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Original Article

A Comparative Study of Point-of-Care Prothrombin Time in Cardiopulmonary Bypass Surgery

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Objective: Point-of-care (POC) devices allow for prothrombin time/international normalized ratio (PT/INR) testing in whole blood (WB) and timely administration of plasma or prothrombin complex concentrate during cardiopulmonary bypass surgery. This study evaluated the sensitivities of a new POC PT test, a dry-hematology method with heparin neutralization technology (DRIHEMATO PT-S [DRI PT-S]; A&T Corporation, Kanagawa, Japan), and compared it with other POC tests currently available.

Design: Prospective, observational study.

Setting: University hospital, single center.

Participants: Healthy volunteers and warfarin-treated and cardiac surgical patients.

Measurement and Main Results: In WB samples obtained from 6 healthy volunteers, PT-INR results of DRI PT-S were not affected by an in vitro addition of heparin < 6.0 U/mL. In warfarin-treated samples (n $=$ 88, PT/INR 0.98-3.87), PT-INR with DRI PT-S showed acceptable correlation with the laboratory method ($r^2 = 0.85$, p $<$ 0.001). In blood samples obtained from cardiac surgical patients (n $=$ 72), heparin prolonged the PT/INR with the laboratory assay, dry-hematology method with non heparin neutralization technology (DRI PT), Coaguchek XS (Roche Diagnostics, Basel, Switzerland), and Hemochron Jr. (Accriva Diagnostics, Edison, NJ), but DRI PT-S was not affected by heparin anticoagulation. In nonheparinized samples, different methods between DRI PT-S and the laboratory method yielded acceptable correlations ($r^2 = 0.76$, p $<$ 0.0001). There was a moderate correlation between factor levels and the PT-INR with DRI PT-S (factor [F]II: $r^2 = 0.63$, FVII: $r^2 = 0.47$, FX: $r^2 = 0.67$; p $<$ 0.0001).

Conclusions: This study demonstrated that PT/INR can be accurately assessed using the dry-hematology method in WB under therapeutic heparin levels. Currently available other POC PT/INR tests are affected by heparin, and thus they are not recommended for coagulation monitoring during cardiopulmonary bypass.

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Key Words: prothrombin time; prothrombin time/international normalized ratio; whole blood; point-of-care testing; cardiopulmonary bypass; coagulopathy

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DECREASED THROMBIN generation can be a major cause of coagulopathy in the perioperative setting.[1] Use of cardiopulmonary bypass (CPB) in cardiovascular surgery is particularly an important cause of coagulation disturbance, and prolonged CPB can increase postoperative bleeding due to hemodilution.[2] Prothrombin time (PT) and PT/international normalized ratio (PT/INR) are used for the titration of warfarin anticoagulation and to guide plasma transfusion or dosing of prothrombin complex concentrate (PCC).[3–6] A typical turnaround time of PT/INR in the centralized laboratory is 20 to 60 minutes because it is performed in plasma separated from the whole blood (WB). During CPB, the use of PT/INR is hindered by heparin anticoagulation.[7,8] Empirical hemostatic intervention often is started in the case of microvascular bleeding without waiting for results of PT/INR obtained after heparin neutralization.

Point-of-care (POC) devices, including the Coaguchek XS (Roche Diagnostics, Basel, Switzerland) and the Hemochron Jr. (Accriva Diagnostics, Edison, NJ), allow for PT/INR testing in WB samples and provide faster turnaround time,[9–12] but their sensitivity to heparin is not well known. The CG02N (A&T Corporation, Kanagawa, Japan) is a portable coagulation analyzer based on the dry-reagent technique.[13,14] A new test cartridge (DRIHEMATO PT-S [DRI PT-S]; A&T Corporation) was developed recently to test PT/INR under systemic heparinization. The authors hypothesized that this new test allows for more accurate PT/INR measurements than do conventional POC PT/INR tests in cardiac surgery. The authors therefore compared different POC PT/INR systems under heparinization in parallel with plasma-based PT/INR in the centralized laboratory.

Methods

Ethics approval (#C-14-1) for the study was provided by the Ethics Committee of Kyoto Prefectural University of Medicine, Kyoto, Japan. To evaluate the effect of heparin on dry-hematology methods for the PT/INR—non heparin-neutralized DRIHEMATO PT (DRI PT), and heparin-neutralized DRI PT-S—a preliminary in vitro study was conducted using WB samples collected from 6 healthy volunteers after informed, written consent. The volunteers had not taken medication(s) that affect coagulation in the preceding 2 weeks. Blood samples were collected into vacutainer tubes including 3.2% sodium citrate (Insepack II-W; Sekisui Medical Co. Ltd., Tokyo, Japan). Unfractionated heparin (Mochida Pharmaceutical, Tokyo, Japan) was added to aliquots of WB samples to 0, 1.0, 2.0, 4.0, and 6.0 U/mL (final concentration). To evaluate the relationship of PT/INR between DRI PT-S and laboratory assay under warfarin anticoagulation therapy, 3.2% citrated plasma samples also were obtained from warfarin-treated patients (n = 88). The laboratory PT/INR was determined with Coagpia PT-N (Sekisui Medical) (international sensitivity index [ISI] = 1.0) on Coapresta 2000 (Sekisui Medical) in the centralized laboratory.

PT/INR is measured in DRI PT and DRI PT-S using WB added to a disposable cartridge containing rabbit brain tissue factor (ISI = 1.73 and 1.02, respectively) and paramagnetic iron oxide particles. The principle of this dry reagent method is based on the technology formerly used in the Thrombolytic Assessment System (Helena Laboratories, Beaumont, TX).[15] Twenty-five microliters of loaded WB sample are moved via capillary action on CG02N and mixed with the paramagnetic iron oxide particles and reagents within the testing chamber.[13] As sample blood is clotted, particle movement is decreased, which is detected optically. The clotting time was measured in seconds (PT) and correlated to the PT/INR determined by the reference laboratory method. A test cartridge of DRI PT-S was developed by the addition of a protamine-like compound to the dry reagent of DRI PT for a PT measurement under systemic heparinization.

The second part of the study was conducted to evaluate the performance of the dry-hematology method in the clinical setting. The authors prospectively collected PT/INR and hematologic data from 18 consenting patients undergoing cardiac surgery with CPB. Inclusion criteria were age >20 years and normal preoperative PT, activated partial thromboplastin time, and platelet count. In this part of the study, patients on warfarin anticoagulation or thrombolytic therapies before surgery and those with preexisting hepatic dysfunction were excluded. Before CPB, patients were given 300 U/kg of intravenous heparin and an additional dose to maintain an activated coagulation time (ACT) >400 s (Hemochron Signature Elite; Accriva Diagnostics). Heparin anticoagulation was reversed after CPB with 150 to 250 mg of protamine sulfate. Blood samples were obtained at the following 4 time points: (1) baseline (before heparin administration), (2) start of CPB (after heparin administration), (3) end of CPB (before protamine administration), and (4) end of surgery. PT/INR data were blinded to the care team, and hemostatic interventions were administered at the discretion of the attending anesthesiologist. The blood samples were processed immediately for WB testing using manufacturer instructions. The POC PT/INR using WB with the DRI PT-S test on CG02N was performed in parallel with the DRI PT test on CG02N, Hemochron Jr. PT test on the Hemochron Jr. Signature Elite, and the Coaguchek XS PT test on Coaguchek XS. To verify the relationship between WB POC PT/INR and laboratory PT/INR, plasma PT/INR also was examined with Coagpia PT-N on Coapresta 2000 in the centralized laboratory.

The remainder of citrated samples were centrifuged at $2{,}000\times$ g for 20 minutes to obtain the platelet-poor plasma for the fibrinogen level (Thrombocheck Fib; Sysmex Co., Kobe, Japan) and batched analyses of prothrombin factor (F)II, FVII, and FX levels using coagulation factor deficiency plasma (Sysmex Co.) with Coapresta 2000. The antifactor activated X activity for unfractionated heparin was determined using Test Team AT (Sekisui Medical) with Coapresta 2000.

Statistical Analysis

Seventy-two measurements were obtained from 18 patients to achieve a $\beta \geq 0.9$ and an $\alpha \leq 0.05$ based on previous study to compare PT/INR derived from laboratory and POC tests.[10,11] Data are expressed as mean (standard deviation). Correlations between different methods were described using

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