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A comparative study of conventional versus new, magnesium-poor Vacutainer® Sodium Citrate blood collection tubes for determination of prothrombin time and INR

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ABSTRACT

Introduction: Conventional Vacutainer® Sodium Citrate blood collection tubes contain a relatively high concentration of contaminating magnesium ions, which may result in shortening of the prothrombin time (PT) and the International Normalized Ratio (INR). Recently the manufacturer of Vacutainer® Sodium Citrate tubes introduced new tubes with a magnesium-poor stopper. The magnesium concentration in the new low-Mg tubes is significantly lower than that in the conventional plastic tubes. The purpose of the present study was to compare PT and INR determined in specimens drawn with the new tubes to those drawn with the conventional tubes.
Materials and Methods: Venous blood specimens were collected from 22 healthy persons and 65 patients treated with vitamin K-antagonists using conventional Vacutainer® Sodium Citrate tubes and new, low-Mg Vacutainer® tubes. PT and INR were determined with four thromboplastin reagents, i.e., three brands of recombinant human tissue factor and one brand of combined rabbit brain reagent. Magnesium concentrations were determined in the citrate plasmas with a colorimetric method.
Results: The differences in PT, INR and International Sensitivity Index (ISI) between the two tubes were significant when using three recombinant human thromboplastin reagents, but were not significant when using the rabbit thromboplastin. The PT and INR differences between the tubes correlated with the magnesium concentration differences ($P < 0.001$). The INR bias between the four reagents was greater for specimens drawn with conventional tubes than the INR bias for specimens drawn with the new tubes.
Conclusion: Agreement of INR between reagents is improved by using magnesium-poor tubes.

Introduction

The prothrombin time (PT) and International Normalized Ratio (INR) are determined by many clinical laboratories for monitoring of treatment with vitamin K-antagonists. The result of the PT test depends on the preanalytical conditions of the specimen. An important preanalytical factor is the system used for drawing the blood specimen. Many commercial blood collection systems are composed of an evacuated tube containing a solution of sodium citrate, and a rubber stopper. Previous studies have shown that the International Sensitivity Index (ISI) of a thromboplastin reagent, which is a measure of its responsiveness to the defect induced by vitamin K-antagonists, may depend on the blood collection system used [1,2]. Furthermore it has been shown that some vacuum tubes are contaminated with magnesium resulting in a shortening of the PT [3–7]. It has been proposed that the magnesium contamination in sodium citrate solutions for blood collection should be less than 1.0 mmol/L [7]. Manufacturers became aware of the undesirable effects of magnesium contamination and started to develop new, magnesium-poor tubes. Recently, the manufacturer of plastic Vacutainer® Sodium Citrate tubes has replaced the conventional rubber stopper by a low-magnesium stopper.

A prototype of a magnesium-poor Vacutainer® Sodium Citrate tube has been evaluated in 2011 [8]. By the end of 2012, a new low-magnesium Vacutainer® Sodium Citrate tube was introduced on the market. At that time, the conventional plastic tube was still being used by clinical laboratories. The primary purpose of the present study was to evaluate the new plastic tube by comparison to the conventional tube, focusing on the PT and INR of healthy persons and patients treated with vitamin K-antagonists. In this study we used three PT reagents made of recombinant human tissue factor and one reagent made of

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rabbit brain combined with adsorbed plasma. Recombinant human tissue factor reagents are more sensitive to variation in magnesium concentration than rabbit brain reagents [4,6,7]. We assessed the INR bias between the four reagents using conventional and low-magnesium tube specimens. Furthermore, we determined the ISI for the low-Mg Vacutainer® tubes relative to the ISI for the conventional Vacutainer® tubes, i.e., the ratio of ISI values.

Materials and Methods

Blood Collection Tubes

Two lots of Vacutainer® Sodium Citrate vacuum tubes were obtained from Becton Dickinson (Plymouth, United Kingdom). Both lots had the same article number (363047) and were made of plastic. The draw volume of blood was 1.8 mL. The tubes contained buffered sodium citrate (0.109 mol/L), with a 9:1 ratio of blood to citrate. The first lot (nr. 2241160, expiry 2013-02) was a lot with conventional stoppers, and the second lot (nr. 2331257, expiry 2013-05) was made with low-magnesium stoppers.

Blood Collection and Processing

Patients treated with vitamin K-antagonists and healthy volunteers were invited to participate in the study. Informed consent was obtained from each individual participant. The healthy volunteers are referred to as normal subjects. Venous blood was collected with the conventional and low-Mg Vacutainer® tubes from the same venepuncture in each subject, according to Clinical and Laboratory Standards Institute document H21-A5 [9]. The order of filling of the tubes was random. All specimens were processed in the same way. The blood specimens were centrifuged and the plasma was transferred to plastic tubes. The samples were frozen and stored at -70 °C until analysis.

Coagulation Instruments

Three automated coagulation instruments were used: Sysmex CA-1500 (Toa Medical Electronics, Kobe, Japan), STA-R (Diagnostica Stago, Asnières, France), and ACL-Advance (Instrumentation Laboratory, Breda, The Netherlands).

Thromboplastin Reagents

Innovin was a recombinant human tissue factor reagent, obtained from Siemens Healthcare Diagnostics (Marburg, Germany). Recombiplastin 2G was a recombinant human tissue factor reagent, obtained from Instrumentation Laboratory (Breda, The Netherlands). Neoplastin R (recombinant human) and Hepato Quick (rabbit brain combined with adsorbed plasma) were obtained from Roche Diagnostics (Almere, The Netherlands). Instrument-specific ISI and Mean Normal Prothrombin Time (MNPT) values for these batches of reagents had been established previously by calibration with the International Standards for thromboplastin (coded rTF/09 and RBT/05), using fresh plasma samples collected with S-Monovette tubes (Sarstedt, Nümbrecht, Germany).

Prothrombin Time and INR Determinations

Plasma samples were thawed in a waterbath at 37 °C and PT's were determined in duplicate with each of the following combinations of reagent and instrument: Innovin and Sysmex CA-1500 (ISI: 1.01; MNPT: 10.7 s); Recombiplastin 2G and ACL-Advance (ISI: 0.98; MNPT: 10.9 s); Hepato Quick and STA-R (ISI: 0.86; MNPT: 28.9 s); Neoplastin R and STA-R (ISI: 0.97; MNPT: 14.6 s). PT's of each subject's samples obtained with the two Vacutainer tubes were determined immediately after each other. Analytical imprecision of the PT systems was calculated from duplicate measurements. All PT determinations were performed in the first author's laboratory. INR's were calculated using the above-mentioned instrument-specific ISI and MNPT values according to the formula: $INR = (PT/MNPT)^{ISI}$.

Magnesium Determination

Magnesium concentration was determined in each citrate plasma sample using a routine colorimetric method on a Modular Analytics P800 System (Roche Diagnostics Nederland).

Statistical Methods

Differences in PT, INR, and magnesium concentration were assessed by using Student's *t*-test on paired observations (SPSS version 20). ISI calibration was performed by means of orthogonal regression analysis [10]. Differences in ISI between the two blood collection tubes were assessed by the method of Poggio et al [11]. Pearson's correlation was calculated using SPSS version 20. *P* values lower than 0.05 were considered as significant.

Results

Effect of tubes on PT, INR, and ISI

Blood specimens of 65 patients treated with vitamin K-antagonists and 22 healthy volunteers were included in the study. The mean PT's of the plasma specimens obtained with the two Vacutainer® tube lots are shown in Table 1. For the three recombinant human thromboplastins Innovin, Recombiplastin 2G, and Neoplastin R, the mean PT's obtained with the conventional tubes were significantly shorter than the corresponding values obtained with the low-Mg tubes. The differences were significant for both normal and patient samples using the *t*-test on paired observations. In contrast, no significant difference was observed for the PT's determined with Hepato Quick. The average imprecision (within-run coefficient of variation) of the PT determinations in the patients' samples ranged from 0.4% to 1.6%. INR's were calculated for each sample using previously established values for the mean normal PT and the ISI (Table 2). The magnitude of the mean differences between the conventional and low-Mg tubes decreased in the order Innovin > Recombiplastin 2G > Neoplastin R > Hepato Quick.

For each thromboplastin reagent, the orthogonal regression equation of log (PT, low-Mg tube) against log (PT, conventional tube) was calculated (Table 3). The slope of the regression line was significantly greater than 1.0 for Recombiplastin 2G and Innovin ($P < 0.001$), and for Neoplastin R ($P < 0.05$). The slope was not significantly different from 1.0 for Hepato Quick.

Effect of Tubes on Magnesium Concentration

The mean and range of magnesium concentrations in the citrate plasma samples are shown in Table 4. The magnesium concentrations in the samples collected with the conventional Vacutainer® tubes were significantly higher than those in the Low-Mg tubes ($P < 0.001$).

Correlation Between Magnesium and INR Differences

For each patient sample, the relative INR difference and the difference in magnesium concentration between the conventional and Low-Mg tube was calculated. A scatterplot of the INR differences versus the magnesium concentration differences is shown in Fig. 1. For INR differences determined with Recombiplastin 2G, Innovin, and Neoplastin R, Pearson's correlation between the differences was highly significant ($P < 0.001$). For INR differences determined with Hepato Quick, the correlation between these quantities was weakly significant ($P = 0.04$).

Table 1
Geometric mean prothrombin times (in seconds) and analytical imprecision of determination.

Tube	Subjects	N	Hepato Quick (rabbit)	Neoplastin R (recombinant human)	Recombiplastin 2G (recombinant human)	Innovin (recombinant human)
Conventional	Normals	22	28.17	13.85	10.64	10.34
Low-Mg	Normals	22	28.19 (N.S.)	14.40 ($P < 0.001$)	10.99 ($P < 0.001$)	10.77 ($P < 0.001$)
Conventional	Patients	65	93.9	39.7	29.0	27.1
Low-Mg	Patients	65	94.2 (N.S.)	41.4 ($P < 0.001$)	31.3 ($P < 0.001$)	29.3 ($P < 0.001$)
Average imprecision of patient PT (CV)			1.6 %	0.5 %	1.4 %	0.4 %

P values: Student's *t*-test for paired data (Low-Mg versus Conventional). N.S. = Not Significant.

Discussion

In the present study a new Vacutainer® Sodium Citrate tube was evaluated by comparison to the conventional Vacutainer® tube. The new Vacutainer® has been developed by the manufacturer using a new rubber stopper with a lower magnesium content than in the conventional stoppers. As expected, using the new Vacutainer® tubes resulted in lower plasma magnesium concentrations when compared to the samples collected with the conventional tubes (Table 4). Prothrombin times in the new tubes were longer than those in the conventional tubes (Table 1), but the differences reached statistical significance only if recombinant human thromboplastins were used. The PT differences between the tubes must be due to the different composition of the tubes because there was no difference in processing of specimens and time delay between venepuncture and analysis. Previous studies have demonstrated that there is no difference in PT between the first and second tube if the two tubes are from the same lot [12]. The PT differences observed with Hepato Quick were not statistically significant and were not of clinical importance (Table 1). In the same way, INR's calculated with fixed values for MNPT and ISI were different when using the recombinant human thromboplastins (Table 2). The magnitude of the INR difference was associated with the concentration of contaminant magnesium in the sample (Fig. 1). In 11 and 13 out of 65 patients samples, the INR differences between the tubes were greater than 10% for Recombiplastin 2G and Innovin, respectively (Fig. 1, panels A and B, respectively). For example, in one patient the INR determined from the new low Mg-tube was 4.2 and the INR from the conventional tube was 3.4. In this case the dosage of VKA would have been reduced if the higher INR had been used but kept constant if the lower INR had been reported. The average VKA dosage for all patients would be reduced if the conventional tubes were replaced by the new low Mg-tubes. Surprisingly, the average INR difference with Innovin and Recombiplastin 2G was almost two times greater than the average difference with Neoplastin R (Table 2). The variation of the mean INR's between thromboplastins in the conventional Vacutainer® Sodium Citrate tubes was greater than the variation observed with the new low-Mg tubes (Table 2). This was to be expected because MNPT and ISI used for calculation of INR were established with low-Mg blood collection tubes. The use of low-Mg blood collection tubes by all laboratories should result in less variation of INR between laboratories.

Magnesium ions can accelerate tissue factor-induced coagulation but the magnitude of the effect depends on the tissue factor species [4]. There are Mg^{2+} binding sites in the γ-carboxyglutamic acid (Gla) domain of Factor VII/Factor VIIa, and Mg^{2+} augments phospholipid binding to Factor VIIa [13]. Furthermore, Mg^{2+} binding to the Gla domain of Factor X may influence the interaction with tissue factor [14]. In crude tissue thromboplastin preparations, differences in phospholipid/protein composition among various species have been reported [15]. In recombinant thromboplastin preparations, relative sensitivities to specific clotting factors are differentially influenced by the content of phospholipid [16]. A comparison of the primary structure of tissue factor among mammalian species showed divergences at regions involved in binding the Factor VII Gla domain and the region interacting with the catalytic domain of Factor VII [17]. We speculate that the different responses to Mg^{2+} ions among thromboplastin reagents may be explained partially by the phospholipid composition and dilution of the system, and partially by the divergences in tissue factor primary structure.

In previous papers it has been shown that the ISI value for a thromboplastin reagent depends on the blood collection system used [2,6]. In one study, blood collection tubes of different manufacturers were compared [6]. Blood collection systems with low-Mg contamination were associated with low ISI values. This association is confirmed by the present study, in which two different tubes from the same manufacturer were compared. The slopes of the orthogonal regression lines shown in Table 3 represent the ratios of the conventional Vacutainer® ISI to the low-Mg Vacutainer® ISI. For Innovin and Recombiplastin 2G, the ISI is approximately 4% higher with the conventional Vacutainer® tube than with the low-Mg Vacutainer® tube. For Neoplastin R, the ISI is approximately 0.6% higher with the conventional Vacutainer® tube than with the low-Mg Vacutainer® tube. For Hepato Quick, there was no significant ISI difference between the tubes.

Table 2
Geometric mean INR of patient samples (N = 65). Mean INR difference between Low-Mg tube and conventional tube relative to the conventional tube is given in %. The range of individual differences is given between brackets. *P* values refer to Student's *t*-test on paired observations.

	Hepato Quick		Neoplastin R		Recombiplastin 2G		Innovin	
	INR	Difference (%)	INR	Difference (%)	INR	Difference (%)	INR	Difference (%)
Conventional	2.83	0.2 (-3.9/+3.0)	2.72	4.2 (1.1/7.1)	2.68	7.8 (3.1/13.3)	2.64	8.1 (2.5/23.1)
Low-Mg	2.84	$P > 0.05$	2.84	$P < 0.001$	2.89	$P < 0.001$	2.87	$P < 0.001$

Table 3
Orthogonal regression lines $\log_e$ (PT low-Mg tube) = $a + b$. $\log_e$ (PT conventional tube).

	Intercept *a*	Slope *b*	SD of slope *b*	Pearson correlation of difference plot (*P* value)
Hepato Quick	-0.008	1.003	0.003	0.353
Neoplastin R	0.020	1.006	0.002	0.012
Recombiplastin 2G	-0.068	1.043	0.004	< 0.001
Innovin	-0.062	1.042	0.005	< 0.001

Table 4
Magnesium concentration in citrate plasma samples.

	Subjects	N	Magnesium (mmol/L), mean	Magnesium (mmol/L), range
Conventional tube	Normals	22	1.14	1.01 – 1.22
Low-Mg tube	Normals	22	0.72	0.66 – 0.83
Conventional tube	Patients	65	1.15	0.99 – 1.37
Low-Mg tube	Patients	65	0.72	0.60 – 0.81

Certified (lyophilized) plasmas are commercially available for local test system ISI calibration or 'direct' INR determination [18]. Certified plasmas may be used for correction of analytical bias but cannot correct for preanalytical errors. The PT of the certified plasma determined by the local (user) laboratory is independent of the preanalytical conditions used by this laboratory. On the other hand, the certified values depend on the preanalytical conditions of the certifying laboratory because ISI and MNPT of the certifying laboratory depend on the preanalytical conditions.

It may be argued that unbiased INR's could be obtained with the conventional Vacutainer® Sodium Citrate tubes if adjusted or corrected values for MNPT and ISI were used. However, in the daily practice of a routine clinical laboratory, it would be difficult to do this because thromboplastin reagent manufacturers do not provide ISI values or correction factors which are specific for any brand or type of blood collection tubes. Other authors emphasized that special attention is required when a change of the brand of sodium citrate vacuum tubes for performing PT tests is to be devised [19]. Apart from magnesium contamination of blood collection tubes, variation of citrate concentration is another source of preanalytical error. INR's of plasma from tubes with 3.8% sodium citrate (approximately 0.129 mol/L) were significantly higher than those from tubes with 3.2% (approximately 0.109 mol/L) [20,21]. It is recommended to use 0.109 mol/L sodium citrate for PT/INR determination [10]. In spite of this, blood collection tubes containing a relatively high sodium citrate concentration (0.129 mol/L) are still being manufactured [22]. In the present study we compared two lots of 0.109 mol/L sodium citrate tubes from the same manufacturer. Although we did not evaluate the current citrate tubes from other manufacturers in this study, we would like to emphasize that all manufacturers of blood collection systems should try and standardize their products so that differences between brands and lots are eliminated. The new plastic Vacutainer® Sodium Citrate tubes contain low

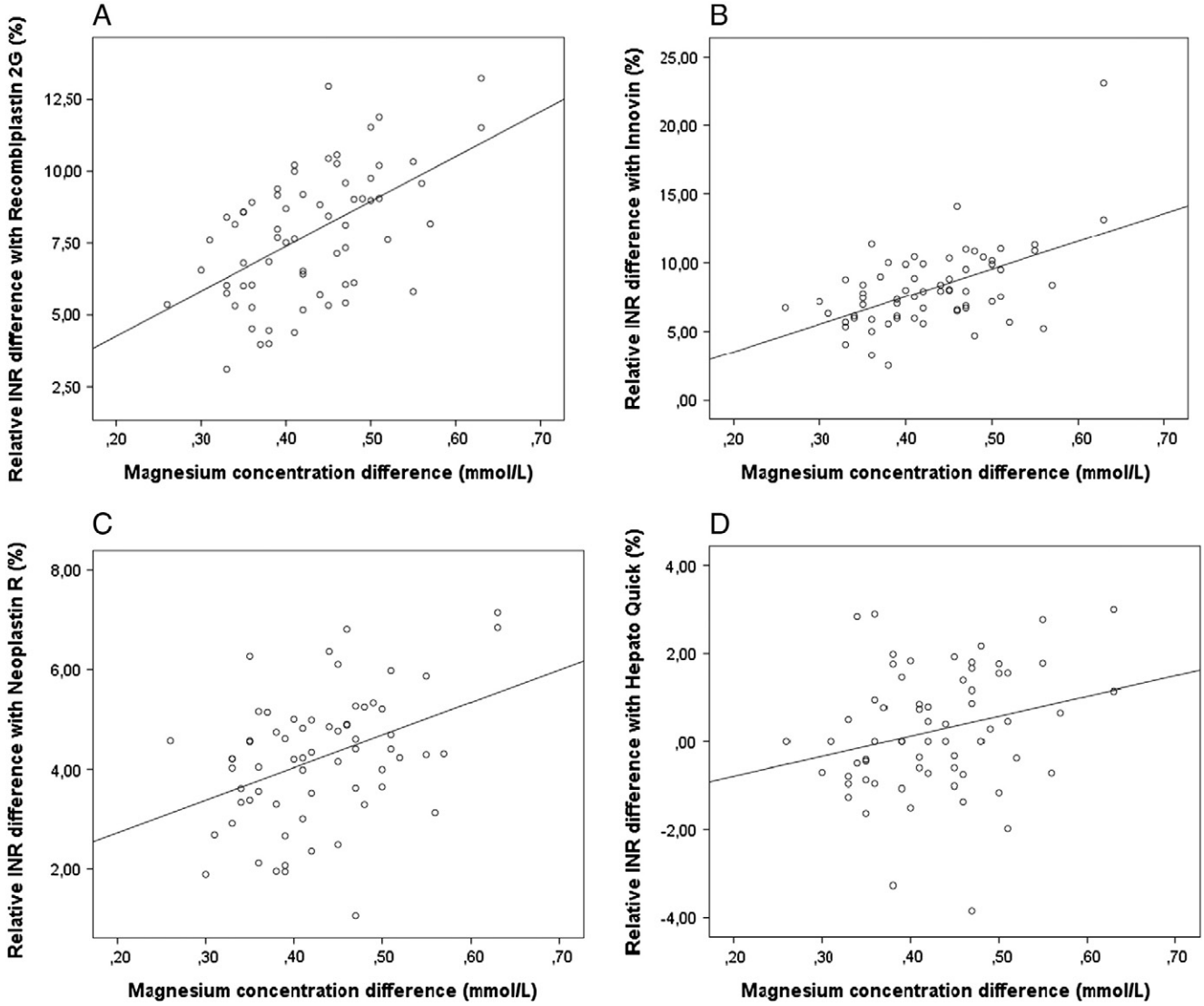

Fig. 1. Scatterplot of relative INR differences, (INR Low Mg tube – INR conventional tube)/INR conventional tube, versus magnesium concentration differences (mmol/L) in 65 patients' citrate plasma samples. Panel A: INR differences (%) determined with Recombiplastin 2G; Pearson's correlation coefficient is 0.538 ($P < 0.001$). Panel B: INR differences (%) determined with Innovin; Pearson's correlation coefficient is 0.532 ($P < 0.001$). Panel C: INR differences (%) determined with Neoplastin R; Pearson's correlation coefficient is 0.396 ($P = 0.001$). Panel D: INR differences (%) determined with Hepato Quick; Pearson's correlation coefficient is 0.255 ($P = 0.04$). In all panels, the linear regression lines are shown as well.

magnesium concentrations (< 0.1 mmol/L), but conventional glass Vacutainer® Sodium Citrate tubes still contain high magnesium concentrations (> 1.0 mmol/L). The manufacturer informed us that the glass Vacutainer® Sodium Citrate tubes will be changed in the near future so that acceptable low magnesium levels will be reached.

Conflict of Interest Statement

None of the authors has any conflict of interest to report.

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