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Reducing transfusion requirements following total knee arthroplasty: effectiveness of a double infusion of tranexamic acid

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Abstract. – OBJECTIVE: Blood loss following joint replacement surgery represents a relevant issue for orthopedic surgeons. The use of tranexamic acid (TXA) to reduce transfusion requirements has become mainstream. However, consensus about the starting time, methods, or volume of usage of TXA in joint replacement surgery has yet to be found. A retrospective study was conducted comparing pre- and post-operative infusion of TXA 15 mg/kg to a single pre-operative infusion.

PATIENTS AND METHODS: 291 patients undergoing TKA were retrospectively reviewed. 109 received a single pre-operative dose of 15 mg/ kg TXA (single dose, SD group), 182 received a single pre- operative dose of 15 mg/ kg TXA followed by a second post-operative dose of 15 mg/kg TXA (double dose, DD group). The primary outcome was blood loss calculated from haematological values and perioperative transfusions. Secondary outcomes included the occurrence of major complications within the first postoperative year.

RESULTS: None of the patients reported adverse events. Blood transfusions were administered to 63 patients (13.5%) in the SD and 36 in the DD group (5.7%). Significant difference between the groups was observed ($p < 0.005$). No significant difference between the two groups was found concerning mean blood loss in drainage after the 24th hour and postoperative hemoglobin values (p = n.s.).

CONCLUSIONS: The study demonstrated that TXA possesses a good safety profile. In addition, pre- and post-operative infusion of TXA 15 mg/kg is more effective compared to single pre-operative infusion in reducing need for transfusion requirements.

Key Words:
Knee osteoarthritis, Total knee arthroplasty, Tranexamic acid, Blood transfusion.

Abbrevations

TKA: total knee arthroplasty; SD: standard deviation.

Introduction

Blood loss following total knee arthroplasty represents a serious issue as it is often associated with postoperative anaemia requiring transfusions[1]. Several treatment strategies are currently adopted to reduce transfusion requirements, including perioperative red cell salvage, hemodilution, controlled hypotension, use of recombinant human erythropoietin[2]. A major cause of bleeding in patients undergoing total knee arthroplasty (TKA) is hyperfibrinolysis, as a result of surgical trauma. Therefore pharmacological agents able to reduce hyperfibrinolysis are currently being used for their ability to inhibit hyperfibrinolysis and stabilize blood clots, thus reducing blood loss[3]. Among these drugs, tranexamic acid (TXA) has demonstrated an excellent safety profile without increasing the risk of adverse events, including thromboembolism in the perioperative period[4,5], and many papers have shown that its use can significantly reduce transfusion requirements following joint replacement surgery[4-9]. However, the optimal volume of usage of TXA has yet to be determined: the most common practice is to administer TXA at an intravenous dose of 15 mg/kg prior to surgery, followed either by a continuous infusion of 1 mg/kg /hour after 4-6 hours or by repeating the initial dose in the post-operative period (6 to 8 hours after surgery)[9], but dosing regimens reported range from 10 to 135 mg/

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kg[8]. Similarly, no consensus exists on regimen duration for TXA in joint replacement surgery, as huge variations in the way in which TXA is administered are reported, with studies showing that a single dose regimen is not as effective as multiple dose regimens[10-12], and authors advocating that a single bolus of TXA of either 20 mg/kg or 30 mg/kg can be as effective as the multiple dose method[13,14]. A retrospective study was conducted comparing the efficacy of TXA in patients undergoing TKA. Study hypothesis was that intravenous administration of TXA reduces blood loss following TKA. In addition, combined pre- and post-operative infusion of TXA 15 mg/kg was compared to single pre-operative infusion.

Patients and Methods

291 patients who underwent primary TKA at our Institution between January 2016 and December 2016 were retrospectively reviewed. 109 patients received a single pre-operative dose of 15 mg/ kg TXA (Single Dose, SD group), while 182 received a single pre- operative dose of 15 mg/ kg TXA followed by a second post-operative dose of 15 mg/kg TXA (Double Dose, DD group). The primary outcome was blood loss calculated from hematological values and perioperative transfusions. Secondary outcomes included the occurrence of major complications within the first postoperative year. Complications, such as thrombotic events and infections as well as adverse events were recorded up to one year from surgery. Blood transfusion was administered at a hemoglobin threshold of 8 g/dl in patients without comorbidities, and a threshold of 10 g/dl in patients with preexisting cardiac pathology, according to international guidelines[15,16].

Statistical Analysis

Statistical analysis was performed using Chi-square test to evaluate differences between the groups. IBM SPSS Statistics for Windows® software, Version 21.0 (IBM Corp., Armonk, NY, USA) was used. Statistical significance was established at $p < 0.05$.

Results

None of the patients who completed TXA therapy reported adverse events. A detailed overview of perioperative blood loss including mean total postoperative drainage volume, hemoglobin concentration and transfusion rate is reported in Table I. No statistically significant difference in the amount of blood loss examined through drainage after the 24th hour were reported between the two groups (p = n.s.). Similarly, no statistically significant differences in the value of postoperative haemoglobin concentrations were reported between patients in the SD and DD group (p = n.s.). Red blood cells transfusions were administered to 63 patients (13.5%) in the SD and 36 patients in the DD group (5.7%). Significant difference between the groups was observed ($p < 0.005$).

Discussion

The most important finding of the present study is that TXA administration represents a safe way to prevent blood loss following TKA surgery. In addition combined pre- and post-operative infusion of TXA 15 mg/kg is more effective compared to single pre-operative infusion reducing the need for postoperative transfusions. Numerous studies reported that TXA can be safely and effectively used to decrease blood loss and reduce transfusion requirements[4,5]. In our case series, no venous or arterial thromboembolic

Table I. Comparison of perioperative blood loss between patients in the Single Dose and the Double Dose group.

	SD group	DD group	*p*-value
Hb change (g/dL)	14.2 (SD: 5.5)	14.4 (SD: 7.6)	p = n.s.
- Pre - operative	10.7 (SD: 0.6)	11.0 (SD: 0.5)	p = n.s.
- Post - operative			
Blood loss (ml)	225 (SD: 151.8)	213 (SD: 151.8)	p = n.s.
Transfusion rate (%)	13/109 (11.9%)	9/182 (4.9%)	$p < 0.05$

SD: standard deviation.

events occurred, and consistently with previous experience reported in literature, among patients undergoing joint arthroplasty, treatment-related reductions in transfusion requirements were associated with intravenous administration of TXA. However, there are huge variations in the way in which TXA is administered in joint replacement surgery, with dosing regimens ranging from 10 to 135 mg/kg, and regimen duration ranging from a single shot to multiple injections, to continuous infusion for up to 3 days[8]. As a result, the optimal dose for TXA in joint replacement surgery has yet to be determined, and no consensus about the starting time, methods, or volume of usage of TXA exists[17,18].

Previous studies have suggested that a single dose regimen is not as effective as multiple dose regimens[10-12]. Iwai et al[10] reported that a double intravenous dose of TXA produced a further reduction of postoperative blood loss in TKA compared to a second administration. Maniar et al[11] observed the efficacy of a three-dose regimen, adding a further postoperative dose.

More recent studies showed that a single bolus of TXA of either 20 mg/kg or 30 mg/kg can be as effective as the multiple dose method[13,14]. In the current study, two dosing regimens of TXA administration were compared: one a single dose and the other a doubled regimen. The total volume of blood loss postoperatively was not significantly lower when administering a doubled-dose regimen. However, low transfusion rate was reported in the DD group compared to the SD group.

Potential limitations in the present work include its retrospective nature and its non-randomized design. Further prospective randomized studies are needed to substantiate these findings.

Conclusions

We found that TXA possesses a good safety profile. In addition, pre- and post-operative infusione of TXA 15 mg/Kg is more effective compared to single pre-operative infusion in reducing need for transfusion requirements.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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