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Celite-activated viscometer Sonoclot can measure the suppressive effect of tranexamic acid on hyperfibrinolysis in cardiac surgery

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Abstract

Purpose. To investigate the usefulness of the celite-activated viscometer Sonoclot for monitoring fibrinolytic status in cardiac surgery, we demonstrated the effectiveness of high doses of tranexamic acid, an antifibrinolytic agent, in reducing postoperative bleeding.

Methods. Thirty-two American Society of Anesthesiologists (ASA) physical status III patients who required cardiac surgery with cardiopulmonary bypass (CPB) were studied. Anesthesia was induced by a high dose of fentanyl and midazolam with oxygen and was maintained by the intermittent administration of these agents. Patients were divided into two groups: the control group ($n = 15$) and patients receiving tranexamic acid (TA; $n = 17$). The TA group received a high dose (50 mg/kg) of TA twice, once before and once after CPB. The percentage diminishing rate of the Sonoclot tracing 15 min after maximum clot signal (DR_{15}) and the amount of postoperative bleeding were measured.

Results. After CPB, DR_{15} in the control group (mean 28.3%) increased significantly by 45%, and the DR_{15} in the TA group (16.1%) was significantly lower than that in the control group. The amount of postoperative bleeding in the TA group (546 ml) was significantly less, by 34%, than that in the control group (829 ml).

Conclusion. Prophylactic administration of high-dose TA in cardiac surgery reduces postoperative bleeding, and this effect is consistent with changes in the diminishing rate using Sonoclot. The celite-activated viscometer Sonoclot is recommended for use in cardiac surgery for rapid assessment of fibrinolytic status.

Key words Fibrinolysis · Tranexamic acid · Viscometer · Celite · Cardiac surgery

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Introduction

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) develop some degree of acquired platelet dysfunction as a result of dilutional, activating, consumptive, and destructive actions [1,2]. Severe platelet dysfunction and/or hypocoagulability may impair hemostasis and result in the need for a transfusion of blood products [3]. Traditionally, the activated clotting time (ACT) has been used to monitor heparinization during CPB. Recently, it has been found that not only hypocoagulability but also hyperfibrinolysis is an important factor in bleeding after taking off the CPB or after cardiac surgery [4,5]. However, fibrinolytic status cannot be evaluated by ACT. Thromboelastography (TEG) is a well-known, reliable method for assessing fibrinolysis as well as coagulability [4–7]. However, it takes at least 2 h to assess fibrinolysis by means of conventional TEG techniques. Recently, we have shown that the celite-activated viscometer Sonoclot (Sienco, Morrison, CO, USA) is a useful technique for the rapid assessment of fibrinolytic status as well as coagulation [8]. Therefore, the aim of present study was to investigate the usefulness of the celite-activated viscometer for monitoring fibrinolytic status in cardiac surgery by demonstrating the effectiveness of high doses of tranexamic acid (TA), an antifibrinolytic agent, in reducing postoperative bleeding. TA is a lysine analog that aggressively binds to the lysine-binding sites of plasmin and plasminogen, leading to the inhibition of fibrinolysis.

Materials and methods

This study was approved by the Sapporo Medical University Ethics Committee on Human Research. After informed consent was obtained, 32 adult patients who had each been scheduled for cardiac surgery (coronary artery bypass grafting ($n = 13$) or valve replacement

(n = 19)) with CPB were enrolled in the study. No patient had preoperative hepatic dysfunction, platelet abnormality, or pulmonary hypertension. Patients who had been treated with antiplatelet or anticoagulant agents within 14 days prior to the operation were excluded from the study. Morphine (0.1 mg/kg) and atropine (0.01 mg/kg) or scopolamine (0.008 mg/kg) were given 1 h before anesthesia.

Anesthesia was induced by a high dose of fentanyl (20–30 μg/kg) and midazolam (3.0–6.0 mg) with oxygen, and was maintained by intermittent administration of fentanyl and midazolam. Nonpulsatile CPB with a membrane-type oxygenator and moderate hypothermia (28–32°C) was used in all cases. In each case, heparin (300 U/kg) was administered before CPB, and additional heparin (100 U/kg) was administered every hour during CPB. Patients were randomly divided into two groups by the coin technique: control patients (n = 15) and patients administered TA (n = 17). As has been reported previously [9,10], the TA group received a high dose (50 mg/kg over 10 min) of TA twice, once before and once after CPB.

Blood samples for ACT and Sonoclot measurements were taken twice during the procedures: before the first administration of TA and systemic heparinization, and 20–30 min after heparin neutralization by protamine [11] and the second TA administration. Samples were drawn from an arterial catheter after approximately 15 ml was aspirated and discarded to avoid heparin contamination [7]. For Sonoclot measurements, blood samples (0.4 ml) were placed in the cuvette of the Sonoclot within 1 min of sampling, and a few drops of mineral oil (Sonoil, Scienco) were spread over the blood surface to prevent the evaporation of blood. The viscometer analysis uses a Sonoclot Coagulation & Platelet Function Analyzer (Scienco), a thermal graphic printer, and a disposable test cuvette (800-0432 SonACT test; consisting of a celite activator, stir bar, and probe) [12,13]. The Sonoclot Analyzer consists of a heating block maintained at 37°C, a head assembly that holds the viscosity transducer, and a cuvette holder. A disposable probe is placed on the transducer so that when the head assembly is closed, the probe is immersed into the blood sample in the cuvette. After filling the test cuvette with whole blood and pressing the start switch, the analyzer provides a timed 10-s mixing cycle to distribute the activator throughout the blood sample. After mixing, the head assembly is manually closed to begin analysis. The analyzer automatically calculates the onset time (which is an ACT for this test) and clot rate results. A typical recording is shown in Fig. 1. As has been reported previously [8], we have defined the diminishing rate of the clot signal over a period of 15 min (DR_{15}) as (ms-S_{15})/ms × 100 (%). The ACT was simultaneously measured at the same points

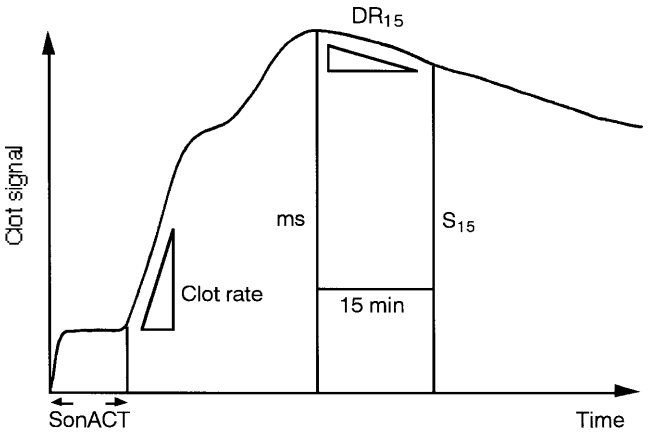

Fig. 1. Typical recording of the celite-activated viscometer (Sonoclot). ms, maximum clot signal; S_{15}, clot signal 15 min after ms; SonACT (s) [8], the time, in seconds, until the beginning of fibrin formation; clot rate (%), the rate of fibrin formation from fibrinogen; DR_{15} (%), diminishing rate defined as (ms − S_{15})/ms × 100, which reflects clot retraction and lysis [12]

by the use of a blood coagulation timer (Hemochron-800; International Technidyne, Edison, NJ, USA). The amount of postoperative bleeding from mediastinal drainage was measured over a period of 24 h following operation.

All data are expressed as the mean ± SD. Comparisons for all data were made using the paired or unpaired two-tailed t-test. For all comparisons, $P < 0.05$ was considered statistically significant.

Results

Thirty-four patients participated in this study and 32 completed the protocol. Two of the 34 patients studied needed intraaortic balloon pumping due to low output syndrome (cardiac index <2.0 l/min per m^2), and they were excluded from the study. The patient characteristics and the operation data are shown in Table 1. The control and TA groups were comparable for gender, age, weight, height, and duration of anesthesia and surgery. Intraoperative variables, such as the duration of CPB and aortic cross-clamping, were also similar.

Table 2 shows the coagulation parameters in both groups before and after CPB, obtained by the use of Sonoclot and ACT monitors. There was no significant differences in each parameter, SonACT, clotting rate or ACT between the groups or between before and after CPB. The DR_{15} before and after CPB and the amount of postoperative bleeding within 24 h are shown in Fig. 2. Before CPB, there was no significant difference in DR_{15} between the two groups. After CPB, DR_{15} in the control

group (28.3 ± 7.3%) increased significantly (by approximately 45%), and DR_{15} in the TA group (16.1 ± 3.7%) was significantly ($P < 0.05$) lower than that in the control group. The amount of postoperative bleeding in the TA group (546 ± 242 ml) was significantly less (by approximately 34%) than that in the control group (829 ± 346 ml; $P < 0.05$). All Sonoclot measurements for both control and TA groups were completed within 30 min (24.5 ± 3.4 and 26.2 ± 2.3 min, respectively).

Table 1. Patient characteristics and operation data

	Control group (n = 15)	TA group (n = 17)
Sex (F/M)	5/10	5/12
Age (years)	62 ± 8	65 ± 7
Weight (kg)	64 ± 9	67 ± 7
Height (cm)	160 ± 12	161 ± 11
CABG/valve replacement (n)	6/9	7/10
Duration of anesthesia (min)	371 ± 82	346 ± 71
Duration of surgery (min)	296 ± 68	288 ± 54
Duration of CPB (min)	188 ± 41	171 ± 35
Duration of cross-clamping (min)	131 ± 34	123 ± 29
Amount of intraoperative bleeding (ml)	874 ± 452	748 ± 365

Data are the mean ± SD or numbers. There were no significant differences between the two groups for any particular variable. TA, tranexamic acid; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass

Discussion

Celite consists of chemically inert particles (silica) that provide a contact surface to activate coagulation factor XII and platelets and, hence, accelerate coagulation in a blood samples. Celite is also known to activate plasmin and plasminogen, leading to hyperfibrinolysis [14]. Therefore, the whole process of coagulation and fibrinolysis can be measured within a short time (<30 min) by the celite-activated viscometer Sonoclot [8].

In the present study, we found that the DR_{15}, measured by the Sonoclot technique, significantly increased (by approximately 45%) after cardiac surgery in the control group, whereas this increase was prevented by the prophylactic administration of a high dose of TA (Fig. 2A). It has been reported that hemostatic abnormalities after cardiac surgery with CPB may be caused

Table 2. Coagulation parameters in control and TA groups before and after CPB obtained from the celite-activated viscometer (Sonoclot) and ACT monitor

Group	SonACT (s)	Clot rate (%)	ACT (sec)
Control (n = 15)			
Before CPB	114.7 ± 11.8	24.3 ± 6.5	127.6 ± 12.8
After CPB	118.6 ± 13.4	21.8 ± 8.2	133.2 ± 14.2
TA (n = 17)			
Before CPB	121.4 ± 10.8	25.4 ± 5.6	125.8 ± 11.9
After CPB	124.2 ± 12.8	22.3 ± 7.3	128.7 ± 14.8

Data are the mean ± SD. SonACT, activated clotting time by Sonoclot; clot rate, linear slope by fibrin formation; ACT, activated clotting time by a blood coagulation timer

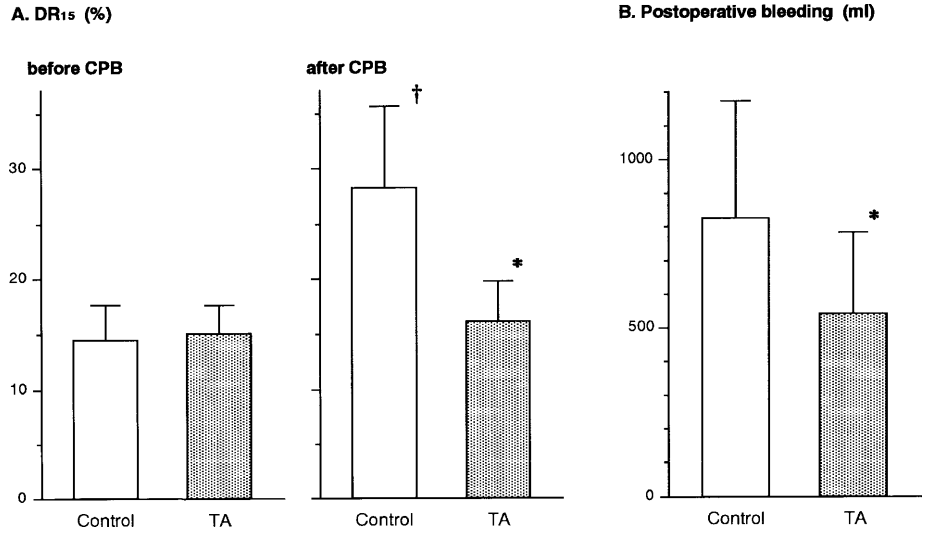

Fig. 2. DR_{15} before and after cardiopulmonary bypass (CPB; **A**) and the amount of postoperative bleeding within 24 h (**B**). *$P < 0.05$ compared with the control group (paired t-test); † $P < 0.05$ compared with the control group before CPB (n = 15 in the control group; n = 17 in the TA groups)

by increased fibrinolytic activity [4,5], as reflected in increased plasmin concentrations and fibrin degeneration products, both of which have detrimental effects on platelet function [15]. Therefore, the prophylactic administration of antifibrinolytic agents, such as TA or ε-aminocaproic acid, would be useful for suppressing the hyperfibrinolysis induced by cardiac surgery with CPB, leading to the reduction of postoperative bleeding, as shown in Fig. 2B. Many investigators have studied the effects of antifibrinolytic agents on postoperative bleeding and transfusion requirements [16–19]. There is controversy over the effects of antifibrinolytic agents on transfusion requirements [20,21], although most researchers, including us, agree on the effectiveness of these agents in reducing postoperative bleeding. The difference in transfusion requirements could be due to differences in the subjects themselves (age, type and time of operation etc.), differences in their protocols (dose and time of administration etc.) and/or differences in the trigger for transfusions among the institutions. We did not investigate the transfusion requirements because it also depends on individual surgeons.

Fibrin degradation products (FDP) and D-dimer are also markers of fibrinolysis. Shore-Lesserson et al. [18] have shown that no patient after cardiac surgery had detectable FDP, despite positive D-dimer levels, and concluded that FDP is an insensitive marker of fibrinolysis. Whitten et al. [22] found that TEG was more sensitive than D-dimer in detecting fibrinolysis after CPB. Moreover, it takes several hours to measure the D-dimer. The diminishing rate of celite-activated TEG is, therefore, the best monitor for a rapid and accurate assessment of fibrinolytic status after cardiac surgery with CPB.

Potential complications of antifibrinolytic therapy include the risk of thromboembolic events. Although several studies have associated the use of antifibrinolytic agents with graft occlusion [20,21], this has not been proven to be statistically significant in any large prospective randomized study, nor were the coagulation parameters of Sonoclot or the ACT value in the present study changed by TA administration (Table 2). Because the current study has a relatively small sample size for the evaluation of side effects, further comparative studies are needed.

In conclusion, the celite-activated viscometer Sonoclot is a useful monitoring derive for rapid assessment of hemostasis, including fibrinolytic status. Prophylactic administration of high doses of TA, an antifibrinolytic agent, in cardiac surgery with CPB reduced postoperative bleeding, and this effect is consistent with changes in the diminishing rate using Sonoclot. Sonoclot is recommended for use in cardiac surgery with CPB for the rapid assessment of fibrinolytic status.

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