

Title Page

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5-fluorouracil Versus Placebo in Periocular Full Thickness Skin Grafts

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1. CLINICAL PROTOCOL

1.1 Background

- 5-Fluorouracil (5-FU) is an antimetabolite that works by irreversibly inhibiting the enzyme thymidylate synthetase resulting in impaired DNA synthesis. This reduces fibroblast proliferation, and inhibits collagen type 1 production which is a key protein in scar formation. This medication is commonly used in ophthalmology after or during glaucoma filtration surgery. We propose a randomized controlled prospective study to evaluate the outcome of periocular full thickness skin grafts with or without the use of 5-FU injected in the post-operative period.
- In oculofacial surgery, full thickness skin grafts are a fundamental tool used to restore function to the eyelid. This can be required after removal of skin cancer, correction of eyelid malposition such as cicatricial eyelid ectropion, retraction, scar formation, or trauma with loss of tissue. These conditions affect patients of all ages, ranging from newborns to nonagenarians. Skin grafting in the periorbital area is relatively safe, although complications may arise. The most common and challenging complication is scarring and graft shrinkage. This can lead to requiring additional surgery to add additional skin or to improve the appearance of the graft. In addition to the morbidity of another surgery, some patients have limited or no additional skin available (e.g. young patients, burn patients). The eyelid skin is the thinnest of the body, so only thin skin can be used as donor material. However, the amount of skin available for this purpose is very little. There are limited options for preventing graft shrinkage and scarring in this situation. The oldest and most commonly used technique is injection of steroid medication. Steroids decrease

proliferation of a fibroblast cells, which create collagen and glycosaminoglycan, two proteins created by the body that contract and cause graft shrinkage. Data in literature shows that one form of steroid, triamcinolone, is effective for this purpose. However, there is a risk of embolization of this solid steroid material that can rarely cause blindness. In addition, in the periocular area, steroids can elevate intraocular pressure causing glaucoma in some cases and accelerate the formation of cataracts.

1.2 Rationale

- There have been two retrospective studies that have investigated the safety and efficacy of 5-FU injected in periorbital skin grafts with or without Kenalog. The first (Massry 2011) used post-operative injections of a 50:50 mixture of 5-FU and triamcinolone for correction of medial canthal webs. In 2 patients, they found it to be safe and effective. The author noted he has used it previously for other scar management cases and was “very pleased with the results and [had] negligible side-effect[s].” The same author performed another study using 5-FU for skin grafts. This study evaluated 19 patients who had skin grafts for various purposes and were injected following surgery (similar to our protocol). This study demonstrated safety of the injection, with no cases of complication. The author concluded that the 5-FU is effective with “minimal scarring, high patient and surgeon satisfaction, and few complications
- Medication will be injected in the periocular skin graft area 2-3 weeks after surgery. The medication will be injected every 2-3 weeks for a total of up to four injections. Concentration of medication is 50mg/ml. Medication will be administered using a 1cc syringe with a 30gauge needle.

- Any competent patient (male or female) from the age of 18 to 89 that presents with any periocular pathology that requires skin graft for reconstruction and consents to participate will be a candidate to be included in the study.
- To your knowledge 5-FU hasn't been withdrawn from research or market in any country for any reason related to its safety or effectiveness.

2. STUDY OBJECTIVES

2.1 Primary Objective

- Determine the effectiveness of 5-FU on the change in measured graft size.

2.2 Secondary Objective(s)

- Patient and surgeon satisfaction using the scar assessment scale (POSAS) developed and previously published by Draaijers et al.
- Treatment related adverse events. Examples are pain, skin thinning, color/texture change, atrophy, telangiectasis, infection and erythema.
- Early post-operative complications (within 2 weeks of surgery). Example of that are wound dehiscence, graft necrosis, infection, bleeding, partial/complete graft failure and/or ectropion.

3. STUDY DESIGN

3.1 Study Design Description

- Randomized double blinded study comparing 5-FU versus placebo.
 - Patients will be randomized between treatment and control group. Double-masked study, neither patient nor physician providing treatment will know which group they are participating. Pharmacy will provide medication (5-FU versus saline).
 - Subject will be evaluated on first visit for the periocular pathology referred to our clinic requiring a full thickness skin graft to reconstruct the affected area. On that same visit patient will be scheduled to have surgery and research study will be presented. Whether or not patients decide to participate on study, surgery will be performed as normal. Then patient will be seen one week post-op as all surgical patients are normally seen. If patients decide to participate, 1-2 weeks later will start injecting medication (5-FU versus saline) on affected area. Injections will be repeated three more times, for a total of up to four, in a period of 2-3 weeks between each injection. After last injection is placed, patient will be seen 2-3 weeks after, and then 6 and 12 months after original surgery date. During each visit after surgery patient will be required to fill a scar assessment questionnaire.

3.2 Allocation to Treatment

- Patients will be randomly allocated between the two arms: treatment or control group by the MEEI Pharmacy Department.

3.2.1 Randomization Procedures

- Randomization will be performed by the research pharmacy per their protocol. The study will be conducted in a double-blind manner.

3.2.2 Masking Procedures

- Pharmacy will provide medication on the same syringe, no matter the group, with only patient's information.

3.2.3 Breaking the Mask (only if proposed study is *masked*)

- If any of the study participants suffer a serious adverse event, the identity of the study drug received by the subject will be given by the pharmacy for effective emergency treatment of the event.

4. SUBJECT SELECTION

4.1 Subject Inclusion Criteria

- Competent patient (male or female)
- Between ages of 18 and 89

Present with any ocular pathology requiring a full thickness skin graft

4.2 Subject Exclusion Criteria

- Women lactating, pregnant or planning to get pregnant
- Minors (<18 years old) or patients over 89 years old
- Immunosuppressed or immunocompromised
- Serious and active infection
- Dihydropyrimidine dehydrogenase enzyme deficiency
- Severe hepatic or renal failure
- Patient unable to consent

5. STUDY DRUG(S)/DEVICE(S)

5.1 Study Drug Information

- Study drug that will be administered to fifteen of our patients is 5-Fluorouracil, FDA-approved systemic chemotherapy medication to treat certain cancers, the concentration 50 mg/ml and will inject less than 1cc total in the subcutaneous tissue of the affected area.
- Study placebo that will be administered to the other fifteen of our patients is sodium chloride 0.9% (PF).
- Medications will be given every 2 to 3 weeks for a total of 4 injections.
- The amount of medication injected will depend on the extension/dimension of the periocular area affected with a maximum dose of 1cc total.

5.2 Study Drug Compliance/Adherence

- Drug will be injected in office by the physician. Medication will be administered every 2 to 3 weeks.
- Patient will be withdrawn from study if patient doesn't follow post-operative instructions or is non-compliant with follow up appointments.
 - If a subject is withdrawn from study participation due to noncompliance/adherence will be replaced for another patient and will receive the corresponding medication.

5.3 Study Drug Supplies

- **Formulation and Packaging**
Medication will be received directly from MEEI Pharmacy department.
Medication will come on a syringe with only patient's information on it.

- **Preparing and Dispensing**

Medication will be prepared on-site by the MEEI Pharmacy.

- **Administration**

Medication will be administered in the Ophthalmic Plastic and Reconstructive Surgery clinic on the main MEEI building. Injection will be placed on the corresponding affected area of each patient.

5.4 Study Drug/Device Storage and Accountability

- Medication will be prepared and stored by MEEI Pharmacy Department as by their protocol.
- Medication disposable or destruction upon completion as per MEEI Pharmacy Department.

5.5 Other Medications

- **Administration**

No limitation in concomitant medication use prior or during the clinical study participation.

- **Rescue Medication or Therapy**

No identifiable rescue medication or therapy that can be used during the participation in the clinical study.

7. STUDY PROCEDURES

7.1 Screening Procedures

- Every patient that comes to the clinic requiring a full thickness skin graft to reconstruct the periocular area (meets the inclusion and exclusion criteria) will be offered the opportunity to participate on the clinical trial study.

7.2 Enrollment/Baseline Procedures

- Every patient will undergo periocular reconstructive surgery with the use of a skin graft. Afterwards (2-3 weeks later) will start receiving the injections.

7.3 Study Drug or Device Procedures

- Every patient that participates on the study will obtain a physical examination with emphasis on the affected area in every visit. Plus patient will be required to fill out a scar assessment questionnaire. Also a photograph will be taken to monitor changes objectively.

7.4 Standard of Care Procedures

- No matter the patient's enrollment in the study, all patients will obtain the appropriate surgical procedure without deviation of the normal surgical routine. Follow up will be kept the same.

7.5 Follow-up Procedures

- After patient receives last injection, he will be followed 3 more times (2-3 week after last injection, and 6 and 12 month post-op from original surgery date). During those visits, patient will be required to fill out a questionnaire and will obtain a physical examination by the physician and photos will be taken.

7.6 Unscheduled Visits

- If patient needs to be seen sooner for any reason, it will be allowed and documented in the study.

7.7 Early Termination

- If early results show that medication have serious adverse reaction, not seen in any of the previous published studies, then study will be stopped and patients will be informed of the event. Study physician may withhold any injections if there is an adverse event like infection.

7.8 Schedule of Activities (Study Table)

	Intervention (injection)	Physical examination	Questionnaire	Photograph
Initial evaluation (screening)		X		X
Surgery				X
First post- operative visit		X		X
2-3 weeks after surgery (1 st injection)	X	X	X	X
2-3 weeks after 1 st injection (2 nd injection)	X	X	X	X
2-3 weeks after 2 nd injection (3 rd injection)	X	X	X	X

2-3 weeks after 3 rd injection (4 th injection)	x	x	x	x
2-3 weeks after 4 th injection		x	x	x
6 months after initial surgery		x	x	x
12 months after initial surgery		x	x	x

8. SAFETY AND EFFECTIVENESS ASSESSMENTS

8.1 Safety Assessments

- Patients will be asked in each visit after surgery for any adverse events or complain from surgery or injection. It will be documented in the record as normally done with any patient.
- The PI will be responsible for safety review. Physician may withhold any injection if there is an adverse event like infection

8.2 Effectiveness Assessments

- Effectiveness of the study medication will be evaluated by measuring skin graft in each visit after surgery. The measurements will be recorded and analyzed at the end of the study to evaluate the graft size change during the whole study and compare the two groups. Photos will be taken also to objectively observe and document changes. Scar assessment will be evaluated with the use of a questionnaire completed by the observer/surgeon and patient. Questionnaire will be stored and at the end of the study values will be analyzed.

9. ADVERSE EVENT RECORDING AND REPORTING

9.1 Recording Requirements

- Research subjects will be routinely questioned about treatment related adverse events at each study visit. All possible, if any, non-serious examples are pain, erythema/redness, skin thinning/atrophy, infection, color/texture change, swelling, telangiectasia, graft shrinkage/rejection and need for additional surgery. Serious adverse events are not expected to be seen at any moment of the study since medication has been shown to be safe to the patient. In addition, patients will be evaluated for early post-operative complications (within 2 weeks of surgery) not related to study drug treatment. Example of that are wound dehiscence, graft necrosis, infection, bleeding, partial/complete graft failure and/or ectropion. Events will be followed until it resolves or stabilizes; if needed other treatment (eg. antibiotics) will be added to manage adverse event.

9.2 REPORTING PROCEDURES

- **Reporting Adverse Events to the Human Studies Committee (HSC)**
- Will follow HSC Policy for “Reporting Adverse Events and Unanticipated Problem”. As follows, any adverse events that are serious, unexpected and related or possibly related to the study will be reported to the HSC within 7 days from the time the PI becomes aware of the event. Any unexpected and study-related death will be reported to HSC within 24 hours of the PI’s knowledge of the event by e-mail or telephone. A completed AE report form will be submitted to HSC within 7 calendar days of initial HSC notification. If the PI becomes aware more than 30 days after the conclusion of a subject’s participation of a serious adverse event that is both related to the research and unexpected, the PI will

report the event to HSC at the time he becomes aware of it. PI will report to the HSC all non-serious adverse events that are unexpected and related or possibly related to the research within 30 calendar days from the time the PI becomes aware of the event. All unanticipated problems (UAP) involving risks to subjects or others will be reported in writing to the HSC within 7 calendar days from the time the PI becomes aware of the event. If a UAP or an unexpected serious adverse event results in a subject's death or was potentially life-threatening, the PI will notify HSC through e-mail or phone within 24 hours from the time the event is identified. A follow-up report will be submitted at a later date when more information is available. The PI will notify HSC through e-mail or phone within 24 hours from the time the event is identified for UAPs that take the form of a data loss.

9.3 Withdrawal of Subjects due to Adverse Events

- If subject presents with a serious event from intervention, he/she will be withdrawn from further study intervention and the investigators will evaluate the reason for event. If patient states a minor adverse event patient will continue unless patient wishes to voluntary withdraw.
- A serious event includes a severe allergic reaction to medication causing systemic symptoms of anaphylaxis.
- Data will continue to be collected from the withdrawn subjects, until 12 months after original surgery date, but without further intervention (no more injections) and patient will not be included in the analysis.

Withdrawn subjects from study participation due to an adverse event will not be replaced for a new patient.

11. DATA AND SAFETY MONITORING

11.1 Data and Safety Monitoring Plan

- Safety review will take place on site on every follow up visit by the examining physician that will monitor all patients for any complication or side effect from treatment; if serious treatment will be stopped. All adverse events and unanticipated problems will be reported to the Human Studies Committee as previously explained. Every examining physician has the expertise and knowledge to identify any complication from the treatment each patient is receiving. Each physician and member of the study has completed MEEI training. Each month, the study will be assessed by the PI and study coordinator to evaluate for significant adverse or treatment effects. All data collected will be stored in a locked cabinet inside the oculoplastics administrative office.

12. DATA HANDLING, RECORD-KEEPING AND MONITORING

12.1 Data Recording, Record-Keeping and Monitoring

- A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The Sponsor-Investigator will review, approve and sign/date each completed CRF; the Sponsor-Investigator's signature serving as attestation of the Sponsor-Investigator's responsibility for ensuring that all clinical data entered on the CRF are complete, accurate and authentic. The physician will review the informed consent, confirm subject eligibility and verify the accuracy of data transfer from the source document to CRF. Data monitoring will occur monthly if new patients have been recruited during that specific time. Data review will be done by PI and study coordinator.
- Source Data are the clinical findings and observations, and test data/measurements, and other information contained in Source Documents. Source Documents are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.
- The electronic data recording data system being used for this clinical research study has not been fully certified as being compliant with the FDA regulations at 21 CFR Part 11 due to the limited scope of this clinical research study.

13. STUDY DISCONTINUATION CRITERIA

13.1 Discontinuation of Individual Research Subjects

- Discontinuation criteria for individual research subjects has been previously addressed under section 5.2 (Withdrawal of subjects due to non-compliance/adherence) and section 9.3 (Withdrawal of subjects due to adverse events) of the clinical protocol. Decision will be done by PI. Data will be collected until subjects are withdrawn. If subjects have already received part of the treatment or withdrawn before treatment has been started then subjects will be replaced using the same eligibility criteria.

13.2 Sponsor-Investigator Discontinuation of the Clinical Research Study

- Clinical research study will be discontinued if treatment is showed during the course of the study to be harmful to the patient or graft. The rest of subjects will be notified and evaluated to make sure harmful side effects have not occurred to them.
- The HSC and the FDA will be notified promptly of discontinuation of the entire clinical study.