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The Knee

The comparative efficacy and safety of topical and intravenous tranexamic acid for reducing perioperative blood loss in Total knee arthroplasty- A randomized controlled non-inferiority trial☆

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ABSTRACT

Background: Total Knee Arthroplasty (TKA) can be associated with significant perioperative blood loss and blood transfusions. This is a prospective randomised non-inferiority trial comparing intraarticular (IA) and intravenous (IV) routes of administering Tranexamic acid (TXA) with regard to efficacy and safety.
Methods: A total of 113 patients who underwent primary unilateral TKA from January to June 2017 randomly received either 1.5 g TXA in 100 mL normal saline solution (IA group, $n = 58$) or 10 mg/kg TXA (IV group, $n = 55$) at 10 min before the tourniquet inflation and at tourniquet release. Haemoglobin (Hb) drop on third day (primary outcome), visible blood loss (VBL), hidden blood loss (HBL), total blood loss (TBL), transfusion requirement, incidence of deep vein thrombosis (DVT), wound complications and renal function derangement (secondary outcomes) were recorded.
Results: The mean difference in haemoglobin drop between both groups was 0.25 g/dL with 90% CI of −0.07 to 0.58. Since the lower bound of 90% CI was above equivalence margin of −0.35, IA group was found to be non-inferior to IV group in terms of Hb drop. The mean difference between both groups of VBL, HBL and TBL were 0.85 mL (p value 0.90), −7.9 mL (p value 0.90) and −6.2 mL (p value 0.93) respectively. Transfusions and wound complications were statistically insignificant. None of the patients had DVT or renal function derangement.
Conclusion: IA TXA is not inferior to IV TXA with regard to efficacy and safety and may be preferred considering ease of administration and lack of systemic absorption.

1. Introduction

Total Knee Arthroplasty (TKA) in the absence of blood conserving measures can be associated with perioperative blood loss up to 2000 mL and blood transfusion rate of 10% to 62% [1]. Hyperfibrinolysis associated with surgical trauma, is thought to be contributory, this being aggravated by tourniquet application [2]. Tranexamic acid (TXA), an anti-fibrinolytic drug which acts by competitively blocking a lysine binding site of plasminogen is one of the several modalities to minimise blood loss in TKA [3].

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Intravenous (IV) TXA has been the standard of care in TKA for over a decade. Both IV and intraarticular (IA) routes have been proven superior to placebo in randomised trials and subsequent meta-analyses [4]. However, there are few studies comparing the two with results supporting IV [5], IA [6] or both [7]. All available meta-analyses suggest equivalent outcomes between both routes [8,9], however none of the included trials was of equivalence design.

Since meta-analyses hinted that one method of therapeutic intervention is unlikely to be superior to the other in terms of outcomes, and there is clear advantage of topical route in terms of ease of administration and lesser chances of systemic absorption, we hypothesised that if non inferiority of IA route was proved, then clinicians would automatically favour topical over systemic route. In addition, the literature provides clear evidence for the superiority of IA over the IV route in renal failure and Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) [4]. Furthermore, the dosage remains standard for all patients in the topical route as opposed to weight dependent dosage regimens in the systemic route, thus keeping the cost lower and avoiding repeat doses as in the systemic route. Also, equivalence trials need a larger sample size and this particular clinical question might equally be served by a non-inferiority design when viewed in conjunction with the previous literature.

The purpose of this study was to compare efficacy and safety profiles of IA versus IV TXA. We hypothesised that IA TXA would not be inferior to IV TXA in terms of outcomes.

2. Patients and methods

This study was conducted as a single centre double blinded randomised non-inferiority trial with 1:1 allocation after approval of the Institutional Review Board. Informed consent was obtained from all patients before the surgery was scheduled. The manuscript was prepared according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines [10].

The inclusion criterion was all patients with osteoarthritis of the scheduled for a primary unilateral cemented TKA between January 2017 and June 2017. The exclusion criteria included those related to the drug (allergy to TXA, elevated renal function tests, history of thromboembolic events, coronary artery heart disease, malignancies) and to outcome measures (severe preoperative anaemia, thrombocytopenia, coagulation test abnormalities, treatment with Aspirin, NSAIDs or anticoagulants within one week of surgery).

2.1. Sample size calculation

Sample-size was calculated based on the difference in the primary outcome [i.e., postoperative decrease in haemoglobin (Hb)] between the two study groups. Though measurement of Total Blood Loss (TBL) consisting of Visible Blood Loss (VBL) and Hidden Blood Loss (HBL) has been followed by many authors previously, we took drop of Hb on the third day (surrogate marker of hidden blood loss) as the primary outcome measure. This is because Hb drop is more objectively measurable and clinically relevant than VBL calculated by visual assessment and HBL calculated by formulae. We assumed that differences in VBL would be insignificant as surgery was done under tourniquet. Also clinicians take decisions on transfusion based on Hb drop and not blood loss.

Sample size was determined using power and sample size calculator for continuous outcome non-inferiority trial from sealedenvelope.com. We chose the smallest value for equivalence limit that would be a clinically important effect [11]. Since this trial lacks a placebo arm, we also had to ensure that we accounted for the effect of standard treatment over no treatment (based on the literature) while determining the non-inferiority limit. Delphi method (subjectively arguing statistical and clinical relevance) was adopted to achieve consensus between investigators and Hb drop of 0.35 g/dL was decided as the inferiority limit. A recent trial comparing two doses of IA TXA versus placebo observed a common mean Hb drop of 2.2 $\pm$ 0.7 g/dL in intervention arms and 2.9 $\pm$ 1.2 g/dL in placebo arm [12]. Thus, the mean effect size in terms of Hb drop of intervention was 0.7 g/dL (subtracting 2.2 from 2.9). We agreed that non-inferiority limit should not be lower than 50% of observed effect size between placebo and active treatment [13]. Another recent non-inferiority design RCT chose a non-inferiority limit of 0.59 g/dLHb drop based on their observations of literature [8]. Thus, our limit of 0.35 g/dL was felt sufficiently narrow to preclude the error of concluding an inferior treatment as non-inferior. Sample size estimations revealed a minimum sample size of 50 per group to be 80% sure (chosen level of power) that the lower limit of a one-sided 95% confidence interval (CI) (or equivalently a 90% two-sided CI) will be above the non-inferiority limit of -0.35 [14].

2.2. Randomization and double-blind implementation

Patients were randomised by an independent allocator using block randomisation method with randomly mixed block sizes of two, four and six, with sizes of block concealed from the executer. The independent allocator made random allocation cards in sealed envelopes using computer generated random numbers. A duplicate set was made in case individual code breaking was required. Patient was blind to the treatment arm as well as one of the authors (J.G.), who stayed out of surgery and collected all the data and outcome measures pertaining to the study.

Patients were assigned treatment in one of the two cohorts:

1. Cohort I (IA group) received TXA as 1.5 g in 100 mL of normal saline solution, which was poured into the joint before wound closure.
2. Cohort II (IV group) received TXA as 10 mg/kg body weight over 10 min before tourniquet inflation and again 10 mg/kg at tourniquet release. Maximum rate of administration did not exceed 100 mg/min to avoid hypotension.

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