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# Balancing Thromboprophylaxis and Bleeding in Total Joint Arthroplasty: Impact of Eliminating Enoxaparin and Predonation and Implementing Pneumatic Compression and Tranexamic Acid

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ABSTRACT

*Background:* Venous thromboembolic disease (VTED) after total hip arthroplasty (THA) and total knee arthroplasty (TKA) poses substantial risk. Pharmacologic prophylaxis against VTED can cause bleeding, transfusion, and associated complications. The ActiveCare+SFT is a portable, intermittent pneumatic compression device (IPCD), providing equivalent VTED prophylaxis to pharmacologic agents without associated bleeding. Tranexamic acid (TXA) is an antifibrinolytic that reduces blood loss after THA and TKA. Our objective was to measure blood transfusion and VTED after eliminating enoxaparin, introducing an IPCD, eliminating autologous blood transfusion, and administering TXA during primary TKA and THA.
*Methods:* Four consecutive cohorts of THA and TKA patients were studied. Group A, the historical control, received enoxaparin VTED prophylaxis. Group B received IPCD VTED prophylaxis. Group C received IPCD VTED prophylaxis along with TXA (1 g intravenous at incision and closure). Groups A, B, and C predonated 1 unit of autologous blood. Group D received IPCD VTED prophylaxis, TXA as above, but did not donate blood preoperatively.
*Results:* Seventeen of 50 patients (34%) in Group A, 7 of 47 (14.9%) patients in Group B, 4 of 43 (9.3%) patients in Group C, and 0 of 46 patients in Group D received transfusions. There were no major symptomatic VTED events.
*Conclusion:* Using an IPCD and TXA and discontinuing enoxaparin and preoperative autologous blood donation eliminated blood transfusion in primary THA and TKA without any increase in VTED. Using an IPCD instead of enoxaparin, adding TXA, and eliminating preoperative autologous donation each had an incremental dose response effect. This protocol provides effective VTED prophylaxis equivalent to pharmacologic methods and eliminates transfusion risk in the primary THA and TKA population.


Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are associated with a documented risk of venous thromboembolic disease (VTED) and significant blood loss leading to anemia, transfusion, and associated complications [1,2]. Traditionally, recommendations for prophylaxis against VTED have involved some form of anticoagulation, which has exacerbated the potential for blood loss [1]. In turn, attempts at minimizing blood loss by less aggressive anticoagulation or topical or systemic medications to enhance coagulation have resulted in a real or perceived risk of an increased incidence of VTED [3]. Optimizing VTED prophylaxis along with minimizing blood loss and its associated complications until recently have been nearly mutually exclusive.

In 2012, the American College of Chest Physicians revised its guidelines to include the use of a unique intermittent pneumatic compression device (IPCD) as an acceptable prophylaxis against VTED after THA and TKA when used for a minimum of 10 to 14 days rather than no antithrombotic prophylaxis (class 1C recommendation) [1]. In particular, the ActiveCare+SFT (synchronized flow technology), a portable, battery-operated, IPCD device, meant to be worn continuously, and sequenced to the respiratory system to enhance peak venous velocity, was specifically referenced in these guidelines [4,5]. The device enhances the peak venous velocity by monitoring the respiratory-related venous phasic flow and

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**Table 1**
Demographic Background Data and Length of Stay by Cohort.

| Treatment Group | Age at Time of Surgery (SD) | Height (SD) | Weight (SD) | BMI (SD) | Female (%) | Right-Sided Procedure (%) | TKA (%) | LOS (SD) |
|---|---|---|---|---|---|---|---|---|
| Enoxaparin/autodonation | 67.9 (10.20) | 65.61 (4.62) | 182.66 (40.84) | 30.13 (7.95) | 33 (66.0) | 33 (66.0) | 31 (62.0) | 2.38 (0.6) |
| ActiveCare/autodonation | 66.63 (9.69) | 67.09 (3.91) | 190.23 (45.98) | 29.35 (4.68) | 30 (63.8) | 25 (53.2) | 28 (59.6) | 2.49 (0.83) |
| ActiveCare/TXA/autodonation | 67.51 (8.17) | 66.42 (4.79) | 189.51 (43.37) | 30.63 (6.76) | 23 (53.5) | 26 (60.5) | 25 (58.1) | 2.56 (1.12) |
| ActiveCare/TXA/no autodonation | 67.79 (9.56) | 66.63 (5.03) | 186.85 (44.55) | 29.32 (5.12) | 23 (50.0) | 24 (52.2) | 30 (65.2) | 2.41 (0.69) |
| *P* value | .91 | .45 | .83 | .71 | .32 | .47 | .91 | .93 |

All data are presented as mean (standard deviation [SD]) or mean (percentage).
BMI, body mass index; TKA, total knee arthroplasty; TXA, tranexamic acid; LOS, length of stay.

triggering compression when resistance is lowest and flow can be maximized. The increased flow resulting from the synchronized compression and respiratory cycle significantly reduces stasis and resultant VTED. The data supporting its use in both THA and TKA demonstrate equivalent VTED prophylaxis efficacy to formal anticoagulation with significantly less bleeding and transfusion risk [5].

Tranexamic acid (TXA), an antifibrinolytic, has become a well-accepted modality to reduce blood loss at the time of THA and TKA [6,7]. The growing body of literature has effectively dispelled the theoretical concern for increased VTED risk [7-11].

We hypothesized that combining a synchronized IPCD with the use of intravenous TXA during THA and TKA would substantially reduce blood loss and the risk of transfusion without increasing the occurrence of VTED.

## Methods

### *Design and Study Population*

The institutional review board approved this study. This study represents a retrospective analysis of prospectively gathered data. Between September 19, 2013 and November 4, 2014, data regarding preoperative care, surgical procedure, postoperative care, hemoglobin (Hb) levels, transfusions, and complications for all TKA and THA patients of a senior orthopedic surgeon were recorded. Patients were chronologically divided into 4 study groups as follows: group A: enoxaparin/autodonation, group B: IPCD/autodonation, group C: IPCD/TXA/autodonation, and group D: IPCD/TXA/no autodonation.

Enoxaparin was administered as a 30-mg subcutaneous injection twice daily starting 18-24 hours after wound closure while the patient was hospitalized, and as a 40-mg daily subcutaneous injection after discharge, for a total of 14 days.

The IPCD was applied in the preoperative holding area to the nonoperative limb and to the operative limb in the operating room on completion of the surgery. The patients were instructed to wear the device at least 20 hours per day for 14 days postoperatively. TXA was administered intravenously at a dose of 1000 mg at the time of incision and again on commencement of closure. Postoperative Hb was measured in the postanesthesia care unit, and then again daily for the first 2 hospital days, and as necessary thereafter. Patients with an Hb level of <8 gm/dL or with symptomatic anemia were transfused 1 unit at a time until stable. Exclusion criteria for this study were patients undergoing a revision TKA or THA, patients who had undergone previous surgery during the study period, patients with diagnosed anemia or blood disorders, patients with a history of VTED, and patients with recent bleeding events.

### *Statistical Analysis*

Statistical analysis was performed using analysis of variance and the Kruskal-Wallis test for numerical variables and the chi-square, Fisher exact, and Cochran-Armitage trend tests for categorical variables. A 2-sided .05 significance level was used throughout. Post hoc power analysis was carried out according to the study's hypothesis and yielded power of ≥95%. Statistical calculations were made using SAS version 9.2 (SAS Institute, Cary, NC) and nQuery Advisor, version 6.0 (Janet D. Elashoff, 2005).

## Results

Two hundred forty-four surgeries were recorded during the study period, and 186 surgeries remained after excluding patients not meeting the inclusion criteria. There were 50 patients in group A, 47 in group B, 43 in group C, and 46 in group D. The age, height, weight, body mass index, sex, operation side, specific procedure performed, and length of stay did not significantly differ between any of the groups (Table 1).

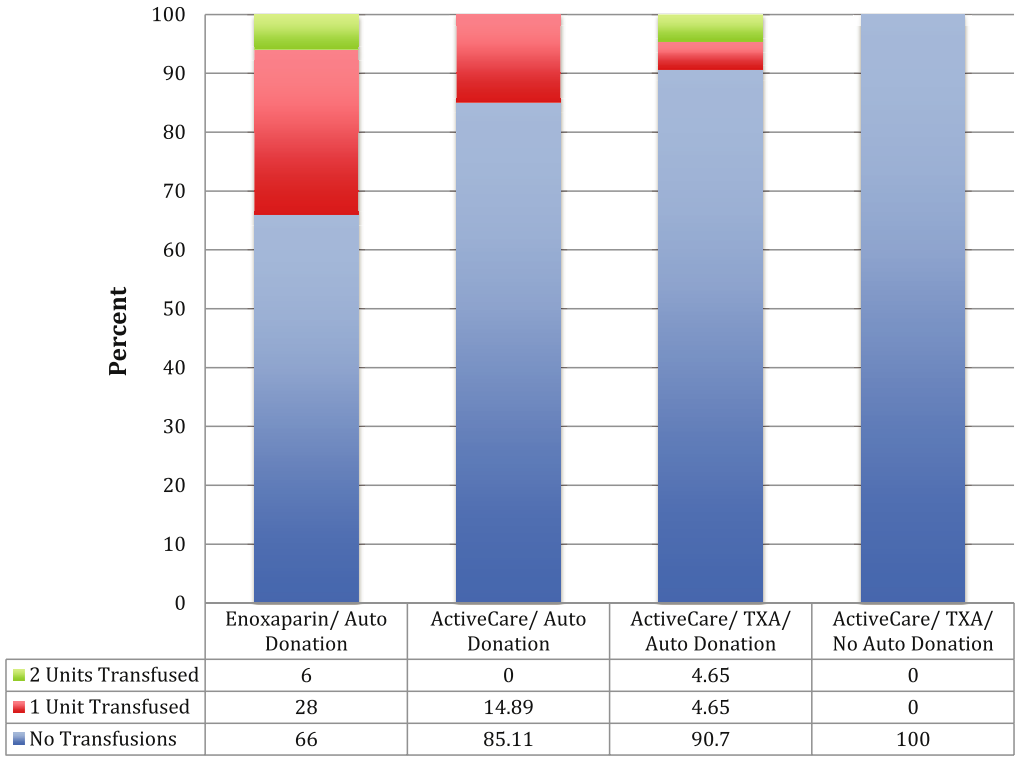
The percent of patients transfused decreased significantly with the addition of each intervention. Thirty-four percent of patients in the enoxaparin/autodonation group were transfused, which decreased to 14.9% of patients in the IPCD/autodonation group, 9.3% of patients in the IPCD/TXA/autodonation group, and 0% of patients in the IPCD/TXA/no autodonation group ($P < .0001$; Table 2, Fig. 1). In addition, the number of units transfused per patient was reduced sequentially with each additional intervention from 0.4 (20 of 50) to 0.15 (7 of 47) to 0.14 (6 of 43) to 0 (0 of 46). This was accomplished without any significant increase in complications ($P = .24$), including no increase in symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE). There were no deaths in this series (Table 3).

Hb levels measured preoperatively and postoperatively, as well as the lowest recorded postoperative Hb level, differed significantly when compared by group ($P = .039$, .043, <.0001, respectively; Table 4). The change in Hb level demonstrated reduced Hb loss with the addition of each intervention. Each intervention sequentially reduced the drop in Hb from postoperative to lowest Hb and from preoperative to lowest Hb. Preoperative to lowest postoperative Hb decreased significantly in a stepwise fashion from 3.98 to 3.84 to 3.41 to 3.39 in each group, respectively ($P = .02$). Changes in postoperative to lowest postoperative Hb levels also decreased significantly in a stepwise fashion from 1.82 to 1.77 to 1.36 to 1.20 for each group, respectively ($P = .003$). Finally, preoperative to

**Table 2**
Transfusion Data by Cohort.

| Treatment Group | Units Transfused/ Patient (SD) | Number Transfused/ Group | Percent Transfused/ Group |
|---|---|---|---|
| Enoxaparin/autodonation | 0.4 (0.61) | 17/50 | 34 |
| ActiveCare/autodonation | 0.15 (0.36) | 7/47 | 14.9 |
| ActiveCare/TXA/autodonation | 0.14 (0.47) | 4/43 | 9.3 |
| ActiveCare/TXA/no autodonation | 0 | 0/46 | 0 |
| *P* value | <.0001 | <.0001 | <.0001 |

SD, standard deviation; TXA, tranexamic acid.




| | Enoxaparin/ Auto Donation | ActiveCare/ Auto Donation | ActiveCare/ TXA/ Auto Donation | ActiveCare/ TXA/ No Auto Donation |
|---|---|---|---|---|
| 2 Units Transfused | 6 | 0 | 4.65 | 0 |
| 1 Unit Transfused | 28 | 14.89 | 4.65 | 0 |
| No Transfusions | 66 | 85.11 | 90.7 | 100 |

**Fig. 1.** Transfusions. All numbers are displayed as percentages. TXA, tranexamic acid.

postoperative Hb levels decreased sequentially, except in group D, from 2.16 to 2.07 to 2.06 to 2.18 (Fig. 2).

## Discussion

The primary outcome of this study demonstrated that using a synchronized IPCD and TXA, while discontinuing enoxaparin and preoperative autologous blood donation, eliminated blood transfusions in primary THA and TKA without increasing VTED.

Blood transfusions after TKA and THA are common. A recent study of 1573 patients showed that 9.27% of TKA and 26.6% of THA patients required transfusions [12]. These transfusions associated with TKA and THA pose risks to the patients including hemolytic reactions, nonhemolytic febrile reactions, allergic reactions, acute lung injury, reactions secondary to bacterial contamination, circulatory overload, air embolism, thrombophlebitis, hyperkalemia, citrate toxicity, hypothermia, clotting abnormalities, transmission of infectious diseases, iron overload, and immune sensitization [13].

Given the blood loss associated with TKA and THA, and to minimize the risks of allogeneic blood transfusions, many surgeons have used preoperative autologous blood donation in TKA and THA. However, Bou Monsef et al demonstrated that donating preoperative autologous blood increases the rate of transfusion to 0.84 per patient from 0.41 ($P < .001$) [14]. Therefore, although preoperative autologous donation eliminates some of the challenges associated with allogeneic transfusion, the overall transfusion rate is increased. Furthermore, even autologous blood transfusion results in risks associated with any transfusion such as increased length of stay, infection, disseminated intravascular coagulation, electrolyte disturbances, dilution coagulopathies, and significant costs [15]. It is noteworthy that because transfusion risk is calculated per unit transfused, the reduction in the number of units transfused per patient demonstrated in this study with successive interventions is significant in terms of reducing risks associated with transfusion even when transfusion itself is not completely eliminated.

Numerous methodologies have been used during TKA and THA in an attempt to decrease blood loss and subsequent transfusions. TXA has been shown to drastically reduce the need for transfusion in TKA and THA patients [6,16]. The safety of TXA is still being debated although many studies have demonstrated no increased risk for VTED with its use [8-10]. Nevertheless, TXA does not eliminate entirely the risk of blood loss and consequent transfusion [17,18].

In the present study, the lowest recorded postoperative Hb and the change from preoperative Hb to postoperative Hb to the lowest postoperative Hb were significantly different between the groups. Our interventions significantly reduced the drop in Hb in a sequential and additive manner with elimination of enoxaparin, addition of a synchronized IPCD, addition of TXA, and elimination of autologous blood. This resulted in a parallel and incremental

**Table 3**
Complication Data by Cohort.

| Treatment Group | Complications | Notes |
|---|---|---|
| Enoxaparin/autodonation | 0 | |
| ActiveCare/autodonation | 2 | 1 Pulmonary embolism without long-term sequelae and 1 new onset atrial fibrillation with rapid ventricular response |
| ActiveCare/TXA/autodonation | 2 | 1 Postoperative aspiration pneumonia and 1 hemorrhage into unknown pituitary adenoma |
| ActiveCare/TXA/no autodonation | 0 | |

TXA, tranexamic acid.

**Table 4**
Preoperative and Postoperative Hemoglobin (Hb).

| Treatment Group | Preop Hb (SD) | Postop Hb (SD) | Lowest Hb (SD) |
|---|---|---|---|
| Enoxaparin/autodonation | 13.17 (1.31) | 11.02 (1.4) | 9.19 (1.47) |
| ActiveCare/autodonation | 13.23 (1.69) | 11.17 (1.5) | 9.39 (1.27) |
| ActiveCare/TXA/autodonation | 13.36 (1.66) | 11.3 (1.42) | 9.95 (1.35) |
| ActiveCare/TXA/no autodonation | 13.99 (1.42) | 11.81 (1.33) | 10.6 (1.1) |
| *P* value | .039 | .043 | <.0001 |

All data are presented as mean (standard deviation [SD]).
Preop Hb = preoperative Hb level.
Postop Hb = first postoperative Hb level.
Lowest Hb = lowest postoperative Hb level.

decrease in transfusion rate, ultimately to 0 in our final group. The individual contribution of each intervention is impossible to assess in this study model, but clearly each intervention had a successive and positive impact on the lowest Hb level and transfusion rate.

One potential confounder in this study is that the preoperative Hb was different between the groups. Despite the fact that analysis of variance analysis can only determine that the starting Hb levels in our 4 groups are not the same, the raw numbers suggest that the groups which predonated autologous blood had preoperative Hb levels which were very close to one another, and each of which was substantially lower than the preoperative Hb for the group which did not predonate. Predonation was the only factor in our study that could have affected preoperative Hb; therefore, it seems most likely that the difference in preoperative Hb was due to the impact of predonation on lowering preoperative Hb. Furthermore, regardless of preoperative Hb, each intervention resulted in a reduced drop in Hb, presumably from a decreased blood loss. The reduced blood loss combined with the higher starting Hb contributed to eliminating transfusion in the IPCD/TXA/no autologous blood predonation group.

Blood management in TKA and THA must be balanced with a VTED prophylaxis because reducing the tendency toward clotting and coagulation may increase the risk of bleeding. Traditionally, the approach to the prevention of VTED has followed guidelines established by the American College of Chest Physicians and has included oral or injectable anticoagulants as first line options [2]. This has been based on the consensus that one of the most dreaded complications is symptomatic and/or fatal PE, and its presumed precursor, DVT. The risk of symptomatic VTED remains a serious problem in TKA and THA. Two percent of patients experience symptomatic VTED within the first 35 postoperative days [1], and the risk of fatal pulmonary embolism remains between 0.1% and 2% [19,20] regardless of the prophylactic measures used. While this incidence of PE is substantial and cannot be ignored, it nevertheless is relatively low, which renders it a difficult primary outcome to study, requiring extremely large numbers to establish enough power to determine the statistical significance of any intervention. Therefore, DVT has frequently been used in studies as a surrogate outcome for PE because its incidence is far greater in an unprophylaxed population of joint replacement patients. These studies have demonstrated powerful reductions in the incidence of DVT using aggressive anticoagulant protocols after THA and TKA.

Not surprisingly, this aggressive anticoagulation has lead to a perception of an increased risk of wound complications, bleeding, transfusion, length of stay, and even deep joint space infection [21,22]. In response to this, and calling into question the traditional causative correlation between DVT and PE, the American Academy of Orthopaedic Surgeons refocused the goal of prophylaxis in its 2005 guidelines [3] on symptomatic and fatal PE. These guidelines stratified patients according to underlying risk and favored less aggressive prophylactic interventions, including aspirin, and mechanical devices, for all but the most high risk patients, despite their proven lack of efficacy at substantially reducing the risk of DVT as sole treatment options [3].

Clearly, the clinical conundrum surrounding VTED prophylaxis is that the more effective modalities tend to increase bleeding, and in turn, methodologies that reduce bleeding increase DVT and PE risk. The 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition, have highlighted the challenge of providing adequate VTED prophylaxis without creating excessive bleeding stating "use of prophylaxis to reduce the patient-important outcomes of fatal and symptomatic PE and symptomatic DVT [must be] balanced against the hazard of an

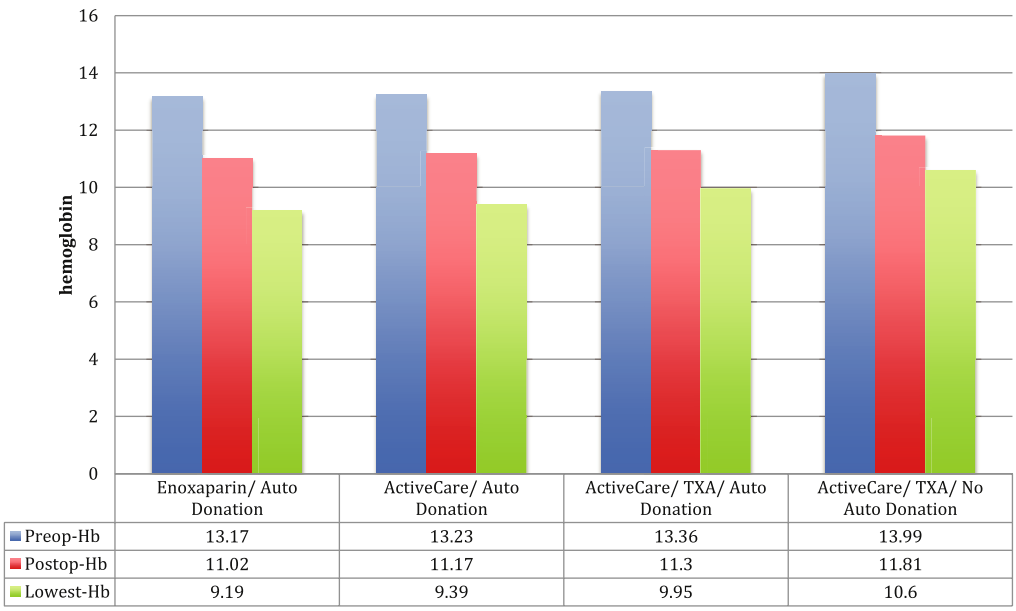



**Fig. 2.** Preoperative, postoperative, and lowest hemoglobin (Hb) levels. All data are represented as means.

increase in symptomatic bleeding events."[1] A major shift in these 2012 guidelines is the recommendation for use of IPCDs instead of no prophylaxis for the prevention of VTED after THA and TKA. The qualification of this recommendation specifies use of only portable, battery-powered IPCDs capable of recording and reporting proper wear time on a daily basis for inpatients and outpatients. Among IPCDS, only the ActiveCare+SFT, which is a portable, battery-operated IPCD, designed to be worn continuously without compromising the patient's ability to fully ambulate and mobilize satisfies the American College of Chest Physicians' recommendations. The compressions provided by this IPCD are sequenced to the respiratory cycle to maximize the peak venous velocity and reduce the force of the compression and the discomfort caused by it and can record and report compliance. In a study of 3060 TKA and THA patients, Colwell et al [5] found that this IPCD provided a non-inferior risk of VTED when compared to a pharmacologic prophylaxis, including warfarin, enoxaparin, rivaroxaban (fell short 0.06% of expected rate only in TKA), and dabigatran. Similar results were found in other studies of orthopedic and nonorthopedic surgeries studying the effectiveness of this device alone or in combination with a pharmacologic prophylaxis [4,23-26]. Using this device and TXA, along with eliminating enoxaparin in our study, succeeded in reducing blood loss without compromising VTED prophylaxis and demonstrated a substantially and significantly reduced drop in Hb and an elimination of transfusion, while avoiding costly and time-consuming preoperative autologous blood donation. The out-of-pocket costs for the ActiveCare+SFT are approximately $300.00. Unfortunately, Medicare, and therefore many other payers, does not reimburse for interventions that are considered prophylactic. Although a formal cost analysis is beyond the scope of this study, we believe that this cost is nominal considering the potential risks of complication which are avoided and when comparing to the acquisition and monitoring costs of other effective prophylactic options.

*Limitations*

This study was retrospective and has the inherent limitations associated with this design. In addition, we added interventions in a stepwise fashion to insure patient safety and to measure incremental improvement of our interventions. Therefore, our ability to measure the impact of the individual interventions in the absence of the others is impossible. Furthermore, not all patients were able to receive the intended protocol because of drug allergies or other medical contraindications. This created exclusions which had they been included may have blunted some of the effects we noticed. However, those excluded patients who were at baseline at increased transfusion risk (revision surgery, recent major surgery creating an already low preoperative Hb, those with bleeding disorders or underlying anemia) would not be expected to respond differently to the modalities we studied. Including them would simply have diluted the results we succeeded in demonstrating. In fact, although these patients were excluded from analysis, each of them was part of the exact same protocol we were using at the point they had the surgery. The statistical methodology used an intention to treat analysis, which may have decreased the observed therapeutic effect because patients with contraindications did not receive TXA but were included in their intended group analysis nonetheless. Finally, we understand that this is a relatively small study and therefore may be underpowered to draw definitive conclusions with regard to complications. However, the results are dramatic. Thus, it would be wrong to ignore the conclusions of this study and not provide this approach to patients in the interest of improving their outcomes and minimizing risks.

*Conclusion*

Using a synchronized IPCD and TXA, and discontinuing enoxaparin and preoperative autologous blood donation, eliminated blood transfusion in primary THA and TKA without any increase in VTED. Using the synchronized IPCD instead of enoxaparin, adding TXA, and eliminating preoperative autologous donation of blood sequentially each had an incremental dose response effect. Furthermore, transfusion risk was further decreased by the reduction of units of blood per patient transfused. Although aggressive VTED prophylaxis has traditionally been associated with increased bleeding and transfusion risk, this protocol provides effective VTED prophylaxis equivalent to pharmacologic methods and eliminates transfusion risk in the primary THA and TKA population.

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