**No: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**RESEARCH PROPOSAL for Graduate Committee (GC)**

**Title (not to exceed 50 words):**

Botox versus Glyceryl Trinitrate in the Treatment of Chronic Anal Fissure: A Randomized Controlled Trial Protocol (BOCHRAN)

**Name of Candidate: DR Nisar Ahmed**

**Name of Supervisor: Dr Abdul Jalil**

**Co-Supervisors:**

**1. Dr Nauman Arif**

**2. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**3. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Duration of Project: 6 Months**

**Institute: Khyber Medical College Peshawar**

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**Budget Required: 0.5 Million PKR**

**Name & Signature of Student/Scholar: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Name & Signature of the Supervisor: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**Name & Signature of Head of Institute: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1. TITLE (not to exceed 50 words):** Should reflect objective of the study.

BOtox versus Glyceryl Trinitrate in the Treatment of CHRonic ANal Fissure: A Randomized Controlled Trial Protocol (BOCHRAN)

**2. Introduction:** (must include problem statement, background information and rationale 250-300 words)

Anal fissure is a linear ulcer in the squamous cell epithelium distal to the mucocutaneous junction, most commonly occurring in the midline posteriorly.1 The predominant clinical features include pain during and after defecation and bleeding.2 The main pathophysiologic cause for fissure formation and non healing is increased anal tone resulting from overactivity of the smooth muscle fibers of the internal anal sphincter 3, compounded by altered bowel movements, especially constipation.4 The surgical option of lateral internal anal sphincterotomy is the gold standard, with healing rates approaching 93 to 100%5, although a few concerns are important for the patients, i.e. the risk of incontinence and the requirement of admission to hospital and general/ regional anaesthesia.6 Among the medical therapies, local application of glyceryl trinitrate ointment (smooth muscle relaxant), diltiazem ointment (calcium channel blocker) and botulinum toxin (presynaptic acetyl choline release inhibitor), are noteworthy.1

The success rates of these medical therapies are variable. Among these modalities, GTN is used widely because of its cost and easy applicability. But certain issues such as variable success rate, side effects profile (29-78%) and poor compliance are associated with its use.5 Pharmaceutical preparation of botulinum toxin A (Botox) has gained a lot of popularity because it is a once only treatment and is used in the outpatients’ setting, and with good fissure healing rates (67-92%).7,8 The efficacy of Botox has been established in many studies across the globe and has been compared against other treatment modalities.7,8

**Rationale:**

Numerous studies including clinical trials have been conducted regarding the comparison of the various medical and surgical treatment modalities, but fewer RCTs have been conducted regarding the comparison of Botox with GTN, with study limitations of small number of participants9, and short follow-up (2 weeks)10.

The limited research about Botox especially in Pakistan11 indicates the lack of confidence of the treating physicians and surgeons on treatment with Botox. Being a relatively recent modality of treatment, Botox has not found its way into the routine use. Moreover, till date, no comparison between botox injection and glyceryl trinitrate has been done in the local setting.11,12 For these reasons, we would like to investigate the role of Botox in the treatment of Chronic Anal Fissure in the local setting.

**3. Objective(s):** (must be stated in measurable terms and starting with an action verb)

To compare the efficacy of Botox Injection (Botox group) with Glyceryl Trinitrate ointment (GTN group) in terms of fissure healing and improvement in mean pain scores.

**4. OPERATIONAL DEFINITIONS:** (All key variables of study must be clearly defined in detectable terms)

**Chronic Anal Fissure:**

A breach in the epithelium of anoderm distal to the anal muco-cutaneous junction with visible fibrosis in the base and a skin tag at the lower end.

**Fissure Healing:**

Defined as re-epithelialization of the previously identified fissure

**Pain Score:**

Pain experienced during defecation on a 0 to 10 visual analogue scale

**5. HYPOTHESIS (If required):** (only the alternate hypothesis must be clearly stated aligned with objective)

Botox injection results in improved fissure healing and lesser pain scores as compared to treatment with local application of GTN ointment.

**6. Materials and Methods:**

**6a. Study Design: Randomized Controlled Trial**

**6b. Study Settings: Department of Surgery, Khyber Teaching Hospital Peshawar**

**6c. Study Duration: Six Months**

**6d. Sample Size:** (with justification of its calculations and reference used):

With 1:1 allocation into either group, 95% significance level (1-$α$), 80 % power (1-$β$), 67% exposed (used Botox) with outcome (Fissure healing) and 33% unexposed with outcome, a sample size of 40 is calculated in both groups.7 The expected loss to follow up is 10%, therefore, the sample size is increased to 44 patients in each group. The sample size is calculated using the online calculator openepi.com.13

**6e. Sampling Technique:**

All consecutive patients presenting to the surgical outdoor department will be assessed for eligibility to the study.

**7. SAMPLE SELECTION:**

**7a. Inclusion criteria :** (What type of subjects or material is to be included in the study)

All the patients with Chronic Anal Fissure above the age of 18 years from both genders will be considered eligible.

**7b. Exclusion Criteria:** (What type of subjects or material is to be excluded from the study and why excluded)

* Known allergy to Botox
* Coexistent other anal conditions like hemorrhoids, fistula in ano etc
* Fissures not located posteriorly or anteriorly
* Coexistent inflammatory bowel disease like ulcerative colitis, Crohn's disease
* History of cluster headaches or migraine

**7c. Study Flow sheet:**

The Standard Protocol Items, Recommendations for Interventional Trials (SPIRIT) guidelines will be followed as per the diagram shown below in Figure 1: Study Flow Sheet

Assessment for Eligibility

Invitation to Participate in the Trial

Informed Consent

Baseline Assessment

Random Allotment into two groups i.e. Botox Group and GTN Group

Botox Group

N = 40

GTN Group

N = 40

8 weeks Assessment

Figure 1: Study Flow Sheet

**7d. Randomization and treatment allocation**

Eligible patients will be randomly assigned to one of the two treatment arms according to computer generated lists. Randomization sequence will be generated by Trials Unit, Institute of Public Health and Social Sciences, Khyber Medical University (IPHSS KMU). The treatment options will be enclosed in opaque envelopes by a researcher not associated with the trial. The randomization code will not be available to the principal investigators before the enrollment of all the study sample.

Upon qualifying for enrollment and consenting to participate in the study, the patient will be asked to pick one envelope and the appropriate treatment revealed.

**7e. Treatment arms**

**Botox group**

A solution of Botulinum Toxin in 0.9% saline will be made in 100 Units/ml concentration. 0.3 ml of the prepared solution will be injected in the inter-sphincteric groove on either side of the midline anteriorly (total amount of Botulinum Toxin used per patient will be 60 Units). The injection would be performed with the patient either in left lateral position or knee-elbow position.

**GTN group**

Glyceryl Trinitrate 0.2% ointment; the patients will be asked to apply the ointment inside the anal canal using the tube applicator three times daily for eight weeks.

In addition to the treatment given, patients in both groups will be encouraged to avoid spicy meals and use diet with abundant fiber. Laxatives will be prescribed where constipation is distressing. Regular pain killers (Tab Paracetamol 375 mg+ Tramadol 37.5 mg) twice daily will be given to all the patients for initial two weeks.

**7f. Outcome measures**

**Primary outcome**

Primary outcome will be complete fissure healing, characterized by complete epithelialization of the fissure mucosa, assessed at 08 weeks after the start of treatment.

**Secondary outcome**

Secondary outcome will be change in pain score from baseline to pain at eight weeks after the start of treatment.

**7g. Masking**

Due to nature of the treatments, where one arm will receive injection and other will receive ointment, masking of the participants or the researchers will not be possible and hence not done.

The researchers measuring the outcome (assessors) will be masked and they will not be allowed to ask about the treatment received.

**7h. Consent**

A detailed written and informed consent will be taken from all the participants on a pre-designed paper-based form. The patients will be given ample time for questions regarding the study. All the potential favorable and unfavorable effects of the interventions will be explained.

**7i. Ethical approval**

The study will be approved by the Institutional Research Evaluation Board (IREB) of Khyber Medical College, Peshawar.

**7j. Adverse events monitoring**

All adverse event (AE) and serious adverse events (SAEs) reported spontaneously by the participant, or observed by research or intervention staff, will be recorded.

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in patients during the trial.

An SAE is defined as any AE that

* Leads to death
* Leads to serious deterioration in health of patient that results in either
	+ Life threatening illness or injury
	+ Permanent impairment of a body structure or body function
	+ In patient or prolonged hospitalization
	+ A medical or surgical intervention to prevent life threatening injury or illness or permanent impairment to a body structure or body function

The chair or a nominated person from the Trial Advisory Board will review SAEs within 48 h, deciding if it is likely related or unrelated to the intervention; and the Trial Advisory Board will review all adverse reactions twice a month. In both instances, the Trial Advisory Board will determine if any appropriate action in respect of ongoing trial conduct is necessary and specify what action this would be (i.e. referral to specialized care). The site PI will inform trial participants and those bodies providing ethical oversight if anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen.

**7k. Retention of study participants**

The participants will be encouraged to comply with the final assessment at 8 weeks. For this reason, monetary reimbursement of the travel expenses of deserving participants will be considered. Moreover, the patients will be encouraged to have telephonic or text message contact in case of any concerns relating to the disease or the follow up.

**8. DATA COLLECTION PROCEDURE:** *(Detailed inclusion of subjects and data collection plan, including briefs about laboratory procedures, surgeries etc. Must clearly explain how the researcher will flow his data collection plan right from start till finishing the follow up on subjects or material.)*

Upon eligibility of a patient for inclusion in the study, a paper based pre-designed data collection form will be used for data collection. Separate forms for individual patients will be used. Sample of the data collection forms is attached here. (***Annexure I***)

The following timeline will be followed for various steps of the data collection, according to the Standardized Protocol Items Reporting for Interventional Trials (SPIRIT) guidelines below: Figure 2: Schedule for various steps of the study

|  |  |
| --- | --- |
|  | **STUDY PERIOD** |
|  | **Enrolment** | **Allocation** | **Post-allocation** | **Close-out** |
| **TIMEPOINT\*\*** | ***-t1*** | **0** | ***t1*** ***(Rx day 0)*** | ***T2******(8 wks)*** | ***tx*** |
| **ENROLMENT:** | X |  |  |  |  |
| **Eligibility screen** | X |  |  |  |  |
| **Informed consent**  | X |  |  |  |  |
| **Allocation** |  | X |  |  |  |
| **INTERVENTIONS:** |  |  |  |  |  |
| ***[Group A (Botox)]*** |  |  |  |  |  |
| ***[Group B (GTN)]*** |  |  |  |  |  |
| **ASSESSMENTS:** |  |  |  |  |  |
| ***Fissure Healing (Yes/No)*** |  |  |  | X |  |
| ***Pain (VAS)*** |  |  | X | X |  |
| ***Side Effects/ Adverse Events*** |  |  |  | X | X |

Figure 2: Schedule for various steps of the study

**9. DATA ANALYSIS PROCEDURE:** *Detailed description of type of analysis plan according to type of variables and study design, statistical tests (if required), stratification of confounders/effect modifiers, presentation of results etc must be clearly mentioned.*

Data analysis will be done by IBM® SPSS® version 26 for macOS. Findings will be reported according to Consolidated Standards of Randomized Trials (CONSORT) statement for RCTs.

Assessed for eligibility

Randomized (n=…)

Excluded (n = …)

Not meeting inclusion criteria (n = …)

Declined to participate (n = ...)

Other Reasons (n = ...)

Allocated to Intervention (n = …)

Received allocated intervention (n = …)

Did not receive allocated Intervention (give reasons) (n = ….)

Allocated to Intervention (n = …)

Received allocated intervention (n = …)

Did not receive allocated Intervention (give reasons) (n = ….)

Lost to follow up (give reasons) (n = …)

Discontinued Intervention (give reasons) (n = …)

Lost to follow up (give reasons) (n = …)

Discontinued Intervention (give reasons) (n = …)

Analyzed (n = )

Excluded from analysis (give reasons) (n = …)

Analyzed (n = )

Excluded from analysis (give reasons) (n = …)

**Enrollment**

**Allocation**

**Follow up**

**Analysis**

Figure 3: Reporting according to CONSORT statement

* The primary and secondary outcome analysis will be done according to intention-to-treat population.
* Comparison of demographics i.e. age and gender of both groups will be done.
* Primary outcome variable i.e. fissure healing (dichotomous variable, healed/non-healed) in two groups will be compared using Chi square test as test of significance. $α\leq 0.05 $will be considered significant.
* Improvement in pain scores (Continuous variable on visual analogue scale) will be compared using independent sample T test, $α\leq 0.05$ will be considered significant.

**10. BIBLIOGRAPHY:** In Vancouver style.

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**ANNEXE:**

**Annexure I: Data Collection Instrument**