Applicability of a Compact PT-INR Measuring Device CoaguChek XS to Perioperative Management

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Objective: In perioperative management, prothrombin time (PT) expressed as the international normalized ratio (INR) is an important preoperative test to assess bleeding risk. It is also used to assess the effect of discontinuing anticoagulant therapy, to determine whether to treat patients with vitamin K or fresh frozen plasma, and to decide whether a deep nerve block (e.g., epidural anesthesia) is needed. Compared with other devices used to measure prothrombin time, the CoaguChek XS is a smaller, lighter and more convenient-to-use PT-INR monitoring system that requires a smaller venous, skin puncture or arterial blood sample than other systems. In a surgical setting, it is often more convenient to collect arterial blood. However, the applicability of arterial blood PT-INR values has not been verified.
Methods: We evaluated the usefulness of the CoaguChek XS in anesthetic management by comparing PT-INR values for arterial blood with those of venous blood in 50 patients who were scheduled for elective surgery under general anesthesia.
Results: Arterial PT-INR values were well correlated with venous PT-INR values ($r^2 = 0.9239$; regression line $y = 0.9537x + 0.0505$).
Conclusion: These results indicate that the CoaguChek XS system can provide arterial PT-INR values and should be available in operating and emergency rooms.

Key words: PT-INR, CoaguChek XS, preoperative assessment, anticoagulant therapy, perioperative management

INTRODUCTION

Prothrombin time (PT) is a coagulation parameter that reflects the activity of the extrinsic coagulation pathway (factors VII, X, V and II, and fibrinogen), starting from tissue factor-induced activation of factor VII and ending in fibrin formation. It is now widely used to screen for abnormal coagulation and monitor oral anticoagulant therapy with warfarin potassium. However, test results can be inconsistent between laboratories because the reactivity of thromboplastin, a reagent used in PT measurement, is very variable and is influenced by the species / tissue used to manufacture it as well as the method of preparation. To address this problem and to standardize results, the World Health Organization proposed that the PT ratio measured using local thromboplastin should be converted into the international normalized ratio (INR) scale using human brain thromboplastin as the international normalized sample. The PT-INR* is now determined by laboratories at many medical institutions [1].

In terms of anesthetic management, PT is commonly used for preoperative assessment of the patient's blood clotting ability, the effect of withdrawal from anticoagulant therapy on the risk of intraoperative / postoperative bleeding, and the need for intraoperative administration of vitamin K preparations / fresh frozen plasma (FFP) and epidural block during anesthetic planning. Therefore, the PT-INR is regarded as an essential preoperative test parameter.

CoaguChek XS (Fig. 1; Roche Diagnostics / F. Hoffmann-La Roche Ltd.) is a hand-sized compact PT-INR device that is able to rapidly measure the PT-INR from a drop of blood. It can be readily used in an operating room and is suitable for perioperative management. The manufacturer limits the use of the CoaguChek XS to samples of fresh whole blood obtained by skin puncture or venous blood sampling. However, in anesthetic management or intensive care settings, blood is often collected through an arterial pressure monitoring line. Thus, it is possible that measurement using arterial blood may reduce data precision and reliability. To investigate the applicability of arterial PT-INR values measured using the CoaguChek XS to anesthetic management, we compared PT-INR values determined from arterial blood samples using the CoaguChek XS with the corresponding measurements determined using a conventional blood coagulation analyzer in our hospital laboratory.

METHODS

A total of 51 patients (31 males and 20 females, mean age: 60.9 ± 10.7 years) with ASA-PS† 1 or 2 who underwent elective surgery in our hospital during a 3-month period between April and July 2009 were included in this study. The study was conducted in

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Fig. 1 The CoaguChek XS (manufactured by Roche Diagnostics / F. Hoffmann-La Roche Ltd.; main unit length 38 mm x width 78 mm x height 28 mm, weight 127 g), the chip for correction and the test strips are shown from left to right.

accordance with the Declaration of Helsinki ethical principles and the "Ethics Guidelines for Clinical Research" (Ministry of Health, Labour, and Welfare Announcement no. 415, revised on July 31, 2008). The protocol was ethically reviewed and approved before commencing the study by the Institutional Review Board for Clinical Research at Tokai University Hospital (No. 08R-144 issued by the Tokai University Institutional Review Board for Clinical Research). The purpose of the study was explained to each subject in writing and orally before obtaining their consent to blood sampling.

After induction of general anesthesia, arterial and venous blood samples were simultaneously collected from each subject and the PT-INR of both samples was measured immediately in the operating room using the CoaguChek XS and later in the laboratory. Arterial blood was collected through the arterial line, i.e., through a three-way stopcock placed 200 mm from the connection point of the catheter to Edwards TruWave® Disposable Pressure Transducers (Edwards Lifesiences Limited). The volume of saline containing heparin (4 U/mL) that filled the circuit and three-way stopcock was 0.56 mL. Blood was collected after discarding more than 4 times the blood volume necessary for elimination of heparin (≥ 2.5 mL for all patients), by which heparin might have been reduced to undetectable levels in arterial blood samples [2, 3]. The sample (required blood volume: 10 μL) was placed onto a test strip containing tissue thromboplastin (Roche PT test strip [ISI = 1.0, Roche Diagnostics / F. Hoffmann-La Roche Ltd.]). After being drawn into the CoaguCheck XS device by capillary flow, the sample reacts with the substrate to initiate conversion of prothrombin to thrombin and thereby degrade the substrate. The PT-INR was calculated from the number of electrons released by oxidation, which was measured for approximately 1 minute using an electrode method. In the laboratory, tissue thromboplastin (HemosIL RecombiPlastTin; ISI = 0.86, Mitsubishi Chemical Medience Corporation) was added to plasma obtained from 0.8 mL of blood, mixed with 0.2 mL of 3.2% sodium citrate to activate the extrinsic coagulation pathway, and the PT-INR (duration of measurement: approximately 7 minutes) was determined using an automated blood coagulation analyzer (ACL-TOP, Mitsubishi Chemical Medience Corporation). The PT-INR levels of arterial and venous blood samples measured in the operating room and in the laboratory were plotted against each other to evaluate the reliability of the CoaguCheck XS data. Pearson's product-moment correlation coefficients were determined to examine the relationship between the operating room and laboratory data. The PT-INR levels measured in arterial and venous blood samples using both methods were normally distributed.

RESULTS

Fig. 2 compares the arterial and venous PT-INRs calculated using CoaguChek XS data, and Fig. 3 compares the arterial and venous PT-INRs calculated using the automated analyzer data. The arterial and venous PT-INRs calculated from the CoaguChek XS data show good correlation (r^2 = 0.9239; regression line: y 0.9537x + 0.0505) and are comparable with those calculated from the automated analyzer data (r^2 = 0.9286; regression line: y = 0.9693x + 0.0244). The correlations between CoaguChek XS data and automated analyzer data were good for both arterial PT-INRs (r^2 = 0.8546; regression line: y = 1.0347x + 0.0248; Fig. 4) and venous PT-INRs (r^2 = 0.8037; regression line: y = 1.0172x + 0.0352; Fig. 5).

DISCUSSION

PT is a coagulation parameter frequently used for the assessment of the extrinsic (tissue factor) and final common pathways. In principle, it measures coagulation time, which represents the time from the addition of tissue thromboplastin and calcium chloride to plasma to the onset of fibrin formation. For many years, PT has played an important role in screening for abnormal coagulation and diagnosis of bleeding

*Abbreviations: PT-INR: prothrombin time–international normalized ratio (PT of patient plasma/PT of reference plasma); FFP: fresh frozen plasma; ISI: international sensitivity index (sensitivity of the sample relative to that of the international normalized sample [1]; NVAF: nonvalvular atrial fibrillation

†ASA-PS: American Society of Anesthesiologists Physical Status Classification System (1. A normal healthy patient: No organic, physiologic, or psychiatric disturbance; excludes the very young and very old; healthy with good exercise tolerance. 2. A patient with mild systemic disease: No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy)

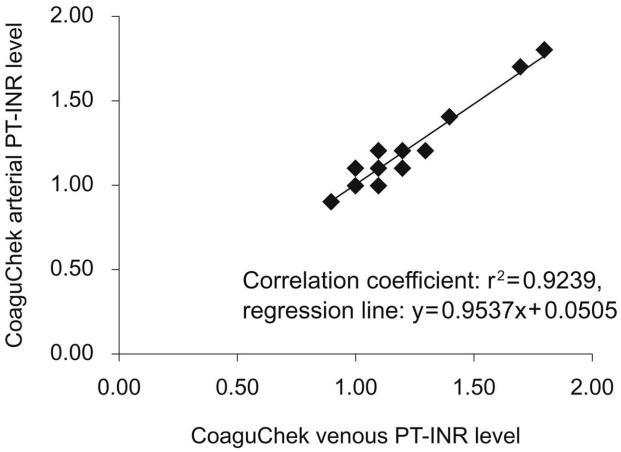

Fig. 2 Correlation between venous and arterial PT-INRs measured using a CoaguChek XS.

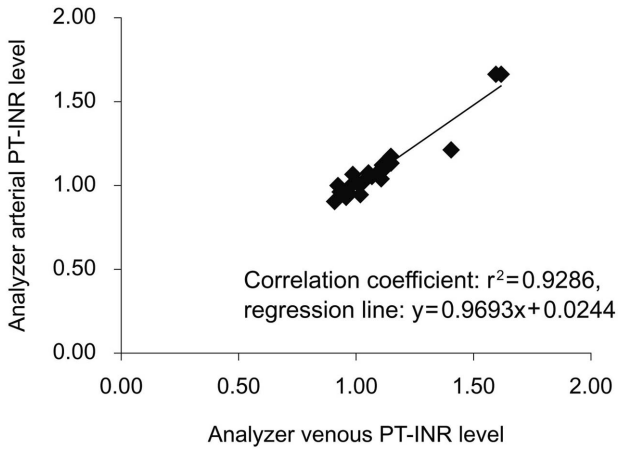

Fig. 3 Correlation between venous and arterial PT-INRs measured using an automated analyzer.

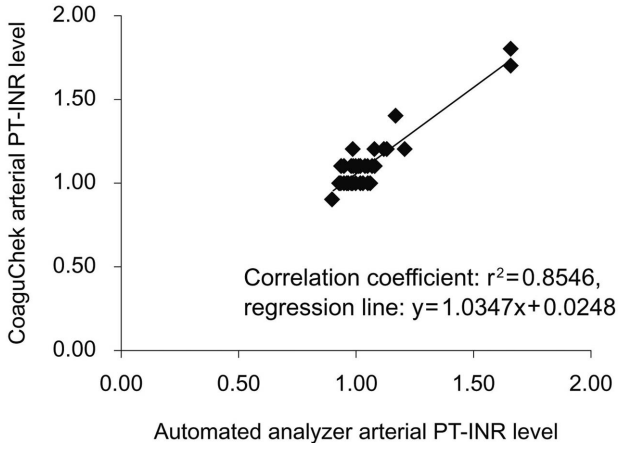

Fig. 4 Correlation between CoaguChek XS-measured and automated analyzer-measured arterial PT-INR values.

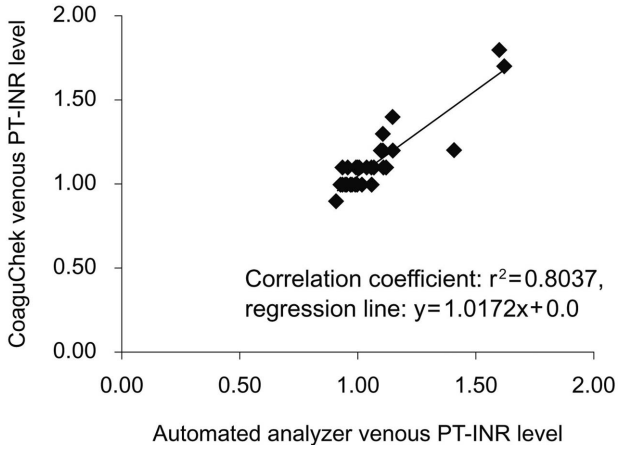

Fig. 5 Correlation between CoaguChek XS-measured and automated analyzer-measured venous PT-INR values.

tendency. In addition, it has frequently been used to evaluate the efficacy of warfarin, the only anticoagulant agent that can be orally administered to prevent thromboembolism. Since the introduction of the INR, the PT-INR has increasingly been recommended in place of conventional PT testing by various guidelines in Japan [4, 5].

CoaguChek XS, used in the present study, is a point-of-care device that was developed to monitor warfarin therapy for the prevention of thromboembolism. In Western countries, warfarin therapy has been self-managed using similar monitoring devices [5]. CoaguChek XS is a compact, portable device for simple and quick measurement of PT-INR and is expected to be suitable for use in operating rooms. However, since the manufacturer limits the use of the CoaguChek XS to venous blood samples, the reliability of measuring PT-INR using arterial blood samples needed to be verified. The results of this study suggested that there provided comparable data when arterial blood was used to determine PT-INRs with the CoaguChek XS for many of the patients scheduled for elective surgery. In addition, the CoaguChek XS data showed good correlation with measurements obtained in the central laboratory, suggesting that data obtained using the CoaguChek XS could be used for a reference. And the slope of the regression line was dosed to 1.0 and the y-axis intercept was near zero (Fig. 2).

Because of the aging of the population, the number of people with nonvalvular atrial fibrillation (NVAF) secondary to hypertensive disease and coronary artery disease, for example, is steadily increasing [6]. In the management of NVAF, oral anticoagulant therapy with warfarin has been shown to prevent cardioembolic stroke [5, 7] and to be more effective than antiplatelet therapy with aspirin and ticlopidine, for example, in preventing cerebral infarction [8, 9] with fewer cases of bleeding complications [10, 11]. Similarly, in surgical care, the importance of measuring the PT-INR preoperatively has increased because the number of patients on warfarin therapy and scheduled for surgical anesthesia has increased. Given that the mean half-life for the inhibitory effect of warfarin on the biosynthesis of blood coagulation factors via competition with vitamin K in the liver is 1 day [12], it has been recommended that warfarin therapy should be discontinued 3 or 4

days before elective surgery to ensure a normal PT-INR on the day of surgery. It is also recommended that those at risk of developing a thromboembolism following withdrawal from warfarin should receive low-dose unfractionated heparin continuously until 4–6 hours before surgery, and receive protamine in a competitive manner during surgery, as needed [4, 13]. When washout fails to normalize coagulation parameters, or if emergency surgery without an opportunity for washout is needed, the use of vitamin K preparations or FFP should be considered.

In Japan, however, the incidence of thromboembolism has recently increased to the level seen in Western countries. Therefore, the risk of thromboembolism caused by inappropriate discontinuation of warfarin in preparation for surgery/anesthesia cannot be ignored. Cardioembolic stroke is often serious and even fatal. The risk of bleeding caused by continued anticoagulant therapy must be weighed against the risk of thromboembolism caused by withdrawing therapy [14] and it is becoming more common to continue anticoagulant therapy in patients at high risk for thromboembolism [15].

In addition, the dose of warfarin is not easily controlled because it varies among patients and may depend on the patient's clinical and physical conditions, such as intake of food containing vitamin K and the use of concomitant drugs such as phenobarbital, rifampicin, ethanol and cholestyramine [6]. Long-term or permanent warfarin therapy requires periodic monitoring of the blood clotting ability to prevent bleeding complications caused by excess warfarin and to prevent thromboembolism if the warfarin dose is too low. Age, sex, race, body weight (liver weight) and liver function may also affect warfarin metabolism, and the elderly, women, those with low body weight, and Asians (including Japanese) are more sensitive to warfarin [16]. In recent years, the difficulty of optimizing the warfarin dose has been attributed to variations (including racial differences) in the CYP2C9 gene, which affects the activity of cytochrome P450 2C9 and is the primary enzyme responsible for hepatic metabolism of warfarin, or in the VKORC1 gene, which affects the activity of hepatic vitamin K epoxide reductase, an enzyme inhibited by warfarin. It has been suggested that both genes may alter the pharmacokinetic and pharmacodynamic properties of warfarin and thereby the relationship between its blood concentration and anticoagulant efficacy [7, 16–18]. Accordingly, pharmacological factors and the time from discontinuation of therapy to normal coagulation (i.e., the elimination rate of warfarin) may vary between patients. Therefore, guidelines that standardize the period and method of washout should not be applied indiscriminately to all patients.

In anesthetic management, it is also desirable to measure the PT-INR immediately before surgery. The PT-INR is a useful parameter that can detect abnormal coagulation, predict the efficacy of anticoagulant therapy for intraoperative bleeding, and determine the usefulness of treatments, including vitamin K preparations, FFP and coagulation factor concentrates. CoaguChek XS can quickly measure PT-INR on demand in an operating room and in other settings in which there is insufficient time or conventional preoperative testing or delivering information on anticoagulant therapy [19]. This device may be particularly useful in emergency situations requiring general anesthesia for hemostasis or hematoma evacuation for bleeding events associated with anticoagulant therapy, as well as for emergency surgery. Considering that epidural anesthesia or spinal (subarachnoid) anesthesia does not increase the risk of extradural hematoma in patients with a PT-INR < 1.5 [20, 21], knowing the PT-INR could help physicians to determine whether deep nerve blockade, including paravertebral block, is an option.

Values of coagulation parameters differ significantly with respect to the source of the blood samples, and it has been reported that arterial and venous bloods cannot be treated as equivalent for the purpose of assessment of coagulation status in disease patients [22, 23]. In this study, we found the arterial PT-INR values comparable with venous ones when measured by CoaguCheck XS for the purpose of assessment of coagulation status in patients with ASA-PS 1 or 2 who underwent elective surgery. Further studies are necessary to clarify the reliability of arterial PT-INR values by CoaguCheck XS and its usefulness in preoperative management of patients with specific disease conditions.

In conclusion, measuring arterial PT-INR using CoaguChek XS provided comparable values with venous blood in a selected patients such as those with ASA-PS 1 or 2 who underwent elective surgery, and can provide anesthesiologist's information for a reference in preoperative management of those in operation room. Use of this device allows the anesthesiologist to quickly determine the risk of bleeding, as needed, in an operating room and select the most appropriate anesthetic method. The CoaguChek XS device should be a standard piece of equipment in operating rooms.

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