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BLOOD LOSS IN TKR: PERSPECTIVE EVALUATION OF THREE POST-OPERATIVE PROTOCOLS

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ABSTRACT – *Objective:* Early patient mobilization and ambulation, as well as blood-saving strategies, are key points in total knee replacement (TKR) surgery. This study compares three blood management protocols for total blood loss, hemoglobin and hematocrit reductions, need for transfusions, length of hospital stays, and complications.

Patients and Methods: Consecutive patients (n=225) were enrolled and divided into 3 groups. Group A: ordinary regimen (drain for 48 hours, ambulation after 48 hours, extended knee); group B: no drain, ambulation after 3 hours, knee flexed 120° for 3 hours; group C: no drain, ambulation after 3 hours, knee extended for 3 hours. Hemoglobin, hematocrit, and blood loss were evaluated on the first (Id) and second post-operative day (IId). Need for blood transfusions, length of hospital stay, and complications were recorded and compared.

Results: The comparison between groups revealed homogeneity for demographics and pre-operative traits. Group A patients showed a statistically significant hemoglobin, hematocrit, and blood volume drop in the second post-operative day compared to groups B and C. Group A patients needed a statistically significant number of blood transfusions (n=10; 13%) compared to groups B (n=0; 0%) and C (n=2; 2.7%). No major bleeding-related complications were observed in either group. A prosthetic joint infection was recorded in group A.

Conclusions: Blood management adopted in groups B and C was superior in terms of blood loss with respect to group A. Given the similar results obtained in groups B and C, the group C protocol seems to be preferable in that keeping the limb extended is easier and more comfortable than keeping a flexion for 3 hours.

KEYWORDS: Fast track, Post-operative management, Blood management, Blood loss, Total knee replacement.

INTRODUCTION

Total knee replacement (TKR) is one of the most performed procedures for knee osteoarthritis. An important concern is blood loss, which can range from 726 to 1,768 ml[1,2]. It derives from soft tissues release, osteotomies on the femur and tibia, and dredging of the marrow cavity[3], seriously impacting patients with co-morbidities and impaired hematopoietic ability, and often requiring blood transfusions and prolonged hospital stays, ultimately increasing health risks and economic costs. While transfusions may be necessary, they can cause anaphylactic reactions, circulatory overload, renal failure, lung injury, infection, immunosuppression, and death[4]. Blood management is, therefore, a key component in optimizing patient care.

Strategies to reduce bleeding include intra-articular injections of tranexamic acid (TXA)[5], pharmacological agents[6,7], blood reinfusion systems, protocols for tourniquets and drains[8], autologous platelet gels[9], minimally invasive or computer-aided surgery[10,11], and continuous passive motion machines. TXA acts by inhibiting plasminogen activation, blocking its lysing-binding sites, and it was shown[12] to provide a significant bleeding reduction without disadvantages like systemic absorption of thromboembolic complications. Similar effects were reported for agents like bupivacaine, epinephrine, and norepinephrine[13], administered locally during the surgical procedure.

In the last decade, those strategies have been combined into an evidence-based multimodal approach called "fast track" (FT), or "enhanced recovery" (ER). Its main concepts are: anesthesia, fluid therapy, pain therapy, and early post-operative mobilization[14,15]. This approach shows[16] a reduction of convalescence time, improved clinical results, reduction in morbidity and mortality, and reduction in length of stay, and it does not compromise patient safety or increased complication rates.

Further improvement is sought, especially for post-operative limb positioning. Traditionally, replaced knees have been placed in extension, with a compressive dressing to reduce bleeding. This has been found to be able to reduce post-operative flexion at 6 weeks follow-up and to minimally influence transfusion rates; therefore, knee flexion has been suggested[17,18]. The rationale is that this position would reduce tension on the popliteal vein, increasing venous return, reducing venous pressure, and reducing hidden blood loss[19]. Moreover, the compression of soft tissues obtained in a flexed knee could decrease the space for bleeding and improve the postoperative range of motion (ROM)[20].

The optimal post-operative position is still under debate, along with the amount of time required for significant blood loss control. Hypothetically, deep flexion should provide greater bleeding control, but low compliance, wound complication, and residual deformities could be expected. On the contrary, lower degrees of flexion could be much more tolerated and have no influence on wound healing but may not reduce the need for transfusions. These protocols may require prolonged flexed positioning for up to 48 or 72 hours and are, therefore, incompatible with an FT regimen.

The main purpose of this paper was to compare three blood management protocols in patients who underwent TKA. The first hypothesis was that a combination of LIA (local infiltration analgesia), TXA, no drain, and a short (3 hours) post-operative high flexion regimen (group B) would drastically reduce blood loss and transfusion rate with respect to our standard protocol (group A). The secondary hypothesis was that a short (3 hours) postoperative high flexion regimen (group B) may be superior to a postoperative knee extension regimen (group C) when the other variables remain unchanged.

PATIENTS AND METHODS

This is a case-control and observational study. The study was conducted according to the guidelines of the Declaration of Helsinki. All patients gave informed consent prior to enrollment. Approval of the Regional Ethical Committee was not deemed necessary by Hospital Direction since some of the proposed strategies were already practiced individually in our institution.

A Fast Track protocol for blood management was applied in our Institution in January 2018. The first consecutive patients undergoing primary TKA for disabling knee osteoarthritis were enrolled in this prospective observational monocentric study. Patients with revision surgery, a history of thromboembolism, bleeding disorders, renal failure, rheumatoid arthritis, or similar conditions were excluded. Patients with previous knee surgery, except for meniscectomy, were excluded as well. The study group was made up of 75 patients. A control group was created to review the same continuous number of previously operated patients, who, therefore, were treated with our standard blood management protocol. Lastly, in order to describe possible differences arising from a different post-operative limb positioning, a third group of 75 consecutive patients (respecting inclusion and exclusion criteria) was enrolled. The final population was made of 225 consecutive patients divided into three groups.

Group A - Control Group (n=74)

A standard blood management protocol was used in this group. A urinary catheter was placed in all cases. Non-selective epidural anesthesia was administered. In the preoperative phase, no premedication was given. No TXA was used either intravenously or intra-articularly. A tourniquet was used throughout the procedure. No LIA was administered. Two drains were placed (under and above the fascia) before wound closure. The limb was left extended with drains in place for 48 hours. A blood reinfusion system was always adopted; blood collected within the first five hours was re-infused. Patient ambulation and CPM (once a day, 20 minutes) were started after drain removal. Cryotherapy was used after each kind of mobilization and at least 5 times a day for 20 minutes. On day 3 or 4, patients were instructed and assisted in climbing and descending a ramp of stairs. Discharge from the hospital was set on days 5 to 6.

Group B - Fast Track Study Group, Knee Flexed (n=73)

This group represents the first cohort of patients undergoing our FT protocol. Urinary catheter was never used. Selective epidural anesthesia was administered, aiming to minimize the effect on the contralateral limb and detrusor muscle. Preoperative pre-medication with hydrocortisone sodium succinate (500 mg/5 mL) i.v. and TXA 1,000 mg i.v. were given half an hour before surgery. Intra-operatively tourniquet was used throughout the procedure. A second dose of 1,000 mg of TXA was given i.v. at tourniquet removal, and a third dose of 1,000 mg was injected intra-articular after capsule watertight closure diluted in 20 cc of saline. Before implantation of the prosthetic components, LIA was administered peri-capsularly and subcuticularly (Chirocaine 150 mg and Adrenalin 0.5 mg diluted in 25 cc of saline). The medullary canal was closed with bone cement. No drain was placed. After skin closure, the limb was placed for three hours in 110-120° flexion on a homemade jig (Figure 1).

Figure 1. Patient's operated leg on the custom-made flexion jig used in this study.

A single pill of methylprednisolone 16 mg was given the morning after surgery. At the removal of the jig, each patient was mobilized under assistance and instructed to walk with crutches and full weight bearing for a short distance (i.e., around the bed). A CPM machine was also applied, one time a day, for 20 minutes starting on day 1 postoperatively. Cryotherapy was used after each kind of mobilization and at least 5 times a day for 20 minutes. On day 2 or 3, patients were instructed and assisted in climbing and descending a ramp of stairs. Discharge from the hospital was set on day 4.

Group C - Fast Track Study Group, Knee Extended (n=73)

An identical FT protocol was applied in this group, only changing the variable of post-operative knee positioning. The patient's knee was kept extended for three hours. After this, patients were allowed to mobilize and walk around the bed.

Each patient of the three groups had antibiotics (Cefazolin 2 gr, intravenously, 30 minutes before surgery and 1 gr the morning after surgery), fluid therapy (2 L/day of electrolytic saline during the first 24 hours and 1 L/day until the 48^{th} hour), and DVT-prophylaxis (sodium enoxaparin, 4,000 IU, subcutaneously; starting 12 hours after surgery, and then 1/day for 35 days).

Surgery was standardized and performed by the two senior authors (NC, DE). It consisted of a medial parapatellar approach to implant a cemented bi- or tri-compartmental knee prosthesis (Attune, DePuy, Warsaw, Indiana, USA).

Pre-Operative and Post-Operative Evaluation

Age at surgery, body mass index, percentage of males and females, pre-operative hemoglobin (g/dl), pre-operative hematocrit (%), and pre-operative blood volume were recorded and evaluated.

Primary outcome tools were hemoglobin and hematocrit values on days 1 and 2 after surgery, blood loss (ml), number of additional blood tests, number of blood transfusions, amount of transfused blood units, and length of hospitalization. Blood volume was calculated with Nadler's formula[21], while blood loss was calculated according to Gross's formula[22]. The trigger for blood transfusion was set for hemoglobin lower than 8 g/dl in healthy patients and lower than 10 g/dl in patients with relevant heart disease.

Statistical Analysis

Statistical analysis was performed to compare each group for homogeneity and to compare pre- and post-operative variables of each group. Continuous and non-continuous values were compared using a Student's *t*-test and Chi-square test, respectively. To improve the results, the ANOVA test was used to compare continuous variables, and the Chi-square (χ^2) test was employed for categorical variables such as gender among the three groups. A *p*-value was considered significant if lower than 0.05.

RESULTS

The study cohort consisted of 225 patients equally distributed into 3 groups. Five patients were excluded (one patient from group A had an incomplete set of data; one patient from group B and three patients from group C were unable to have TXA for deep vein thrombosis history and severe heart disease). Age, BMI, gender, preoperative hemoglobin values, hematocrit values, and estimated blood volume (according to Nadler's formula) are reported in Table 1. Comparisons between groups for each item did not show any significant difference ($p>0.05$), demonstrating an appropriate homogeneity except for BMI and preoperative hematocrit.

Postoperative outcomes are shown in Table 2. Comparisons between the results of group A and group B showed statistical differences for all variables ($p<0.05$). Specifically, on the second postoperative day, there was a significantly higher hemoglobin drop and blood volume loss in group A (3.9 g/dl and 1,450 ml) compared to group B (2.6 g/dl and 892 ml). Moreover, patients in group A required a significant number of blood transfusions compared to patients in group B (13% *vs.* 0%). The length of hospital stays significantly decreased from 6.5 days to 6 days ($p<0.05$). Analysis was also confirmed with multigroup testing.

Table 1. Pre-operative values for each group.

	Group A (n=74)	Group B (n=73)	Group C (n=73)	*p*-value A;B	*p*-value A;C	*p*-value B;C	*p*-value
Age	73.3 ± 8.0	72.2 ± 6.6	71.1 ± 7.6	$p > 0.05$*	$p > 0.05$*	$p > 0.05$*	$p > 0.05$
BMI	27.8 ± 3.8	29.7 ± 4.5	28.6 ± 4.2	$p > 0.05$*	$p > 0.05$*	$p > 0.05$*	$p < 0.05$*
Male (%)	27 (36.4%)	24 (32.8%)	21 (28.7%)	$p > 0.05$§	$p > 0.05$§	$p > 0.05$§	$p > 0.05$
Hb Pre-op. (g/dl)	14 ± 1.3	13.9 ± 1.4	13.5 ± 1.2	$p > 0.05$*	$p > 0.05$*	$p > 0.05$*	$p > 0.05$
HCT Pre-op (%)	43.1 ± 3.1	42.8 ± 3.9	42.0 ± 3.6	$p > 0.05$*	$p > 0.05$*	$p > 0.05$*	$p < 0.05$*
EBV (ml)	4372 ± 694	4580 ± 686	4342 ± 892	$p > 0.05$*	$p > 0.05$*	$p > 0.05$*	$p > 0.05$

BMI=body mass index; Hb=hemoglobin; HCT=hematocrit; EBV=estimate blood volume. *: Student's *t*-test; §: Chi-Square test.

Table 2. Results obtained comparing each post-operative regimen.

	Group A (n=74)	Group B (n=73)	Group C (n=73)	*p*-value A;B	*p*-value A;C	*p*-value B;C	*p*-value
Hb II day post-op (g/dl)	10.1±1.3	11.2±1.2	11.1±1.2	$p < 0.05$*	$p < 0.05$*	$p > 0.05$*	$p < 0.05$
Hb drop (g/dl)	3.9 ± 1	2.6 ± 0.9	2.5 ± 1	$p < 0.05$*	$p < 0.05$*	$p > 0.05$*	$p < 0.05$*
HCT II day post-op (%)	31.1 ± 5.2	35.1 ± 3.7	34.5 ± 4.6	$p < 0.05$*	$p < 0.05$*	$p > 0.05$*	$p < 0.05$*
HCT drop (%)	12 ± 4.7	7.7 ± 1.9	7.5 ± 2.1	$p < 0.05$*	$p < 0.05$*	$p > 0.05$*	$p < 0.05$*
Blood loss (ml)	1450 ± 868	892 ± 400	886 ± 618	$p < 0.05$*	$p < 0.05$*	$p > 0.05$*	$p < 0.05$*
N° transfusion (%)	10 (13%)	0 (0%)	2 (2.7%)	$p < 0.05$§	$p < 0.05$§	$p > 0.05$§	$p < 0.05$*
Length of stay (days)	6.5 ± 0.6	6 ± 0.8	5.2 ± 0.8	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*	$p < 0.05$*

Hb=hemoglobin; HCT=hematocrit. *: Student's *t*-test; §: Chi-Square test.

Comparisons between the results of group A and group C showed statistical differences for all variables ($p<0.05$). Specifically, on the second postoperative day, there was a significantly higher hemoglobin drop and blood volume loss in group A (3.9 g/dl and 1,450 ml) than in group B (2.5 g/dl and 886 ml). Moreover, patients in group A required a significant number of blood transfusions compared to group C (13% *vs.* 2.7%). The length of hospital stays significantly decreased from 6.5 days to 5.2 days ($p>0.05$).

Comparisons between groups B and C did not show statistical differences for any of the examined variables ($p>0.05$), but the length of hospital stay decreased from 6 days to 5.2 days ($p>0.05$).

DISCUSSION

This study describes a monocentric experience of blood management in TKR. The previous ordinary protocol (group A) was compared to a recently adopted “Fast Track” protocol (group B) with its slightly modified version in order to assess the most advantageous post-operative knee position (group C). The main strengths are the large cohort of consecutive patients evaluated and the standardization in surgical technique, prosthetic implants, and post-operative rehabilitation.

Results provided show that both FT groups (B and C) obtained significantly better values in terms of hemoglobin drop and need for blood transfusions, compared to group A. Similarly, a significant reduction in the length of hospital stay was seen, favoring the application of FT protocols, with an average reduction of 0.5 to 1.3 days compared to group A (Table 2). Instead, no statistically significant differences were found between groups B and C for hemoglobin drop, blood loss, or need for transfusions. Therefore, it can be assumed that a high post-operative knee flexion positioning (110-120°), kept for 3 hours, does not influence post-operative bleeding. The three-hour period of flexion was selected for a practical reason: it is a relatively short period of time that can allow for early mobilization and ambulation even for a patient operated on in the late afternoon. If a six-hour period of flexion were to be chosen, in fact, those patients operated on in the afternoon would not have been able to walk on the same day of surgery. Lastly, a statistically significant difference was observed in the length of hospital stay, among all groups. If this could be expected by comparing group A with B and C, it is somewhat unexpected comparing the two FT groups (6±0.8 days for group B *vs.* 5.2±0.8 days for group C). Since no difference in bleeding was seen among these two groups, the difference could be explained by increased confidence and familiarity developed by surgeons, physicians, and rehabilitators, while adopting FT protocols. Group C, in fact, being the latest group of consecutive patients, could suffer from a sort of "confidence bias", which ultimately led to a reduction in hospitalization.

In terms of general outcomes, the reported results are in line with the published literature. Several studies[23] advocated the application of many of the strategies included in the FT regimen, especially for TXA, a synthetic antifibrinolytic agent which retards fibrinolysis and blood clot degradation. It was recommended for routine use in primary THA and TKA to reduce blood loss by several meta-analyses[24-26], and it was also shown to reduce total blood loss by intra-articular injection of a 30 mg/ml dose[27]. Moreover, non-use of TXA was demonstrated to be a risk factor for blood transfusions[28] and the strongest independent risk factor among octogenarians and nonagenarians[29]. But "Fast Track" protocols are a set of strategies working together as a whole. Comprehensive protocols, in fact, were demonstrated to be extremely helpful[30] even after revision surgeries[31]. Similar results were published by Rostund and Kehlet[32], and by Holm et al[33] showing consistent pain relief, along with recovery of an appropriate health-related QoL, efficiency, functionality, and high patients' satisfaction, which should be considered the ultimate goal of joint replacement. Even early mobilization is important to reduce the risk of thrombosis and to initiate rapid recovery, as demonstrated by several authors[34-36].

Regarding post-operative limb positioning, a debate is ongoing, and our results seem to suggest little to no influence on the overall outcomes. Knee flexion is thought to decrease the tension of the popliteal vein, increasing venous return and diminishing venous pressure, therefore leading to a lower hidden blood loss[37]. This reduction was demonstrated to help to restore the functional ROM by diminishing the degree of joint effusion and swelling, allowing patients to perform simple quadriceps exercises earlier[38,39]. Several protocols of knee flexion have been proposed[40-43]. However, only those promoting 3 or 6 hours of flexion may be useful in an FT setting aimed at patients' ambulation on the same day of surgery. There are few studies available in literature in which high knee flexion was adopted for a short period of time. Napier et al[39] did not find significant differences in blood loss and ancillary findings among the group with the knee in extension and the group with the knee kept flexed at 120° for 3 hours. Instead, they found a significant reduction of blood loss in patients who kept 120° flexion for 6 hours with respect to 3 hours or knee extended. There was no significant difference in blood transfusion among the three groups. This study, however, differed from ours in that TXA was not used, patient mobilization and ambulation were started on day 1 after surgery, and the threshold for blood transfusion was also different[39]. Antinolfi et al[44] compared a control group, a flexion group (3 hours flexed at 90° and 3 hours flexed at 50°), and a TXA group (500 mg intra-articular at the end of TKR procedure). The authors[44] found no significant differences in blood loss and hemoglobin drop among the control and flexion group[44]. However, there was a significant decrease in blood loss and an increase in hemoglobin values (only on day 1) for the TXA group with respect to other groups. In contrast to our study, drainage was used and kept for 48 hours, and the blood loss was considered as the actual amount of blood present in the drainage 44 instead of calculating it from the hematocrit values[22]. Panni et al[27] compared a flexion group (6 hours, 90°) and an extension group as well. They found a significant decrease in calculated blood loss (24 hours) and hemoglobin drop (24 and 72 hours) in the flexion group compared to the extension group. There were 5 transfusions in the extension group and 0 in the flexion group. Suction drainage was positioned and kept for 24 hours. All the patients had 1,000 mg TXA iv before skin incision[27]. Madarevic et al[45] compared a flexion group (6 hours, 90°) and an extension group. They were unable to prove any statistical difference in blood loss (from suction drainage) and hemoglobin loss among the two groups. TXA was not used in this study[45].

Lastly, FT regimens have been associated with some complications. A little concern arose regarding the risk of wound and skin complications with high knee flexion. Yashar et al[37] studied continuous passive movement (CPM) with early flexion and reported an episode of skin necrosis among 104 patients having an accelerated CPM regimen. Skin necrosis has also been reported[38] with intra-articular injections of adrenaline (epinephrine) without using a drain post-operatively. However, a more recent study by Napier et al[39], did not show a single episode of wound breakdown or skin necrosis despite an early passive high knee flexion up to 6 hours post-operatively. Other authors showed how keeping the knee in a flexion position could induce a flexion contracture, reducing ROM and increasing wound complications due to a lower oxygen tension at the wound edges, delaying the healing of the wound[45]. On the contrary, flexed knee position was also shown[46] to be effective in reducing blood transfusions and improving ROM by a recent metanalysis in which no complications of any sort were noted.

In this study, two major complications were observed, all regarding group A: a deep prosthetic infection, acute atrial fibrillation, and consequent heart failure, which required the patient to be moved into the intensive care unit. This female patient had a preoperative Hb of 11.1 g/dl and a second-day Hb of 9.8 g/dl. She received two blood units (the trigger was 10 g/dl in patients with known heart disease), but this was not enough to prevent atrial fibrillation and heart failure. No major complications occurred in groups B and C. Minor skin blistering was observed once in group B and twice in group C. No wound problems were observed in either group.

Limitations

This paper has some limitations. First, the comparison between groups A and B/C could have only a descriptive value because of the many different variables characterizing each group. However, there is not a single factor that can provide optimal post-operative bleeding control by itself. Therefore, a comparison between an old-fashioned yet widespread blood management protocol and newer approaches able to allow for early mobilization and recovery was deemed appropriate. Second, factors that may have had a role in bleeding, such as chronic drug therapies, smoke habits, comorbidities, surgical time, and tourniquet time, were not taken into account, although those were not seen as a limit for the application of one regimen or another. Third, pre-operative and post-operative ROM evaluations were not recorded, but the study was focused on bleeding control over the immediate post-operative timespan, and therefore, ROM was not considered a useful outcome tool.

CONCLUSIONS

In conclusion, our results support the application of a newer “Fast Track” comprehensive regimen for total knee replacement despite a more traditional protocol with drain application.
High knee flexion for three hours was not statistically superior to an extended limb position in terms of blood loss, need for blood transfusions, and complications. Therefore, the adoption of an FT protocol with an extended limb for three hours before ambulation is preferred.

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Conflicts of Interest:
The authors declare no conflicts of interest.

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Data Availability:
Data sets are available in Excel format upon direct request to the corresponding author.

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