Journal of Orthopaedics 16 (2019) 513–516

Contents lists available at ScienceDirect

Journal of Orthopaedics

journal homepage: www.elsevier.com/locate/jor

Reducing perioperative blood loss with antifibrinolytics and antifibrinolytic-like agents for patients undergoing total hip and total knee arthroplasty

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ARTICLE INFO

Keywords:
Antifibrinolytic
Tranexamic acid
Aminocaproic acid
Fibrin tissue adhesive
Aprotinin
Total joint arthroplasty

ABSTRACT

Total hip and knee arthroplasties may be associated with a significant amount of perioperative blood loss. The severity of blood loss may be great enough to require the use of blood transfusions to treat perioperative anemia. Various methods of blood preservation have been studied. The use of antifibrinolytics and antifibrinolytic-like agents to reduce perioperative bleeding has been researched in orthopaedics and other surgical subspecialties. This review aims to evaluate the current evidence supporting the use of tranexamic acid, aminocaproic acid, fibrin tissue adhesive, and aprotinin in the reduction of perioperative blood loss in total hip and knee arthroplasties.

1. Introduction

Total hip (THA) and total knee (TKA) arthroplasties are common surgeries that provide a well-documented improvement in functionality and quality of life. However, they are also associated with significant perioperative blood loss, often resulting in the need for blood transfusions. Estimated total blood loss during THA, which is more indicative of actual blood loss compared to measured blood loss, has been shown to range from 630 to 2292 mL.[1] It has been shown that both TKA and THA can result in a 4 g/dL drop in hemoglobin.[2] Moreover, it has been demonstrated that up to 74% of patients may meet the criteria to receive blood transfusions,[3] which could potentially increase the risk of immunological and non-immunological adverse effects, such as a higher rate of postoperative infection, intravascular hemolysis, transfusion-induced coagulopathy, acute kidney injury, and even increased mortality.[4] As a result of the potential severity of THA and TKA perioperative blood loss and its consequences, researchers have pursued more effective means for minimizing these losses, such as the use of preoperative erythropoietin, intraoperative blood salvage, regional anesthesia, and antifibrinolytic agents.[5–9] Therefore, the purpose of this review was to evaluate the recent evidence on various antifibrinolytics and antifibrinolytic-like agents for patients undergoing lower extremity total joint arthroplasty in an effort to minimize the perioperative blood losses. Specifically, we reported on the effects of: (1) tranexamic acid; (2) aminocaproic acid; (3) fibrin gel; and (4) aprotinin.

2. Tranexamic acid

Tranexamic acid (TXA) is a synthetic lysine analog antifibrinolytic agent that is approximately 7–10 times more potent than aminocaproic acid. It competitively blocks the lysine-binding site of plasminogen, plasmin, and tissue plasminogen activator, preventing their association with fibrin.[10] As a result of its affinity to plasmin and plasminogen, TXA decreases the proteolytic action of these entities, thus increasing the temporal and functional effectiveness of hemostasis. Adverse effects of TXA are rare and mainly limited to nausea, which is usually elicited by rapid intravenous infusion of the agent.[11]

The use of TXA injection in TKA can be considered an effective method to control and minimize perioperative blood loss.[12] Kundu et al.[13] demonstrated that patients who received TXA had a total measured blood loss of 146 mL compared to the 578 mL in the placebo group ($p < 0.0001$). The same study showed that the placebo group was transfused 32 units of blood compared to the TXA group that received 3 units, and the hemoglobin after 6 and 24 h postoperatively was considerably lower in the placebo group compared to the TXA group.[13] Similarly, a meta-analysis that included 46 randomized controlled trials consisting of 2925 patients found that the use of TXA reduced total blood loss by a mean of 408.33 mL (95% confidence interval [CI],

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https://doi.org/10.1016/j.jor.2019.06.025
Received 14 May 2019; Accepted 30 June 2019
Available online 02 July 2019

−505.69 to −310.77), intraoperative blood loss by a mean of 125.65 mL (95% CI, −182.58 to −68.72), and postoperative blood loss by a mean of 214.58 mL (95% CI, −274.63 to −154.52).[14] Additionally, TXA was found to decrease the number of blood transfusions per patient by 0.78 units (95% CI, −0.19 to −0.37) as well as the volumes of blood transfusions per patient by 205.33 mL (95% CI, −301.37 to −109.28).[14]

There is a concern that antifibrinolytics place patients in a state of hypercoagulability and increase the risk of developing a deep vein thrombosis (DVT). Studies have also been performed to analyze the safety of TXA with respect to DVT occurrence. It has been shown in a number of studies that patients being treated with TXA and concurrent chemical thromboprophylaxis do not have an increased risk of DVT.[14] A study published by Shen et al.[15] used Doppler ultrasonography examination to demonstrate that 4 cases of DVT were detected in the TXA group compared to 4 cases in the placebo group at postoperative day 7 ($p > 0.05$). Similarly, a meta-analysis performed by Tan et al.[16] showed that the incidence of venous thromboembolism (VTE) was 2.2% in the TXA group and 2.3% in the placebo group, and the rate of VTE was not affected by the use of TXA when the TXA group was compared with the placebo group (RR, 0.89 [95% CI, 0.43–1.85]; $p = 0.76$). In addition to having no demonstrated association with increased DVTs, TXA has not been shown to increase the risk of acute renal injury, as previously suggested.[17]

Researchers have also investigated the most effective means of administering TXA. In a meta-analysis that included 20 randomized clinical trials with 1800 patients, Chen et al.[18] compared topical versus IV TXA use in patients who underwent THA and TKA. The analysis found that there were no significant differences in terms of blood loss, drain output, or transfusion rates. Similarly, Li an Li[19] performed a meta-analysis that included 5 randomized controlled trials with 333 patients and compared oral versus IV TXA administration during THA and TKA. The analysis found that there were no significant differences between the two routes of administration in terms of blood transfusion rate, drain output volume, or length of hospital stay.

The timing of TXA administration has also been evaluated. Tanaka et al.[20] evaluated 99 patients who underwent TKA and received TXA preoperatively, intraoperatively, preoperatively and intraoperatively, or saline (control group). They found that the preoperatively dosed TXA cohort had less blood loss than the intraoperatively dosed TXA cohort (776 mL vs. 896 mL), and the group that received both preoperative and intraoperative TXA had the lowest total blood loss (528 mL). In a similar study, Imai et al.[6] reported on 107 patients who underwent THA and received different dosing regimens of TXA. The study found that the cohort that received TXA preoperatively had a significantly lower intraoperative blood loss compared to the cohort that received TXA at the end of surgery (280 vs. 377 mL, $p < 0.01$). The cohort that received TXA doses both preoperatively and 6 h after the first dose had the least amount of postoperative blood loss when compared to the cohort that received TXA at the end of surgery (579 vs. 781 mL, $p < 0.01$). Therefore, postoperative blood loss may be most effectively mitigated by administering TXA twice, i.e. one preoperative dose as well as another dose either intraoperatively or approximately 6 h after the first dose.

In addition to mitigating the amount of perioperative blood loss, TXA has been shown to reduce the costs of care by decreasing the number of blood transfusions. A case-control study performed by Harris et al.[21] investigated the cost associated with blood transfusions in patients who underwent THA. Prior to the use of TXA, there were 1047 THAs that had 208 blood transfusions, which cost the hospital $287 per THA. However, with the use of intravenous TXA, there were 478 THAs that had 21 blood transfusions and cost the hospital $123 per THA. When topical TXA was used, there were 70 THAs that had 9 blood transfusions, which cost the hospital $132 per THA. This demonstrated that intravenous TXA decreased the costs associated with blood transfusions by 57%, and topical TXA decreased the costs associated with blood transfusions by 54%. Furthermore, compared to controls, the personnel time associated with blood transfusions was decreased by 84% when IV TXA was used and by 69% when topical TXA was used.[21]

Therefore, the use of TXA in orthopaedic procedures has been shown to be effective in decreasing perioperative blood loss, decreasing the frequency and need for blood transfusions, and has not been demonstrated to be associated with increased rates of DVT or renal impairment. In addition, the use of TXA has been shown to be cost effective when compared to the cost associated with blood transfusions. Nevertheless, more studies are needed in order to evaluate potential complications as well as the most effective dosage, timing, route of administration, and infusion rate.

3. Aminocaproic acid

Aminocaproic acid, also known as epsilon-aminocaproic acid (EACA), is an antifibrinolytic that has been explored as a method to minimize perioperative blood loss in lower extremity total joint arthroplasty. It has been shown to have a mechanism of action that is similar to TXA. EACA is a lysine analog that competitively binds to the activating site of plasminogen and plasmin, thereby inhibiting their fibrinolytic properties.[22]

In a Cochrane review of antifibrinolytics used perioperatively, Henry et al.[23] reported that EACA reduced perioperative blood loss by approximately 300 mL (mean difference [MD] = −299.69 mL; 95% CI, −522.54 to −76.84 mL) compared to controls in two orthopaedic trials. Additionally, Ray et al.[24] reported the interim results of a randomized clinical trial that included 45 patients who underwent THA and were randomized to receive EACA, aprotinin, or placebo. They found the EACA group had a 53% decrease in blood loss ($p < 0.01$) compared to the placebo group at 24 h postoperatively. Additionally, they reported that no DVTs occurred in the treatment group.[24] While EACA was effective in reducing perioperative blood loss, the Cochrane review by Henry et al.[23] found no significant benefit of EACA in terms of intraoperative blood loss when compared to controls (MD = −40.66 mL; 95% CI, −236.71–155.38 mL).

When compared directly to TXA, EACA showed no significant differences in terms of total blood loss or number of allogeneic blood transfusions [24 25]. Camarasa et al.[26] performed a randomized study on 67 patients who had a mean age of 72 years and received antifibrinolytics (EACA [n = 32], TXA [n = 35]). The treatment group was compared to 60 patients who did not receive antifibrinolytics (controls) after undergoing TKA. The antifibrinolytic groups had significantly less blood loss and transfusions compared to the controls ($p < 0.001$). However, there were no significant differences between the EACA and TXA sub-groups in terms of mean total blood loss (1104 vs. 1095 mL, $p = 0.998$) or transfusion units per patient ($p = 0.248$). Although there are concerns regarding hypercoagulability and other adverse effects with the use of EACA, Henry et al. observed no significant increase in the risk of mortality, myocardial infarction (MI), stroke, DVT, pulmonary embolism (PE), or decline in renal function with the use of EACA compared to controls.[23]

EACA was successful in decreasing perioperative blood loss and the number of blood transfusions in patients who underwent lower extremity total joint arthroplasty. In addition, EACA has been shown to be relatively cost effective as the mean medication acquisition costs after arthroplasty are reported to be $2.23 for EACA per surgery compared to $39.58 for TXA per surgery.[25] However, EACA was not shown to decrease the length of hospital stay when compared to controls.[23] Therefore, EACA may be an efficacious and safe method to reduce perioperative blood loss in lower extremity joint arthroplasty.[26]

4. Fibrin tissue adhesive

Fibrin tissue adhesive, also known as fibrin glue, fibrin sealant, or fibrin gel, achieves its local hemostatic effects by facilitating the last

step of the coagulation cascade and allowing for the formation of a stable fibrin clot and subsequent hemostasis.[27,28] The main components of fibrin tissue adhesive are fibrinogen, factor XIII, and thrombin. In addition, some formulations contain an antifibrinolytic agent, such as aprotinin or TXA.[29] Since 1972, fibrin tissue adhesives have been increasingly used as hemostatic agents in a variety of surgical specialties, including, recently, in orthopaedic surgery TKA.[29] There have been several commercial products available in Europe, but none in the United States due to the current regulatory stance against pooled plasma blood products.[30] In orthopaedic surgery, the literature has been limited, and there are only a few reports on TKA due to the fact that fibrin tissue adhesive has not yet been used routinely.[29]

A meta-analysis performed by Wang et al.[27] demonstrated that the use of fibrin sealant significantly reduced postoperative drainage (weighted mean difference (WMD) = 346; 95% CI, −496.29 to −197.54; $p < 0.00001$) and blood transfusions (risk ratio (RR) 0.47; 95% CI, 0.35 to 0.63; $p < 0.00001$). However, using fibrin sealant did not significantly reduce total blood loss (WMD = 305.25; 95% CI, −679.44 to 68.95, $p = 0.11$).[27] In a similar study, Sabatini et al.[29] compared patients who underwent TKA and received treatment with fibrin tissue adhesive (treatment group) with patients who were managed postoperatively with blood recovery and reinfusion (control group). Sabatini et al. found that the median apparent postoperative blood loss at drain removal (third postoperative day) was significantly less in the fibrin tissue adhesive group compared to controls (910 vs. 1250 ml, $p < 0.0001$). Also, compared to controls, the fibrin tissue adhesive group had a lower rate of blood transfusions ($p = 0.03$).[29]

A systematic review and meta-analysis by Liu et al.[31] included 8 studies that reported on 558 patients who underwent TKA. The meta-analysis compared fibrin sealants to controls and found statistically significant differences in many hematological measurements. The authors found that the fibrin sealant group had decreased intraoperative drainage blood loss (MD = −354.02 mL; 95% CI, −500.87 to −207.18; $p < 0.05$) as well as a reduction in calculated total blood loss (MD = −402.12; 95% CI, −599.16 to −205.08); $p < 0.05$), hemoglobin loss (MD = −0.86 g/dL; 95% CI, −1.10 g/dL to −0.61 g/dL; $p < 0.05$), and transfusion rate (RR = 0.62; 95% CI, 0.45 to 0.86; $p < 0.05$) compared to the control group.

When complications were evaluated, Wang et al. found that fibrin sealant did not significantly increase the risk of adverse events, such as infection, fever, hematoma, or DVT when compared to no fibrin sealant or placebo.[27] However, the Italian Agency of Drugs had reported that the use of a spray device to apply fibrin tissue adhesive can produce massive pulmonary emboli (two cases, one fatal reported), and recommended using a spray device with a pressure less than 2.0 to 2.5 barometers, applying sealant from a minimum distance of 10–15 cm, and monitoring patients during spray application.[29]

When assessing the cost-effectiveness of fibrin sealants, it was found to be comparable in terms of cost to the use of a device used to salvage and reinfuse blood intraoperatively. Nevertheless, the costs are not insignificant as 1 mL, which can be used for a wound surface area of 10 cm^2, costs approximately $175 [32]. However, at least one operator is needed to prepare and reinfuse the blood using the blood salvage device, which could contribute to an increased cost and widen the gap in cost between the device and fibrin sealants.[32]

5. Aprotinin

Aprotinin differs from the lysine analog antifibrinolytics (e.g. TXA, EACA) in its mechanism of action and efficacy profile.[33] Aprotinin is a polypeptide with serine protease inhibitory activity of key enzymes associated with inflammatory, fibrinolytic, and hemostatic pathways.[34] The exact mechanism of aprotinin is still unknown, but one theory suggests that it interacts with platelet glycoprotein Ib receptors and improves their function. Aprotinin may also have an anti-kallikrein effect, which prevents activation of plasminogen to plasmin.[35] Current literature suggests that the direct anti-inflammatory effects of aprotinin are due to modulation of neutrophil activation, attachment, and transmigration, with resultant reduction in the rise of proinflammatory cytokine levels.[34]

Huang et al.[36] reviewed 18 randomized controlled trials that included 1276 patients who underwent orthopaedic procedures including TKA (n = 21), THA (n = 14), hip fracture surgery (n = 2), and spine surgery (n = 8) and reported on the efficacy of aprotinin. The authors found that the use of aprotinin reduced the mean total blood loss by 498.88 mL (95% CI, −735.03 to −262.72), intraoperative blood loss by 246.11 mL (95% CI, −352.11 to −140.11), postoperative blood loss by 169.11 mL (95% CI -234.06 to −105.55), and number of blood transfusions per patient by 0.93 units (95% CI, −1.36 to −0.51). In addition, the use of aprotinin led to a reduction in the transfusion requirements (RR = 0.59; 95% CI, 0.51 to 0.69).[36]

In a Cochrane Review that included over 252 studies, Henry et al.[23] reviewed ten studies involving orthopaedic surgery cases that included a total of 430 patients who were randomized to receive aprotinin or were controls. They found that aprotinin reduced the mean total blood loss by 399 mL per patient (MD = −399.09 mL; 95% CI, −562.81 to −235.37 mL). Similarly, a study by Petsatodis et al. examined the effects of aprotinin in 50 patients who underwent THA. Compared to controls, the aprotinin group had a significantly reduced mean intraoperative blood loss (1073 vs. 1496 mL, $p = 0.0001$).[37] In their Cochrane Review, Henry et al.[23] also investigated the use of aprotinin with respect to the rate of postoperative blood transfusions. They reported on 15 studies that included 1146 patients who had orthopaedic procedures. When compared to controls, Henry et al. found that the use of aprotinin significantly reduced the rate of blood transfusions by 32% (RR = 0.68; 95% CI, 0.52 to 0.89).[23]

There have been studies that have shown that aprotinin may be slightly more efficacious than other antifibrinolytics, but aprotinin was not as cost-effective and carried an increased risk for the development of anaphylaxis.[26] However, the risk of hypersensitivity reactions is low after primary exposure to aprotinin. The risk associated with anaphylaxis is highest between the 4th and 30th days after initial exposure, and the use of aprotinin is not recommended for the first 6 months after primary exposure.[38] Moreover, in 2006, the use and safety of aprotinin were questioned due to its potential association with postoperative renal failure, myocardial infarction, cerebral vascular accident, and death in patients who underwent cardiac surgery.[23] In 2007, the distribution of aprotinin was temporarily suspended in the United States by the Food and Drug Administration based on preliminary safety results from a Canadian heart study.[36]

Lastly, it should be noted that aprotinin treatment did not reduce the lengths of hospital stay (MD = −0.25 days; 95% CI, −0.71 to 0.20 days).[23]

6. Conclusion

Strategies to reduce blood loss and the need for transfusions in surgery include enhancement of coagulation and inhibition of fibrinolysis. The effectiveness of antifibrinolytic and antifibrinolytic-like agents to reduce perioperative blood loss in lower extremity total joint arthroplasty has been investigated. Each of the 4 agents reviewed (TXA, EACA, fibrin tissue adhesive, and aprotinin) was associated with significantly reduced blood loss. The lysine analog antifibrinolytic agents, TXA and EACA, were similar in terms of efficacy to aprotinin, less expensive, and have not been associated with increased incidence of complications or death.[39] Fibrin tissue adhesive was also found to be an effective means to decrease the amount of perioperative blood loss that occurs with lower extremity total joint arthroplasty. However, this agent is comparatively expensive, and cost related concerns may lead to the more routine use of alternative products. Future studies are needed to further evaluate the possible combination of these therapies, the most efficacious means of administration, and potential adverse effects.

Funding

No sources of funding were solicited or utilized in the completion of any aspect of this study.

Author contributions

Bhaveen H: Kapadia: study conception and design, data analysis, manuscript writing, manuscript editing; **Barrett Torre:** data analysis, manuscript writing, manuscript editing; **Nicholas Ullman:** data analysis, manuscript writing, manuscript editing; **Andrew Yang:** study conception, data analysis, manuscript writing; **Matthew A. Harb:** study conception, manuscript writing, manuscript editing; **Preston W. Grieco:** study conception, manuscript writing, manuscript editing; **Jared M. Newman:** study conception, manuscript writing, manuscript editing; **Steven F. Harwin:** study conception, data validation from orthopaedic surgery standpoint, manuscript editing; **Aditya V. Maheshwari:** study conception, data validation from orthopaedic surgery standpoint, manuscript editing.

Conflicts of interest

There are no relationships or conflicts of interest directly related to this paper or that could influence or bias this work. The following authors have no disclosures to report: Kapadia, Torre, Ullman, Yang, Harb, Grieco, Newman, Maheshwari. The author Harwin reports personal fees and other from Stryker and Thieme, Inc., Journal of Knee Surgery and Journal of Hip Surgery, and editorial or governing board for Orthopaedics journal, SLACK Incorporated, and Thieme, Inc., Journal of Knee Surgery and Journal of Hip Surgery.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jor.2019.06.025.

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