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The Use of Tranexamic Acid in Joint Replacement Surgery

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Perioperative bleeding is a prevalent risk of elective joint replacement surgery that can lead to allogeneic blood transfusions, delayed discharge, and slowed physical therapy progress. Antifibrinolytics such as tranexamic acid (TXA) have been used in various surgical procedures to reduce bleeding; however, the use of TXA in orthopaedic surgery is not widespread. The purpose of this article is to determine whether the use of TXA in joint replacement surgery reduces total blood loss and lowers the need for allogeneic blood transfusions without adding additional surgical risk and cost. All reviewed meta analyses and systematic reviews analyzed did show a statistically significant reduction in total blood loss and reduction in the need for allogeneic blood transfusions. Therefore, researchers conclude that intravenous TXA use does decrease total blood loss and allogeneic blood transfusion needs. Thus, its use should be included in orthopaedic clinical practice guidelines due to its overall positive effect on outcomes.

Total joint replacement is one of the most common elective orthopaedic surgeries. It aims to provide pain relief and improve quality of life. However, the surgery is not free of complications and risks; a significant risk is bleeding. Perioperative bleeding often leads to a significant drop in hemoglobin level from baseline, allogeneic blood transfusion, and delays in discharge and physical therapy evaluation (Dang & Schwarzkopf, 2013). Up to 20% of joint replacement patients require blood transfusions, with the average total blood loss from joint replacement surgery being 591 ml (Alshryda et al., 2011). The mean units of blood received after joint replacement surgery is 1.8, which also results in an increased length of stay by 0.76 days once a transfusion occurs (Raveen & Wong, 2014). The cost of a blood transfusion in a U.S. hospital begins at $1,000. This includes the unit of blood, storage and retrieval costs, follow-up blood work, and additional length of stay in the hospital (Gillette et al., 2013). As a result of these concerns such as the cost of transfusion, transfusion safety, and an increase in rapid discharge after surgery, recent research has focused on introducing antifibrinolytics during the procedure to minimize blood loss (Henry et al., 2011).

Antifibrinolytics have been used to control bleeding in surgical cases for more than 20 years, although not in total joint replacement. The three most common antifibrinolytics used in orthopaedic surgery are aprotinin, tranexamic acid (TXA), and epsilon-aminocaproic acid (Wera, Garcia, & Goldberg, 2012). Because of its efficacy, ease of use in intravenous and topical form, lower cost, and few postoperative complications, TXA is the most commonly used and researched antifibrinolytic in orthopaedic surgery. Studies show that with the use of TXA intraoperatively, total hospital stay cost has declined by nearly $900, and the need for transfusions in the postoperative period has been reduced by more than 75% (Gillette et al., 2013; Raveen & Wong, 2014).

TXA Pharmacology

Tranexamic acid is a synthetic derivative of the amino acid lysine that acts on the lysine-binding sites on plasminogen to reduce the local breakdown of fibrin by plasmin, thus acting on the fibrinolytic system and reducing intraoperative and postoperative bleeding (McCormack, 2012). It must be stored at 25ºC and can be administered at a rate of 100 mg/min i.v. The cost is approximately $80 per 10 ml at a concentration of 100 mg/ml. Administration is typically 10 mg/kg i.v. over 30 minutes before inflation of tourniquet and 10 mg/kg at tourniquet release. Dose adjustments must be made for patients with renal impairment and serum creatinine must be monitored as TXA is excreted in urine. Side effects include visual changes, seizures, thrombotic events such as deep vein thrombosis (DVT), and hypersensitivity reactions (Astedt, 1987).

Use in Orthopaedic Practice

Although recently approved for use in other surgical and medical procedures by the U.S. Food and Drug Administration, TXA use in orthopaedic surgery is still considered "off label." Currently the use of TXA in

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Table 1. Literature Reviewed Table

Citation	Sampling/ Setting	Research Design	Data Analysis	Findings/Results	Level of Evidence	Comments
Henry et al.	211 RCTs, surgical patients with antifibrinolytics (27 RCTs of orthopaedic patients with intravenous TXA vs. control)	Cochrane-Systematic Review	*p* value, 95% CI , I^2	51% reduction in allogenic blood transfusion needs in TXA group (27 trials, I^2 54%). Total blood loss in orthopaedic patients was 446 ml less with TXA than no TXA (20 trials).	Level 1	Significant reduction in blood loss and transfusion needs in orthopaedic patients. High heterogeneity due to outside variables but net reduction in blood loss and transfusion needs was uniform and in the same direction.
Sukeik et al.	11 RCTs total hip replacement, TXA intravenous vs. control	Meta-analysis	*p* value, 95% CI, I^2	TXA reduced allogenic blood transfusions by 20% with no significant heterogeneity (I^2 15%). 289.4 ml reduction in blood loss in TXA group vs. control.	Level 1	Looks at specifically total hip replacement patients, thus lowering I^2 and reducing heterogeneity. Again net reduction in total blood loss.
Zhou et al.	19 RCTs total hip replacement, TXA intravenous vs. control	Meta-analysis	*p* value, CI 95%, I^2	TXA reduced transfusion rate by 28% in TXA group than placebo group (I^2 11%). Total blood loss 305.27 ml less with TXA than control. In 19 RCTs, 15 patients who received TXA developed DVT and 3 developed PE. In those that did not receive TXA, 19 developed DVT and 1 developed PE. $N = 382$	Level 1	No statistical heterogeneity in reduction of transfusion rate and total blood loss when looking at total hip replacement. Data analysis reveals no statistically significant difference in risk of developing DVT or PE when odds ratio explored.
Yang et al.	15 RCTs, total knee replacement, TXA intravenous vs. control	Meta- analysis	*p* value, 95% CI, I^2	The rate of patients requiring blood transfusion was significantly less (16%) in the TXA group compared with placebo (I^2 3%). Total blood loss was 504.9 ml less with TXA than control. In 15 RCTs, 10 patients who received TXA developed DVT and 2 developed PE. In those that did not receive TXA, 13 developed DVT and 4 developed PE. $N = 837$	Level 1	When looking at 15 RCTs of total knee replacement statistically significant reduction in transfusion rates with very low heterogeneity. Total net decrease in blood loss in TXA group. Data analysis reveals no statistically significant difference in risk of developing DVT or PE when odds ratio explored.
Zhang et al.	15 RCTs, total knee replacement, TXA intravenous vs. control	Meta-analysis	*p* value, 95% CI, I^2	Showed 37% reduction in the proportion of patients who required blood transfusion (I^2 39%). Total blood loss was 486.7 ml less in TXA group than control.	Level 1	Looking at total knee replacement showed the highest percent reduction in blood transfusion in patients receiving TXA vs. control. Net decrease in total blood loss.

Note. CI = confidence interval; DVT = deep vein thrombosis; I^2 = index of heterogeneity; PE = pulmonary emboli; RCT = randomized controlled trial; TXA = tranexamic acid.

joint replacement is not universal; however, studies continue to show that the hemodynamic benefits seen in other surgeries outweigh the risk of adverse reactions in this population. Many university medical centers and other joint replacement research institutions currently use TXA in their practice and have studied its positive effects on bleeding since 2011. The American Academy of Orthopaedic Surgeons does not currently have guidelines on the use of antifibrinolytics intraoperatively.

Looking at the best available evidence, meta-analyses show that the use of intraoperative intravenous TXA leads to a reduction in the need for allogeneic blood transfusions in joint replacement patients without an increase in surgical complications (Yang, Chen, & Wu, 2012, Zhou, Tao, Li, & Wu, 2013). Studies show that despite transfusion triggers, patient population, and administration protocol differences, there is an overall total net effect of a decrease in total blood loss and reduction in transfusions once TXA is implemented in total joint replacement (Henry et al., 2011; Sukeik, Alshryda, Haddad, & Mason, 2011; Zhang, Chen, Chen, & Que, 2012).

Recent randomized control trials went further to examine the benefit of TXA use on common surgical side effects such as DVT and pulmonary emboli (PE) as well as financial cost of use. Sukeik et al. (2011) concluded that there was no statistically significant difference among study groups in relation to higher risk of developing DVT or PE. Yang et al. (2012) and Zhou et al. (2013) also concluded that the rate of developing a DVT and PE was not affected by using TXA. The literature reviewed reached these conclusions after following patients up to 14 days postoperatively when clinical screening was performed for DVT and PE in the follow-up visit. Looking at allogeneic blood transfusion, Zhou et al. (2013) concluded that the economic cost-effectiveness of administering TXA outweighed the high cost of allogeneic blood transfusion. Long-term effects have yet to be determined, but because of the immediate benefits and net positive outcomes, orthopaedic surgeons have begun to implement its use (see Table 1).

With its introduction into practice, TXA will, in turn, reduce hospital stay costs for patients related to the reduction in length of stays, the lower cost of TXA administration when compared to blood transfusion costs, earlier return to prehospitalization wellness and activity levels, and the unintended additional burden of risks associated with blood transfusions (Gillette et al., 2013). In a small population group such as Jehovah's Witnesses, TXA can improve outcomes and reduce risk for patients who refuse blood transfusions for religious reasons.

Tranexamic acid offers a pharmacological option to decrease the amount of blood loss during elective orthopaedic surgery and thus improve outcomes and safety for patients who refuse blood transfusion. Although TXA is still contraindicated in patients with hypersensitivity to TXA, acquired defective color vision, active intravascular clotting, and subarachnoid hemorrhage, the benefits reach a large section of joint replacement patients and can overall lead to better outcomes (Astedt, 1987).

Nursing Considerations

With the introduction of TXA intraoperatively, orthopaedic nurses must ensure accurate communication in reporting shift to shift as to which patients received TXA. Those patients will require increased monitoring for signs of DVT, PE, decreased kidney function, and bleeding. Preoperative patient education about the use of TXA and screening for contraindications will be completed by the physician, physician assistant, or nurse practitioner, and the nurse will continue this patient education thread through discharge by answering patient and family questions and educating about complications.

Conclusion

It is hoped that orthopaedic nurses gain an increased understanding about TXA, its safety and efficacy, contraindications, and indications for use in joint replacement in today's orthopaedic surgeries. Decreased length of stays, decreased blood transfusion rates, increased return to prehospitalization wellness and activity levels, and decreased financial costs specifically related to no longer needing blood transfusions are all benefits of the introduction of TXA in joint replacement surgery. With that introduction also comes a decreased overall risk of side effects associated with blood transfusions. Tranexamic acid as an antifibrinolytic agent is safe and effective, produces both patient and facility cost-savings, and is recommended for use in joint replacement surgeries as evidenced by this literature review.

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