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Prophylactic hemostatic drugs do not reduce hemorrhage: thromboelastographic study during upper abdominal surgery

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Abstract: Although a number of hemostatic drugs are currently used during surgery to reduce hemorrhage, their effects on bleeding are still controversial. Furthermore, few studies have been made on their prophylactic effects. The purpose of this study was to clarify the effects of hemostatic drugs on bleeding. Thirty adult patients undergoing upper abdominal surgery were randomly assigned to receive carbazochrome sodium sulfonate and tranexamic acid immediately after induction of anesthesia (group H, $n = 15$) or no hemostatic drugs (group C, $n = 15$). Common coagulation-tests [prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB)], thromboelastography [reaction time (R), coagulation time (K), maximum amplitude (MA), clot formation rate (α)], and determination of bleeding time were conducted before induction of anesthesia and just before the completion of surgery. PT, R, and K decreased significantly in both groups, while MA and α increased and FIB decreased significantly in group C. No significant difference in blood loss was observed between the groups. Our findings, therefore, suggest that these two hemostatic drugs do not have prophylactic effects on intraoperative bleeding. Further studies are, however, necessary before applying these results to all surgical patients.

Key words: Carbazochrome sodium sulfonate, Tranexamic acid, Thromboelastography

Introduction

Concern over the transmission of infection or other complications arising from blood transfusion has recently led to a reduction in the use of blood products. Autologous blood transfusion has gradually been introduced in various surgical procedures. Thus, donor blood may be avoided to some extent during surgery in order to prevent the complications of blood transfusion, but the need for donor blood is not eliminated.

Reducing the amount of intraoperative blood loss is another means of avoiding transfusion. A number of hemostatic drugs have therefore been used during and after surgery to reduce hemorrhage. Although some of these drugs have been reported to be effective in some clinical situations, their effects on intraoperative bleeding have not been established. Thus, it is necessary to reevaluate their clinical effects on hemorrhage.

In the present study, the prophylactic effects of hemostatic drugs, such as carbazochrome sodium sulfonate (CS) or tranexamic acid (TA), on hemorrhage during surgery were investigated using common coagulation tests, thromboelastography (TEG), and bleeding time among patients receiving hemostatic drugs and those who did not. In this study, CS and TA were used as hemostatic drugs because they have been most frequently and routinely used during the perioperative period in Japan and because they are the drugs that are most likely to be administered during surgery.

Patients and methods

With approval of the Onomichi General Hospital Ethical Committee and informed consent of all the patients, 30 adult patients scheduled for elective major upper abdominal surgery were studied. All were ASA physical status I or II; patients with preoperative coagulopathies receiving anticoagulant or antiplatelet medication were excluded from this study.

Before induction of general anesthesia, an epidural catheter was inserted using the standard hanging drop technique and the radial artery was cannulated for blood sampling and arterial blood pressure monitoring. Blood samples for thromboelastography and common coagulation tests [prothrombin time (PT), activated

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partial thromboplastin time (APTT), and fibrinogen (FIB)] were obtained before induction of anesthesia. TEG was performed using whole uncitrated blood (0.35 ml) with a thromboelastograph (CLOT-TRACER TE-400, ERMA, Tokyo, Japan). The common coagulation tests were conducted using whole citrated blood (1.8 ml) by means of a commercially available automated coagulation analyzer (ACL 100, Instrumentation Laboratory, USA). Bleeding time (BT) was determined by Duke's method using a specially designed blade (Blood Lancets, Feather Industries, Tokyo, Japan). Thereafter, general anesthesia was induced with 3–5 $mg \cdot kg^{-1}$ of thiamylal sodium and vecuronium bromide 0.1 $mg \cdot kg^{-1}$ was administered to facilitate tracheal intubation. Anesthesia was maintained with low concentrations of isoflurane or sevoflurane (≤1.0% inspired) in 67% N_2O/33% O_2, ≤5 $\mu g \cdot kg^{-1}$ of intravenous fentanyl, and intermittent administration of 1.5% mepivacaine through the epidural catheter to achieve regional anesthesia. Lactated Ringer's solution was infused intravenously to all patients at a rate of about 10 $ml \cdot kg^{-1} \cdot h^{-1}$ during surgery. Patients were then randomly assigned to one of the following groups:

Group H (n = 15): Patients received CS 50 mg and TA 1000 mg
intravenously within about 30 min
after induction of general anesthesia.
Group C (n = 15): Patients did not receive any drug having an effect on the hemostatic system during surgery.

Blood samples for TEG and common coagulation tests were again obtained 2 h after the administration of hemostatic drugs in group H and 2 h after the beginning of surgery in group C. BT was also measured simultaneously at the time of blood sampling in both groups.

Age, height, weight, blood loss, and duration of operation were compared between the two groups using the Mann-Whitney U-test. TEG variables [reaction time (R), coagulation time (K), clot formation rate (α), maximum amplitude (MA), and amplitude 60 min after MA/MA (A60/MA)], PT, APTT, FIB and BT were compared between the two groups using the Mann-Whitney U-test. Additionally, the data obtained before induction of anesthesia and 2 h after the administration of hemostatic drugs in group H and 2 h after the beginning of the operation in group C were compared using Wilcoxon's signed rank test. Data were expressed as mean ± SD. P values < 0.05 were considered to be statistically significant.

Table 1. Patient characteristics

	Group H	Group C	P value
Age (years)	62.0 ± 11.3	54.8 ± 11.7	0.136
Height (cm)	153.9 ± 10.9	157.9 ± 28.9	0.268
Weight (kg)	50.9 ± 12.1	57.1 ± 23.8	0.123
Duration of operation (min)	112.2 ± 49.1	128.4 ± 18.3	0.285
Blood loss (g)	108.9 ± 62.0	83.8 ± 101.4	0.161

Values are mean ± SD.

Results

There were no statistically significant differences in age, height, weight, blood loss, and duration of operation between the two groups (Table 1). The data in Table 2 show that PT in group H decreased significantly 2 h after administration of hemostatic drugs compared to the preanesthetic value, but the results of other common coagulation tests remained unchanged. On the other hand, as shown in Table 2, PT and FIB decreased significantly two hours after the beginning of surgery in group C. There were no statistically significant differences in the corresponding data between the two groups.

The TEG variables presented in Table 3 demonstrate that the patients in group H became hypercoagulable 2 h after administration of hemostatic drugs; R and K decreased significantly from 13.1 ± 0.6 min to 9.5 ± 0.5 min (P = 0.012) and from 7.0 ± 0.7 min to 5.1 ± 0.4 min (P = 0.038), respectively. Moreover, patients in group C also became hypercoagulable 2 h after the beginning of surgery compared to the preanesthetic values; MA and α increased significantly from 49.3 ± 2.8 mm to 55.3 ± 3.1 mm (P = 0.036) and from 36.1 ± 2.8 degrees to 44.5 ± 3.5 degrees (P = 0.036), respectively. Nevertheless, no statistically significant differ-

Table 2. Coagulation tests

	Pre	Post	P value
Group H			
PT (%)	80.4 ± 20.3	73.8 ± 17.6	0.024*
APTT (s)	33.3 ± 17.2	28.9 ± 6.6	0.161
FIB (mg/dl)	349.7 ± 242.2	308.3 ± 192.3	0.075
BT (min)	1.75 ± 1.05	1.81 ± 0.74	0.666
Group C			
PT (%)	79.8 ± 20.7	71.3 ± 11.7	0.028*
APTT (sec)	34.0 ± 11.3	31.1 ± 10.1	0.107
FIB (mg/dl)	318.0 ± 179.8	247.1 ± 108.0	0.012*
BT (min)	1.71 ± 0.70	2.14 ± 0.94	0.276

* $P < 0.05$ versus pre-value. Values are mean ± SD.
Pre, before induction of anesthesia; Post, 2 h after administration of hemostatic drugs (group H) or after beginning of surgery (group C); PT, prothrombin time (70%–120%); APTT, activated partial thromboplastin time (25–35 s); FIB, fibrinogen (200–400 mg/dl); BT, bleeding time (1–5 min).

Table 3. TEG variables

	Pre	Post	*P* value
Group H			
R (min)	13.1 ± 2.3	9.5 ± 2.0	0.012*
K (min)	7.0 ± 2.7	5.1 ± 1.6	0.038*
MA (mm)	52.0 ± 11.7	57.7 ± 6.6	0.051
A60/MA	0.837 ± 0.098	0.832 ± 0.055	0.138
α (degrees)	41.0 ± 10.9	43.6 ± 12.9	0.553
Group C			
R (min)	14.6 ± 3.1	12.5 ± 2.0	0.012*
K (min)	7.3 ± 3.1	5.5 ± 2.3	0.024*
MA (mm)	49.3 ± 10.9	55.3 ± 12.1	0.036*
A60/MA	0.863 ± 0.055	0.867 ± 0.078	0.674
α (degrees)	36.1 ± 10.9	44.5 ± 13.7	0.036*

* $P < 0.05$ versus pre-value. Values are mean ± SD.
Pre, before induction of anesthesia; Post, 2 h after administration of hemostatic drugs (group H) or after beginning of surgery (group C); R, reaction time (7–12 min); K, coagulation time (4–8 min); MA, maximum amplitude (50–58 mm); A60, amplitude 60 min after MA (A60/MA > 0.85), α = clot formation rate (40–60°).

ences were observed in the corresponding data between the groups.

Discussion

Hemostatic drugs are often indicated during surgery when the direct approach fails to stop bleeding or when no other causes for abnormal bleeding can be found. Many of the currently available hemostatic drugs have been reported to reduce blood loss during and after surgery [1]. Indeed, we have often employed these drugs, especially CS and TA, before any bleeding starts during surgery. However, few studies have been done to examine the prophylactic effects on intraoperative bleeding. It was, therefore, necessary to investigate whether these drugs actually have preventive effects on bleeding.

The common coagulation tests conducted in the present study showed decreased prothrombin activity in both groups. This result differs from that of Collins et al. [2] who observed no significant changes in PT in response to operative stress. In the present study, decreased prothrombin activity means either the existence of intravascular coagulation or the activation of the fibrinolytic system. Engqust and Winter [3] and O'Brien et al. [4] demonstrated the enhancement of fibrinolysis due to surgical stress. Thus the present results might reflect the increased fibrinolytic activity. Although the mechanism of the current PT change is not known, it is unlikely that it is due to hemostatic drugs because similar changes were observed in both groups. Common coagulation tests also showed a significant decrease in FIB level in only group C; the reason for this is unclear, but the possibility that more than one mechanism is involved should be considered. One such mechanism is that FIB was consumed significantly in group C, and the other is that hemodilution caused a significant decrease in the FIB level in group C. If significant consumption of FIB occurred, the level of fibrinogen degradation products (FDP) should increase and some signs of abnormal coagulation should be observed clinically. Therefore, although we did not measure FDP, it is unlikely that FIB was consumed significantly in only group C. While it is more likely that hemodilution occurred in group C to a greater extent than in group H, there is no evidence of hemodilution such as reduced plasma protein levels.

TEG provides information on hypercoagulability, platelet function, and fibrinolysis which other tests are unable to provide. TEG is thus a reliable guide for intraoperative therapy for bleeding [5]. TEG has also been reported to be useful for the in vitro assessment of platelet function in whole blood because significant correlations have been demonstrated between TEG variables and platelet aggregometry responses to ADP and collagen [6]. We therefore used TEG with the expectation of gaining additional information on coagulation and fibrinolysis. In the thromboelastographic data, significant decreases in the R and K values in group H and significant increases in the MA and α values in group C were observed. This suggests that patients in both groups became hypercoagulable after surgery. These variables were, however, all within the normal range and no statistical significance was observed between the groups. Thus, it seems that CS and TA do not have any effect on coagulability. It is thus suggested that our findings are caused by hypercoagulability due to surgical stress, consistent with the results of previous studies [2,7].

CS is a drug that inhibits the increase in vascular permeability [8], strengthens vascular fragility [8], and reduces BT without affecting the coagulation-fibrinolysis system. The effect of CS should have, therefore, appeared in BT, but our data did not show a significant change in BT. We measured BT using Duke's method, which is convenient and is very commonly used in Japan. There are, however, substantial problems concerning sensitivity, specificity, and reproducibility of Duke's method [9]. If we had used a more sensitive method to measure BT, the effect of CS might have been detected.

TA has been reported to be effective in cardiac surgery [10,11], and is not likely to affect platelet function or other hemostatic parameters in patients with subarachnoid hemorrhage [12]. The former cases seem to involve a high fibrinolytic state. In our study, TA might play an important role in maintaining the FIB level after surgery. Thus, TA is considered to exert a beneficial effect in cases where fibrinolytic activity is increased.

Haynes et al. [13] have recently demonstrated that when coagulation studies are performed using blood samples from an arterial cannula, they may provide clinically misleading information because of the contamination of small amounts of heparin. In this case, a separate venipuncture is recommended. Although we used blood samples from an arterial cannula after 5 ml of blood was withdrawn to avoid contamination with heparin, it might be better to employ venipuncture in future studies.

In conclusion, prophylactic administration of CS and TA does not reduce the intraoperative blood loss during upper abdominal surgery. However, the number of patients in each group is small, and the dosage of hemostatic drugs and the degree of surgical stress should be taken into account when evaluating the effect of hemostatic drugs. Further studies are, therefore, necessary before applying our results to all patients scheduled for surgical operation.

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