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Combined intravenous, topical and oral tranexamic acid administration in total knee replacement: Evaluation of safety in patients with previous thromboembolism and effect on hemoglobin level and transfusion rate

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ABSTRACT

Background: The aims of this study were to investigate the safety of combined intravenous, oral and topical tranexamic acid (TXA) in primary total knee replacement. We assessed dose-related efficacy on hemoglobin level, transfusion, length of stay and thromboembolic complications. In addition, TXA safety in patients with previous history of thromboembolism >12 months ago was monitored specifically.

Methods: From January 2013 until January 2016, 922 patients were included who received TXA after primary total knee replacement. Patients without TXA administration or with thromboembolic events <12 months ago were excluded. TXA dosage groups were divided into ≤10 mg/kg, >10–25 mg/kg and >25–50 mg/kg.

Results: Between the three TXA groups no significant difference was found in thromboembolic complications (deep venous thrombosis (DVT) and pulmonary embolism (PE)), wound leakage and transfusion rate. For patients with DVT or PE in their history >12 months ago specifically, no more complications were noted in higher-TXA-dosage groups compared to the low-dosage group. Length of stay was shorter in the highest-TXA-dosage group compared with lower-dosage groups (median two vs three days). With high TXA dose a smaller difference between pre- and postoperative Hb was found: the >25–50 mg/kg TXA group had a 0.419 mmol/l smaller decrease in postoperative hemoglobin compared to the lowest-dosage group ($P < 0.05$).

Conclusion: Combined intravenous, oral and topical TXA is effective in knee replacement and can safely be given to patients with a thromboembolic history >12 months ago. High dosage (>25–50 mg/kg) TXA resulted in the smallest decrease in postoperative hemoglobin.

1. Introduction

Multiple studies have shown that tranexamic acid (TXA) gives a significant reduction in blood loss after knee replacement, and results in lower blood transfusion rates [1–3]. Consensus is lacking though regarding the administration route and optimal dose of TXA administration after total knee arthroplasty (TKA) [4]. Intravenous TXA is most often used, and has been found to be very safe and effective [5]. Oral TXA has been shown to give an equivalent reduction in blood loss, and has a lower cost than intravenous use [6,7]. Besides oral and intravenous administration, topical TXA offers the advantage of intra-articular administration at

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the site of bleeding and minimizes its systemic absorption [1,2,8,9]. Topical TXA administration during joint replacement surgery has been described as a safe and cost-effective alternative to intravenous use [1,2,10,11]. For transfusion rates a similar odds ratio is found with significantly less transfusion in the topical as well as in the intravenous TXA groups when compared with control groups [8,10,11]. No increased risk of deep venous thrombosis (DVT) or pulmonary embolism (PE) has been reported in several meta-analysis studies on the use of TXA in arthroplasty, even at higher and repeated dosages [1,2,11–15]. Combined intravenous and topical administration has also been studied, and a further reduction in blood loss and transfusions was found [16–18]. Recent meta-analysis of different methods of tranexamic acid administration did not show any significant differences, but more studies on efficacy are warranted [19]. Subgroup analysis on the dose-related effect of tranexamic acid has shown that a higher and repeated dose of TXA may be better at reducing bleeding and transfusions than a lower single TXA dose [20,21]. Although TXA is widely administered in different administration forms, no previous study has been performed to investigate the combined effect of intravenous, oral and topical use in order to achieve a prolonged anti-fibrinolytic effect. Besides determination of its dose-related efficacy, also the safety profile has not been studied before in patients with thromboembolic events in the past. Therefore, the present study was conducted to assess the effect of different TXA dosages on the outcomes of hemoglobin (Hb) decrease, transfusion rates, length of stay (LoS), thromboembolic and wound complications, and referral to home or a care facility. In addition, the effect of TXA in patients that had a DVT or PE longer than 12 months ago was monitored specifically and incidence of thromboembolic complications in this group was compared with patients without a previous thromboembolic event in the past.

2. Patients and methods

2.1. Study design

Data was prospectively gathered in all consecutive primary TKA patients from January 2013 until January 2016, and retrospectively analyzed. Data was collected by the Department of Orthopedics at the Alrijne Hospital Leiden, The Netherlands. Data was extracted from patient files until six months after total knee replacement surgery. Subjects were included in case of primary total knee replacement surgery in which TXA was administered. Subjects that had revision knee arthroplasty, unicondylar knee replacement, fracture or tumor prosthesis were excluded from the study. Exclusion was also the case if no TXA was given or with a recent thromboembolic event less than 12 months ago. Consecutive series of subjects with total knee replacement surgery were compared in the following dosages: ≤10 mg/kg, >10–25 mg/kg, and >25–50 mg/kg administration of TXA. The retrospective cohorts consisted of a group with only a single dose of intravenous TXA administration, a group with combined intravenous and oral administration, and a group with combined intravenous, oral and topical administration.

2.2. Study procedure

From 2013 until 2014 pre-operative intravenous TXA was administered, from 2014 to 2015 patients received pre-operative intravenous and postoperative oral TXA, and from 2015 until 2016 topical administration of TXA was added intra-articularly after closure of the knee joint in addition to the intravenous and oral administration as per earlier time periods. The method of TXA administration and the total dosage of TXA were recorded for every patient. The anesthetist administered 10 mg/kg intravenous TXA just before the start of surgery, and one gram of oral TXA was given postoperatively after transfer from the recovery room. Topical TXA was administered in the joint during surgery after closure of the knee capsule in the standard dose of two grams. Three consultant orthopedic surgeons performed all surgeries through a medial parapatellar approach using a cemented Nexgen posterior stabilized high flex total knee prosthesis (Zimmer Biomet, Warsaw, US). All patients had rehabilitation by the same enhanced recovery protocol including multimodal opioid sparing pain management, a pre-operative dose of intravenous dexamethasone, per-operative local infiltration analgesia, and in the case of spinal anesthesia a low dose enabling early mobilization out of bed within three hours after operation. An upper-leg tourniquet was used during surgery to achieve a bloodless field, so no blood loss was seen during operation. As no postoperative wound drains were used, the amount of lost blood was assessed by measuring the difference in pre-operative and postoperative Hb levels, which was checked the month before and the day after surgery in every patient. A daily subcutaneous dose of low-molecular-weight heparin was used for one month as DVT prophylaxis in all patients. No urinary catheters, and no patient-controlled anesthesia pain pumps were used in any of these patients. To investigate the incidence of postoperative symptomatic DVT and PE, the hospital electronic patient data files of each patient were surveyed including the regional general practitioners' referral system with a follow-up of six months postoperatively. In addition, the radiology patient database was checked for positive results on ultrasound or computed tomography scans for proven DVT and PE.

2.3. Statistical analysis

To summarize continuous data, a mean and standard deviation was used. If data was not normally distributed, a median and range was reported. Absolute and relative frequencies were used to summarize categorical data. To evaluate differences between the TXA dosage groups (≤10 mg/kg, >10–25 mg/kg, and >25–50 mg/kg) and the primary outcomes, the appropriate statistical test for each outcome was used. Differences were significant if $P < 0.05$. As we identified body mass index (BMI), age, gender and pre-operative Hb levels as possible confounders between TXA dosage and the outcome measures Hb level and referral to home or facility care, we first assessed whether these variables were significantly associated with TXA dosage and with the

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