Validation of a Portable Coagulometer for Routine In-Hospital Use for Newborns

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Objectives: To verify the reliability and clinical benefits of the coagulation tests made by a point of care device in newborn admitted to a neonatal unit.

Design: We made a statistical comparison between results obtained by the point of care device versus conventional laboratory analysis.

Setting: Level 3 neonatal unit.

Patients: Thirty-one infants admitted to the neonatal unit at the San Cecilio University Hospital (Granada, Spain) were recruited to this study.

Interventions: All underwent a double analytical determination: a small drop of blood was taken for analysis with a portable coagulometer (qLabs Electrometer Plus) and the rest of the blood sample was analyzed with conventional hospital laboratory equipment.

Measurements and Main Results: According to the linearity test performed, the measuring methods presented a good linear regression fit. Lin's concordance coefficient showed a "good" agreement for activated partial prothrombin time and international normalized ratio (>0.61) and a moderate one for prothrombin time (0.41–0.6) for the sample of newborns.

Conclusions: The portable coagulometer qLabs Electrometer Plus device has the potential to be an alternative to standard hospital coagulation autoanalyzers in a subset of patients where the amount of blood drawn can have significant risks. Our study is the first of its kind to analyze the use of this device with severely ill newborns. (*Pediatr Crit Care Med* 2017; XX:00–00)

Key Words: blood coagulation; coagulation test; coagulometer; newborn; point of care system

Third-level neonatal units treat newborns of any gestational age and weight presenting highly complex medical situations. Critically ill infants are admitted to neonatal ICUs (NICUs) to receive the support and care appropriate to their condition. The technological resources that form part of these hospital units, together with other factors, have contributed decisively to the achievement of diagnostic and therapeutic improvements and, consequently, to reducing mortality rates and long-term sequelae. Laboratory procedures, such as coagulation tests, are essential in clinical and therapeutic monitoring.

Vitamin K is routinely provided as appropriate prophylaxis in newborns to counter the physiologic tendency to bleeding in the hours immediately after birth. A single 1-mg dose of vitamin K at birth, by intramuscular injection, is effective against hemorrhagic disease in full-term newborns (1). In neonates admitted to the NICU who present other risk factors, such as prematurity, sepsis, asphyxia, liver disease, or metabolic disease, serial coagulation tests form part of the daily diagnostic procedure. Depending on the characteristics of the hospital laboratory, the volume of blood required for this process varies, but may be as much as 1.9 mL of total blood extracted.

The total blood volume of the newborn is relatively low, and especially so in newborns of very low birth weight or extremely low birth weight, and therefore the extraction of blood for testing inevitably presents a high risk of provoking anemia. Neonatal anemia is a common cause of clinical decompensation, especially in preterm infants, and sometimes requires medical treatment (erythropoietin and/or oral iron) or blood transfusion. Strategies are needed in neonatal units to avoid the latter necessity, with its associated risks and costs. Numerous studies have been published regarding the adverse effects of transfusion activity in newborns, such as infection, necrotizing enterocolitis (2, 3), bronchopulmonary dysplasia, retinopathy of prematurity, neurodevelopmental disorders, and increased mortality (4).

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In this study, the international normalized ratio (INR), prothrombin time (PT), and activated partial PT (aPTT) were determined in newborns using a qLabs Electrometer Plus portable coagulometer (Micropoint Biotechnologies, Guangdong, People's Republic of China) and comparing the results obtained with those of conventional hospital laboratory equipment. Our aim was to determine the degree of agreement between the two procedures in order to use the portable device as the sole reference in the future for the basic measurement of coagulation in newborns. This portable device offers several advantages, especially those of immediacy (in time and space) and, above all, the fact that considerably less blood is needed for analysis (10 μL, equivalent to a small drop). We also analyze the economic impact of using this type of coagulometer.

Very few previous studies have been conducted in this respect for very young patients and fewer still for newborns. For over 20 years, home-use devices for pediatric patients being treated with warfarin have been proven safe and to promote clinical control (5). In 2014, it was concluded that portable coagulometers are useful for monitoring the INR in healthy infants and established values of 0.90–1.30 as a normal range (6). To the best of our knowledge, no previous studies have analyzed the in-hospital use of portable coagulometers for newborns.

MATERIALS AND METHODS

This article reports a validation study of diagnostic testing in newborns. Over a period of 7 months (February to September 2016), 31 infants admitted to the neonatal unit of the San Cecilio University Hospital (Granada, Spain) were recruited to the study. Gestational age ranged between 23 and 41 weeks (mean: 38.8 ± 4.4 wk) and their birthweight between 596 and 3,979 g (mean: 2,736 ± 864 g). Coagulation assessment was made between first and 20th day of life (mean: 4.5 ± 5.9 d). Medical indications for needing of coagulation tests included perinatal asphyxia and encephalopathy (12 newborns), sepsis (7), bleeding (5), suspicion of thrombosis (2), and necrotizing enterocolitis (2) (**Table 1**). Coagulation tests were performed after obtaining prior informed consent from the parent or guardian of the newborn. Blood collection was performed by direct venipuncture by nurses from the neonatal unit. With the sample obtained, two tests were performed; a single drop was used for portable coagulation analysis and the rest of the sample, in sufficient quantity, for routine laboratory analysis. The study protocol was approved by the hospital's ethics committee.

Only venipuncture techniques were performed because each blood samples were used, not only for coagulation analysis but also to determine several hematimetric and plasma biochemical variables in those critically ill newborns. Therefore, capillary samples (from heel stick or others) were not done to avoid one more painful procedure.

The portable coagulation test was performed with a qLabs Electrometer Plus (Micropoint Biotechnologies), which is a small portable device that can provide measurements of PT, INR, and aPTT, using specific disposable test strips. The test is carried out in whole blood obtained by venous, arterial, or capillary puncture. It requires a small drop of blood (10 μL), which is deposited on the test strip and provides the result in 7 minutes. To guarantee an accurate result, since the blood is dropped on the strip until result is displayed, this device should be on a level surface and no movement is allowed. That is the reason because nurses did not bring this portable coagulometer closer to the patients during each procedure.

It has an international sensitivity index (ISI) of 1.02. During bedside analysis, a test strip is inserted into the device and the drop of blood is deposited on the strip. The analysis is performed by the attending physician or nurse.

In accordance with the standard laboratory method, blood was collected by venipuncture and placed in a sterile vacuum container containing one part citrate (solution at a concentration of 3.2%: 0.105 mmol/L) to which nine parts of venous blood were added, avoiding foaming.

The samples were transferred to the laboratory, where they were centrifuged at 1,500*g* for 15 minutes at room temperature. All samples were processed within 4 hours of collection. The resulting serum was analyzed by BCS XP autoanalyzers (Siemens Healthcare Diagnostics, Marburg, Germany). The reagents used were Thromborel S (Siemens Healthcare Diagnostics, Marburg, Germany) with an ISI of 0.979 for PT and INR, and Pathromtin SL (Siemens Healthcare Diagnostics, Marburg, Germany) with a range (5–95th percentiles) of 25.9–36.6 seconds for aPTT.

In the laboratory analysis, techniques are needed to detect systematic errors. In our study, the statistical method used was that proposed by Passing and Bablok, which consists of making a nonparametric estimation of the orthogonal regression slope. This method enables us to determine whether there are constant or proportional differences between two measurement methods, according to whether the 95% CI of the constant in the regression slope includes the value 0 and whether that of the slope includes the value 1. Lin's concordance coefficient, on the other hand, allows us to graduate the agreement between two measurement methods. All statistical analyses were performed using SPSS 20.0 statistical software (IBM Corporation, New York, NY).

RESULTS

The newborns enrolled in this study had a median gestational age of 40 weeks, with an interquartile range (IQR) of 36–41 weeks. The median birth weight was 3,320 g (IQR: 2,100–3,979). Measurements were taken, on average, during the second day of life (IQR: 1–20).

For the three variables examined, the constant (α) was not statistically different from 0 (the 95% CI included the value 0) and the slope (β) was not statistically different from 1 (the 95% CI included the value 1). It follows, therefore, that these two measurement methods are comparable in preterm infants because there were no constant or proportional differences. The linearity test based on the coefficient indicates that both measuring methods fit a linear regression, whose mathematical expression is shown in **Table 2**. This table also shows Lin's

TABLE 1. Clinical Characteristics of Recruited Newborns

Patient Number	Gestational Age (Wk)	Birthweight (g)	Days of Life	Clinical Indication
1	41	3,000	3	Perinatal asphyxia. Encephalopathy
2	41	3,190	1	Perinatal asphyxia. Encephalopathy
3	38	2,240	1	Bleeding
4	38	3,475	19	Sepsis
5	35	2,400	7	Perinatal asphyxia. Encephalopathy
6	40	3,520	19	Sepsis
7	40	3,035	1	Perinatal asphyxia. Encephalopathy
8	40	3,035	4	Perinatal asphyxia. Encephalopathy
9	40	3,979	10	Sepsis
10	40	3,270	2	Perinatal asphyxia. Encephalopathy
11	23	596	4	Sepsis
12	36	1,950	1	Suspicion of thrombosis
13	37	2,610	1	Perinatal asphyxia. Encephalopathy
14	36	2,940	0	Bleeding
15	36	1,950	3	Suspicion of thrombosis
16	37	3,350	20	Sepsis
17	38	3,120	4	Sepsis
18	41	3,740	2	Sepsis
19	40	3,000	2	Sepsis
20	25	761	11	NEC
21	37	1,860	1	Perinatal asphyxia. Encephalopathy
22	32	2,100	1	Sepsis
23	32	1,800	1	Sepsis
24	39	3,645	1	Perinatal asphyxia. Encephalopathy
25	39	3,645	2	Perinatal asphyxia. Encephalopathy
26	35	1,950	2	Bleeding
27	40	3,500	13	Bleeding
28	40	3,500	1	NEC
29	34	2,200	1	Perinatal asphyxia. Encephalopathy
30	41	3,590	1	Perinatal asphyxia. Encephalopathy
31	31	1,866	1	Bleeding

NEC = necrotizing enterocolitis.

concordance coefficient, which reflects "good" agreement for aPTT and INR (*r* value for aPTT = 0.75; *r* value for INR = 0.71) and moderate agreement for PT (*r* value for PT = 0.54) with respect to our sample of newborns.

DISCUSSION

The qLabs portable coagulometer is a small device, which is capable of making a basic measurement of coagulation, quickly and safely, at the patient's bedside. It requires only 10 µL of blood, and the result is obtained in 7 minutes. The technique is simple and requires minimal staff (one nurse or doctor). Our results demonstrate good agreement between the results obtained and those of the hospital laboratory. All samples were obtained by venipuncture and none by heel stick; therefore, correlation of heel stick results with venipuncture results was not determined.

The determination of biological variables by means of handheld devices is a growing trend in different areas of

TABLE 2. Comparison of the Accuracy of a Portable Coagulometer With That of an Instrumental Laboratory Method, by the Passing-Bablok Method

Test	Standard Method (Laboratory) ($n = 31$), Mean (SD)	Portable Coagulometer ($n = 31$), Mean (SD)	Passing-Bablok Regression, Mean (95% CI)		Lin's Coefficient
			Constant (α)	Slope (β)	
Activated partial prothrombin time	40.4 (12.6)	40.7 (19.3)	1.7 (−19.7 to 8.7)	0.71 (0.51–1.2)[a]	0.75
Prothrombin time	14.3 (2.8)	11.5 (2.8)	2.7 (−1.8 to 5.8)	0.90 (0.61–1.3)[a]	0.54
International normalized ratio	1.26 (0.27)	1.09 (0.27)	0.26 (−0.06 to 0.6)	0.85 (0.52–1.18)[a]	0.71

Linearity test: CUSUM test for deviation from linearity:
[a]$p < 0.01$.

hospital treatment, and these techniques have been reviewed in scientific literature for many years. They can provide results in situ, faster than a conventional laboratory, and therefore enable treatment decisions to be made immediately. These advantages are translated into improved clinical care, both for hospitalized patients and for those being treated at home (8), and even in cases of pediatric emergency (9).

Conventional coagulation testing in the laboratory requires considerable analysis time, due to the processing and centrifugation necessary to deliver results; 45–60 minutes are usually needed to obtain a reliable result (10).

In accordance with the standard laboratory method, blood samples were placed in a sterile vacuum container containing sodium citrate (solution at a concentration of 3.2%: 0.105 mmol/L). We did not take into account high hematocrit levels because there is sufficient scientific information demonstrating that a hematocrit up to 60% does not result in a statistically significant prolongation in PT, aPTT, or INR values (7).

Numerous studies have been conducted of adult patients in which the use of a portable coagulometer is compared with standard hospital laboratory methods, particularly for patients being treated with oral anticoagulants. Consequently, their performance has been optimized for the INR in this patient population. The use of point of care (POC) devices is increasingly common, both in outpatient treatment and in consultation and hospitalization because of its proven reliability (INR agreement), safety, and acceptability. The INR values we are reporting were not obtained on infants receiving vitamin K antagonist therapy; therefore, the less strong correlation of PT between POC and laboratory results must be considered when making clinical decisions.

Our literature review found the CoaguChek portable coagulometer (Roche Diagnostics, Basel, Switzerland) to be the object of most such comparative studies (10–14). Other devices (such as the ProTime Microcoagulation System, International Technidyne Corporation, Edison, NJ) have been corroborated for over a decade by institutions and scientific groups and have been shown to maintain (even under home testing conditions) INR levels within the therapeutic range and thus avoid complications arising from oral anticoagulation (15).

In 2012, the Canadian Agency for Medicines and Health Technologies conducted a review of systematic reviews, searching for studies comparing portable and laboratory analyses for various biological markers in blood, such as INR, glucose, electrolytes, blood gas analysis, troponin, liver function, and blood count. However, the only comparative studies found in these areas were for INR and glucose in adult patients. Among the conclusions drawn, and emphasizing the very limited amount of quality research conducted, it was observed that the portable coagulometers evaluated (CoaguChek XS, Roche Diagnostics; INRatio, Alere Inc, Waltham, MA; ProTime/ProTime 3, International Technidyne Corporation; and the SmartCheck INR System, Unipath, Bedford, United Kingdom) can be considered reliable and cost-effective (16).

Clinical and analytical testing is often more difficult for pediatric patients than for adults and can require a greater number of determinations (5, 17). Other specific problems caused by age are the absence of collaboration and the technical difficulty for the nurse in performing a venipuncture for blood extraction. The use of portable devices reduces the anxiety associated with serial measurements of INR in these patients and their parents and furthermore provides rapid results (18, 19). Of the few published studies that have included patients of pediatric age, one of the first was conducted by Marzinotto et al (20) in children between 3 months and 18 years old, treated with oral anticoagulation and recruited in outpatient clinics, although some cases were only monitored in the home setting. This study measured INR and PT in 80 children and reported good acceptability and good agreement between the values obtained with the CoaguChek portable coagulation device (Roche Diagnostics) and those obtained by hospital laboratory analysis (20). In addition, satisfactory correlation has been obtained between measurements with CoaguChek XS (Roche Diagnostics) for patients younger than 16 years old receiving anticoagulant therapy (21, 22), and its routine use is recommended, even for outpatients with heart disease and receiving anticoagulation treatment (23).

However, statistically, levels of agreement between these two methods may not always be the same and may depend on the INR values measured. In a study of 129 determinations from nine anticoagulated patients, younger than 18 years old, CoaguChek S (Roche Diagnostics) was reported to be a valid instrument for home monitoring of INR, if the values were between 2.0 and 3.0. However, for values above 3.5, the results should be viewed with caution, and confirmed with a second test if they are greater than 4.0 (24). Similar conclusions were

drawn in a study conducted in 19 American children, comparing several different portable coagulometers (CoaguChek, Roche Diagnostics; Hemochron Jr. Signature, International Technidyne Corporation; Microcoagulation ProTime System, International Technidyne Corporation; and Rapidpoint Coag, PharmaNetics Inc, , Raleigh, NC). The authors concluded that these portable devices provide accurate results if INR values are within the therapeutic range, but suggest that values outside this range should be confirmed by laboratory tests (18).

With respect to pediatric patients admitted to an ICU, CoaguChek XS Plus (Roche Diagnostics) seems to offer reliable results, according to a recent study of children younger than 13 years old (25). In another, however, little correlation was obtained for infants younger than 1 year old, treated with heparin. In addition, the portable coagulometer used (CoaguChek Pro, Roche Diagnostics) seems prone to overestimate aPTT values in these patients (26).

Among the few studies carried out in newborns, Iijima et al (6, 27) compared the INR results obtained by a portable coagulometer of the same brand as those mentioned above (CoaguChek XS, Roche Diagnostics). These studies included 488 healthy at-term infants and analyzed determinations obtained on the fourth day of life. The results obtained show that this device provides a safe, fast, and suitable method for determining INR in this newborn population, and the authors proposed its use as a neonatal screening test. By contrast, other devices, such as the GEM PCL Plus (Instrumentation Laboratory, Bedford, MA), offer very poor agreement for PT and aPTT in cord blood (28). To the best of our knowledge, no previous studies have compared both intrinsic and extrinsic coagulation pathways, measuring PT, INR, and aPTT in a population of critically ill newborns. Therefore, the study we present is the first one including a nonhealthy neonatal population, admitted in a neonatal unit.

Another advantage offered by portable coagulometers is that their use can avoid the need for the frequent, and often difficult, collection of blood samples from fragile infants admitted to neonatal units, thus reducing the risk of iatrogenic anemia. This is especially the case with preterm infants, in whom anemia is a common cause of respiratory, cardiac, or hemodynamic decompensation and is associated with higher morbidity and mortality (29). There are several causes of anemia in newborns, including those derived from prematurity or severe diseases (as the population of our study). If we associate iatrogenic causes to that previous situation of vulnerability, we could be increasing the opportunity of suffering a more intense and early decrease of hemoglobin and hematocrit levels.

Treatment may then require the administration of oral iron therapy for several months (if the enteral route is feasible) combined, in extreme preterm infants, with hematopoietic stimulants such as subcutaneous erythropoietin. If the anemia is more intense and/or the patient's clinical condition is worse, the transfusion of blood products (usually packed RBCs) becomes necessary.

In this study, we also quantified the cost associated with the use of portable coagulometers, in comparison with standard laboratory procedures. The reactive strips in the handheld device cost €10 each. In the hospital laboratory, the citrate tube and the coagulation reagents cost about €2. In this analysis, we did not take into account the not inconsiderable costs of the nurses who perform the venipuncture, the transfer of samples and the laboratory personnel. If neonatal anemia occurs, this will require oral iron therapy for at least 3 months (at least one pack required: price €3 each), the amount depending on the weight of the newborn (approximate cost €0.40 per kilogram body weight). Sometimes, oral iron therapy is associated with the use of hematopoietic stimulants such as recombinant human erythropoietin for several weeks. The financial cost of erythropoietin treatment is constituted not only of the price of the drug (approximately €20–50 per kilogram body weight) but above all that of the time and medical personnel necessary to ensure accurate dosing, according to the weight of the newborn. In addition, many times anemia occurs during hospitalization (first weeks of life) and erythropoietin should be administered by nursing staff.

If all these measures fail or the clinical situation requires, a blood transfusion must be administered. The cost of this process will certainly be high, especially if complications or post-transfusion reactions occur. In addition, we must consider the intrinsic price of cross matching and of the irradiated pediatric leucodepleted erythrocyte concentrate, which amounts to almost €164 (30)

CONCLUSIONS

In this study, we show that the portable coagulometer tested could have the potential of complement conventional hospital coagulation autoanalyzers in neonates admitted to neonatal units. They are a vulnerable subset of patients where the amount of blood drawn can have significant risks, like iatrogenic anemia and its consequences. It is a safe and simple technique that can be done by clinicians and allows early medical diagnosis and treatment. Due to the good agreement obtained between the two coagulation procedures, we propose that more use be made of this type of device, as part of a strategy to minimize iatrogenic blood loss. We believe a detailed cost-benefit analysis would show this to be a cost-effective recommendation.

Nevertheless, further research, focused on the neonatal population, is needed to corroborate the findings reported in this article.

REFERENCES

1. Puckett RM, Offringa M: Prophylactic vitamin K for vitamin K deficiency bleeding in neonates. *Cochrane Database Syst Rev* 2000:Cd002776
2. Paul DA, Mackley A, Novitsky A, et al: Increased odds of necrotizing enterocolitis after transfusion of red blood cells in premature infants. *Pediatrics* 2011; 127:635–641
3. Mohamed A, Shah PS: Transfusion associated necrotizing enterocolitis: A meta-analysis of observational data. *Pediatrics* 2012; 129:529–540
4. dos Santos AM, Guinsburg R, de Almeida MF, et al; Brazilian Network on Neonatal Research: Red blood cell transfusions are independently associated with intra-hospital mortality in very low birth weight preterm infants. *J Pediatr* 2011; 159:371–376.e1

5. Massicotte P, Marzinotto V, Vegh P, et al: Home monitoring of warfarin therapy in children with a whole blood prothrombin time monitor. *J Pediatr* 1995; 127:389–394
6. Iijima S, Baba T, Ueno D, et al: International normalized ratio testing with point-of-care coagulometer in healthy term neonates. *BMC Pediatr* 2014; 14:179
7. Austin M, Ferrell C, Reyes M: Do elevated hematocrits prolong the PT/aPTT? *Clin Lab Sci* 2013; 26:89–94
8. Gialamas A, St John A, Laurence CO, et al; PoCT Management Committee: Point-of-care testing for patients with diabetes, hyperlipidaemia or coagulation disorders in the general practice setting: A systematic review. *Fam Pract* 2010; 27:17–24
9. Hsiao AL, Santucci KA, Dziura J, et al: A randomized trial to assess the efficacy of point-of-care testing in decreasing length of stay in a pediatric emergency department. *Pediatr Emerg Care* 2007; 23:457–462
10. Kalcik M, Yesin M, Gursoy MO, et al: Comparison of the INR values measured by CoaguChek XS coagulometer and conventional laboratory methods in patients on VKA therapy. *Clin Appl Thromb Hemost* 2017; 23:187–194
11. Cosmi B, Palareti G, Moia M, et al: Accuracy of a portable prothrombin time monitor (Coagucheck) in patients on chronic oral anticoagulant therapy: A prospective multicenter study. *Thromb Res* 2000; 100:279–286
12. Jackson SL, Bereznicki LR, Peterson GM, et al: Accuracy, reproducibility and clinical utility of the CoaguChek S portable international normalized ratio monitor in an outpatient anticoagulation clinic. *Clin Lab Haematol* 2004; 26:49–55
13. Nam MH, Roh KH, Pak HN, et al: Evaluation of the Roche CoaguChek XS handheld coagulation analyzer in a cardiac outpatient clinic. *Ann Clin Lab Sci* 2008; 38:37–40
14. Meneghelo ZM, Barroso CM, Liporace IL, et al: Comparison of the international normalized ratio levels obtained by portable coagulometer and laboratory in a clinic specializing in oral anticoagulation. *Int J Lab Hematol* 2015; 37:536–543
15. Oral Anticoagulation Monitoring Study Group: Point-of-care prothrombin time measurement for professional and patient self-testing use. A multicenter clinical experience. Oral Anticoagulation Monitoring Study Group. *Am J Clin Pathol* 2001; 115:288–296
16. Canadian Agency for Drugs and Technologies in Health: Rapid Response Report: Summary With Critical Appraisal. Point-of-Care Testing: A Review of Systematic Reviews on Testing Accuracy and Cost-Effectiveness. Ottawa, ON, Canada, Canadian Agency for Drugs and Technologies in Health, 2012
17. Newall F, Bauman M: Point-of-care antithrombotic monitoring in children. *Thromb Res* 2006; 118:113–121
18. Nowatzke WL, Landt M, Smith C, et al: Whole blood international normalization ratio measurements in children using near-patient monitors. *J Pediatr Hematol Oncol* 2003; 25:33–37
19. Ignjatovic V, Barnes C, Newall F, et al: Point of care monitoring of oral anticoagulant therapy in children: Comparison of CoaguChek Plus and Thrombotest methods with venous international normalised ratio. *Thromb Haemost* 2004; 92:734–737
20. Marzinotto V, Monagle P, Chan A, et al: Capillary whole blood monitoring of oral anticoagulants in children in outpatient clinics and the home setting. *Pediatr Cardiol* 2000; 21:347–352
21. Bauman ME, Black KL, Massicotte MP, et al: Accuracy of the CoaguChek XS for point-of-care international normalized ratio (INR) measurement in children requiring warfarin. *Thromb Haemost* 2008; 99:1097–1103
22. Greenway A, Ignjatovic V, Summerhayes R, et al: Point-of-care monitoring of oral anticoagulation therapy in children. Comparison of the CoaguChek XS system with venous INR and venous INR using an International Reference Thromboplastin preparation (rTF/95). *Thromb Haemost* 2009; 102:159–165
23. Moon JR, Jeong SI, Huh J, et al: Accuracy of CoaguChek XS for point-of-care antithrombotic monitoring in children with heart disease. *Ann Clin Lab Sci* 2010; 40:247–251
24. Hill J, Perreault S, Dorval M: Validity of CoaguChek S for home monitoring of anticoagulant therapy in pediatrics. *Can J Cardiol* 2007; 23:47–50
25. Urwyler N, Staub E, Staub LP, et al: Point-of-care prothrombin time testing in paediatric intensive care: An observational study of the ease of use of two devices. *Eur J Anaesthesiol* 2012; 29:75–81
26. Klein RH, van der Vorst MM, de Wilde RB, et al: Evaluation of a bedside device to assess the activated partial thromboplastin time for heparin monitoring in infants. *Blood Coagul Fibrinolysis* 2013; 24:327–331
27. Iijima S, Baba T, Ueno D, et al: International normalized ratio testing with a point-of-care coagulometer in 1-month-old infants: A comparison with Normotest. *Thromb Res* 2016; 145:72–77
28. De Luca R, Fontana P, Poncet A, et al: Evaluation of the GEM®PCL Plus point-of-care device for neonatal coagulation assessment: An observational study on cord blood. *Thromb Res* 2014; 134:474–478
29. Aher S, Malwatkar K, Kadam S: Neonatal anemia. *Semin Fetal Neonatal Med* 2008; 13:239–247
30. Boletín Oficial de la Junta de Andalucía No 228. 2015. Sevilla. Spain. Available at: http://www.juntadeandalucia.es/boja/2015/228/BOJA15-228-00009-19572-01_00080482.pdf. Accessed July 1, 2017