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Original Research Article

A STUDY ON COMBINED USE OF INTRAVENOUS AND TOPICAL TRANEXAMIC ACID FOLLOWING CEMENTLESS TOTAL HIP ARTHROPLASTY- A RANDOMISED CLINICAL TRIAL

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Abstract

Purpose: This study was designed to compare the efficacy and safety of the combined use of tranexamic acid (TXA) with the intravenous (IV) or local use alone in total hip arthroplasty (THA).

Methods: 21 patients were randomised to a IV group, a local group or a combined group. Participants received 1.5 g IV-TXA in the IV group, 3 g local TXA in the local group, or 1 g IV-TXA combined with 2 g local TXA in the com- bined group. The primary outcomes were total blood loss (TBL), maximum haemoglobin drop, and the incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE).

Results: TBL was (77.65 \pm 18.95) ml in the combined group, which was significantly lower than in the IV group or the local group (p = 0.015, p = 0.001 respectively). Likewise, the mean values of maximum hemoglobin drop in the combined, IV, and local groups were 2.98 \pm 0.78, 3.36 \pm 0.78, and 3.89 \pm 0.72 g/dL, respectively, with a significant intergroup difference (p<0.001 for all). Asymptomatic DVT was detected in 1 patient of the IV group, and 2 patients of the combined group with the use of ultrasound. There were no episodes of PE, and no significant differences were seen between groups in terms of complications.

Conclusions: Combined use of intravenous TXA and local TXA in primary unilateral THA can effectively decrease total blood loss and increase postoperative haemoglobin levels without influencing complication rates. It is sug- gested that this combined TXA regimen is more effective in decreasing blood loss in cementeless THA than intra- venous or local administration alone.

Keywords: Tranexamic acid, Total hip arthroplasty, Blood loss, Transfusion, Combined treatment

Introduction

Total hip arthroplasty (THA) is an excellent surgical proce- dure for patients with end-stage hip disease However, it is still associated with a considerable amount of blood loss which can be as much as 700-2000 ml (1), and 16% to 37% of patients may need allogenic blood transfusion (ABT) postoperatively (1). Although the incidence is low, ABT is not short of risks; some serious complications have been reported, such as im- munological reaction, and disease transmission (2-4). More- over, ABT may increase the risk of surgical site infection (5). Substantial blood loss during THA may be caused by 2 factors: one is the overt blood loss caused by surgical trauma; the other is hidden blood loss caused by fibrinolysis which accounts for approximately 60% of total blood loss (6). In order to reduce blood loss

ABT, and the need for multimodal blood management protocols have been introduced. Of these, control of bleeding with antifibrinolytic agents may be the most effective choice. Tranexamic acid synthesised antifibrinolytic competitively inhibits the activation of plasminogen by blocking the lysine binding sites, thus inhibiting clotting breakdown which results in the re-duction of blood loss and transfusion requirement (7).

There is a body of evidence provided by prospective ran-domised controlled trials (8-14) and meta-analysis studies (15, 16) that have shown that TXA, applied either intrave-nously or locally, can reduce the amount of total blood loss, haemoglobin reduction and requirement for ABT following primary THA without risking a high complication rate. However, the optimal regimen, dosage, and timing still

remain unclear. Traditionally, TXA was injected intravenously prior to skin incision in primary THA, and concerns about the safety of systemic administration of TXA in high dosage hindered its wide application. Compared with IV-TXA, local administration is easy to administer, inhibiting clot breakdown directly withmaximum concentration at the bleeding site, and being asso- ciated with little systemic absorption (17). Another method, the combined use of IV-TXA and local TXA, has been put un- der the spotlight in total knee arthroplasty (TKA), and shown satisfactory results (18, 19). Unlike the procedure of TKA, there was high overt blood loss in THA. Based on the above findings, we propose the hypothesis that the combination of IV injection of TXA before skin incision and local administration of TXA during surgery will be more effective than either regimen alone. However, there is a paucity of studies on the combined regimen following primary THA, and the 3 methods of TXA administration have not been compared head to head. Therefore, we conducted this prospective randomised controlled clinical trial in order to address the following questions: 1) Is there any difference in terms of efficacy and safety? 2) Can the combination of IV injection and local administration of TXA further reduce blood loss and haemoglobin drop when compared with either regimen alone? 3) Is it safe to combine the 2 methods?

Materials and Methods

This prospective, randomised, controlled trial was performed on patients who were scheduled for primary unilaeral THA from May 2018 to February 2019. Before starting this trial, the study protocol was approved Jawahar lal Nehru Medical college Wardha sawangi DMIMS. Written informed consent and research authorisations were obtained prospectively prior to surgery from all participants.

All patients, aged 18 years and older, who were scheduled primary unilateral for THA osteoarthritis or osteonecrosis of the femoral head were considered eligible for inclusion in the trial. Exclusion criteria were: patients with cardiovascular disease (history of myocardial infraction, angina, and atrial fibrillation), cerebrovascular pathology (previous history of stroke), clotting disorders, thromboembolic disorders (history of DVT or PE), and known allergy to TXA.

Recruited patients were assigned randomly to either an intravenous group (IV Group), local group (Local Group) or a combined application group (Combined Group) using opaque sealed envelopes opened just prior to surgery. The surgeons and anaesthesia staff were not blind to the treatment arms because of the nature of different administration methods, but the patients, postoperative nursing staff and data analyst were blind to the administration routes.

All operations were performed by the same surgical team, which was composed of 4 senior surgeons. With the applica- tion of same cementless acetabular cup and femoral stem (Pin- nacle cup, Corail stem; Depuy synthes, USA), all procedures were performed via a posterolateral approach, under general anaesthesia. In the IV Group, patients were given 1 single in-travenous dose of 1.5 g of TXA, 15 minutes before skin incision. For the Local Group, we refer to the methods described in our previous study (12), 3 g TXA in 150 ml physiological saline was used as follows: gauze full of 50 ml TXA solution was used to soak the acetabulum and also the femoral canal for 3 minutes respectively after acetabulum and femur preparation; the re- maining 50 ml TXA was injected into the joint space through the drainage tube after fascia closure. In the Combined Group,1 g TXA was administered intravenously, in the IV Group, and 2 g TXA dissolved in 150 ml saline was used locally in the Local Group. All drainage tubes of both groups remained clamped for 30 minutes, and the drainage was removed the morning following the operation. A half dose of Enoxaparin (0.2 ml 2000 IU) was initiated 6 h postoperatively and repeated at 24-h intervals with a full dose (0.4 ml 4000 IU) administered on subsequent days until discharge. Additionally, an intermittent pneumatic compression device was used routine practice to prevent thromboembolism events (VTE). After discharge, 10 mg Rivaroxaban was administered orally to patients for 30 days. Patients were examined daily for clinical symptoms of DVT during hospitalisation. Doppler ultrasound was used to detect DVT at different time points (preoperative, time of discharge, 1- and 3months follow-up). If there was a clinical suspicion of VTE, ultrasound was performed immediately for DVT, and Computed Tomography was performed to confirm PE.

Total blood loss (TBL), maximum haemoglobin drop and the incidence of DVT and PE were the primary outcomes. Haemoglobin (Hb) and haematocrit (Hct) levels were tested preoperatively and on postoperative day one (POD 1), POD 3, POD 5 routinely. TBL was calculated by the Gross and Nadler formula as in our previous study (12). Overt blood

loss was defined as intraoperative blood loss plus drainage tube loss, and hidden blood loss was defined as TBL minus overt blood loss. Other secondary outcomes included the length of hospi- tal stay (LOHS), transfusion rate, complications (wound leak- age, haematoma, superficial infection and deep infection) and other adverse events (defined as cardiac infarction, stroke, and acute renal failure).

The necessity for transfusion was determined by the National Ministry of Health guidelines. Thus, transfusion was allowed for those patients presenting symptomatic anaemia (defined as lightheadedness, presyncope, fatigue precluding participation in physiotherapy, palpitations, or shortness of breath not due to other causes) with Hb levels between 7 g/dl and 10 g/dl, or any Hb levels below 7 g/dl.

Sample size calculations were performed using PASS 2011 (NCSS, LLC. Kaysville, Utah, USA) software with a one-way analysis of variance designed for RCTs. To detect a difference of 100 ml of primary end point, with a power of 0.90 and significance level of 0.05, 68 patients per arm were needed. We compared the quantitative data between groups utilising the one-way ANOVA and Tukey's post hoc. The Pearson Chisquared test or Fisher exact test was used in order to analyse qualitative comparative parameters. All analyses were per- formed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) software and statistical significant difference was defined as P<0.05.

Results

During the study period, a total of 25 primary THAs were performed in our institution. Of these, 3 patients were ineligible based on the exclusion criteria, 1 patients declined to participate. The remaining 21 patients were included and followed up, with 7 patients randomised to the IV group, 7 to the Local Group, and 7 to the Combined Group (Fig. 1). Baseline characteristics with regard to age, gender, BMI, ASA grade and preoperative laboratory parameters were comparable between the 3 groups (Tab. I).

Primary outcome data and complications in the 3 groups are shown in Table II and Table III. As for primary outcomes, significant differences were observed in TBL, and maximum Hb drop. The TBL was 77.75 ± 18.95 ml in the Combined group, which was significantly lower than in the IV group and the Local group (p = 0.015, p = 0.001 respectively). Although the mean value of TBL in the IV group was less than in the Local Group, the difference failed to reach significance (p = 0.734)

(Fig. 2). Likewise, the mean values of maximum Hb drop in the Combined, IV, and Local group were 2.98 \pm 0.78, 3.36 \pm 0.78, and 3.89 \pm 0.72 g/dL, respectively, with a significant intergroup difference (p<0.001) . The Combined group had the lowest Hb drop (p<0.001). Also, the Hb drop was significantly lower in the IV group than in the Local group (p<0.001).

No episodes of PE occurred during the 30-day follow-up period. Asymptomatic DVT was detected in 1 patient of the IV group, and in 2 patients of the Combined group us- ing ultrasound. The difference was not statistically significant (p = 0.774). As for secondary outcomes, overt blood loss was also lower in the Combined group when compared to the other 2 groups (p<0.001 for both), while the difference between the IV group and Local group was not statistically

significant (p=0.241)(Fig.4). Nopatient in the Combinedg roup,4inthe Local group, and 3 in the IV group required transfusion (non statistically significant difference). No patient needed intra- operative blood transfusion. No episode of other adverse events like cardiac infrac- tion, stroke, or acute renal failure occurred during the 30-day follow-up period. In 1 wound leakage was observed patients postoperatively, which was controlled with wound dress changing and infrared ray treatment. 6 patients developed superficial infection, which was controlled with wound dress changing and antibiotics. Regarding wound complications or other adverse events, all groups showed similar results with no statistically significant differences.

Discussion

Patients undergoing THA have a relatively high risk of re- quiring ABT. The increasing awareness of the importance of preventing the risks associated with ABT has prompted the evaluation of multimodal blood management strategies (18). Abundant literature (8-16) regarding intravenous and local TXA in primary THA has confirmed the efficacy and safety of reducing blood loss and the need for transfusion when com- pared with placebo. Recently, another mode of TXA admin- istration combining the use of intravenous and local TXA has been introduced in TKA, showing promising results (18-20). The main characteristics of current RCTs on this topic have been reviewed and listed in Table IV. So far, studies on this regimen in THA are still obscure, and the effect of combin- ing the use of TXA is unclear, when compared with IV or local administration alone. Also, direct comparisons between the 3 methods of TXA

administration in THA are scarce. This RCT was conducted in order to address these issues. We did not aim to confirm the efficacy and safety of TXA, an already established fact, but rather to identify a novel, effective and safe administration regimen following primary THA. Furthermore, it was not in accordance with ethical standards to expose patients to a high risk of blood loss and allogenic blood transfusion, because several studies have already verified the efficacy and safety of TXA in primary THA. Therefore, a control group with no active treatment was not included in this study design.

When IV-TXA is given preoperatively, it is widely distrib- uted throughout the extracellular and intracellular compart- ments, and rapidly reaches maximum plasma concentration in 5 to 15 min (21). Then local fibrinolysis can be inhibited at the initial stage as soon as surgery is commenced. In THA, bleeding mostly occurrs during the process of acetabula, fem- oral canal preparation and soft tissue release. Local administration of TXA may maintain maximum local levels to induce partial microvascular haemostasis by stopping fibrin clotting breaking down (22). So, it is logical to combine the preoperative IV injection with an intraoperative local application. In this randomised controlled clinical study, the most important finding was that the combination of preoperative IV and in-traoperative local administration of TXA seemed to be more effective without increasing the incidence of complications, when compared with application alone. Compared to IV-TXA or local TXA, combined TXA administration can further reduce TBL by 12%, and 14%, respectively. Less perioperative blood loss would result in higher postoperative haemoglobin levels. Although not reaching levels of statistical significance, the number of patients needing ABT was zero in the combined group, less than in the other groups. Group sample size was not large enough to detect significant differences in terms of transfusion rates.

TXA has a biological half-life in the blood or joint fluid of 3 hours (23). Fibrinolysis activated by surgical trauma is initi- ated at the beginning of surgery, lasting for 18 to 24 hours (24, 25). When a combined TXA administration regime is used, the duration of action would be longer than intrave- nous injection alone. In terms of equal total dose, the plas- ma TXA concentration of combined administration would be higher than the local application alone. This may explain the less overt blood loss observed in the

combined group. Interestingly, the results revealed no differences in regard to hidden blood loss. Because of the lack of control group, we cannot comment on the efficacy of the combined TXA administration on hidden blood loss. So, further research is needed in order to investigate the influence of repeated administration of TXA on hidden blood loss.

The administration of IV-TXA in primary THA has been well established in the literature (8-11). Different doses, rang- ing from 10 mg/kg to 30 mg/kg, have been administered by different methods, for example single IV bolus, repeated bo- luses and prolonged infusion. Rajesparan et al (26) conducted a RCT which compared 1 g IV-TXA to placebo and found that a single IV dose of 1 g TXA could reduce total blood loss by 18% and improve maximum haemoglobin levels by 20%. In our centre, a single IV bolus administration of 1.5 g TXA has been widely used since 2012, and satisfactory clinical results have been reported. Recently, concerns regarding systemic com- plications of IV-TXA administration have prompted the local application of TXA. In our previous study (12), a total dose of 3 g TXA was locally applied to the acetabulum, femoral canal and joint cavity before implant insertion. The results revealed a significant reduction in total blood loss and transfusion requirement. However, direct comparisons of TXA intravenous and local administration are rare. In the current study, the regimen used in the IV group was effective in improving postoperative haemoglobin reduction in patients undergoing primary THA. Although not significant, blood loss and transfu- sion requirements were lower in the IV group. Therefore, sim- ilar to previous study (27), it seem that intravenous injection of 1.5 g TXA shows better, or at least comparable haemostatic effect when compared to local use of 3 g TXA.

The main concern regarding TXA has been the incidence of vascular occlusive events, which were observed in hip fracture surgery (28). In a retrospective study conducted by Duncan and his colleagues (29), Poeran et al (30) reported a protective effect on clinically significant PE (0.2% vs 0.4%), mortality (0.04% vs 0.1%), and acute myocardial in- farction (0.1% vs 0.2%) in patients receiving TXA. In contrast to the previous studies, we did not observe symptomatic DVT and PE and we report an incidence of 1.4% asymptomatic DVT. No differences in adverse events or other complications were found between the 3 modes of administration.

Therefore, we are now convinced of the efficacy and safety of combined TXA administration in THA and we routinely use it in our current practice.

There are limitations in the current study. The surgeon and the anaesthetist were not blind to the randomisation, although the data collector and analyst were. Furthermore, the perioperative blood management protocol was consistent, including careful electrocoagulation haemostasis controlled hypotension anaesthesia, and the operation time was also comparable, so we believe that this limitation does not affect the validity of the study. We did not evaluate postoperative function outcomes and satisfaction levels in patients receiving TXA in primary THA. Therefore, the relationship between clinical outcomes and blood loss or Hb level remain uncertain. Blood concentrations of TXA were also not available. There are several strengths to this randomised controlled study. It was carefully and strictly designed and performed. So the the effect of bias is minimal and the sample size was powerful enough to detect statistical significance in terms of primary outcomes. The transfusion protocol was clear and strict, which makes the results of the transfusion rate convincing. Total blood loss was calculated using the Gross formula, which has been proven to be more accurate than clinical methods, and overt and covert blood loss were evaluated between the three different regimens. Lower limb ultrasonographic examination was conducted routinely for every patient during hospital stay and for a 3-month followup period. Additionally, the follow-up period is thought to be long enough to identify known adverse events (31). So, our results for safety profile are reliable.

Conclusion

Combined administration of intravenous and local TXA in primary unilateral THA can effectively decrease total blood loss and elicit higher postoperative haemoglobin levels without the risk of higher complication rates. This TXA administration regimen may serve as an alternative to intravenous or local administration alone.

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