Arthroplasty Today 2 (2016) 77–82

Contents lists available at ScienceDirect

Arthroplasty Today

journal homepage: http://www.arthroplastytoday.org/

Original research

Effects of tranexamic acid and bipolar sealer alone or in combination in primary total knee arthroplasty: a prospective, randomized, controlled trial

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ARTICLE INFO

Article history:
Received 16 October 2015
Received in revised form
28 December 2015
Accepted 31 December 2015
Available online 31 March 2016

Keywords:
Tranexamic acid
Blood loss
Total knee arthroplasty
Bipolar sealer system
Hemoglobin change

ABSTRACT

Background: The purpose of this study was to compare 2 blood management interventions, tranexamic acid (TXA) and bipolar sealer system (BSS) used independently or in combination with a control group during primary total knee arthroplasty (TKA).
Methods: A total of 127 TKA patients were enrolled and randomized into 4 groups: Intravenous TXA plus the BSS (N = 29, group 1); TXA only (N = 29, group 2); BSS only (N = 31, group 3); and intravenous normal saline as a control group (N = 32, group 4).
Results: Changes in hemoglobin from baseline to postoperative follow-up were significantly lower among patients who received TXA plus BSS and those receiving TXA only when compared with the control. BSS only did not differ significantly when compared to the control group. In addition, TXA plus BSS was as efficacious as TXA only in preserving postoperative hemoglobin.
Conclusions: In other terms, using bipolar sealer did not add to the effect of TXA in reducing the postoperative hemoglobin drop in primary TKA.

Introduction

Total knee arthroplasty (TKA) is associated with significant blood loss, subsequent anemia, and the periodic need for intraoperative or postoperative blood transfusions [1,2]. The anemia could lead to unwanted hemodynamic changes in patients with underlying medical conditions such as coronary artery disease or valvular disease and may have a negative impact for patients' functional recovery during rehabilitation [3].

Likelihood of transfusion in total joint arthroplasty is largely dependent on 4 factors: (1) baseline hemoglobin (Hb) and hematocrit before surgery; (2) surgical blood loss (volume); (3) the "transfusion trigger," that is, Hb level below which the surgeon and/or anesthesiologist are likely to make a decision to transfuse; and (4) body size and hence total blood volume. Considering the potential risks of blood transfusion [4,5], various preoperative, intraoperative, and postoperative methods have been used to reduce the amount of bleeding associated with surgery. These methods include administration of erythropoietin, autologous blood donation and retransfusion, intraoperative red cell salvage, acute normovolemic hemodilution, controlled hypotension, meticulous operative technique, and use of antifibrinolytic drugs. In terms of reducing surgical blood loss, success has been achieved with intraoperative use of different drugs and cautery systems.

Tranexamic acid (TXA) is an antifibrinolytic agent that blocks the conversion of plasminogen to plasmin on the surface of fibrin and consequently inhibits fibrinolysis. Intravenous TXA has been

No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work. For full disclosure statements refer to http://dx.doi.org/10.1016/j.artd.2015.12.007.

Clinicaltrials.gov registration no.: NCT02374398.

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http://dx.doi.org/10.1016/j.artd.2015.12.007

successfully used in joint arthroplasty. TKA is usually performed using a tourniquet, which offers better visibility of the surgical site and reduces intraoperative blood loss; on the other hand, the tourniquet may activate fibrinolysis. Under those circumstances, the use of TXA should contribute to reduction of intraoperative and postoperative blood loss. Overall various studies have shown that TXA is effective in reducing blood loss and transfusion requirements for TKA [6-12] and does not increase the risk of thromboembolic complications such as deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral vascular accident (CVA), or myocardial infarction [9].

Another important method of reducing perioperative blood loss for TKA is represented by surgical hemostasis. Standard electrocautery, which uses monopolar radiofrequency energy, is the most common method used to obtain intraoperative hemostasis. However, monopolar electrocautery is associated with local tissue damage from charring and a greater risk of postoperative bleeding and anemia [13]. The bipolar sealer system (BSS) works at a molecular level by heat-driven transformation of the collagen triple helix structure. Local temperatures under 100°C are sufficient to shrink collagen fibers in the walls of blood vessels, effectively sealing the blood vessels. The device can be used to coagulate vessels that are actively bleeding or to cauterize tissue surfaces to prevent bleeding or treat active oozing. The result is a reduction of the bleeding from both soft tissue and bone. In addition, because of its mechanism of action, the bipolar sealer, as opposed to the standard electrocautery, will not char, burn tissue, or produce smoke. The saline-coupled bipolar sealing has been used successfully for other types of orthopaedic surgeries including hip and spine procedures. Several studies have shown that, compared with standard electrocautery, the additional use of saline-coupled bipolar sealer technology results in reduced blood loss and rates of transfusion and less decrease of the postoperative Hb from the preoperative level [13-18].

The mechanisms of action of TXA and bipolar sealer as described previously are very different. One is a drug, whereas the other is a device, but use of both is aimed at minimizing blood loss and improving outcomes after surgery. Although TXA and the bipolar sealer were shown to be effective in preserving postoperative Hb independently, there is a significant gap in the literature justifying

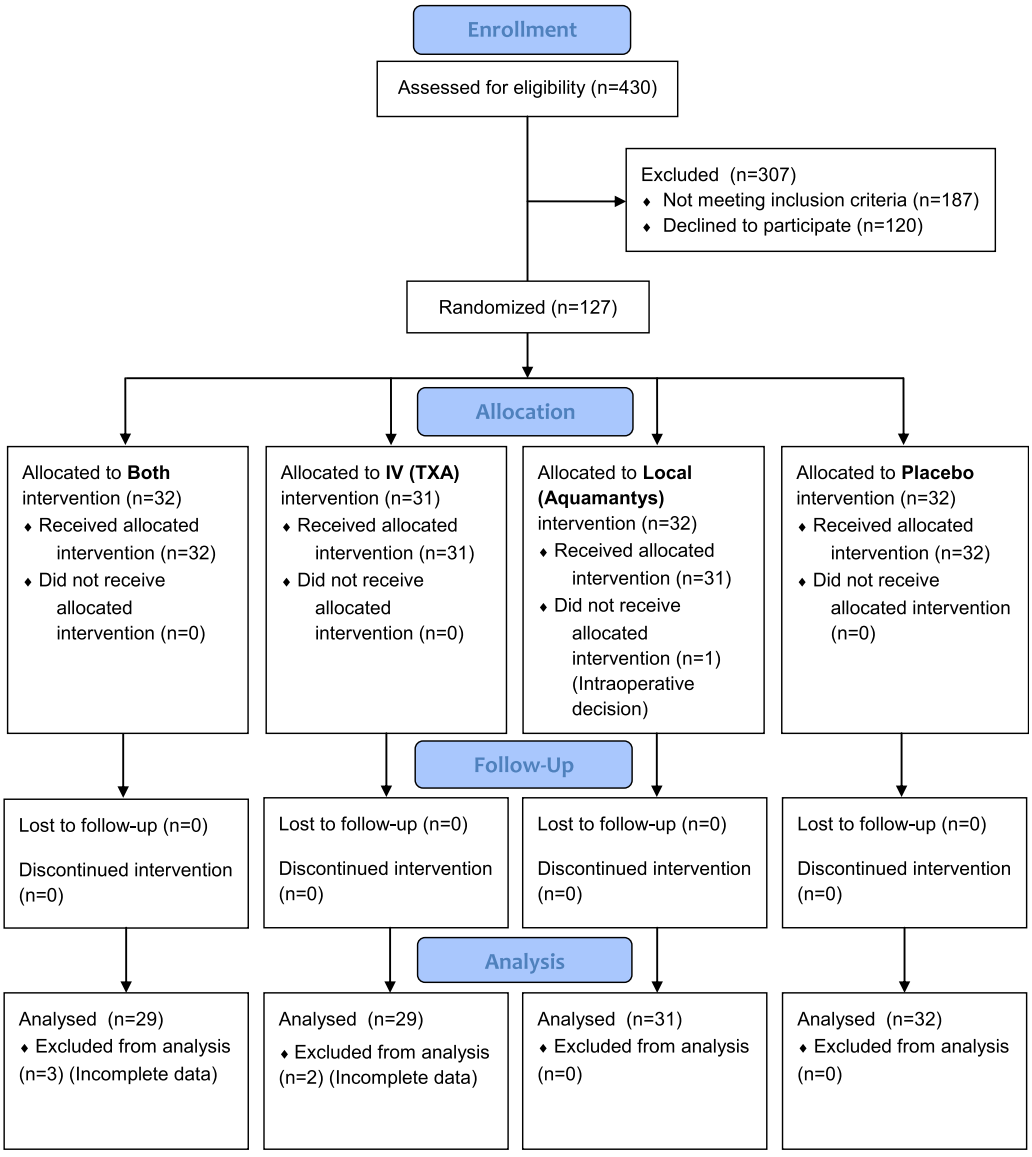

Figure 1. Study enrollment flow diagram. Both: TXA plus BSS (group 1); IV (TXA): TXA only (group 2); local: Aquamantys: BSS only (group 3); placebo: control (group 4).

the use of bipolar sealer in combination with TXA. As the theoretical benefits of bipolar sealer such as reduced pain and swelling are unsupported and the costs associated with the procedure are high, further evaluation of the BSS in primary TKA was necessitated.

In this study, our objective was to determine how TXA, bipolar sealer, both in combination, and control compare in terms of conserving Hb, reducing total blood loss, length of stay, operating time, and complications after primary TKA.

Material and methods

The study was approved by Eastern Maine Medical Center's (EMMC) institutional review board (IRB). All patients were enrolled after informed consent was obtained. Enrollment was completely voluntary. To ensure safety, data on complications and adverse reactions were recorded and reported to the IRB.

Participants

Between April 2011 and November 2014, 127 patients undergoing voluntary primary TKA consented to participate in this IRB-approved trial (Fig. 1). Five patients with missing laboratory data were excluded from the study. One patient was disqualified from participation because of a change from cemented to uncemented implant. Preoperative teaching and perioperative management were the same for patients in all groups. Patients over 18 years of age undergoing elective total primary knee arthroplasty, under spinal anesthesia, were included in the study. Patients with adverse reaction to TXA; congenital or acquired coagulation disorder; preoperative platelet count <100,000/μL or international normalized ratio >1.4; history of DVT, PE, or CVA; acquired defective color vision; renal insufficiency (glomerular filtration rate <20 mL/min); severe liver disease; coronary stents; or pregnant patients were excluded from the study. All enrolled patients were informed of the goals of this trial, which were to reduce intraoperative and postoperative blood loss and transfusion rate, length of stay, surgery time, and complications.

Trial design and setting

This was a randomized double-blind placebo-controlled study of 127 TKA patients conducted at EMMC in Bangor, Maine. The only exception to blinding was represented by the surgeon, who could not be blinded to using the BSS. Enrolled subjects were assigned to one of 4 groups (Table 1) by block randomization of alternating 4, 8, and 12 patients per block. All study subjects received standard electrocautery. Intervention subjects received an intravenous (IV) bolus of TXA, the BSS (Aquamantys, Medtronic, Minneapolis, MN), or both. Blinding the interventions and randomly varying the block size helped reduce the problem of predictability of the sequence. An equal allocation ratio of 1:1:1:1 was predetermined for each group at the commencement of the trial. The Pharmacy Department at EMMC provided the IV placebo or the IV TXA according to the randomization process.

Table 1
Treatment and control group composition.

Group/treatment	Group 1	Group 2	Group 3	Group 4
	TXA ± BSS	TXA only	BSS only	Control
Intravenous TXA (20 mg/kg)	✓	✓		
Intravenous saline (0.9%)			✓	✓
BSS	✓		✓	
Standard electrocautery	✓	✓	✓	✓

Drug and device

As per the clinical recommendations by the medical advisory panel published in December 2014 [19], doses of intravenous TXA in orthopaedic surgery varied greatly. In a systematic review of randomized controlled trials by Kagoma et al. [20], 21 trials showed prescribing a dose of TXA ranging from a 10- to 20-mg initial bolus followed either by an infusion of 1-10 mg/kg/h for 4-30 hours or repeated doses of the initial dose of TXA every 3 hours for 1 to 4 doses. In TKA, an intraoperative dose of 10 mg/kg initial bolus of TXA followed by a second similar dose at 3 hours is most common. Literature suggests a dose of 20 mg/kg of TXA is suitable for TKA [21,22]. Owing to the drug's prolonged extravascular effectiveness, we decided to use one 20 mg/kg intravenous dose of TXA which was given as a bolus over 20 minutes starting at the beginning of surgery (skin incision) to all patients in groups 1 and 2 (TXA plus the BSS and TXA only, respectively). We chose to administer the drug after tourniquet inflation and skin incision so as to allow enough time to address the potential drop in blood pressure and correct it before IV TXA bolus administration. Clinical recommendations suggest that therapeutic level for TXA can be maintained for approximately 8 hours after surgery [19].

The BSS is Food and Drug Administration approved with surgical indications that include TKA and was used by the orthopaedic surgeon in patients in groups 1 and 3 (TXA plus the BSS and bipolar system only, respectively).

All surgeries were performed by one surgeon under spinal anesthesia with a femoral nerve block. A tourniquet was used at 250 mmHg, inflated at the time of incision and let down before closing. All knees were a cemented, cruciate-retaining design (Zimmer NexGen, Warsaw, IN). A mini-midvastus approach was used with meticulous hemostasis in all cases. The bipolar sealer was used in a standard fashion "painting" the posterior capsule and synovium with care in an attempt to seal all of the available surface area. No postoperative drains were used and patients were mobilized on the day of surgery.

Outcome measures

The change in Hb at day 3 was chosen as the primary end point. About 33% of the patients were missing Hb data on day 3 because of early discharge. To reduce the attrition bias, we decided to replace missing Hb values on day 3 with Hb values taken on day 2. The decision to study Hb change as the primary end point was made looking at our previous success in reducing and nearly eliminating transfusions via our preoperative anemia management program. Our institution's transfusion trigger threshold as a part of the patient blood management program is between 7 and 8 g/dL of Hb in stable medical or surgical patients. It is worth noting that the mean transfusion rate at our institution for primary TKAs over a 5-year period (2010-2014) after the implementation of the patient blood management program in 2009 was 4.04% (Supplementary Table 1), and the average transfusion rate of our lead surgeon was zero. Secondary end points for the 4 groups were transfusion rates and total packed red blood cells transfusion or units administered (if any), length of stay, surgery time, complications such as DVT, PE, myocardial infarction, CVA, and estimated blood loss (EBL).

The EBL was determined with the Gross formula [23]. According to a review article published in 2013, Gross's formula although developed in 1983 is still widely used as reported [24]. The formula which is relatively easy to use is described as follows:

$$\text{Patient blood volume(PBV)} = K(1) \times \text{height(m)}^3 + K(2) \times \text{weight(kg)} + K(3),$$

where K(1) = 0.3669 (male), 0.3561 (female); K(2) = 0.03219 (male), 0.03308 (female); and K(3) = 0.6041 (male), 0.1833 (female).

$$\text{Estimated blood loss} = \text{PBV}\left[\text{Hematocrit}_{\text{initial}} - \text{Hematocrit}_{\text{final}}\right] / \text{Hematocrit}_{\text{mean}},$$

where mean hematocrit is the sum of initial and final hematocrit divided by 2.

Statistical methods

Comparisons between the 4 groups were made using a 1-way analysis of variance and Fisher's least significant difference post hoc test for continuous variables, and Pearson's chi-square test for categorical variables. Normality was assessed using the Shapiro-Wilk test; variance homogeneity was assessed using the Levene's test of homogeneity of variances. All analyses were carried out using SPSS version 21, and statistical significance was accepted for P values <.05. Sample size calculations were determined with the software nQuery using a 1-way of analysis design with 4 groups. Assumptions were that the standard deviation of change for all groups would be 1.3 g/dL and that the control group (group 4) would have an average Hb loss of 3.5 g/dL, the bipolar sealer group (group 3) a loss of 3.0 g/dL, the TXA group (group 2) a loss of 2.5 g/dL, and for the combination group (group 1), we assumed the most conservative result for sample size calculations, a loss of 3.0 g/dL. The average loss value and standard deviation came from averaging results of past studies [12,25]. A sample size of 35 subjects per group provided 80% power to detect the differences described previously.

Results

A total of 127 patients were enrolled, and 121 had complete data for analysis (29 in group 1; 29 in group 2; 31 in group 3, and 32 in group 4). There were no significant demographic differences among the 4 groups (Table 2). Descriptive data for each of the 4 groups are shown in Table 2. Data are presented as mean ± standard deviation. Compared to the preoperative Hb level, postoperative Hb decreased by 2.6 ± 1, 2.6 ± 0.9, 3.2 ± 1.1, and 3.7 ± 1.1 mg/dL in groups 1, 2, 3, and 4, respectively, and the differences between these treatment groups were statistically significant, $F(3,117) = 7.088$, $P = .0002$ (Table 3). Least significant difference analysis revealed that both TXA groups (groups 1 and 2) scored a statistically significantly lower drop in Hb than the control (group 4; $P < .05$). Bipolar sealer (group 3) did not differ significantly from the control. Within the TXA groups, our study could not detect a difference between groups 1 and 2 (Table 4). Findings were corroborated in the secondary outcomes of change in hematocrit and EBL. Hospital stay and operating time did not differ statistically between the groups (Table 3). There were no red blood cell transfusions, complications, or adverse events reported intraoperatively or postoperatively. Analysis of the cost data indicated mean total direct cost of the procedure to be higher in the bipolar sealer group than in the TXA group. However, the total direct cost per case difference was not statistically significant between the groups.

Table 3
One-way analysis of variance results for primary and secondary outcomes.

Variable	Group 1	Group 2	Group 3	Group 4	P value
	TXA + BSS	TXA only	BSS only	Control	
Change in Hb (g/dL)	2.6 ± 1.0	2.6 ± 0.9	3.2 ± 1.1	3.7 ± 1.1	.0002[a]
Change in Ht (%)	6.8 ± 2.58	7.1± 2.51	8.6 ± 3.22	10.0 ± 3.38	.00008[a]
EBL (mL)	746.6 ± 270	747.9 ± 298	938.9 ± 376	1077.6± 371	.0002[a]
Hospital stay (d)	2.6 ± 0.77	2.9 ± 0.88	2.5 ± 0.56	2.6 ± 0.47	.208
Operating time (min)	92.7 ± 12.5	87.2 ± 10.1	90.6 ± 11.8	89.1 ± 11.6	.312

Ht, hematocrit.
The data are reported as mean ± standard deviation.
[a] One-way analysis of variance P values are significant at $P < .05$.

Discussion

The results of our trial indicate that TXA alone is as efficacious as TXA plus the BSS in preserving postoperative Hb. In other terms, use of bipolar sealer did not enhance the effects of TXA in improving outcomes of primary TKA.

A review published in 2014 by Saltzman et al. [13] listed 4 randomized controlled trials and 1 case control study which demonstrated that BSS is not superior over standard electrocautery. Two of the five studies were in TKA [26,27] and 3 were in total hip arthroplasty [16,17,28]. Outcome measures of drain output, postoperative Hb drop, transfusions, length of stay, and surgery time were studied. A meta-analysis by Yang et al. [29] also reported that bipolar sealer is not superior to standard electrocautery in primary hip arthroplasty.

Our institution's total direct cost of using bipolar sealer and TXA in combination is 15 times higher than the cost of using TXA alone in primary TKA. This rise in cost for this step in the procedure did not translate well into a rise in overall direct cost per case. Although

Table 2
Participant characteristics.

Characteristic	Group 1	Group 2	Group 3	Group 4	Total
	N = 29	N = 29	N = 31	N = 32	N = 121
Age (y)	61.1 ± 10.5	65.7 ± 8.6	64.8 ± 8.0	62.9 ± 8.4	63.6 ± 8.9
Gender (F:M)	16:13	13:14	17:14	18:14	64:55
BMI (kg/m^2)	33.76 ± 7.8	32.31 ± 7.20	31.58 ± 6.4	32.23 ± 6.4	32.4 ± 6.9
Height (m)	1.7 ± 0.07	1.69 ± 0.08	1.69 ± 0.08	1.66 ± 0.09	1.69 ± 0.08
Weight (kg)	98.4 ± 25.6	92.5 ± 25.9	90.6 ± 20.4	89.4 ± 17.9	92.9 ± 22.6
Preop Hb (g/dL)	13.92 ± 1.22	14 ± 1.10	13.85 ± 1.16	13.99 ± 1.32	13.9 ± 1.20
Preop Ht (%)	41.1 ± 3.28	41.7 ± 3.20	41.1 ± 3.09	41.4 ± 3.85	41.3 ± 3.36

F, female; Ht, hematocrit; M, male.
The data are reported as mean ± standard deviation.
Group 1: TXA plus BSS; group 2: TXA only; group 3: BSS only; group 4: control.

Table 4
Post hoc group comparisons of mean Hb change.

Treatment group (A)	Treatment group (B)	Mean difference in Hb (A − B)	SE	*P* value	CI (L-U)
Group 1	Group 2	−0.02	0.27	.940	−0.56 to 0.52
Group 1	Group 3	−0.57[a]	0.27	.035	−1.11 to −0.04
Group 1	Group 4	−1.05[a]	0.27	.0001	−1.58 to −0.52
Group 2	Group 3	−0.55[a]	0.27	.042	−1.09 to −0.02
Group 2	Group 4	−1.03[a]	0.27	.0002	−1.56 to −0.50
Group 3	Group 4	−0.47	0.26	.074	−1.00 to 0.05

CI (L-U), confidence interval (lower-upper); SE, standard error.
Group 1: TXA plus BSS; group 2: TXA only; group 3: BSS only; group 4: control.
[a] Least squared difference test *P* values are significant at .05.

mean cost per case is greater in the BSS groups (group 3 > group1 > group 2 > group 4), the cost per case difference is not significant statistically. There are several direct hospital and patient characteristics and indirect physician preferences which should be considered while estimating overall cost per case. Therefore, a comprehensive cost-effectiveness analysis can help us better understand the individual procedural impacts on overall costs. Our TXA dosing regimen might decrease the costs associated with administering TXA, but its effect on the cost difference with bipolar sealer would be negligible as TXA is a relatively inexpensive drug. Considering the cost difference between the IV TXA and the BSS and based on our findings from the present study, our team's practice has decided to stop the use of bipolar sealer for primary TKAs. It will be of interest to see how our current change in practice can impact procedural costs in future. Morris et al. [17] also reported that their teams' practice has stopped using bipolar sealer for total hip arthroplasty. They found in their randomized trial that bipolar sealer use did not improve hemostasis but increased the costs several times compared to standard electrocautery. Nevertheless, we recommend specific cost-effectiveness studies before implementing our findings. We anticipate that the results of such studies may be different depending on the patient- and surgeon-related factors.

None of the patients in our study suffered complications related to administration of TXA, electrosurgery, or arthroplasty in general. Nonetheless, further research will be required to add to the safety profile of the device and assess long-term effects of not using the bipolar sealer. Also, patient-specific conditions such as vascular abnormalities or elevated bleeding risks should be studied in terms of bipolar sealer use to assess its significance in these patients. Although our study results showed no significant postoperative Hb reduction in the BSS group compared to the control, other studies have found BSS to be better than the control [14,15]. As suggested in a review by Saltzman et al. [13], complex revision cases, patients with coagulation defects, might experience some benefit using this technology.

Limitations of our study are as follows: (1) All surgeries were conducted by one physician at one hospital; hence, findings might be different in other settings hence less generalizability. (2) Because we used a block randomization design and did not enroll the planned number of 35 subjects in each group, sample sizes are similar but not equal within each group. In spite of this, power was not compromised as the mean Hb loss was higher with lower standard deviations than what was assumed for power calculations. (3) Our study had no transfusion patients because transfusion rates for primary total knees performed were zero during the study period. This could be due to the successful overall approach to primary TKA cases at our institution, including timely preoperative anemia screening and optimization of day of surgery Hb, anesthesia techniques, methodical surgical hemostasis, and a conservative transfusion threshold. Success with the transfusions at our institution was published previously [30]. These changes were in place before the onset of the present study and directed our primary outcome to be change in Hb given the success of our existing program at eliminating transfusions. (4) Hb at day 3 was our primary end point. About 33% of the enrolled patients were missing Hb values on day 3 because of early discharge. To reduce attrition bias, we replaced the missing Hb values on day 3 with Hb values on day 2 causing smaller follow-up times in 33% of patients. We understand that this procedure might be seen as underreporting of the Hb drop. Data are presented in Supplementary Table 2. Intraoperative bleeding, cost data, and functional outcomes such as pain, rehabilitation were not assessed. These are important variables but were not the focus of this study.

Overall, although our study had several limitations, it is a high-quality randomized controlled trial with good homogeneity. Our study adds to the current knowledge about the use of bipolar sealers and can help inform long-term organizational decisions. It also makes considerable connections to previous research in this important area and provides insight for further research that can put emphasis on using or not using bipolar sealers.

Conclusions

In conclusion, our study showed that the mean Hb drop from baseline to postoperative day 2 or 3 was significantly lower in the TXA alone and TXA-plus-BSS groups than in the control group. In addition, TXA alone was as efficacious as TXA plus the bipolar sealer system in preserving postoperative Hb. The hospital stay and operating time were not statistically different among the 4 groups.

Acknowledgments

The authors wish to thank their colleagues James Caddell, Misti Guerin, and Danita Richbell at Down East Orthopedics; Renee Ford, RPh at EMMC Pharmacy; Gail Tudor, their Biostatistician; and Barbara Sorondo, MD, and Janet Bayleran, PhD, at EMMC Clinical Research Center for their support and assistance.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.artd.2015.12.007.

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