J Anesth (1994) 8:368–372

Journal of
Anesthesia

Effect of Gabexate mesilate on postoperative blood loss in cardiovascular surgery using cardiopulmonary bypass

ARIFUMI KOHYAMA[1], RITSUKO GOH[2], KEI-ICHI MORI[2], SATOSHI YASUMOTO[1], HIDEYUKI KIMURA[1], and HIROSHI KITAHATA[1]

[1] Department of Anesthesiology, Tokushima University School of Medicine, 2-50-1 Kuramoto-cho, Tokushima, 770 Japan
[2] Department of Anesthesiology, Komatsushima Red Cross Hospital, 28-1 Shingai, Chuden-cho, Komatsushima, Tokushima, 773 Japan

Key words: Gabexate mesilate, Postoperative blood loss, Cardiopulmonary bypass

Summary and conclusion

The aim of this study was to evaluate the effects of FOY on postoperative hemorrhage in patients undergoing cardiovascular surgery using CPB. FOY was administered at a rate of 20 $mg \cdot kg^{-1} \cdot hr^{-1}$ during CPB in 20 patients (FOY group). This was compared with a control group which received no FOY (control group). The amount of postoperative hemorrhage was significantly smaller in the FOY group than in the control group ($P < 0.05$). No significant correlation was found between the duration of CPB and amount of postoperative hemorrhage in the FOY group, although a significant correlation was found within the control group ($r = 0.556$, $P < 0.05$). In conclusion, administration of FOY during CPB appears to effectively decrease the amount of postoperative hemorrhage.

Introduction

In patients undergoing cardiovascular surgery using cardiopulmonary bypass (CPB), a bleeding diathesis may appear postoperatively, leading to profuse hemorrhage. This is caused either by a decrease in coagulation factors or a fall in platelet function as a result of hyperfunction of the blood coagulation and fibrinolysis systems [1,2]. In recent years, attempts to minimize hemorrhage during surgery were performed along with autotransfusion [3] to avoid complications of transfusion using preserved homologous blood. To protect the platelets during CPB, prostacyclin [4,5], dipyridamole [6], aprotinin [7–9], and desmopressin [10] were used to inhibit hemorrhage after CPB.

Gabexate mesilate (FOY), a proteolytic enzyme inhibitor, acts on trypsin, thrombin, plasmin, and kallikrein to inhibit the extrinsic and intrinsic coagulation and fibrinolysis systems [11]. FOY has the advantages of rapid degradation [12], no need for antagonists, and small molecular weight minimizing the risk of anaphylactic shock. It has been effectively used in place of heparin during artificial hemodialysis [13,14]. The effects of FOY on the coagulofibrinolytic system during CPB have been investigated [15–18]; however, whether FOY reduces the amount of postoperative hemorrhage in patients undergoing CPB is not clear.

In the present study, the effect of FOY on postoperative hemorrhage was evaluated in patients undergoing cardiovascular surgery using CPB.

Patients and methods

This study was conducted on 39 patients undergoing surgery of the heart and great vessels. The profiles of patients are summarized in Table 1. Anesthesia was induced with fentanyl and thiamylal, and intratracheal intubation was performed after the administration of vecuronium bromide. Anesthesia was maintained by inhalation of 50% nitrous oxide in oxygen and intermittent administration of fentanyl. Inhalation of sevoflurane or halothane at low concentrations was continued until the beginning of CPB. During CPB, fentanyl and diazepam were administered intravenously. Hypertension during CPB was treated with

Address correspondence to: A. Kohyama
Received for publication on July 12, 1993; accepted on January 20, 1994

Table 1. Patient's and intraoperative characteristics

	Control group ($n = 19$)	FOY group ($n = 20$)
Age (years)	59.1 ± 10.1	63.1 ± 8.4
Procedure (numbers of patients)		
MVP or MVR	4	6
AVR	4	4
CABG	10	8
TAA	1	2
Duration of surgery (min)	194.6 ± 37.8	203.7 ± 90.1
Duration of CPB (min)	82.5 ± 29.7	87.2 ± 47.3
Type of oxygenator (numbers of patients)		
Membrane type	13	19
Bubble type	6	1

Mean ± SEM.
MVP, mitral valve plasty; MVR, mitral valve replacement; AVR, aortic valve replacement; CABG, coronary artery bypass graft surgery; TAA, thoracic aortic aneurysm surgery; CPB, cardiopulmonary bypass; FOY, gabexate mesilate.

prostaglandin E_1 as a vasodilator in continuous or intermittent intravenous injection. Flow rates of CPB were 2.0–2.41·min^{-1}·m^{-1}. Either a heparin-coated or nonheparin-coated circuit was used. The oxygenator used was either a membrane type such as the Maxima (Medtronics Minnesota USA) or bubble type such as the Sarns 16310 (3 M, Minnesota USA). Priming of the CPB circuit was performed without blood. Mild hypothermia was maintained during CPB. For myocardial protection, cooled glucose-insulin-potassium (GIK) solution was used by the heart cooling method with ice slush. Using Cell Saver (Haemonetics Co. Massachusetts USA), blood from the operative wound during surgery and blood filling the CPB circuit after surgery was washed and returned to the patient's circulation.

After the induction of anesthesia, 10 ml tranexamic acid was administered intravenously in all patients. The dose of heparin was 50 IU·kg^{-1} with the heparin-coated circuit and 300 unit·kg^{-1} with the noncoated circuit. Heparin was antagonized with protamine in a ratio of 1.0 mg protamine per 100 IU of heparin after CPB.

FOY was administered continuously at the rate of 20 mg·kg^{-1}·hr^{-1} during CPB in 20 patients (FOY group). This was compared with 19 patients who received no FOY (control group). The amount of postoperative hemorrhage was defined as the total amount of blood obtained from the thoracic cavity and pericardial drain on the day of surgery and the 1st postoperative day. Blood analysis, prothrombin time (PT), and activated partial thromboplastin time (APTT) were determined pre- and postoperatively.

The results were statistically analyzed by Student's t-test and Mann-Whitney u-test, using $P < 0.05$ as the level of significance. Data are expressed as mean ± standard deviation.

Results

The duration of CPB and surgery (Table 1) was not significantly different between the two groups. No difference was noted in platelet count, PT and APTT between the two groups (Table 2). The amount of postoperative hemorrhage was significantly lower in FOY group (control group: 472.3 ± 165.5 ml, *vs* FOY group: 384.7 ± 196.0 ml, $P < 0.05$). Although a significant correlation between the duration of CPB and the amount of postoperative hemorrhage was found in the control group ($r = 0.556$, $P < 0.05$), no significant correlation was noted in the FOY group (Fig. 1). No significant difference was observed in the amount of postoperative hemorrhage between the membrane type and bubble type oxygenators in the control group (membrane type: 466.5 ± 158.6 ml, *vs* bubble type: 484.8 ± 194.9 ml, NS).

Discussion

In view of the significantly smaller amount of postoperative hemorrhage in the FOY group compared to controls and the absence of a significant correlation between the duration of CPB and the amount of postoperative hemorrhage in the FOY group, FOY apparently protected the coagulation and fibrinolysis systems during CPB.

In cardiovascular surgery using CPB, the amount of hemorrhage increases markedly with prolonged bypass time [3,9]. In the present study, hemorrhage during surgery was low in both groups due to the use of Cell Saver to recover the patient's own blood. The amount of postoperative hemorrhage correlated with the duration of CPB in the control group ($r = 0.556$, $P < 0.05$). The

Table 2. Changes in blood analysis and coagulation time pre- and postoperatively

	Preoperative	Postoperative days 1	2
Hemoglobin ($mg \cdot dl^{-1}$)			
Control	13.5 ± 1.7	11.4 ± 1.5*	11.6 ± 1.5*
FOY	12.7 ± 1.7	11.8 ± 1.3*	12.1 ± 1.4
Platelets ($104 \cdot \mu l^{-1}$)			
Control	20.2 ± 3.3	14.3 ± 3.2*	13.0 ± 3.9*
FOY	23.9 ± 6.2	15.1 ± 4.1*	16.2 ± 5.8*
PT (s)			
Control	10.9 ± 0.4	14.4 ± 1.5*	11.7 ± 0.6*
FOY	11.4 ± 1.3	14.4 ± 1.7*	11.4 ± 1.5
APTT (s)			
Control	30.0 ± 3.0	37.5 ± 5.7*	35.2 ± 4.2*
FOY	31.6 ± 3.5	41.7 ± 10.9*	33.0 ± 4.6

* $P < 0.05$ Compared with preoperative value. Mean ± SD.
Control, control group; FOY, FOY infusion group; PT, prothrombin time; APTT, activated partial thromboplastin time.

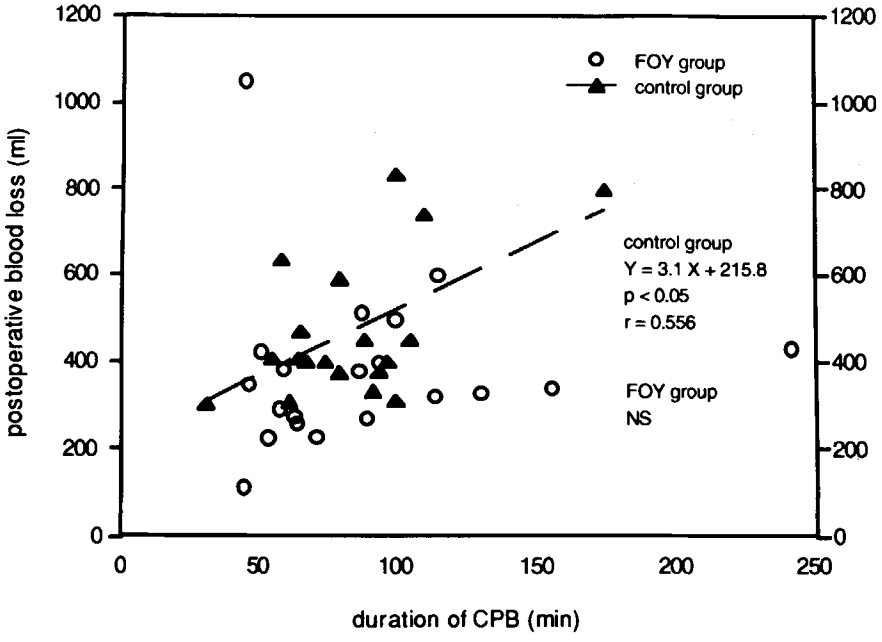

Fig. 1. Correlation between postoperative blood loss and duration of cardiopulmonary bypass (CPB) in the gabexate mesilate (*FOY*) group (*open circles*) and the control group (*closed triangles*). Significant correlation between postoperative blood loss and duration of CPB was demonstrated in control group (dotted line)

hemorrhagic tendency during cardiovascular surgery is reportedly influenced by hypothermia during surgery, the extracorporeal circuit, the pump, the membrane-type or bubble-type oxygenator, heparin overdose, and protamin [1]. The postoperative hemorrhagic tendency is thought to be caused by augmentation of the fibrinolysis system or decreased coagulation function due to the fall of blood coagulation factors including platelets. After CPB, coagulation factors decreased but not to the extent explaining the excessive hemorrhage [1]. Primary fibrinolysis system is augmented during CPB but recovers quickly after discontinuation [19,20]. These are therefore unlikely candidates for the cause of postoperative hemorrhage; decreased platelet aggregation or adhesion is probably responsible. Platelet transfusion is useful for hemostasis when the hemorrhagic tendency persists despite maintenance of the platelet count postoperatively [21,22]. In the present study, the platelet count did not differ between the two groups postoperatively and remained above the level causing hemorrhage clinically. The fall in platelet count during CPB has been explained by adhesion of platelets to the circuit and elsewhere [23,24], or by the augmentation of the coagulation system triggered by the contact of blood with a foreign body such as the surface of the extracorporeal circuit, oxygenator, or compression roller. Immediately after initiation of CPB, platelets adhere to the circuit and elsewhere causing a market fall in the

platelet count, followed by release of platelets from the circuit and partial recovery [4,25]. The decrease in the function of platelets released from the circuit is thought to be the most important cause of postoperative hemorrhage. To suppress the hemorrhage after CPB inhibition of coagulation, platelet function and the fibrinolytic system becomes important.

FOY inhibits the actions of thrombin, plasmin, and kallikrein without requiring antithrombin III [11]. Contact of blood with a foreign body surface such as an extracorporeal circuit or oxygenator activates contact factor, leading to augmentation of the coagulation and fibrinolysis systems, and complement activity [26]. FOY inhibits these endogenous systems through its anti-kallikrein action [11,14,18,27], and subsequently platelet aggregation. Since FOY inhibits platelet aggregation directly [14,18], it may sustain platelet number and function circulating through the CPB circuit. Although the platelet count did not change in the present study, the amount of postoperative hemorrhage decreased in response to the use of FOY. Especially since postoperative hemorrhage did not increase even after long CPB when FOY was used in this study, FOY probably protected the platelet function during CPB. The inhibition of the fibrinolytic system through the antiplasmin action of FOY was probably effective to decrease the amount of hemorrhage after CPB along with inhibition of the coagulation system.

In the present study, 20 $mg \cdot kg^{-1} \cdot h^{-1}$ of FOY was used. As FOY is degraded by esterase in blood, with a plasma half-life of 1 min followed by disappearance within 2 min, continuous administration is necessary [12]. Generally, 1–10 $mg \cdot kg^{-1} \cdot hr^{-1}$ [13,14] of FOY is required for disseminated intravascular coagulation (DIC) and 50 $mg \cdot kg^{-1} \cdot h^{-1}$ is necessary for the protection of hepatic lysosomal enzyme in hemorrhagic shock. During hemodialysis using FOY alone within the circuit, 20 $mg \cdot kg^{-1} \cdot h^{-1}$ is required to inhibit blood coagulation. In the present study, heparin was used and continuous administration of 20 $mg \cdot kg^{-1} \cdot h^{-1}$ FOY was employed to ensure the effect of FOY [28]. The optimum dose of FOY, as well as platelet function, coagulation, and fibrolytic function during FOY administration require further study.

References

1. Harker LA (1986) Bleeding after cardiopulmonary bypass. N Engl J Med 314:1446–1448
2. Bachman F, Mckenna R, Cole ER, et al. (1975) The hemostatic mechanism after open-heart surgery. Studies on plasma coagulation factors and fibrinolysis in 512 patients after extracorporeal circulation. J Thorac Cardiovasc Surg 70:76–85
3. Love TR, Hendren WG, O'Keefe DD, et al. (1987) Transfusion of predonated autologous blood in elective cardiac surgery. Ann Thorac Surg 43:508–512
4. Addonizio VP, Macarac EJ, Nicolaou KC, et al. (1979) Effects of prostacyclin and albumin on platelet loss during in vitro simulation of extracorporeal circulation. Blood 53:1033–1042
5. Fish KJ, Sarnquist FH, Steennis CV, et al. (1986) A prospective, randomized study of the effects of prostacyclin on platelets and blood loss during coronary bypass operation. J Thorac Cardiovasc Surg 91:436–442
6. Teoh KH, Christakis GT, Weisel RD, et al. (1988) Dipyridamole preserved platelets and reduced blood loss after cardiopulmonary bypass. J Thorac Cardiovasc Surg 96:332–341
7. Royston D, Taylor KM, Bidstrup BP, et al. (1987) Effect of aprotinin on need for blood transfusion after repeat open heart surgery. Lancet 2:1289–1291
8. Bidstrup BP, Royston D, Sapsford RN, et al. (1989) Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). J Thorac Cardiovasc Surg 97:364–372
9. Dietrich W, Spannagl M, Jochum M, et al. (1990) Influence of high-dose aprotinin treatment of blood loss and coagulation patterns in patients undergoing myocardial revascularization. Anesthesiology 73:1119–1126
10. Salzmann E, Weinstein MJ, Weintraub RM, et al. (1986) Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. N Engl J Med 314:1402–1406
11. Muramatu M, Fujii S (1968) Inhibitory effects of ω-guanidino acid esters on trypsin, plasmin, thrombin and plasma kallikrein. J Biochem 64:807–714
12. Miyamoto T, Hirata H (1978) Metabolic fate of Etyl p-(6-Guanidinohexanoyloxy) Benzoate Methanesulfate (FOY) 2. Absorption, excretion and metabolism after intravenous administration in rabbit. Ouyou Yakuri 15:15–20
13. Matsui N, Nakagawa S, Sasaoka T, et al. (1979) Reduction of unfavourable effects of heparin with use of gabexate mesilate in dialysis. Proc Eur Dial Transp Assoc 16:135–140
14. Taenaka N, Shimada Y, Hirata T, et al. (1982) New approach to regional anticoagulation in hemodyalysis using gabexate mesilate (FOY). Crit Care Med 10:773–775
15. Matsumura M, Isono M, Ishikawa M, et al. (1981) Effects of FOY on coagulofibrinolytic system during extracorpored circulation. Gendai Iryou 13:1231–1235
16. Tanaka K, Wei CM, Shimono T, et al. (1987) Alteration of hemostatic parameters during open heart surgery and the effects of Gabexate Mesilate (FOY) on these parameters. Jpn J Artif Organs 16:522–525
17. Murakawa S, Mori Y, Yamada T, et al. (1991) The effect of gabexate mesilate on coagulofibrinolytic system and platelet function during extracorporeal circulation. Jpn J Artif Organs 20:1181–1185
18. Arima T, Tsuji Y, Genda T, et al. (1985) The effects of gabexate mesilate on blood coagulation factors during surgery with cardiopulmonary bypass. Masui 34:1336–1342
19. Kucuk O, Kwaan HC, Frederickson J, et al. (1986) Increased fibrinolytic activity in patients undergoing cardiopulmonary bypass operation. Am J Hematol 23:223–229
20. Stibbe J, Kluft C, Brommer EJP, et al. (1984) Enhanced fibrinolytic activity during cardiopulmonary bypass in open-heart surgery in man is caused by extrinsic (tissue-type) plasminogen activator. Eur J Clin Invest 14:375–382
21. Harker LA, Malpass TW, Branson HE, et al. (1980) Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective α-granule release. Blood 56:824–834
22. DelRossi AJ, Cernaianu AC, Vertrees RA, et al. (1990) Platelet-rich plasma reduces postoperative blood loss after cardiopulmonary bypass. J Thorac Cardiovasc Surg 100:281–286
23. Wenger RK, Lukasiewicz H, Mikuta BS, et al. (1989) Loss of platelet fibrinogen receptors during clinical cardiopulmonary bypass. J Thorac Cardiovasc Surg 97:235–239

24. Gluszko P, Rucinski B, Musial J, et al. (1987) Fibrinogen receptors in platelet adhesion to surfaces of extracorporeal circuit. Am J Physiol 252:H615–H621
25. Edmunds LH (1989) Letters to the editor: Blood platelets and bypass. J Thorac Cardiovasc Surg 97:470–471
26. Kluft C (1991) Pathomechanisms of defective hemostasis during and after extracorporeal circulation: contact phase activation. In: Friedel N (ed) Blood use in cardiac surgery 10–15. Springer, Berlin Heidelberg New York, pp 1:10–15
27. Ishihara H, Matsuda M, Tatsuta T, et al. (1980) The effect of FOY on the levels of plasminogen and high molecular weight kininogen during extracorporeal circulation with use of heart-lung machine. Arch Jpn Chir 49:187–194
28. Miyawaki T, Sameshima T, Miyao J, et al. (1983) Effects of FOY on lysosomes in hemorrhagic hypotension—a histological analysis. Masui 33:263–268