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Intravenous versus intra-articular tranexamic acid in total knee arthroplasty: A double-blinded randomised controlled noninferiority trial

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ABSTRACT

Background: Despite the proven efficacy of both intravenous (IV) and intra-articular (IA) tranexamic acid (TXA) in reducing blood loss during total knee arthroplasty (TKA), the ideal route of administration remained debatable. This study aimed to compare the effect of IV versus IA TXA on transfusion incidences, perioperative blood loss and postoperative lower limb swelling during TKA.
Methods: One hundred patients were prospectively randomised into two groups: 1) IV TXA; and 2) IA TXA. In both groups, TXA was administered intraoperatively after cementing the prostheses. The perioperative blood loss was calculated using the haemoglobin balance method. The thigh, suprapatellar, and calf girths were measured preoperatively and on postoperative day (POD) 4.
Results: Two patients in the IV group and one patient in the IA group required blood transfusion ($p = 0.500$). The median and interquartile range (IQR) of perioperative blood loss on POD1 and POD4 was 530 (IQR 386,704) and 730 (IQR 523,925) ml for the IV group, compared with 613 (IQR 506,703) and 799 (IQR 563,1067) ml for the IA group ($p = 0.090$ and $p = 0.232$ respectively). The median increment in thigh, suprapatellar, and calf girths were 1.5 (IQR 0, 3.0), 2.0 (IQR 0.5, 4.0) and 0 (IQR 0, 1.0) cm for the IV group, compared to 2.0 (IQR 1.0, 4.0), 2.0 (IQR 0, 4.5) and 0 (IQR 0, 1.5) cm for the IA group ($p = 0.246$, $p = 0.562$, and $p = 0.937$ respectively).
Conclusions: Both IV and IA TXA had comparable effect on transfusion incidences, perioperative blood loss, and postoperative lower limb swelling during TKA. IA TXA is an alternative to IV TXA.
Level of evidence: I.

1. Introduction

Total knee arthroplasty (TKA) is a cost-effective and efficacious treatment modality for severe osteoarthritic knees but it can be associated with significant blood loss, with 10 to 38% of patients requiring allogenic blood transfusion perioperatively [1–4]. The risks and costs of blood transfusion, together with challenges in obtaining sufficient labile blood products, have generated interest in blood-conserving strategies.

Tranexamic acid (TXA) is a synthetic anti-fibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, procoagulant factors V and VIII. At higher concentration, TXA also acts directly to inhibit plasmin activity. Consequently, there is a decrease in proteolytic action on the fibrin monomers and fibrinogen, which results in clot stabilization [5]. It has proven to reduce the risk of receiving blood transfusion by a third in a meta-analysis of all surgeries [6]. The trauma of surgery activates fibrinolysis by promoting the release of tissue plasminogen activator [7]. Although the body naturally inhibits fibrinolysis by 24 h after surgery, anti-fibrinolytic agents such as TXA can block the activation of plasminogen to plasmin earlier and thereby decreasing the perioperative blood loss [8,9].

While the use of intravenous (IV) TXA is a common practice, intra-articular (IA) TXA in joint replacement surgeries has only started to gain popularity in recent years. The use of tourniquet in TKA results in negligible intraoperative blood loss but notable postoperative blood loss, which is the ideal scenario for using topical haemostatic agents intraoperatively. Despite several meta-analyses proving the efficacy of both IV and IA TXA in reducing blood loss during TKA [10–14], the ideal route of administering TXA remains debatable [15–21].

Postoperative blood loss and soft tissue inflammation from healing result in significant lower limb swelling and bruising after TKA. While a previous study has shown that IA TXA reduces knee joint swelling after TKA [22], there is a lack of prospective studies comparing the effect of IV and IA TXA in reducing postoperative lower limb swelling. This

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study aims to investigate the effect of IV versus IA TXA on transfusion incidences, perioperative blood loss, and postoperative lower limb swelling during TKA. The authors hypothesize that IV and IA TXA would result in comparable transfusion incidences, perioperative blood loss and postoperative lower limb swelling.

2. Materials and methods

This study was approved by the Centralised Institutional Review Board of SingHealth (CIRB: 2011/745/D) and carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all the patients recruited.

A single institution, double-blinded, prospective randomised controlled noninferiority study was conducted. All patients between the ages of 50 and 85 who were diagnosed with osteoarthritis of the knee and scheduled for an elective primary TKA by the two senior authors (PLC and SJY) were eligible for recruitment. Patients with history of renal impairment, cardiovascular diseases (previous myocardial infarction, atrial fibrillation) or cerebrovascular conditions (previous stroke or peripheral vascular surgery) were excluded from the study. Patients with history of thromboembolic disease, bleeding disorder or receiving anticoagulant drug treatment were also excluded. Between October 2013 and March 2014, 100 patients were successfully recruited and randomised into two groups: 1) IV TXA; and 2) IA TXA.

To maximize the power of this study, the authors designed only two treatment groups, IV and IA TXA, with exclusion of a placebo group. A previous study performed by the authors already reported that 1500 mg of IA TXA wash reduced blood loss during TKA when compared to placebo treatment [23]. Furthermore, several meta-analyses have also shown the superiority and efficacy of TXA compared to placebo in TKA. In this study, the authors aimed to compare the IA group with the currently accepted standard route of administration, IV TXA [11–14].

This study proposed 1: 1 randomisation into IV and IA TXA. Each successfully recruited study patient was assigned a unique study number and randomised according to a computer-generated procedure (random number table). This random number table listed the unique study numbers and the corresponding group allocated. The randomisation numbers were held by an independent observer to ensure masked randomisation. The randomisation was stratified according to the surgeon performing the TKA. Patients and the reviewer responsible for evaluating the outcomes in this study were kept blinded, while the two senior authors were informed of the randomisation results on the day of surgery.

All surgeries were performed using the standard medial parapatellar quadriceps splitting approach with patella eversion under tourniquet control at 300 mm Hg. The distal femur was prepared using an intramedullary rod while the proximal tibia was prepared using an extramedullary jig. A bone plug was used to block the femoral medullary cavity after the femoral cuts. Previous study had shown that there was no difference between weighted versus uniform dose of IV TXA in reducing perioperative blood loss during TKA [24]. There was also no difference in total blood loss if IV TXA was given within or after 30 min of the anaesthetic induction [25]. In the IV group, 1500 mg of TXA (Cyklokapron®, Pfizer, New York, USA) diluted in 100 ml of 0.9% sodium chloride was given as an infusion over 20 min after cementing the prostheses. In the IA group, the same preparation of 1500 mg of TXA (Cyklokapron®, Pfizer, New York, USA) was given as an IA wash also after cementing the prostheses. Similarly, previous study concluded that there was no difference in the efficacy of 1500 mg versus 3000 mg of TXA wash in reducing perioperative blood loss during TKA [26]. At least five minutes of contact time was allowed before just enough TXA was suctioned from the wound to allow the repair of the retinaculum [15,23,27].

A drain was placed and the closure of wound was performed in a standard fashion in all cases. The tourniquet was deflated only after dressing had been applied to the operated knee at the end of the surgery. All patients received one litre of IV fluid substitution in the form of 0.9% sodium chloride perioperatively.

Postoperatively, all patients underwent a standard institution thromboembolic prophylaxis protocol. Pneumatic calf pumps were given immediately postoperative until the patient started ambulating. In January 2010, the National Institute for Health and Care Excellence (NICE) introduced a recommendation to use low-molecular-weight heparin in joint replacement surgeries; hence, subcutaneous Clexane 40 mg once daily (Sanofi, Paris, France) was given to all patients on the first postoperative day (POD) and continued until discharge from hospital. All patients underwent inpatient postoperative physiotherapy with the aim of early mobilization. No deep vein thrombosis screening was done in the post-operative period to detect asymptomatic occurrence. For symptomatic patients, they were evaluated with ultrasonography of the lower limb deep veins and CT scan of the chest. The patients were considered fit for discharge once they had achieved at least 90° of knee flexion and were able to ambulate independently with or without walking aids.

The primary outcomes of this study were transfusion incidences, drain output, postoperative drop in serum haemoglobin level, perioperative blood loss, and postoperative increment in lower limb girth measurements, while the secondary outcomes include duration of surgery, length of hospital stay, wound complications, and thromboembolic events within 30 days of surgery.

At the institution where this study was performed, a serum haemoglobin level of less than 8.0 g/dl was considered the transfusion trigger. For patients presenting with anaemic symptoms or any anaemia-related organ dysfunctions, the transfusion trigger was less than 10.0 g/dl. The drain output was recorded at 24 h after surgery, before it was removed.

The perioperative blood loss was calculated using the haemoglobin balance method [15,23,27,28]. Each patient's total blood volume (TBV) was first calculated using the formula of Nadler et al. [29] as follows:

$$\text{Male}: \ \text{TBV}\,[\text{ml}] = (0.0003669 \times \text{height}^3[\text{cm}]) + (32.19 \times \text{body weight}\,[\text{kg}]) + 604;$$

$$\text{Female}: \ \text{TBV}\,[\text{ml}] = (0.0003561 \times \text{height}^3[\text{cm}]) + (33.08 \times \text{body weight}\,[\text{kg}]) + 183.$$

The perioperative blood loss was then calculated as follows:

$$\text{Perioperative blood loss}[\text{ml}] = \text{TBV}\,[\text{ml}] \times (\text{Hb}_i - \text{Hb}_e)/\text{Hb}_i + \text{Sum of blood products transfused}[\text{ml}],$$

where Hb_i [g/dl] was the preoperative serum haemoglobin level, and Hb_e [g/dl] was the postoperative serum haemoglobin level.

Postoperative lower limb swelling was measured preoperatively and on POD 4 at three regions: 10 cm above the superior patellar border (thigh girth); at the superior patellar border (suprapatellar girth); and at the maximum circumference of the calf (calf girth). The suprapatellar girth was recognized as the index of the IA swelling.

2.1. Statistical analysis

Power analysis for noninferiority was performed prior to the conduct of this study. Based on previous studies [26,30,31] reporting a zero transfusion incidence with IV or IA TXA treatment as the primary end point, this study with 100 patients (50 in each group) provided 90% power to demonstrate noninferiority at a one-sided level of significance of 0.025 to detect a treatment difference (delta value) of 7.5%.

Statistical analysis was carried out in consultation with the in-house biostatistician, using SPSS® 19.0 (IBM, Armonk, New York, United States). Statistical significance was defined as a p-value of ≤0.05. Testing for normality was done with the Shapiro–Wilk test. The Mann–Whitney U test was used to compare the two groups for continuous variables