TRANEXAMIC ACID OCCLUDES CORONARY ARTERY GRAFTS

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ABSTRACT:

INTRODUCTION: Postoperative bleeding is a common problem after CABG operations. Various antifibrinolytic agents including Tranexamic Acid have been used to combat this problem.

AIMS: This was a part retrospective and part prospective study. The first part of this study was conducted in patients who underwent emergency reopening for postoperative bleeding between Jan-Dec 2002, and were found to have occluded coronary artery grafts. The one common factor in these patients was that most had received postoperative Tranexamic Acid to control haemostasis. To further ascertain whether this was an incidental finding or had any significance, the second part of this study was conducted between Jan-Dec 2003, where no Tranexamic Acid was used for haemostasis after coronary artery bypass surgery.

MATERIAL AND METHODS: From Jan-Dec 2002, 582 patients underwent CABG procedures. There were 52 (8.9%) emergency reopenings. All CABG patients, independent of the operating surgeon, were included in this study. Patients undergoing redo CABG surgery were excluded. During re-operation, after the emergency had been dealt with, graft patency was checked and occluded grafts identified. Between Jan-Dec 2003, 565 CABG operations were carried out. No Tranexamic acid was used for the control of postoperative bleeding. Data for the years 2002 and 2003 was collected and compared.

RESULTS: Between Jan-Dec 2002, 8/582 (1.3%) patients had occluded grafts. 5 patients had 1 occluded graft, 2 patients had 2 occluded grafts and 1 patient had three occluded grafts. 6/8 (75%) patients with occluded grafts were given Tranexamic acid postoperatively to achieve haemostasis. Between Jan-Dec 2003, in 46 reopenings, when no Tranexamic Acid was used, only 3/565 (0.53%) patients with occluded grafts were identified. All these patients had single graft occlusions.

CONCLUSION: Intravenous use of antifibrinolytic agents have been associated with graft occlusions in post CABG patients. This data suggests that the intravenous use of Tranexamic Acid might also be liable to cause graft occlusions. However, this needs additional assessment and randomized prospective trials are necessary for further evaluation.

INTRODUCTION:

Diffuse microvascular bleeding remains a common problem after myocardial revascularization on cardiopulmonary bypass (CPB). This results from a multifactorial coagulopathy in which the predominant factors are thrombocytopenia, loss of clotting factors, non neutralized heparin, and increased fibrinolysis.[1,2] Of these, fibrinolysis has been attributed to excessive bleeding in 25-40% of patients.[3] Various antifibrinolytic agents have been used to combat this problem. These include E-Aminocaproic acid, Aprotinin and Tranexamic acid, amongst others.[4,5,6] One potential adverse effect of these agents is postoperative graft occlusion.[7]

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AIMS

The first part of this study was retrospective, carried out in patients who were re-operated to explore for bleeding or tamponade after coronary artery bypass surgery and were incidentally found to have occluded grafts.

Data was collected to identify the factors that could have led to graft occlusion. The one common factor in these patients was that most patients had received postoperative Tranexamic Acid to control haemostasis.

The second part of this study was prospective. This was carried out to ascertain whether this was an incidental finding or had any significance. No Tranexamic Acid was therefore used in the second part of the study between

Jan – Dec 2003 to control haemostasis after coronary artery bypass surgery. Data was collected on all re-openings for bleeding and tamponade during this period.

MATERIAL AND METHODS

From January - December 2002, 582 patients underwent coronary artery bypass grafting (CABG) surgery. There were 52 (8.9%) emergency re-openings in these patients. All CABG patients, independent of the operating surgeon, were included in this study. Patients undergoing redo CABG surgery were excluded. Out of the total, 31 (5.3%) re-openings were for post operative bleeding while 21 (3.6%) were for cardiac tamponade (tab 2).

	All indications	Percentage	Bleeding / Tamponade	Percentage
CABG	059	5.5	52	4.8
VALVE	013	1.2	05	.46
CHD	015	1.4	09	.83
MICS	004	0.4	02	.18
TOTAL	091	8.4	68	6.5

Table-1
Emergency re-operations for all indications, Jan – Dec 2002.

In patients who bled more than 200 mls in the first hour, an ACT was done, and if this was prolonged to more than 110 seconds, 50 mg of Protamine was administered. This was followed by an intravenous infusion of 1 gram of Tranexamic acid over one hour, if the bleeding did not settle. Two units of fresh whole blood were also arranged. At this time, blood was sent to the laboratory for a full blood count and clotting profile.

	2002	2003
Total CABG procedures	582	565
Total re-operations	52 (8.9%)	51 (9%)
Re-operations for bleeding	31 (5.3%)	37 (6.5%)
Re-operationsfor tamponade	21 (3.6%)	14 (2.5%)

Table -2
Summary of re-operations 2002,2003.

If the clotting profile was found to be abnormal, four units of fresh frozen plasma (FFP) were arranged. Four units of platelets were also arranged even if the platelet count was found to be normal. These were transfused to the patient.

1. ACT
2. CLOTTING PROFILE
3. PLATELET COUNT
4. CXR
5. CHOCARDIOGRAPHY

Investigations for postoperative bleeding / tamponade

	BLEEDING
1	> 500 ml over 2 hours
2	> 1000 ml over 3 hours
3	> 100 ml / hour, over 6 hours
4	> 5 ml per kg / hour over 3 hours

Table-3
Criteria for re-operation due to excessive bleeding.

The locations of bleeders identified at re-operation responsible for the haemorrhage or tamponade are summarized in Table 5.

Patients were re-opened, as per standard criteria (tab-3), if they did not respond to conservative measures and continued to bleed. Emergency re-openings were also carried out for suspected cardiac tamponade. If a diagnosis of tamponade was in doubt, a CXR was arranged. Echocardiography was used to settle difficult diagnostic problems.

TREATMENT PROTOCOL

- ACT > 120....PROTAMINE 50mg
- Prolonged PT & INR....Arrange 4 units FFP
- Tranexamic acid 1G IV stat
- Whole blood transfusion, preferably fresh
- 4 units of platelets, even if count normal

Table-4
Protocol for control of bleeding.

The criteria for diagnosing cardiac tamponade are set out in table 5. Re-openings were carried out if three, or at times even two criteria were met.

TAMPONADE
■ Tachycardia
■ Raised CVP
■ Decreasing urinary output
■ Poor gasses
■ Haemodynamic instability
■ Widned mediastinum on CXR
■ Echocardiographic evidence of significant pericardial collection

Table-5
Criteria for diagnosis of cardiac tamponade.

The mean reopening time was 5.6 hours (range 1.2-94 hours), of which 45/52 (86.5%) were reopened within the first 12 hours, 5/52 (9.6%) between 12-72 hours, and 2/52 (3.9%) after 72 hours (fig-1). During re-operation, after haemostasis was controlled, graft patency was checked and occluded grafts identified.

	Jan-Dec 2002	Jan-Dec 2003
■ Side branch of IMA	16	14
■ IMA bed	07	06
■ Distal end of graft	04	05
■ Venous tributaries	04	03
■ Top end of graft	04	03
■ Sternal wire site	04	06
■ Mediastinal fat	03	04
■ Aortic root cannula site	03	02
■ Aortic cannulation site	01	00
■ Atrial cannulation site	01	01
■ Pacing wire site	01	00
■ No bleeder	04	05

Table-6
Source of postoperative bleeding.

In the second part of this study, between January - December 2003, 565 CABG operation were carried out by all surgeons at this institute. There were 51 (9%) emergency re-openings in these patients. Out of the total, 37 (6.5%) re-openings were for post operative bleeding while 14 (2.5%) were for cardiac tamponade (tab 2).

The mean reopening time was 4.7 hours (range 1-81 hours), of which 44/51 (86.3%) were reopened within the first 12 hours, 5/51 (9.8%) between 12-72 hours, and 2/51 (3.9%) after 72 hours (fig-1)

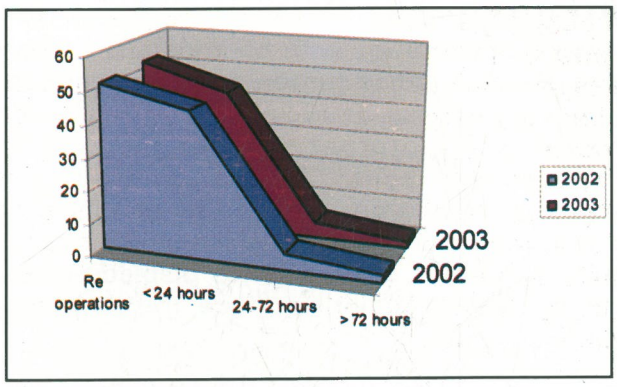

Fig-1
Re-opening data 2002, 2003.

RESULTS

Between Jan-Dec 2002, 8/582 (1.3%) patients had occluded grafts. 5 patients had 1 occluded graft, 2 patients had 2 occluded grafts and 1 patient had three occluded grafts. 6/8 (75%) patients with occluded grafts were given Tranexamic acid postoperatively to achieve haemostasis. 2/8 (25%) patients had not received Tranexamic acid. These were patients with single graft occlusions. Between Jan-Dec 2003, where no Tranexamic Acid was given, in 51 re-openings, 3/565 (0.53%) patients with occluded grafts were identified. All these patients were found to have single graft occlusions (tab-7)

	2002	2003
CABG procedures	582	565
Reopenings	52 (8.9%)	51 (9%)
No of occluded grafts	8 (1.3%)	3 (0.53%)

Table-7
Comparative analysis 2002,2003

CONCLUSION

Tranexamic Acid has been widely used in the control of postoperative bleeding not only in cardiac surgery, but also in various other surgical disciplines. However, the intravenous use of antifibrinolytic agents have been associated with graft occlusions in post coronary artery bypass grafting patients. This data suggests that the intravenous use of Tranexamic Acid might also be liable to cause graft occlusions. However, this needs additional assessment and randomized prospective trials are necessary for further evaluation.

DISCUSSION

Amongst the drugs with haemostatic properties used in cardiac surgery following cardiopulmonary bypass, Tranexamic acid has raised increasing interest in recent years. Tranexamic acid (TA) is a synthetic antifibrinolytic drug that acts by attaching to the lysine binding sites of plasmin and fibrinogen. Saturation of these sites displaces plasminogen from its fibrin surface, thereby inhibiting fibrinolysis.[8]

Tranexamic acid, molecular weight 157 daltons, is the trans isomer of 4-aminoethylccyclohexane carboxylic acid. Only the trans isomer has anti-fibrinolytic activity. It is six to ten times s potent as alpha aminocaproic acid and has a half life in vivo of 80 minutes.[9,10] After intravenous administration, only 3% is protein bound, all to plasminogen . More than 95% is excreted by the kidneys.[11] Adverse reactions reported include nausea, vomiting, diarrhoea, hypersensitivity reactions, hypotension and an increased tendency for thrombosis.[12] Extensive efforts have been made over the last few decades to reduce excessive blood loss following cardiopulmonary bypass. Numerous blood conservation techniques have been developed.[13,14] Of these, pharmacological means of curtailing blood loss have increasingly been reported.[15,16,17,18,19] They all have shown variable effectiveness in diminishing bleeding after CPB (20,21, 22 23, 24 ATS1995;59:438-442.). All the same, they carry a theoretical risk of thrombosis. Various studies have documented this deleterious impact of these antifibrinolytics both in cardiac and non cardiac surgical procedures.[25,26,27,28,29,30] An interplay of preventable and unpreventable factors account for early graft occlusions after coronary artery bypass grafting. Multiple graft and recipient coronary vessel characteristics are known to affect saphenous vein graft patency, including the quality of vein (varicosities, thickened wall), the size of the vein(< 1.5 mm in diameter) and quality and size of the recipient coronary arteries. Of these, indiscriminate use of antifibrinolytics is one possible avoidable factor. Our study endorses this last fact. In Pakistan, where Diabetes Mellitus is widespread, its expression as far as the coronary artery is concerned, is diffuse disease. This is different from the western world where coronary artery disease tends to be more localized. The other important concern is the size of the coronary artery. Coronary arteries in Asians are generally of a smaller caliber as compared to Caucasians, a factor that may lead to earlier graft occlusions due to a poor runoff. Considering all these facts, the use of antifibrinolytic agents for control of postoperative haemostasis in our region needs to be looked at and managed much more carefully. This study recommends that Tranexamic Acid should be used very cautiously and watchfully in our patients, and only where there is a definite indication. It is quite possible that graft occlusions may occur when a combination of these risk factors, rather than individual risk factors, are present. Diffuse disease and small coronary artery size are factors inherently native to the patient, whereas the use of antifibrinolytic agents is an exogenous risk factor, the use of which can be avoided. It is quite possible that the combination of exogenous and endogenous factors may be the vital determinant leading to coronary graft occlusions. However, further studies are necessary in our set up, to determine the place of antifibrinolytic agents in the control of haemostasis following coronary artery bypass surgery.

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