MMC during trabeculectomy at Shiley Eye Institute. As it is our standard practice to always give MMC to trabeculectomy patients there is no added risk

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

None

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Every reasonable effort will be made to keep records confidential. To protect privacy, the information obtained as a result of participation in this research will not be included with any medical records and will be kept in a locked cabinet. Information from which patients may be personally identified will be maintained in a confidential, secure location at the Shiley Eye Center, accessible only by authorized members of the study, and will not be disclosed to third parties except as described in the consent form, or as may be required by law.

17. POTENTIAL BENEFITS

A better understanding of optimal delivery of MMC will benefit future patients requiring trabeculectomy who require maximal IOP lowering.

18. RISK/BENEFIT RATIO

It is standard practice to deliver MMC during trabeculectomy by either route discussed above; all patients excluding high myopes receive MMC during trabeculectomy at Shiley Eye Institute. As it is our standard practice to always give MMC to trabeculectomy patients there is no added risk.

19. EXPENSE TO PARTICIPANT

None

20. COMPENSATION FOR PARTICIPATION

None

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

The research team will be responsible for randomizing patients, consenting patients, collecting all –preoperative patient data as well as all subsequent post-operative measurements during follow-up visits. The research team will be responsible for all statistical analysis.

22. BIBLIOGRAPHY

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11. **Lee, et al.** Trabeculectomy surgery augmented with intra-Tenon injection of mitomycin C**.** Acta OphthalmologicaVolume 86, Issue 8, 28 June 2008.

23. FUNDING SUPPORT FOR THIS STUDY

No funding.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

26. IMPACT ON STAFF
None
27. CONFLICT OF INTEREST
none
28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES
29. OTHER APPROVALS/REGULATED MATERIALS
30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT