PROTOCOL

A double blind randomised controlled trial assessing the effect of oral ibuprofen on outcome of flexor tendon repairs

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Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC *National Statement on Ethical Conduct in Human Research (2007) – Updated May 2015*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95)*.

STUDY INVESTIGATORS:

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Sponsor: Gold Coast Hospital and Health Service for logistics and infrastructure support to the study. No financial considerations.

STUDY SYNOPSIS

(please provide a brief information)

Title:	A double blind randomised controlled trial assessing the effect of oral ibuprofen on outcome of flexor tendon repairs
Short Title:	Ibuprofen Flexor Tendon Trial (IFTT)
Design:	Double Blind Randomised Controlled Trial
Hospital/s:	Gold Coast Hospital and Health Service
Study Question:	Does oral ibuprofen influence outcome in patients post flexor tendon repair?
Study Objectives:	As below
Primary Objectives:	Assessment of the effect of oral ibuprofen on outcome of flexor tendon repairs in humans: 1) Range of motion assessment using Strickland criteria and ASSH criteria 2) Grip strength assessment 3) Michigan Hand Outcomes Questionnaire for

	evaluation of hand outcome
Secondary Objectives	1) Assessment of finger circumference 2) Assessment for delayed wound healing, rupture of tendons, and need for tenolysis/follow up surgeries.
Inclusion Criteria:	18 years of age and above
Exclusion Criteria:	Contraindication to NSAIDs/ibuprofen, systemic conditions/diseases like cardiac, renal, CNS, GI and others, documented allergy to NSAIDs
Number of Planned Subjects:	66
Investigational product:	Oral Ibuprofen
Safety considerations:	Coexisting cardiovascular, gastrointestinal and renal diseases; certain drugs
Statistical Methods:	Two arm trial- interventional and control. Two-sample t-test for a type 1 error (alpha) of 0.05 and a power of 90% for sample size calculation.

1. Glossary of Abbreviations & Terms

Abbreviation	**Description (using lay language)**
ROM	Range of motion
mg	milligram- unit of weight measurement
NSAID	Non-steroidal anti-inflammatory drug- specific class of drugs that are not steroid derivatives but have a good anti-inflammatory properties
OTC	Over The Counter- drugs that people can buy without prescription, also called non-prescription medication
COX	Cyclo-oxygenase inhibitor- inhibitors of specific inflammation enzyme by same name

MHQ	Michigan Hand Outcomes Questionnaire- questionnaire to assess hand function
DIPJ	Distal interphalangeal joint- joint in finger nearest to tip
PIPJ	Proximal interphalangeal joint- joint in finger between tip and palm
MCPJ	Metacarpo-phalangeal joint- joint in hand midway between finger and palm
ASSH	American Society for Surgery of the Hand
TAM	Total Active Motion- combined total number of degrees that a specified joints can move
SD	Standard Deviation- statistical value for deviation of data set on both sides

2. Study Sites

    a. Study Location/s

Site	**Address**	**Contact Person**	**Phone**	**Email**
Gold Coast Hospital & Health Service	Hospital Boulevard, Southport, QLD 4215	Ms Holly Campbell	0756870334	GCUHOrthoAcademics@health.qld.gov.au

3. Introduction/Background Information

    a. Introduction

Flexor tendon lacerations in the hand are a clinical challenge to manage, as they often develop stiffness post operatively. The common complications after flexor tendon repair in the hand are rupture and reduced range of motion and grip strength. (1,2). As with other wounds, tendons heal with an initial inflammatory phase. Excessive scarring of the healing tendon causing adhesions to the surrounding structures will reduce excursion of the healed tendon and thereby cause stiffness of the injured finger with a measurable decrease in range of motion (ROM). After tendon repair, patients have to undergo a minimum of six weeks of

hand therapy in a special splint to protect from rupture and with regular controlled exercises to minimise scarring of the repaired tendon. Patients who develop excessive scarring usually require a second operation months later to remove the scar and allow the tendon to glide.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen inhibit cyclooxygenase (COX) activity and are commonly used as over the counter (OTC) analgesics to treat pain and swelling arising from trauma. Animal studies suggest that ibuprofen as an adjunctive therapy to surgical tendon repair can decrease scar tissue around the tendon (2,3). There is limited clinical evidence on beneficial effect of ibuprofen after tendon repair in human patients with only one published report that utilised high doses of the drug.

The research question is 'Will giving the patient regular ibuprofen at therapeutic doses following flexor tendon repair in the hand will result in better movement?'. The aim of this study is to examine the effect of ibuprofen on flexor tendon injury outcome in patients undergoing flexor tendon repair. This study will be a randomised control trial with two arms, one interventional arm where the patient will be given ibuprofen for three weeks and another control (paracetamol) arm where patients will only receive paracetamol as painkiller. Outcome assessment will include range of motion, grip strength, functional grade, finger circumference and Michigan Hand Outcomes Questionnaire (MHQ) (4-7).

If ibuprofen is shown to have a positive effect on outcome of tendon repair it can become a low-cost and low-risk routine intervention to provide better finger movement and hence better function following flexor tendon repair. It may also reduce the need for additional surgery for scarring.

b. Background information

Tendon injuries in the hand are a clinical challenge as it is very difficult to recover full finger movement due to stiffness. The common complications after flexor tendon repair in the hand are rupture and reduced range of motion and grip strength. (1,2). As with other wounds, tendons heal with an initial inflammatory phase. Excessive scarring of the healing tendon to the surrounding structures will reduce excursion of the healed tendon and thereby cause stiffness of the injured finger with a measurable decrease in range of motion (ROM). After tendon repair, patients have to undergo a minimum of 6 weeks of occupational and physiotherapy and wear a special splint to protect from rupture and with regular controlled exercises to minimise scarring of the repaired tendon. Patients who develop excessive scarring usually need a second operation a few months later to remove the scar and restore

function. Flexor tendon injuries can seriously affect the functionality of injured hand thus increasing morbidity as hand contributes a large proportion of the total work done by upper limb.

NSAIDs like ibuprofen have been specifically implicated in reducing scar and adhesions in different clinical scenarios including tendon healing.(8-10) NSAIDs could decrease peritendinous fibroplasia by reducing endogenous local damage after trauma through the decrease in inflammatory agents like prostaglandins.(8,10) Most of the studies regarding NSAIDs use for improving flexor tendon outcomes have been conducted using animal models. All the quoted studies have provided overwhelming evidence of the beneficial effects of NSAIDs regarding outcome after flexor tendon repairs especially ibuprofen. These positive effects of NSAIDs on tendon healing are due to the influence on remodelling of collagen matrix. Administration of the drug did not adversely affect tendon healing in previous reports. (3,8,10,11)

Prior studies have used ibuprofen for 2 weeks to 4 weeks and shown positive effect on flexor tendon repair outcome both in animals as well as humans. (2,3,8,11). In the only clinical study of 35 patients, ibuprofen was administered for 4 weeks with reported positive outcome compared to control group (11).We have selected 3 weeks duration as laboratory studies demonstrate the maximum healing occurs during the first 3 weeks after repair. Additionally, this will improve patient compliance as patients no longer have pain after 3 weeks and are less likely to continue taking the medication.There is a paucity in present literature regarding benefit of NSAIDs use in humans after flexor tendon repair and further well-designed randomized trials are needed before their use becomes routine practice. Ibuprofen is commonly used after surgery on an ad-hoc basis for pain relief. We propose giving patients a therapeutic dosage of ibuprofen of 400 mg three times a day for a period of three weeks after surgical repair of tendons in order to reduce scar formation. We will use a control arm where the patient is not given any ibuprofen but will be given paracetamol for pain relief and both arms will receive breakthrough medication (oxycodone 10 mg) on an as-needed basis. This study will be a double-blinded randomised controlled trial with patients either randomised to ibuprofen arm or control arm at the time of enrollment. Based on previous reports and our own experience with flexor tendon repairs, we expect to achieve 85% of the normal range of motion for joints of fingers and hence plan to recruit 66 patients (4,12). This study will critically appraise the outcome using descriptive outcome indicators and analysis of range of motion, grip strength, functional grade, finger circumference and Michigan Hand Outcomes Questionnaire (MHQ) (4-7).

If ibuprofen is shown to have a positive effect on outcome of tendon repair it can become a low-cost and low-risk routine intervention to provide better finger movement and hence better function. It may also reduce the need for additional surgery for scarring.

4. Study Objectives

    a. AIMS:

    1) The primary objective of this study is to assess the effect of oral ibuprofen on outcome of flexor tendon repairs in humans using:

1. Range of motion assessment using Strickland criteria and ASSH criteria
2. Grip strength will be recorded as percentage of contralateral hand
3. Michigan Hand Outcomes Questionnaire for evaluation of hand outcome

    2) The secondary objectives of this study are:

1. Assessment of finger circumference at PIPJ in comparison to contralateral hand
2. Patients will also be assessed and followed up for delayed wound healing, rupture of tendons, and need for tenolysis/follow up surgeries.

    b. Hypothesis

    1) Use of oral ibuprofen after flexor tendon repair will result in improved outcome in comparison to control arm that will only receive paracetamol for pain relief.

    2) Oral ibuprofen will result in reduction in finger circumference in patients randomised to interventional arm as compared to patients randomised to control arm

5. Study Design

    a. Study Type & Design & Schedule

Study will be a double-blinded randomised control trial with two arms: one interventional that will receive oral ibuprofen after flexor tendon repairs and the other being the control arm that will receive active drug not containing ibuprofen or any other NSAID that is paracetamol in this study.

Population studied will be 18 years of age and above. It will be a single centre study.

Data will be collected by investigators through in clinic and stored electronically. It will include injury details, operative details and follow up outcome indicators including range of motion,

grip strength, functional grade, finger circumference and Michigan Hand Outcomes Questionnaire (MHQ). Data will be identifiable to investigators and administrators who are involved in study. They will ensure confidentiality of data.

Recruitment will be open till the enrollment of all participants and we expect that to be around 12 months from enrollment of first participant, follow up will be concluded in further 3 months and data analysis will take further 1 month. We expect study analysis should be completed within 16 months of first enrollment.

This study will not require any home visits and protocol is not planned to be used for a student project as of now.

1. Specify how the design will achieve the aims and objective

    b. Randomisation

Participants and investigators will be blinded. The ralloc command of the Stata statistical program will be used to create a Block Randomisation. The randomization list (Participant Number, Ibuprofen or Paracetamol) will be forwarded to the GCUH Pharmacy where the appropriate drug sufficient for 3 weeks use will be packaged along with dosing instructions and the packages labeled with the name of the trial and the participant number. Participants will be provided with consecutive participant numbers upon consent.

    c. Study methodology

All patients undergoing hand flexor tendon repairs under Gold Coast Hospital & Health Service - Gold Coast University Hospital and Robina Campus fulfilling the inclusion criteria will be randomised to study to either interventional or control arm. (n=33 for each arm.)

Flexor tendon repair will be done with non absorbable core and/or epitendinous sutures that are standard of care.

Patients in interventional arm will receive 400 mg oral ibuprofen three times a day for a period of three weeks and will be monitored for any adverse events of interest. Patients in control arm will receive 1000 mg of paracetamol three times a day for three weeks. Dosing instructions for both arms will be identical and drugs will not be identifiable.

Patients in both arms will be put on an identical early active motion tendon rehabilitation protocol under supervision of the hand therapy unit.

Patients in both arms will be instructed to take breakthrough pain medication on an as-needed basis tablet oxycodone 10mg per oral six hourly) when visual analog score (VAS) is more than 4 out of 10.

Clinical assessments for the purpose of trial will be performed at 6 and 12 weeks post surgery. Other regular follow up visits as per standard of care will occur including a clinical evaluation on post-operative day 10 and appointments with hand therapy that start as early as a couple of days post surgery and take place every week or sooner during initial rehabilitation phase. Compliance and adverse drug reactions will also be monitored through verbal communication on follow up visits post surgery.

Assessment criteria:

1) Range of Motion assessments for MCPJ, PIPJ and DIPJ:

i) Strickland criteria for range of motion assessment for PIPJ and DIPJ with contralateral hand as normal. If contralateral hand is not normal, 175 degrees ROM for both joints is considered the normal value. The sum of the degrees of active PIPJ and DIPJ flexion less the degrees from full extension is taken as motion range.

Function Grade assessment is reported as: Excellent 85-100%, Good 70-84%, Fair 50-69%, Poor <50% (expressed in percentage of normal). (4)

ii) ASSH criteria- Total Active Motion under this criteria is calculated in a similar manner as the range of motion under Strickland criteria, but also includes the MCPJ range of motion: Active Range of Motion (AROM) from MCPJ, PIPJ and DIPJ with contralateral as normal, if contralateral hand is normal. If contralateral hand is not normal, 260 degrees TAM for all three joints is considered the normal value. The sum of the degrees of active MCPJ, PIPJ and DIPJ flexion less the degrees from full extension is taken as motion range.

Function grade assessment is reported as: Excellent 100%, Good >75%, fair >50%, Poor <50% (expressed in percentage of normal). (6)

2) Grip Strength: Grip strength is recorded as percentage of the contralateral hand grip strength using hand dynamometer and is considered normal if it is more than the uninjured non-dominant hand or >70% of the uninjured dominant hand.(5)

3) Michigan Hand Outcomes Questionnaire for evaluation of hand outcome for each hand separately and it will approximately take 15 minutes to complete (7).

4) Assessment finger circumference:

Finger circumference of the finger with repaired tendon at PIPJ will be taken and compared with contralateral hand at each visit using a measuring tape around PIPJ and will be recorded in millimetres.

5) Patients will also be assessed and followed up for delayed wound healing, rupture of tendons, and need for tenolysis/follow up surgeries

Clinical examination is expected to take approximately 15 minutes in total.

We expect to achieve 85% of normal range of motion for the finger joints in intervention arm at the end of 12 weeks. We hypothesize that finger movement in the ibuprofen group will be better than the control arm. In the clinical setting, this means a difference of about 35 degrees of the total movement of the finger. The number has been derived from prior studies where a difference of 35 degrees moves a patient from the good to the excellent category. (4,12).

6. Study Population

a. Recruitment Procedure

Subjects will be recruited from the group of patients who will present to the hospital for repair of flexor tendon injuries. Patients to both interventional and control arms will be recruited from same group of patients. Allotment to either arm will be decided on the basis of pre-randomised envelopes/containers and will not be known to either investigators or patients. Relevant information will be provided, all queries will be answered and written consent will be taken upon agreement.

b. Inclusion Criteria

- Adults (aged 18 years and above) undergoing repair with acute (less than 14 days) sharp laceration to single or multiple fingers flexor tendon injury – flexor digitorum

superficialis (FDS) / flexor digitorum profundus (FDP) or both, with or without neurovascular injury.

- Able to participate in early active therapy protocol.

c. Exclusion Criteria

- Non-english speaking patients.
- Patients who do not wish or are unable to follow the protocol (intellectual impairment)
- Crush or avulsion injuries.
- Replantation or revascularization procedures (both neurovascular bundles damaged with pre-operative vascular compromise) (as this will change the rehabilitation)
- Polytrauma patients (that would affect the ability to undertake appropriate hand therapy).
- Previous hand injury or arthritis with pre-existing hand stiffness, which limited hand range of motion
- Patients on warfarin or similar anticoagulants and patients already on NSAIDs or paracetamol containing medications.
- Pregnant or breastfeeding females
- Contraindications to ibuprofen or paracetamol use including:
    - Hypersensitivity or allergy to ibuprofen , paracetamol or other NSAIDs ex. aspirin -induced asthma
    - Liver or renal impairment, heart failure, diabetes or malignancy
    - Asthmatics without any prior history of NSAID intake
    - History of peptic ulcer or gastric bleeding

d. Consent

Individual consent will be obtained after patient agrees to participate in the trial after all information has been given to patient and queries are answered.

7. Participant Safety and Withdrawal

a. Risk Management and Safety

Recent National Health and Medical Research Council, Australia guidelines will be followed for reporting adverse events of interest during the trial.

We will monitor for following adverse events of interest associated with ibuprofen:

- Dark urine, clay coloured stools, yellowing of skin and whites of eyes.
- Drooping of face, limb weakness or paralysis, chest pain, unconsciousness
- Vomiting blood, blood in urine or black stools

We will also monitor for following adverse events of interest associated with paracetamol:

- Dark urine, clay coloured stools, yellowing of skin and whites of eyes.

Serious adverse events will be reported to the institution within 24 hours of investigators becoming aware of the event. Other adverse events of interest will be tracked using an adverse event log and then the combined events from the log and all serious adverse events are reported annually to the HREC in a report.

All patients will be instructed to not take any other painkiller while on trial medications and in rare case of pain being not under control even after taking prescribed medications they should contact the research team orthopaedics outpatient clinic during office hours or emergency department, out of office hours and be directed to orthopaedic registrar on call. This is the standard practice for all of our postoperative patients. Similarly they will be instructed to follow the above mentioned procedure in case of patients experiencing adverse events of interest. Adverse events of interest will be managed appropriately as indicated and subjects may be removed from the trial if clinically indicated. Compliance and adverse events of interest will also be monitored through verbal communication on follow up visits post surgery.

b. Handling of Withdrawals

Participants may withdraw from the study for the following reasons: participant has chosen to withdraw from the study, protocol violation, or participant has experienced an adverse event. Withdrawals will be appropriately notified to concerned authority and will be excluded from final analysis. All data will be deleted. There will be no blood samples or scans. Unblinding of participants in case of adverse reactions and removal of trial will involve department of pharmacy and principal investigator.

8. Statistical Methods

Sample Size Estimation & Justification:

We expect to achieve 85% of normal range of motion for the finger joints in intervention arm at the end of 12 weeks. We hypothesize that finger movement in the ibuprofen group will be better than the control arm. In the clinical setting, this means a difference of about 35 degrees of the total movement of the finger. The number has been derived from prior studies where a difference of 35 degrees moves a patient from the good to the excellent category. (4,12).

This study is designed to detect a difference of 35 degrees in the PIPJ+DIPJ ROM between control arm and ibuprofen (interventional) arm where the mean angle of control arm is 114

degrees and the ibuprofen arm is 149 degrees. The difference is considered the smallest clinically relevant difference. Based on using a two-sample t-test with a SD of 45 in each group, for a type 1 error (alpha) of 0.05 and a power of 90% we will require a total of 60 participants, 30 in each arm. Considering 10% withdrawal rate, sample size will be kept at 66 participants, 33 in each arm. (12)

Statistical methods have been written in direct collaboration with Dr. Ian Hughes, Biostatician, Office of Research Governance and Development, Level 2, Block E- Pathology and Education, Gold Coast University Hospital, Gold Coast Health.

9. Storage of Blood and Tissue Samples

Not applicable to our study

10. Data Security & Handling

a. Details of where records will be kept & How long will they be stored

Data will be stored with Department of Orthopaedics, GCUH. Records will be kept for 5 years or until publication of findings whichever is later.

b. Confidentiality and Security

Data will be directly entered into electronic form in excel spreadsheet and will be only accessible to investigators or administrators involved in conduction of study. Confidentiality will be ensured by the users.

c. Ancillary data

Data will be stored for 15 years after closure of trial or until publication whichever is later. Data will only be accessible to investigators or administrators involved in conduction of study and they will ensure confidentiality.

11. Dissemination Plan

Research findings will be presented in scientific meetings/published in journal of repute.

Potential target journal: Journal of Hand Surgery

Rahul Bamal: study design, study draft, recruitment, data acquisition, data analysis

Randy Bindra (Principal investigator): study design, data interpretation, critical revision, final approval

David James Graham: study conception, study design, data interpretation, critical revision, final approval

References:

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