An Original Study

Using Aminocaproic Acid to Reduce Blood Loss After Primary Unilateral Total Knee Arthroplasty

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Abstract

Extensive blood loss after total knee arthroplasty (TKA) is common, and affected patients often require blood transfusions. Studies suggest that antifibrinolytic agents such as aminocaproic acid (ACA) reduce blood loss and blood transfusion rates in patients undergoing TKA.

We conducted a study to evaluate whether a single intravenous 10-g dose of ACA given during primary unilateral TKA would decrease perioperative blood loss, raise postoperative hemoglobin levels, and reduce postoperative blood transfusion rates. We retrospectively reviewed the charts of 50 comparable cemented primary unilateral TKAs. Twenty-five patients had been given a single intraoperative 10-g dose of ACA (antifibrinolytic group), and the other 25 had not been given ACA (control group).

Postoperative drain output was decreased significantly ($P < .0001$) in the antifibrinolytic group (155 mL) compared with the control group (410 mL), as was the number of units of blood transfused after surgery (antifibrinolytic group, 0 units; control group, 10 units; $P < .002$). There were no adverse events in the antifibrinolytic group.

In TKA, perioperative blood loss and blood transfusion rates were reduced significantly in patients given a single intraoperative intravenous 10-g dose of ACA compared with patients not given antifibrinolytics. The positive effects of ACA were obtained without adverse events or complications.

During total knee arthroplasty (TKA), traditionally a thigh tourniquet is used to minimize blood loss. Although intraoperative blood loss is negligible, postoperative blood loss can be extensive, and patients often require blood transfusions. Transfusions expose patients to clinical risks and increase costs. Well-documented transfusion complications include allergic reaction, transfusion-related acute lung injury, transfusion-associated circulatory overload, venous thromboembolism, graft vs host disease, bloodborne infections, and immunomodulation.[1] Although measures are taken to reduce these risks, the costs associated with transfusions continue to escalate.[2]

Postoperative bleeding is attributed to fibrinolytic system activation. The antifibrinolytic agent aminocaproic acid (ACA), a synthetic analogue of the amino acid lysine, acts by competitively blocking the lysine-binding site of plasminogen, inhibiting fibrinolysis.[3] Multiple studies have shown that ACA and a similar drug, tranexamic acid, can reduce postoperative blood loss when used intravenously in unilateral TKA.[4,5] However, more studies are needed to evaluate antifibrinolytic agents with comparative controls using standardized procedures and documented outcome measures. In addition, the majority of studies have used tranexamic acid rather than ACA, despite the lower cost and similar efficacy of ACA.[1,4] ACA is an inexpensive medication with a low risk profile, making it an attractive alternative to historical post-TKA management (which has a higher rate of blood transfusions) and a viable replacement in protocols already implementing tranexamic acid, the more expensive antifibrinolytic.[5,6] It has been proposed that ACA use reduces equipment (drain) costs, blood transfusion costs, exposure to complications of blood loss, and transfusion reactions and reduces or eliminates the need for costly medications, such as erythropoiesis-stimulating agents.

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Kagoma and colleagues[5] reported that antifibrinolytic agents may reduce bleeding by at least 300 mL and may reduce the need for transfusions by 50% or eliminate this need altogether. Other antifibrinolytic agents have been studied in unilateral TKA, with results showing decreased drainage and improved postoperative hemoglobin (Hb) levels.[6]

We conducted a study to evaluate the effectiveness of a single intraoperative dose of ACA in reducing postoperative blood loss and the need for blood transfusions with increased preservation of postoperative Hb levels.

Methods

In October 2011, Dr. Anderson initiated an intraoperative intravenous (IV) ACA protocol for primary unilateral TKA. Given the decreased drain output immediately observed, and patients' increased postoperative Hb levels, a retrospective study was proposed. After obtaining full Institutional Review Board approval for the study, we retrospectively reviewed the medical charts of 50 consecutive patients who underwent primary unilateral TKA—the last 25 who had the surgery before the IV ACA protocol was initiated (control group) and the first 25 who were given the IV ACA medication during the surgery (antifibrinolytic group). Inclusion criteria were primary unilateral TKA, no bleeding dyscrasia, no history of anaphylactic response to antifibrinolytic agents, no history of deep vein thrombosis, and normal preoperative coagulation parameters, international normalized ratio (INR), and partial thromboplastin time. Exclusion criteria included lateral corner release, lateral retinacular release, combined extensive deep and superficial medial collateral ligament releases, and cardiac or peripheral stent in place.

Each surgery—a standard primary unilateral TKA with an intramedullary femoral component and an extramedullary tibial component—was performed by Dr. Anderson. Each component was cemented. Each patient underwent a posterior cruciate ligament release and/or a deep medial collateral ligament release. A well-padded thigh tourniquet was inflated before surgical incision, and it remained inflated until all postoperative surgical dressings were applied. Each patient in the antifibrinolytic group was given a 10-g dose of IV ACA at the start of implant cementation; the dose was administered over 10 minutes and was completely infused before tourniquet deflation. For each patient in the control group, a suction drain (Constavac, Stryker) was used. As postoperative drainage was so insignificant in the first 12 antifibrinolytic cases, use of the drain was then discontinued.

All patients received standard postoperative deep vein thrombosis prophylaxis in the form of warfarin in accordance with existing practice. Warfarin was given once a day starting the night of surgery and was continued until discharge based on daily INR values with an agreed-on target of 2.0. Thigh-high compression stockings and calf sequential compression devices were used in all cases. No patient in either group predonated blood or was given erythropoietin injections before or after surgery. Postoperative allogeneic transfusions were given to patients who were clinically symptomatic or short of breath; patients with hypotension uncorrectable with IV volume supplementation and an Hb level under 9.0 g/dL; and patients with an Hb level under 7.0 g/dL regardless of symptoms. All patients were monitored for postoperative adverse events and complications.

Postoperative blood loss (drain output), Hb levels on postoperative days 1 and 2 (POD-1, POD-2), blood transfusion amounts, and complications were recorded for all patients. Group means were compared with 2-sample *t* tests for independent samples. Data are reported as group means and SDs. All significance tests were 2-tailed, and statistical significance was set at $P < .05$.

Results

Fifty patients enrolled in the study: 25 in the control group and 25 in the antifibrinolytic group. **Table 1** compares the main characteristics of the 2 groups. No significant differences were found between these groups for any of the characteristics considered.

There was significantly ($P < .0001$) more postoperative drainage in the control group: Mean drain output was 410.9 mL for the control group and 155.0 mL for the antifibrinolytic group (**Table 2**). Patients in the antifibrinolytic group did not receive any blood transfusions, whereas 40% of patients in the control group received transfusions ($P = .022$). On average, the transfused patients received 0.4 unit of packed red blood cells.

Although there was no statistically significant difference in POD-1 or POD-2 Hb levels between the antifibrinolytic and control groups, the antifibrinolytic group trended higher on POD-1 (11.1 g vs 10.7 g; $P = .108$) and POD-2 (11.5 g vs 10.2 g; $P = .117$) (**Table 3**). Mean Hb level was 8.1 g for control patients transfused on POD-1 and 7.9 g for control patients transfused on POD-2. For control patients

who were not transfused, mean Hb level was 10.7 g on POD-1 and 10.2 g on POD-2.

There were no adverse events (eg, anaphylaxis, hypersensitivity) in either group, and there was no difference in incision drainage or returns to operating room between the groups.

Discussion

In TKA, a tourniquet is used to minimize intraoperative blood loss; postoperative bleeding, however, is often extensive. Both surgery and tourniquet use are reported to enhance local fibrinolytic activity within the limb.[8] The synthetic antifibrinolytic ACA

Table 1. **Characteristics of Patient Groups**

Characteristic, Mean (Range)	Patient Group: Control (n = 25)	Patient Group: Antifibrinolytic (n = 25)	*P*
Age, y	66.6 (45-82)	65.2 (39-82)	.645
Sex	15 women 10 men	21 women 4 men	.1137
Body mass index	31.1 (20.9-42.6)	33.5 (23-49)	.243
Preoperative hemoglobin, g/dL	13.8 (11.4-18)	13.7 (11.6-16)	.871
Preoperative hematocrit, %	41.1 (30.2-54)	41.5 (37-48)	.701

Table 2. **Blood Losses and Transfusion Requirements by Patient Group**

Mean (Range)	Patient Group: Control (n = 25)	Patient Group: Antifibrinolytic (n = 25)	*P*
Postoperative drain output, mL	410.9 (40-1075)	155.0 (0-320)[a]	<.0001
Units transfused	0.4 (0-2)	0.0	.022
Reinfusion	42.7 (0-553)	0.0	.108

[a]n = 12 because drain was removed.

Table 3. **Changes in Hemoglobin and Hematocrit by Patient Group**

Hemoglobin, g/dL	Patient Group: Control (n = 25)	Patient Group: Antifibrinolytic (n = 25)	*P*
Preoperative	13.8 (11.4-18)	13.7 (11.6-16)	.871
Postoperative day 1	10.7 (8.1-13.1)	11.1 (9.4-13.7)[a]	.108
Postoperative day 2	10.2 (7.3-12.5)	11.5 (8.9-27.5)[b]	.117
Hematocrit, %			
Preoperative	41.1 (30.2-54)	41.5 (37-48)[a]	.701
Postoperative day 1	32.2 (23.9-38.8)	33.5 (27-40.9)	.223
Postoperative day 2	30.8 (23.1-37.7)	32.4 (26.9-38.9)[b]	.136

[a]n = 24.
[b]n = 23.

reduces blood loss by clot stabilization rather than by promotion of clot formation.[8]

In the present study, a single intraoperative dose of IV ACA administered in primary unilateral TKA significantly reduced postoperative wound drainage and eliminated the need for postoperative allogeneic blood transfusions. In addition, patients who received ACA had higher Hb levels on POD-1 and POD-2. These results are similar to those of other clinical trials in which external blood losses were measured.[4-7] The postoperative drain output differences (~250 mL) in our study are clinically relevant, as they indicate significant reductions in postoperative blood loss with the implementation of an antifibrinolytic operative protocol.

In a study by Ponnusamy and colleagues,[1] blood transfusion after orthopedic surgery accounted for 10% of all packed red blood cell transfusions, but use varied widely. National TKA transfusion rates vary from 4.3% to 63.8% among surgeons and hospitals.[9] This evidence calls for standardization and critical review of practices to ensure more efficient use of blood products, effectively protecting patients from unneeded complications and reducing hospital costs. Mounting evidence supporting the efficacy of ACA in reducing perioperative blood loss and lowering postoperative blood transfusion rates points toward including antifibrinolytic therapy in standard TKA protocols. In our study, 40% of control patients and no antifibrinolytic patients required a transfusion—a stark contrast.

Although our antifibrinolytic group's postoperative Hb levels were not statistically significantly higher, their being elevated illustrates the protective effect of intraoperative use of antifibrinolytics in TKA. This elevation in Hb levels is especially valid given the similarity of the antifibrinolytic and control patients' preoperative Hb levels ($P = .871$) (Table 1). Other studies have shown similar upward trends in postoperative Hb levels, many of which were statistically significant.[5-8,10]

Conclusion

This study showed that a single intraoperative 10-g dose of IV ACA significantly reduced perioperative blood loss and lowered blood transfusion rates in TKA. In addition, postoperative Hb levels were higher in the patients who received ACA than in patients who did not receive an antifibrinolytic. The positive effects of ACA were obtained without adverse events or complications, making use of this antifibrinolytic a relevant addition to TKA protocols.

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