Does Tranexamic Acid Decrease Bleeding in Patients Undergoing Cardiopulmonary Bypass?

Neil Roy Connelly\textsuperscript{a}, Brian M. Kiessling\textsuperscript{b} and Sorin J. Brull\textsuperscript{c}

\textsuperscript{a,b}Department of Anesthesiology, Baystate Medical Center, Tufts University School of Medicine, and \textsuperscript{c}Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut

(Received June 22, 1994; sent for revision October 12, 1994; accepted October 24, 1994)

We reviewed the records of 66 patients who underwent cardiopulmonary bypass; half of these patients received the plasmin inhibitor, tranexamic acid. The demographics were not different between the group who received tranexamic acid and the group who did not (control group). There was no difference in the heparin or protamine requirements between the two groups. There was a significantly greater amount of 12-hr chest tube bleeding in the control group (495 ± 484 vs. 863 ± 655 in the control and tranexamic acid groups, respectively; \(p < .02\)). There was no difference between the groups in either the post-operative hematocrit, platelet count or the number of patients requiring transfusion. Although tranexamic acid decreased the amount of chest tube output, there was no demonstrable patient benefit derived from its use.

\section*{INTRODUCTION}

Cardiopulmonary Bypass (CPB)\textsuperscript{d} can be complicated by significant post-operative bleeding. CPB frequently induces a low-grade fibrinolytic state, which lasts several hours postoperatively. Despite full heparin anticoagulation on CPB, thrombin activity during CPB may not be completely inhibited, and fibrinolysis may result [1]. A method recently introduced at our institution in an attempt to decrease postoperative bleeding in cardiac surgery patients is the use of a plasmin inhibitor, tranexamic acid (TA). Preventing fibrinolysis and platelet activation during CPB may improve hemostatic function postoperatively. TA, which is a \textit{trans} isomer of 4-aminoethylcyclohexanecarboxylic acid, has an in vitro half-life of 80 min and is 95 percent renally excreted [2]. It exerts its effect by attaching to the high-affinity binding sites of plasminogen and plasmin with a resultant blockade of fibrin lysis.

When TA became introduced to our clinical practice, it was instituted as a “routine” part of our care. We therefore had the opportunity to investigate whether TA affected heparin requirements, bleeding, or transfusion requirements in patients undergoing CPB. To determine these issues, records were reviewed for a period of time before and after the use of TA became a standard part of our anesthetic care.

\section*{METHODS}

Following Institutional Review Board approval, the charts from 33 patients who received TA and from 33 patients who did not receive TA (control group, non-TA) were reviewed. All patients underwent either coronary artery bypass grafting or a single valve replacement. Patients in the TA group received 10 gm of intravenous TA over a 1-hr period; the infusion was started immediately after anesthetic induction and completed before

\textsuperscript{a}To whom all correspondence should be addressed: Neil Roy Connelly, M.D., Department of Anesthesiology, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199. Tel: (413) 784-4325; Fax: (413) 784-5349.

\textsuperscript{d}Abbreviations: CPB, cardiopulmonary bypass; TA, tranexamic acid; ACT, activated clotting time.
initiation of CPB. Heparin requirements (total, per patient weight and per patient weight per time of CPB) were evaluated. The activated clotting time (ACT) was maintained greater than 600 sec throughout the time of CPB. The amount of protamine required to return the ACT to baseline and measured heparin concentration to zero was also recorded. The platelet count prior to CPB, 1 hr following CPB and the next morning were compared between the two groups. Bleeding during the time of CPB was suctioned with the use of a pump suction apparatus, and following protamine neutralization of heparin, with a cell-saver device. Chest tube output every hr for the first 12-hr period, blood transfused in the operating room and the blood transfused in the intensive care unit were also recorded. As per our usual protocol, chest tube drainage was auto transfused to all patients. Data are presented as mean ± SD. Analysis was performed with two tail t-Test; p < .05 was considered statistically significant.

RESULTS

There was no difference between the TA and control groups with respect to age, sex, height, weight or duration of CPB.

See Table 1 for a tabular display of the results. The duration of CPB was 135 ± 65 in the TA group and 132 ± 48 in the control group (p = NS). The heparin dose was 54,682 ± 22,486 units (u) and 48,545 ± 16,175 u in the TA and non-TA groups, respectively (p = NS).

The amount of heparin per body weight per time of CPB (u/kg/min) was 5.5 ± 2.1 and 5.1 ± 2.0 in the TA and control groups, respectively (p = NS). The dose of protamine necessary to achieve adequate heparin neutralization was 338 ± 102 mg and 311 ± 50 mg in the TA and control groups, respectively (p = NS). Twelve-hr chest tube drainage was 495 ± 484 ml and 863 ± 655 ml in the TA and control groups, respectively (p < .02) (See Figure 1). Average blood transfusion requirements were 0.7 ± 1.8 u in the TA group (eight of 33 patients, 24 percent) and 0.6 ± 1.3 u in the control group (nine of 33 patients, 27 percent) (p = NS). There was no significant relationship between the duration of CPB and the amount of chest tube output. The hematocrit levels on the morning following surgery were not significantly different between the two groups (27 ± 5 percent vs. 26 ± 3 percent in the TA and control groups, respectively).

There was no significant difference between the groups with respect to initial platelet count (255,000 ± 101,000 vs. 228,000 ± 48,000 in the TA and control groups, respectively) or in the platelet count the morning following surgery (122,000 ± 50,000 vs. 115,000 ± 39,000 in the TA and control groups, respectively). The platelet count 1 hr following discontinuation of CPB (126,000 ± 49,000 vs. 101,000 ± 34,000 in the tranexamic acid and control groups, respectively) likewise was not significantly different, although a trend towards a higher platelet count was evident in the group who received TA (p < .06).

Table 1. The characteristics of the patients in the control and tranexamic acid groups.

| Group | CPB* (min) | Heparin (u) | Protamine (mg) | Chest tube output (ml) | Hematocrit (next day) | Platelet count (next day) |
|-------|------------|-------------|----------------|------------------------|-----------------------|--------------------------|
| Control | 132±48     | 48,545±16,175 | 311±50         | 863±655                | 26±3                  | 115,000±34,000           |
| TAa    | 135±65     | 54,682±22,486 | 338±102        | 495±484                | 27±5                  | 122,000±50,000           |

*a=cardiopulmonary bypass duration; a=tranexamic acid.

Results are expressed as mean ± SD. The chest tube output represents the output for the first twelve postoperative hr. The only significant difference between the first two groups was in the chest tube output.
DISCUSSION

Fibrinogen, which is synthesized in the liver, is cleaved by thrombin to form fibrin monomers. Factor XIIIa cross-links the fibrin monomers stabilizing the fibrin mesh. Plasminogen normally binds to fibrinogen prior to its conversion to fibrin. Physiological cleavage of plasminogen to plasmin only occurs on the surface of fibrin. Plasmin splits fibrin into peptide fragments (i.e., fibrin split products). Fibrinolysis inhibitors bind to plasminogen and plasmin, interfering with the ability to cleave fibrin. Fibrinolysis inhibitors are contraindicated in disseminated intravascular coagulation because one would not want to prevent lysis of intravascular clots [3]. Antifibrinolytics have been successfully utilized in patients undergoing cardiac surgery [1, 4, 5], prostate surgery [6], head and neck surgery [7], liver transplantation [8], in cancer patients treated with cytotoxic agents [9] and in patients with subarachnoid hemorrhage [10]. CPB induces a fibrinolytic state as evidenced by an increase in fibrin split products, a decrease in plasminogen and active formation of fibrinopeptide A (a degradation product of fibrinogen) [11].

As in previous studies [3, 4], TA significantly decreased the chest tube output but had no effect on blood transfusion requirements. The routine use of a device that allows autotransfusion of blood shed through the chest tube probably was responsible for the similar transfusion requirements and similar postoperative hematocrit levels. This brings to light the question of cost effectiveness: if antifibrinolytics do result in a decreased amount of bleeding, but not a decreased need for transfusion, are they worth the price? At our institution, the hospital charge for the commonly used antifibrinolytics are as follows: TA (10 gm), $128; aprotinin (2,000,000 kallikrein inhibitor units), $300; epsilon aminocaproic acid (1750 mg), $4. The patient charges for these medications are approximately four times these costs. While these regimens are not necessarily therapeutically equivalent, they do represent the clinical doses of the commonly-used antifibrinolytics. On the other hand, the hospital acquisition cost for the chest tube drainage system is $66 for the basic system and $83 for the autotransfusion system.
TA is not without side effects. Some of the less serious side effects include nausea, vomiting and diarrhea following oral administration and hypotension following rapid intravenous injection. The more serious theoretical side effects include development of a hypercoagulable state, which could cause thrombosis of vascular grafts or result in thromboembolic events. Concern has been expressed about the potential of antifibrinolytics causing thrombosis with resultant myocardial infarction in patients undergoing cardiac surgery [1]. While these concerns are theoretical, in the absence of a clear benefit to patients (i.e., a decreased need for transfusion, shorter time to hospital discharge, etc.), it would seem prudent to avoid an expensive medication that may also have potentially significant side-effects.

Heparin and protamine requirements were also examined in order to rule out any alterations in bleeding due to an effect of TA on heparin or protamine requirements. TA did not affect the heparin required to maintain the ACT ≥ 600 or the amount of protamine required to return the ACT to baseline. Thus, the effect of TA on the amount of postoperative bleeding is not due to an effect on heparin or protamine requirements. Although the platelet count tended to decrease less in the patients who received TA (p < .06), this was not significantly different nor long-lasting, as the platelet counts the following morning were very similar (p = .58). The clinical action of TA is competitive inhibition of plasmin by blocking binding sites of fibrinogen and fibrin; whether it also blocks platelet receptors is unknown. It is interesting to postulate, however, that a part of the mechanism for the decrease in bleeding found in the TA group is a platelet-sparing effect.

In conclusion, tranexamic acid decreased chest tube bleeding in patients undergoing cardiopulmonary bypass. This decrease was unaccompanied by a decreased need for transfusion, or an increased postoperative hematocrit. Our data suggest that until such an effect is shown, the routine use of TA (and perhaps of similar antifibrinolytic agents) should be reevaluated in cases where autotransfusion of shed blood is practiced.

REFERENCES

1. Ovrum, E., Holen, E.A., Abdelnoor, M., Oystese, R., and Ringdal, M.L. Tranexamic acid (Cyklokapron) is not necessary to reduce blood loss after coronary artery bypass operations. J. Thorac. Cardiovasc. Surg. 105:78-83, 1993.
2. Eriksson, O., Kjellman, H., Schamong, P., and Pilbrant, A. Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. Euro. J. Clin. Pharmacol. 7:375-380, 1974.
3. Horrow, J. Desmopressin and Antifibrinolytics. Int. Anesth. Clin. 28:230-236, 1990.
4. Horrow, J.C., Hlavacek, J., Strong, M.D., Collier, W., Brodsky, I., Goldman, S.M., and Goel, I.P. Prophylactic tranexamic acid decreases bleeding after cardiac operations. J. Thorac. Cardiovasc. Surg. 99:70-4, 1990.
5. Horrow, J.C., Van Riper, D.F., Strong, M.D., Brodski, I., and Parmet, J.L. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. Circulation 84:2063-2070, 1991.
6. Sharifi, R., Lee, M., Ray, F., Millner, S.N., and Dupont, P.F. Safety and efficacy of intravesical aminocaproic acid for bleeding after transurethral resection of prostate. Urology 27:214-219, 1986.
7. Woog, J., Dortzbach, R.K., Wexler, S.A., Shahidi, N.T. The role of aminocaproic acid in lacrimal surgery in dyskeratosis congenita. Am J. Ophthalmol. 100:728-732, 1985.
8. Kang, Y., Lewis, J.H., Navalgund, A., Russell, M.W., Bontempo, F.A., Niren, L.S., and Starzl, T.E. Σ-Aminocaproic acid for treatment of fibrinolysis during liver transplantation. Anesthesiology 66:766-773, 1987.
9. Avvisati, G., Buller, H.R., Wouter ten Cate, J., Mandelli, F. Tranexamic acid for control of haemorrhage in acute promyelocytic leukaemia. Lancet ii:122-124, 1989.
10. Schisano, G. The use of antifibrinolytic drugs in aneurysmal subarachnoid hemorrhage. Surg. Neurol. 10:217-222, 1978.
11. Holloway, D.S., Summara, L., Sandesara, J., Vagher, J.P., Alexander, J.C., and Caprini, J.A. Decreased platelet number and function and increased fibrinolysis contribute to postoperative bleeding in cardiopulmonary bypass patients. Thromb. Haemost. 59:62-67, 1988.