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The effectiveness of low dose tranexamic acid in primary cardiac surgery

Purpose: This randomized controlled clinical trial compared three doses of tranexamic acid (TA) in primary cardiac surgery in terms of blood loss and transfusion requirements.

Methods: Patients presenting for primary coronary artery bypass grafting (CABG) and/or valve replacement were randomly assigned to one of three TA regimens : 20 mg·kg^{-1} (LD), 50 mg·kg^{-1} (MD), and 100 mg·kg^{-1} (HD). All participants and staff were blinded to the allocation. Haemoglobin (Hgb), haematocrit and platelet count were determined preoperatively, after bypass, at CCA arrival, and 12 and 24 hr after surgery. Coagulation parameters were measured before and after surgery. Blood loss was measured intraoperatively and for 24 hr postoperatively following a standardized protocol. Blood products were administered in a standardized fashion.

Results: Two hundred twenty patients completed the trial over 10 months: 74 in LD, 75 in MD and 72 in HD dose groups. All patient groups were comparable; similar procedures were performed in each group. No differences were identified for blood loss intra-operatively (490 ± 232 ml, 523 ± 413 ml, 488 ± 357 ml, respectively), 24 hr post-operatively (543 ± 223 ml, 544 ± 231, 458 ± 210 ml, respectively), and overall (1032 ± 358 ml, 1067 ± 502 ml, 946 ± 459 ml, respectively). Blood product administration was similar in the three groups. No differences in postoperative complications were found.

Conclusions: This study demonstrates the equivalency of the three doses of TA in primary cardiac surgical procedures. The use of low dose (20 mg·kg^{-1}) TA results in comparable outcomes, without additional complications.

Objectif : Cet essai clinique contrôlé randomisé a comparé trois doses d'acide tranexamique (AT), lors d'une cardiochirurgie primaire, en termes de pertes sanguines et de besoins transfusionnels.

Méthodes : Des patients qui se présentent pour un pontage aorto-coronaire primaire et / ou pour un remplacement valvulaire ont reçu de façon aléatoire l'un des trois régimes d'AT : 20 mg·kg^{-1} (dose faible DF), 50 mg·kg^{-1} (dose moyenne DM) et 100 mg·kg^{-1} (dose élevée DE). La répartition dans les groupes s'est faite à l'insu des participants et du personnel. Les taux d'hémoglobine (Hb) et d'hématocrites ainsi que le décompte des plaquettes ont été faits avant l'opération, après le pontage, à l'arrivée à l'unité des soins intensifs coronariens et, 12h et 24h après la chirurgie. Les paramètres de coagulation ont été mesurés avant et après la chirurgie. Les pertes sanguines ont été mesurées pendant l'opération et pendant les 24 heures qui ont suivi l'intervention, selon un protocole standardisé. Les produits sanguins ont été administrés de façon classique.

Résultats : L'essai a exigé 10 mois et la participation de deux cent vingt patients : 74 dans le groupe à DF, 75 à DM et 72 à DE. Tous les groupes de patients étaient semblables ; des traitements similaires ont été réalisés dans chaque groupe. Aucune différence de perte sanguine n'a été identifiée pendant l'opération (490 ml ± 232 ml, 523 ml ± 413 ml, 488 ml ± 357 ml respectivement) et au total (1032 ml ± 358 ml, 1067 ml ± 502 ml, 946 ml ± 459 ml respectivement). L'administration de produit sanguin était similaire dans les trois groupes. Aucune différence n'a été constatée dans les complications postopératoires.

Conclusion : Cette étude démontre des effets équivalents de trois doses d'AT dans la conduite de la cardiochirurgie primaire. L'utilisation d'une dose faible (20 mg·kg^{-1}) d'AT amène des résultats comparables à l'utilisation d'une dose moyenne ou élevée sans complications supplémentaires.

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IMPAIRED haemostasis and excessive postoperative bleeding are common complications of cardiopulmonary bypass.[1] One method to reduce bleeding in the post-operative period is the use of tranexamic acid (TA).[2] In this study we evaluated whether reducing the dose of TA used in our institution would modify blood loss and transfusion requirements in patients undergoing primary cardiac surgery requiring cardiopulmonary bypass.

Methods

After Ethics Review Board approval, informed consent was obtained from 225 patients 18 yr scheduled for primary coronary artery bypass grafting (CABG) and/or valve replacement during 1996. Patients were randomized to one of three groups using the Moses-Oakford method.[3] Patients were excluded if they were: actively bleeding, receiving *iv* heparin, emergency cases, in renal failure, had received Warfarin within seven days, had a personal/ family history of bleeding, were Jehovah's witnesses or were having redo surgery. Four were excluded later due to inappropriate inclusion (2 HD, 1 LD) and late refusal (1HD).

After anaesthesia induction, all patients received TA (20 $mg \cdot kg^{-1}$, 50 $mg \cdot kg^{-1}$, or 100 $mg \cdot kg^{-1}$) as a single bolus infusion over 30 min using coded infusion bags which were identical in appearance, transparency, and volume. Standard transfusion and perfusion protocols were employed.

Haemoglobin (Hgb), haematocrit and platelet count were determined before surgery, after bypass, at CCA arrival, and 12 and 24 hr after surgery. Prothrombin time (PT), activated partial prothrombin time (aPTT), fibrinogen and D-dimers were determined before and after surgery.

Demographic data (age, sex), medical history, and outcome (length of stay, blood loss, transfusion requirements, complications) information were collected.

The primary outcome was total blood loss. Secondary outcomes included red blood cell transfusion requirements, perioperative mortality, re-thoracotomy and postoperative CNS complications. Intra-operative and post-operative blood losses were measured in a standardized fashion.

Sample size was determined using data from a pilot study. Data were analysed using the SPSS-PC statistical software program (Version 4.0.1: SPSS, Inc.; Chicago, IL). Categorical values are reported as counts (%), and compared using ^{2} statistics. Continuous variables are reported as means and analysed using analysis of variance (ANOVA). $P < 0.01$ was used as the threshold for statistical significance. Intraclass correlation coefficient

TABLE I Post-operative blood work and main outcomes

Characteristic	*Low Dose* (*n* = 74)	*Med Dose* (*n* = 75)	*High Dose* (*n* = 72)
Total blood loss	1032.8 ±358.4	1067.4 ±502.1	945.9 ±459.3
Intra operative blood loss	489.7 ±231.9	523.1 ±413.3	488.0 ±357.8
CCA total blood loss*	543.1 ±222.8	544.3 ±231.4	457.9 ±210.1
CCA 12 hr post-op	321.9 ±172.8	315.6 ±163.3	275.4 ±170.7
CCA 12-24 hr post-op†	221.16 ±86.4	228.7 ±114.4	182.5 ±69.6
Blood loss 750 12 hr post-op	3 (4%)	2 (3%)	2 ± (3%)
CCA Arrival			
HBG	106.8 ±16.1	105.0 ±15.1	107.3 ±13.5
HCT	.31 ±.05	.31 ±.05	.31 ±.04
Placelet	135.9 ±40.3	138.2 ±39.7	142.0 ±35.7
Post-op 12 hr			
HBG	109 ±16	107 ±15	110 ±16
HCT	0.32 ±.05	0.31 ±.04	0.32 ±.05
Platelet	146.5 ±44.8	147.1 ±41.6	149.4 ±38.1
Post-op 24 hr			
HBG	106 ±14	103 ±14	105 ±14
HCT	0.31 ±.04	0.30 ±.04	0.31 ±0.4
Platelet	142.0 ±43.2	140.4 ±43.1	139.1±34.0

*$P < .05$;†$P < .01$; loss of blood results do not include two patients who died.

Mean ± SD

TABLE II Blood product administration

Total blood products	*Low Dose*		*Med Dose*		*High Dose*	
	Pts (%)	*Total # Units*	*Pts (%)*	*Total # Units*	*Pts (%)*	*Total # Units*
RBCs	14 (19%)	39	17 (23%)	36	17 (24%)	40
Plasma	4 (5%)	7	4 (5%)	5	7 (10%)	8
Platelet	2 (3%)	3	2 (3%)	8	1 (1%)	8
Cryoprecipitate	3 (4%)	10	1 (1%)	8	0	0

(ICC) or kappa (k) agreements were calculated for major outcomes.[4]

Results

Two hundred twenty one patients completed the study. All patient groups were comparable; similar procedures were performed in each group.

All patient groups had similar laboratory values in the post-operative period (Table I). No differences were found among the groups with respect to blood loss in any period except the 12-24 hr while in the CCA. Compared with the LD and MD patients, HD patients lost less blood during this period ($P = 0.01$). There were no differences in the number of patients with blood loss > 750 ml in the first 12 hr after surgery (Table I).

Twenty two percent of patients in the study received PRBCs. There were no differences among the groups in the amount of PRBCs, fresh frozen plasma, platelets, or cryoprecipitate transfused.

The PRBCs were transfused within the first 24 hr in 12 (71%) patients with haemoglobin concentration < 80 $g \cdot l^{-1}$ and 8 (24%) patients with haemoglobin 80-90 $g \cdot l^{-1}$. Of the 50 patients who received PRBC transfusions, most received either one (19) or two (17) units (Table II).

The groups demonstrated similar hospital stays of 6.38 ± 1.8 (LD), 6.47 ± 1.62 (MD) and 6,49 ± 1.7 (HD) days respectively. Four patients had neurological complications (1 LD, 3 HD), 1 patient (LD) required re-thoracotomy and 2 patients died (both MD).

Discussion

The use of TA reduces postoperative blood loss, the amount of homologous blood used, the incidence of chest re-exploration and the volume and frequency of homologous transfusion in cardiac surgery.[5,6] Questions remain, however, concerning the optimal dose of TA and the timing of its administration.

In this study we compared three different doses of TA in terms of their ability to reduce blood loss and the need for transfusion of blood products following primary CABG and/or valve replacement. For this patient population and setting, there was no statistically or clinically significant difference in either blood loss or transfusion requirements in doses between 20 and 100 $mg \cdot kg^{-1}$ of TA.

The only large prospective dose comparison study to evaluate the lower limits of TA administration in cardiac surgery was conducted by Horrow *et al.*[7]. They found that the optimum dose of TA was a loading dose of 10 $mg \cdot kg^{-1}$ followed by an infusion of 1 $mg \cdot kg^{-1} \cdot kg^{-1}$ for 12 hr. Our results confirm their findings and show that the same total dose may be given as a bolus infusion at the time of induction with comparable results. Karski and colleagues were able to reduce the incidence of excessive postoperative bleeding (>750 ml blood loss within six hours after surgery) from 18% to 2% by the prophylactic administration of a standard dose of 10 g TA.[8] The 4% incidence of excessive postoperative bleeding (>750 ml blood loss within six hours postoperatively) that we found using a 20 $mg \cdot kg^{-1}$ dose of TA compares favourably with their results. The lack of a placebo group and the exclusion of redo procedures are areas of weakness in this study. Both will be addressed in subsequent work.

In conclusion, this study has demonstrated that there is no advantage to administering > 20 $mg \cdot kg^{-1}$ of TA to patients having primary CABG and/or valve replacement. By reducing the dose of TA from 100 to 20 $mg \cdot kg^{-1}$ we have been able to reduce the drug costs of our cardiac surgical program without increasing complications.

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