Study Protocol

Title: Comparison of combined topical tranexamic acid with Floseal® with intravenous tranexamic acid on blood loss in total knee arthroplasty

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Study Design and Protocol

We plan to compare acute blood loss (every two hours for 8 hours), total blood loss and risk of blood transfusion, after primary total knee arthroplasty (TKA) within three groups.

- Group I (N=35): Primary total knee replacement with application of Floseal® on potential bleeding sitesbefore prosthesis implantation and intraarticular application of tranexamic acid 3g in 40 ml normal saline into knee joint after closure of the joint capsule.
- Group II (N=35): Primary total knee replacement with intraarticular application of tranexamic acid 3g in 40 ml normal saline into knee joint after closure of the joint capsule.

A : How to enroll the patient

Patients who plan to undergo primary total knee replacement were recruited to this study first. Second, we exclude the patients according to our exclusion criteria. Then we will explain the study design, purpose and risk to the patient and the family. At last, we will enroll the patient into this study after patient and family agree and sign the informed consent.

Inclusion criteria :

1. Patients who have advanced knee osteoarthritis are scheduled to undergo primary, unilateral elective total knee replacement surgery
2. Age > 50 years and < 90 years
3. Failure of medical treatment or rehabilitation.
4. Hemoglobin > 11g/dl,
5. No use of non-steroid anti-inflammatory agent one week before operation

Exclusion criteria

1. Preoperative Hemoglobin ≦11 g/dl
2. History of infection or intraarticular fracture of the affective knee
3. Renal function deficiency (GFR <30 ml/min/1.73m2)which is relative contraindicated for chemical venous thromboembolism
4. Elevated liver enzyme, history of liver cirrhosis, impaired liver function and coagulopathy (including long-term use anticoagulant)
5. History of deep vein thrombosis, ischemic heart disease or stroke

6. Contraindications of tranexamic acid, floseal, or rivaroxaban
7. Allergy to tranexamic acid, floseal, rivaroxaban, or the excipients
8. History of heparin-induced thrombocytopenia (HIT)
9. Coagulopathy or bleeding tendency caused by organ dysfunction, such as cirrhosis, bone marrow suppression etc.
10. Patient who have active bleeding disorder, such as intracranial hemorrhage, upper GI bleeding, hematuria.
11. Patients with known allergies to materials of bovine origin.

Withdrawal criteria

Patients can refuse to participate this study and withdraw from this study at any time of this study, even if the TKA has been done. The data will not be collected for statistics.

Regulations of self-medications of participants

1. Every participant should follow the physician's instructions to use anti-coagulants. Any drug which influences the hemostatic status [including aspirin, clopidogrel, warfarin, etc] should not be used in this study.
2. Drugs which do not influence the hemostasis can be used during the period of this study

Study grading :

Prospective, randomized control trial, single-blinded

Ongoing procedure :

1. All patients receive primary total knee replacement with cemented prosthesis
2. Skin incision using midline longitudinal incision with midvastus approach
3. All operative procedure is performed through minimally invasive technique (8-12 cm)
4. Use of intramedullary guide system for femoral bone cutting, extramedullary guide for tibia cutting.
5. Use of bone plugs in the femoral canal
6. No hemostasis or release of tourniquet before wound closure
7. The hemostasis strategy is different depending on which group the patient is assigned in:
    i. Patients in the first group will receive Floseal® 5ml on potential

bleeding sites before insert implantation, then receive injection tranexamic acid 3g in 40 ml normal saline into knee joint after closure of the joint capsule and before deflating the tourniquet.

ii. Patients in the second group will receive injection tranexamic acid 3g in 40 ml normal saline into knee joint after closure of the joint capsule and before deflating the tourniquet

8. A hemovac drain is in place before wound closure
9. Deflate the tourniquet after wound closure, and the hemovac drain will be clamped for 1 hour after topical TXA injection.

- Postoperative management
  - Estimating blood loss

    Amount of hemovac drainage

    postop 0-2 hours

    2-4 hours

    4-6 hours

    6-8 hours

    8-16 hours

    16-24 hours

    24-32 hours

    32-40 hours
  - Deep vein thrombosis (DVT) prophylaxis with oral rivaroxabam 10mg Qd Day 1 to 14.
    - Start ambulation immediately after operation
  - Check Hb/Hct preoperatively and postop. Day 1, 2, 3 and 14.
  - Indication for allogenic blood transfusion
    - Hb < 8.0g/dl with clinical manifestation of anemia (dizziness, palpitation, palor etc) or Hb < 9.0g/dl in elderly paitents with risk of cardio pulmonary complications
  - Bulking dressing x 2 days
  - Ice packing q6h
  - Ward exercise training starting from 1st post op day
  - Check D-Dimer preoperatively and postop. Day 1.
- 結果測量

1. <u>Primary outcome measure:</u>

   Total Blood Loss

   The total blood loss was calculated according to Nadler et al., which uses maximum postoperative decrease of the Hb level adjusted for weight and height of the patient. Total blood loss

consists of amount of blood loss calculated from the maximum Hb loss and amount of blood transfused

Total blood volume =(K1 x height^3[ml]) + (K2 x weight [kg]) + K3

Where K1 =0.3669 , K2=0.03219, and K3=0.6041 for men and K1=0.3561, K2=0.03308, and K3=0.1833 for women

Total blood loss ={total blood volume * (preop. Hb level – 3th day postop. Hb level)+ hemoglobin count of transfused blood}/preoperative hemoglobin x 1000

- Secondary outcome measure
  1. Blood transfusion rate
     We will record the event of blood transfusion, and calculate the incidence of transfusion,
  2. Thrombosis risk evaluation:
     We will record all thrombotic events in our study, and calculate the incidence of them. The diagnosis of them as followings:
     - Deep vein thrombosis (DVT): Bilateral ascending venography of the legs if symptomatic DVT is suspected according to Well's criteria, ie, limb edema with thigh or leg circumference > 3cm compared at contralateral limb
     - Pulmonary embolism (PE) evaluation : Chest CT scan if PE is highly suspicious
     - Coronary artery disease evaluation: 12 - lead electrocardiogram (ECG), cardiac enzyme level was checked if chest pain, exertional dyspnea, or heart attack was highly suspicious
     - Cerebrovascular accident evaluation: Brain CT or MRI if the patient has change of consciousness or focal neurologic sign.

- Discharge Criteria

1. Clear operative wound without discharge
2. Knee range of motion : 90 degree or more
3. Able to ambulate with walker support.

Out patient department Follow up

- 2 weeks after operation : Check Hb/Hct, Remove stitches, clinical evaluation of the knee, Record range of motion of the knee and continue rehabilitation program, watch signs of DVT.
- 6 weeks after operation : Record range of motion of the knee and clinical evaluation of the knee, record knee score and functional score, watch for

signs of DVT.

- 3 months after operation : Knee radiography follow up, record knee score and functional score, watch for signs of DVT

4. The Duration of the Trial: one year

Statistical Analysis Plan

- . Sample size calculation

  The sample size estimation is based on the difference in the primary outcome (postoperative blood loss) in the three study groups. No clinicial research was found to investigate the blood saving effect of combination of topical TXA and Floseal® in TKA. We refer to our primitive data of eight patients who received combination of topic TXA and Floseal® resulting in 518ml (SD=225ml) blood loss. The Efficacy of Combined Use of Intraarticular and Intravenous Tranexamic Acid on Reducing Blood Loss and Transfusion Rate in Total Knee Arthroplasty" by SY Lin which topical application of TXA group resulted in 705.1± 213.9 mL.

  We set the null hypothesis (H0) is that the values of total blood loss of both group is equal. Alterna-tive hypothesis (H1) is that the total blood loss of two groups are different. We used G-power soft-ware to calculate the sample size. To refuse the H0, under the level of alpha =0.05, and the power =0.95, the smallest sample size is 31 patients in each group (total case number is 62 patients. We plan to recruit 35 patients in each group (total case number is 70 patients to compensate for ex-pected dropouts and incomplete data.

- Statistical Analysis

  The independent t- test was used to determine the differences between two groups in the distribution of demographics, preoperative clinical data, total blood loss, postoperarive drainage amount, postoperative hemoglobin level, length of hospital stay, and wound length.

  Descriptive data, including gender, ASA level, the incidence of thromboembolic events, the blood transfusion rate between the three groups were compared using chi-square test or Fisher's exact test. All statistical comparisons were made using the Statistical Package for Social Sciences (SPSS) (version 18; SPSS Inc., Chicago, Illinois).