**OFFICIAL TITLE:** EFFECTIVENESS OF PERI-OPERATIVE COMBINED USE OF 2 DOSES OF DEXAMETHASONE WITH TRANEXAMIC ACID IN LOWER LIMB JOINT REPLACEMENTS, A RANDOMIZED CONTROLLED TRIAL

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## 1 INTRODUCTION/BACKGROUND

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are highly effective interventions 45 for end-stage arthritis of the knee and hip. Controlling postoperative pain and nausea after total joint arthroplasty remains an important challenge. Perioperative corticosteroids are safe, facilitate earlier discharge, and improve patient recovery following unilateral total knee arthroplasty and total hip arthroplasty. Higher doses (15-20 mg of dexamethasone) are associated with further reductions in dynamic pain and PONV, and repeat dosing may further reduce LOS. It was found that neither one nor two doses of 24 mg intravenous dexamethasone demonstrated prolonged effects on overall pain or sleep quality on postoperative days 3–7 after total knee arthroplasty, also have no effect on patients satisfaction, but it reduced the opioid consumption. Tranexamic acid (TXA) reduces rates of blood transfusion for total hip arthroplasty (THA) and total knee arthroplasty (TKA) . Hence, it was proved that the combination of TXA and DEX has positive impacts on the usage of oxycodone and metoclopramide, postoperative range of motion, postoperative nausea and vomiting and reduces the length of hospital stay .The administration of 10 mg dexamethasone 1 h before the surgery, and repeated at 6 h postoperatively can significantly reduce the level of postoperative CRP and IL-6. There is insufficient evidence on perioperative dexamethasone in primary TJA to determine the optimal dose, number of doses, or risk of postoperative adverse events.

## 2 .Background of interventional procedure

Total joint arthroplasty (TKA) is viewed as one of the most successful orthopedic surgeries for most end-stage joint diseases. In recent years, the concept of enhanced recovery after surgery (ERAS) has greatly improved the speed of rehabilitation after total joint arthroplasty. Patients feel more comfortable during the perioperative period and have shorter hospital stays with the administration of steroidal administration. Dexamethasone plays an important role in ERAS due to its anti-inflammatory and pain reduction role. As, TXA can prevent the activation of plasminogen and delay fibrinolysis and reduce blood loss and the rate of blood transfusion perioperatively. Recent studies showed that dexamethasone may be administered multiple times peri operatively. A large number of studies confirmed that dexamethasone can reduce post operative pain and inflammation and shortens the length of hospital stay and combination pre operative tranexamic acid with dexamethasone reduces the limb swelling that improves the joint range of motion. There will be no risk of the interventional drug

Benefits will include that the drug is cost effective, easily available, reduce the post operative complications

## 3. Rationale

Previous studies showed the effects of peri-operative use of single dose of dexamethasone, and there is very little data available on effects of peri-op use of multiple doses of dexamethasone. There is no study that has been conducted yet, which compared the effects of peri-op use of 1 dose of dexamethasone and tranexamic acid with 2 doses of dexamethasone and tranexamic acid, on post operative range of motion and pain during rest and weight bearing on operated limb, length of stay in hospital and C-reactive protein.

## 4. Study Objectives

### 4.1 Primary Objective

To evaluate the effectiveness of peri operative intravenous 2 doses of dexamethasone in lower limb joint/s replacement surgeries on postoperative C-reactive protein, post operative fatigue, postoperative joint range, post operative pain during rest and weight bearing, and length of hospital stay.

### 4.2 Hypothesis:

If hypothesis will get confirmed, then the peri operative use of 2 doses of dexamethasone with intravenous tranexamic acid, reduces the postoperative C-reactive protein, post operative fatigue, pain during rest and weight bearing, and length of hospital stay and improves the post operative joint range of motion.

If hypothesis will not get confirmed, then the peri operative use of 2 doses of dexamethasone with intravenous tranexamic acid, will not reduces the postoperative C-reactive protein, post operative fatigue, pain during rest and weight bearing, and length of hospital stay and and will not improve the post operative joint range of motion.

## 5. Material and Methods:

### 5.1 Study Design:

Randomized controlled trial with 2 arms

**Arm 1**: GROUP A will receive 1 dose of dexamethasone (10mg) with tranexamic acid (20mg/kg), peri operatively .

**Arm 2**: GROUP B will receive 2 doses of dexamethasone (2*10mg) with tranexamic acid (20mg/kg), peri operatively.

### 5.2 Study setting & target population

Study settings: Orthopedics Department, Indus Hospital and Health Network.

Targeted Population: patients having knee/hip osteoarthritis scheduled for joint replacement of one or both sides.

### 5.3 Duration of study

12 months

8 patients per month will be enrolled

### 5.4 Trial Population:

**Screening Criteria**

After giving the informed signed consent, participants will have a detailed examination and will assess for eligibility as defined in inclusion/exclusion criteria.

### 5.5 Clinical contraindications

Not any

### 5.6 Excluded medications

Not any

### 5.7 Known allergy/sensitivity or any hypersensitivity to components of study drug(s) or their formulation

Not any

### 5.8 Active drug or alcohol use or dependence that would interfere with adherence to study requirements

**Serious illness requiring systemic treatment and/or hospitalization within 3-4 days prior to entry**

Not any

## 6 Study enrollment procedures including informed consent

Prior to commencing the study, protocol and protocol consent form will be approved by the institutional review board (IRB). Once the identification will be completed, details will be carefully discussed with the subject.

If the patient or representative will not able to read and sign then informed, then it will be signed and dated by an impartial witness who will independent of the Investigator. A witness who will sign and date the consent form will certify that the information in this form and any other written information had been accurately explained to and understood by the patient or his / her representative.

## 7 STUDY TREATMENT (OR INTERVENTION)

7.1 Regimens (or Intervention), Administration, and Duration

All patients will randomize into two groups,

**Group A**: 1 dose of IV Dexamethasone 10mg+ tranexamic acid (20 mg/kg**);**

**Group B**: 2 doses of IV Dexamethasone 10mg+ tranexamic acid 20 mg/kg.

In group A, 1 dose of 10 mg of intravenous dexamethasone and 20mg/kg of intravenous tranexamic acid administered at 10 minutes before surgery.

In group B, dose of 10 mg of intravenous dexamethasone and 20mg/kg of intravenous tranexamic acid administered at 10 minutes before surgery and then 10mg of intravenous dexamethasone will be again administered before incision closure.

### 7.2 Concomitant Medications

**7.2.1 Required Medications:** IV TXA 20 mg/kg

IV Dexamethasone 10mg

**7.2.2 Prohibited Medications:** not any

**7.2.3 Precautionary Medications:** not any

### 7.3 Treatment Compliance (adherence assessment)

**Treatment compliance:**

If patient will come on follow up visits at 1st and 4th week for outcomes assessment, after discharge.

**Treatment non compliance:**

If patient will not come on follow up visits at 1st and 4th week for outcomes assessment, after discharge.

## 8 CLINICAL AND LABORATORY EVALUATIONS

**8.1. Timing of Evaluations**

8.1.1 Screening: Screening will be done during pre operative evaluations, prior to the enrollment in study. In addition to data being collected on subjects who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a screening log and entered into the database.

**8.1.2 Pre-Entry**

Pre-entry evaluations will complete at 15 days after screening evaluations have been completed.

**8.1.3 Follow-up**

Follow up will take place at 1st and 4th week, after discharge.

**8.2 Laboratory Evaluations**

Pre Operative laboratory evaluations will include:

Complete Blood Count (CBC)

C-Reactive Protein (CRP)

Renal Function Test (RFT)

Hepatitis B and C

Electrocardiogram

Chest X-ray

Activated Partial Thrombin Time (aPTT)

Prothrombin Time (PT)

Hemoglobin A1c (HbA1c)

Post operative laboratory evaluations

Complete Blood Count (CBC)

C-Reactive Protein (CRP)

from which investigators will take data of C-reactive protein values in our study, to compare pre and post operatively.

### 8.3 Questionnaires

- Post operative identity consequences fatigue rating scale
- Numeric Pain rating Scale

## 9 CRITERIA FOR DISCONTINUATION

### 9.1 Permanent Treatment Discontinuation

- Drug-related toxicity
- Requirement for prohibited concomitant medications .
- Not completion of treatment as defined in the protocol.
- Request by subject to terminate treatment.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

### 9.2 Premature Study Discontinuation

- Failure by the subject to attend consecutive clinic visits at 1st week and 4th week after discharge.
- Request by the subject to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject.
- Subject judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- A defined study endpoint reached.
- At the discretion of the IRB or investigator.

from which investigators will take data of C-reactive protein values in our study

## 10 STATISTICAL CONSIDERATIONS

### 10.1 Blinding Procedures

The patients, trial participants, anesthesiologists, and data collectors will be blinded to allocation while assessors will know the allocation.

### 10.2 Sample Size and Accrual

IBM SPSS Statistics 21 software will be used to analyze the data.

Methods of analyzing the data will include interferential and descriptive statistics

### 10.3 Determination of Sample Size and Power Calculation

The calculated sample size, using total blood loss is 25 in each group and after adding 20% dropout the sample size will be 25+5=30 in each group. The sample size is calculated using following information.

Z1-$\alpha$/2 Level of significance=95%

$\mu$1 Expected mean change in total blood loss in Group A=93.80

$\mu$2 Expected mean change in total blood loss in Group B= 95.98

$\delta$1 Expected standard deviation in group A=3.88

$\delta$2 Expected standard deviation in group B=2.82

Z1-$\beta$ power of the study= 80%

sample size in a group(n)= 38

After adding 20% drop out 38+8=46 in each group.

Total sample size will be 92

No of groups/arms in study:

Type of comparison:

Superiority comparison

Type of configuration:

Parallel designs

Level of significance (Alpha level): 95 %

Power: 0.8 or 80 %

Allocation ratio: 1:1

Underlying population event rate:

Almost 90 percent of population undergoing total joint replacement, whether uni or bilateral would show the positive clinical outcomes with the use of 2 doses of dexamethasone.

Effect size of therapy: the clinical guidelines shows that each group of clinical trial must have at least 30 participants, so effect size is 92 more than sample size calculated, drop out patients percentages added.

Estimated loss to follow-up or refusals: Based on previous work in this population, 20 % will be lost to follow up or drop out from the trial.

### 10.4 Underlying population event rate:

The population enrolled in previous studies undergoing total joint replacement, whether unilateral or bilateral showed the positive clinical outcomes with the use of dexamethasone with tranexamic acid.

**10.5 Estimated loss to follow-up or refusals:** Based on previous work in this population, 20 % will be lost to follow up or drop out from the trial.

## 11 DATA MANAGEMENT AND MONITORING

### 11.1 Key personal description

ROLE OF INVESTIGATOR: supervise and guidance of all study protocols

ROLE OF CO-INVESTIGATOR: allocation, screening and reassessments, at follow ups, of patients.

ROLE OF NURSING STAFF: taking data from patients under supervision of co-investigators.

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### 11.2 Monitoring of clinical staff involved in research

Nursing staff will be trained about data collection by mentioning the pre and post op CRP, measuring the knee ROMS with goniometer, post operative fatigue scoring, length of hospital stay, post operative pain scoring that will be measured as under supervision of co-investigators.

### 11.3 Records to be kept

Total 4 questionnaires will be provided for each subject to record the data pre and post operative 1st day, 1st and 4th week after discharge. Subjects will be identified by the patient medical record number (MR no).

### 11.4 Management of Clinical Data

The patient's data will be kept on the red cap software, and assessor will assign the patients into 2 groups such that group A and B, according to the doses of dexamethasone will be given, but data collector and patients will be unaware of the group randomization.

### 11.5 Lost to Follow-up Procedures

. A documented reasonable effort i.e., documented telephone calls will be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts will be documented in the research file in the case of patients who fail to return for a follow-up examination.

### 11.6 Follow-up of Discontinuations

The research team will complete all scheduled safety follow-ups with any patient who has prematurely terminated the trial because of a Serious Adverse Event, non-compliance with the protocol, or loss of eligibility, including definite contraindications

### 11.7 Clinical Site Monitoring and Record Availability

Data will be collected from patients in orthopedics ward, and records will be available on Red Cap forms.

## 12 ADVERSE EVENTS DATA MANAGEMENT & REPORTING

### 12.1 Safety Definitions

12.1.1 Adverse Event (AE):

Not any

12.1.2 Adverse Reaction:

Not any

## 13 HUMAN SUBJECTS

IRB OF INDUS HOSPITAL AND HEALTH NETWORK

APPROVAL LETTER BY IRB-INDUS HOSPITAL

Expedited v2- IRB Approval letter.pdf

## 14. Data collection instruments

It includes 4 questionnaire forms per patient

Pre operative form:

PreOpt_EFFECTIVENESSOFPERIOPER.pdf

Post operative 1st day form

PostOp_EFFECTIVENESSOFPERIOPER.pdf

Post operative 1st week after discharge from hospital, form

1stWeekAfterDischarge_EFFECTIV.pdf

Post operative 4th week after discharge from hospital, form

4thWeekAfterDischarge_EFFECTIV.pdf