Intra-articular Tranexamic Acid in Primary Total Knee Arthroplasty Decreases the Rate of Post-operative Blood Transfusions in People with Hemophilia: A Retrospective Case-Control Study

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Abstract *Background:* Blood transfusion rates after total knee arthroplasty (TKA) in patients without hemophilia have diminished with the use of a standardized multimodal blood loss prevention method (MBLPM) that includes intra-articular tranexamic acid (TXA) (MBLPM-TXA). However, the topic has not been addressed in people with hemophilia. *Questions/Purposes:* Our aim was to investigate whether the MBLPM-TXA prevents blood loss in patients with hemophilia A who undergo TKA, thereby decreasing the need for post-operative blood transfusion. *Methods:* This retrospective case-control comparative study involved 30 TKA patients who had a severe degree of hemophilia A without inhibitions: one group treated with the MBLPM-TXA ($n = 15$) and a second group treated without it ($n = 15$). In all cases, the pre-operative hemoglobin level was greater than 13 g/dL. *Results:* The MBLPM-TXA group had a transfusion rate of zero, whereas 46.6% of the patients (seven of 15) in the non-MBLPM-TXA group needed transfusion. *Conclusion:* This retrospective case-control study showed that the use of an MBLPM-TXA in patients with hemophilia A who underwent TKA was effective in reducing rates of transfusion. We recommend its use.

Keywords hemophilia · total knee arthroplasty · post-operative blood loss · blood loss prevention · tranexamic acid · multimodal blood loss prevention method

Introduction

Total knee arthroplasty (TKA) has traditionally been associated with blood loss necessitating allogeneic blood transfusion, with rates ranging from 9 to 84% (mean, 44%) [13]. Allogeneic blood transfusion remains a standard treatment in cases of post-operative anemia after TKA, and at many institutions, clinicians prepare 2 units of packed red blood cells before TKA is performed. However, the risks associated with allogeneic blood transfusion are well established [7]. Many authors have reported the efficacy and safety of intravenous [4, 5, 8, 9, 14, 16, 17] and intra-articular [2, 3, 6, 10–12, 15, 18, 19] tranexamic acid (TXA) in preventing blood loss during TKA.

The use of a multimodal blood loss prevention method (MBLPM) that includes intra-articular TXA (MBLPM-TXA) has been shown to diminish the transfusion rate in TKA patients without hemophilia [2, 3, 5, 6, 12, 15, 18, 19]. In addition to the TXA, the MBLPM includes two other important elements: a tourniquet with pressure 100 mmHg above systolic pressure, released after skin closure, and sealing of the femoral canal with bone graft. However, when the MBLPM-TXA is used in patients with hemophilia, the transfusion rates, hematological parameters used to assess blood loss, clotting factor consumption, and costs of surgery have not yet been well defined.

In a preliminary retrospective comparative study published as a letter to the editor in 2016, we found that the use of the MBLPM-TXA in primary TKA decreased the rate of post-operative blood transfusion in ten patients with

Level of Evidence: Level III, Retrospective Case-Control Study

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Table 1 Methods used in the two study groups to prevent blood loss

MBLPM-TXA group (<i>n</i> = 15)	Non-MBLPM-TXA group (<i>n</i> = 15)
Tourniquet with pressure 100 mmHg above systolic pressure, released after skin closure	Tourniquet with 350 mmHg pressure, released before skin closure for electrocoagulation of bleeding
Femoral canal obturation with bone graft	No limits or treatment regarding pre-operative hemoglobin level
Intra-articular infiltration of posterior capsule, medial and lateral capsule, and ligaments, before closure, with 80 mL saline with adrenalin 300 µg, morphic chloride 10 mg, tobramycin 100 mg, betamethasone sodium phosphate 6 mg, betamethasone acetate 6 mg, and ropivacaine 200 mg	No femoral canal obturation
Intra-articular injection of 35 mL of a combination of TXA (25 mL, 2500 mg) and sodium chloride (10 mL, 18 mg)	24–48-h vacuum drain, opened with skin closure
	No intra-articular infiltration or TXA administration

MBLPM-TXA multimodal blood loss prevention method with intra-articular tranexamic acid

hemophilia [10]. To try to confirm these findings, we designed a similar study of a larger number of cases.

The purpose of this study was to further investigate whether the MBLPM-TXA decreases the rate of post-operative blood transfusion in patients with severe hemophilia A undergoing primary TKA.

Materials and Methods

We conducted a retrospective case–control comparative study using data on 30 patients with hemophilia A who underwent unilateral primary TKA at our institution. The surgery was performed during a 3-year period (January 2010 to December 2012). All patients with severe hemophilia A without inhibitors who were undergoing TKA over the study period were included. The patients were divided into two groups: in one group, the MBLPM-TXA was used (*n* = 15), and in one group, it was not (*n* = 15). In addition to TXA, the MBLPM included a tourniquet with pressure 100 mmHg above systolic pressure, released after skin closure, and femoral canal obturation with bone graft. In the MBLPM-TXA group, 75% of the clotting factor used was recombinant (25% plasmatic), whereas in the non-MBLPA-TXA group, 50% of the factor used was recombinant (50% plasmatic). There were no significant differences in terms of demographic or clinical data between the two groups.

In order to achieve correct hemostasis in patients with hemophilia A during surgery, our protocol involves infusion of clotting factor pre-operatively until a minimum level of 100% of normal is achieved; afterward, the level is maintained at 60% of normal for 14 post-operative days (continuous infusion with a pump), and hematologic treatment is then continued (in intravenous bolus infusions) to achieve a level of 30% of normal before 8 to 10 weeks of rehabilitation. In other words, in hemophilia A patients, the peak plasma factor level must be 80 to 100 IU/dL pre-operatively. In the post-operative period, the levels should be 60 to 80 IU/dL on days 1 through 3, 40 to 60 IU/dL on days 4 through 6, and 30 to 50 IU/dL on days 7 through 14.

The mean weight of the patients in the MBLPM-TXA group was 73.3 kg, compared with 66.4 kg in the non-MBLPM-TXA group. The mean patient age was similar (41.6 years in the MBLPM-TXA group,

43.3 years in the non-MBLPM-TXA group). In all cases, the pre-operative hemoglobin level was greater than 13 g/dL. Blood transfusion was indicated when the post-operative hemoglobin level was less than 9 g/dL. In other words, if the hemoglobin level fell below 9 g/dL, a transfusion was automatically given.

Surgery was performed in a standard operating room, and general anesthesia was always used. The patients were placed in the decubitus supinus position, and a parapatellar medial incision was made. The prosthesis used was a cemented (gentamicin bone cement) NexGen (Zimmer, Warsaw, IN, USA), posterior stabilized model. Patellar resurfacing was performed in all patients. Drains were not inserted in the MBLPM-TXA group but were used (for 24 h) in the non-MBLPM-TXA group. Three surgeons (the three authors of this study) performed the surgery (Table 1).

Intravenous antibiotic prophylaxis was administered at the time of anesthesia induction and for the first 48 h after surgery (three additional doses). Thromboprophylaxis was not used during the study period. Through our post-operative Physical Medicine and Rehabilitation program, patients began active exercises on post-operative day 1. Joint load aided by the use of two crutches was allowed from post-operative day 2. On post-operative days 3 through 7, patients increased knee movement, performed isotonic muscle exercises, and progressively increased bipedal standing and walking. In weeks 2 to 4, progress in the range of motion, muscle strength, and joint balance was encouraged, as were re-education of the gait pattern and recovery of functional skills. From week 4 through week 8, walking around obstacles and using ramps and stairs were encouraged. Finally, re-education in the performance of everyday activities (personal grooming and dressing, for example) was recommended [1]. The first post-operative follow-up visit was at 8 weeks.

Results

In the MBLPM-TXA group, no patient needed a post-operative blood transfusion, as opposed to seven (46.6%) patients in the non-MBLPM-TXA group. Neither hemorrhagic nor thromboembolic complications were seen in this series.

The mean pre-operative hemoglobin concentrations ($\pm$ standard deviations) were 14.25 ± 0.75 g/dL in the MBLPM-TXA group and 14.27 ± 0.80 g/dL in the non-MBLPM-TXA group (difference not significant). The mean post-operative hemoglobin concentrations were 14.16 ± 0.85 g/dL in the MBLPM-TXA group and 9.52 ± 0.90 g/dL in the non-MBLPM-TXA group (difference significant). Medications that stimulate an increase in red cell mass were not used before or after surgery. No complications were encountered.

Discussion

Over the past decade, there have been numerous studies of transfusion rates in primary TKA in patients both with and without hemophilia [13]. Recently, most hospitals have adopted protocols to decrease the allogeneic blood transfusion rate in patients without hemophilia, and today, the standard allogeneic blood transfusion rate is well under 10% [4, 5, 7, 8, 14]. We have tried to achieve the same goal in patients with hemophilia.

This retrospective case–control comparative study has several limitations. A prospective, randomized study would be ideal for comparing blood loss management techniques, but it is unlikely that a comparison with placebo or with surgery performed without any blood loss prevention measures in place would be ethically acceptable today, given the available meta-analyses and systematic reviews confirming its benefits [4, 14]. Also, the number of patients in this study is small.

Although there were two study groups, a standardized surgical technique was used in both groups, and the surgeons' qualifications were deemed equivalent; the only difference was the approach to blood loss management. We achieved a transfusion rate of zero, which was noted previously in our setting [5, 8, 9], as in other studies [2, 3, 6, 12, 15, 16, 18, 19], in patients without hemophilia. Our results in patients with hemophilia are in agreement with the literature on patients without hemophilia, highlighting the potent effects of TXA in reducing blood loss [2–4, 6, 10, 12, 14, 17–19]. Our preliminary data in cases of hemophilia B and revision TKA in patients with hemophilia show similar results (data pending publication).

We used intra-articular rather than intravenous TXA administration; studies have shown the methods to have similar efficacy [5], and anesthesiologists are not needed for intra-articular administration.

In conclusion, we found that in patients with hemophilia A who underwent primary TKA, a multimodal approach to blood loss prevention that included intra-articular TXA administration was effective, with a transfusion rate of zero (as compared with 46.6% in the control group). Therefore, we recommend the use of an MBLPM-TXA in primary TKA patients with hemophilia A.

Compliance with Ethical Standards

Conflict of Interest: E. Carlos Rodriguez-Merchan, MD, PhD, Carlos A. Encinas-Ullan, MD, and Primitivo Gomez-Cardero, MD, declare that they have no conflicts of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Informed Consent: Informed consent was waived from all patients for being included in this study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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