Received: 7 November 2018 | Revised: 4 April 2019 | Accepted: 13 April 2019

DOI: 10.1111/ijlh.13043

ORIGINAL ARTICLE

WILEY ISLH International Journal of Laboratory Hematology

Establishing a reference range for thromboelastograph parameters in the neonatal period

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Funding information
Science and Technology Project of Zhejiang Province, Grant/Award Number: Grant No. 2018C37008; Wuhan Scientific Research Projects, Grant/Award Number: Grant No. WX15C22

Abstract

Introduction: Acquired coagulation disorders are a common cause of neonatal bleeding. The thromboelastograph (TEG) comprehensively assesses haemostatic processes in the body. Unfortunately, the reference range of TEG parameters in the neonatal period has not yet been evaluated, which limits the use of the TEG in neonates. In this study, we aimed to establish the reference range of TEG parameters for the neonatal period.

Methods: This study included 371 full-term infants (≥37 weeks of gestation), and we divided these infants into three groups according to age as follows: 1, 2-7 and 8-28 days. We measured their peripheral blood using TEG, coagulation routine and platelet count tests. We analysed differences among the groups.

Results: The reference ranges for TEG parameters are presented as medians and reference ranges (2.5th and 97.5th percentiles) as follows: *R* (clot reaction time, seconds) 4.80 (2.80-7.17), Angle (fibrin production rate) 69.90 (44.91-78.89), *K* (clot kinetics, min) 1.40 (0.80-4.50), MA (maximum amplitude, mm) 63.50(44.34-74.66) and LY30 (lysis at 30 minutes, %) 0.10 (0.10-6.95). There were significant differences in Angle, *K*, MA and LY30 values between the different neonatal day age groups.

Conclusion: This study preliminarily establishes a reference range for TEG parameters during the neonatal period. The age of a newborn had a large influence on TEG parameters. Additionally, we demonstrated a correlation between laboratory tests and TEG parameters for this age period. The reference values provided herein are meaningful for future studies.

KEYWORDS
neonatal period, neonate, reference range, thromboelastograph

1 | INTRODUCTION

The period from newborn to 28 days after birth is defined as the neonatal period. During this period, the blood coagulation system in infants is undergoing continuous improvements and maturation. Especially in newborn infants, several blood coagulation factors are not fully functional, the development of coagulation factors is not balanced, and the body is in a low coagulation state. In addition, the consumption of coagulation factors increases at birth, and the liver function is not mature, except for the coagulation factor V and factor

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VIII. The coagulation factors are lower in concentration neonates than in adults.[1-5] In addition, neonates have a different balance of haemostasis than adults or infants. It is in balance, but this balance is more labile, so in situations of an ill neonate, the risk of bleeding is increased. It is necessary to monitor the blood coagulation functions of newborns.

Routine coagulation tests, as the most common method to evaluate coagulation function, have certain limitations. Routine coagulation tests can indicate the time of fibrin formation through either the intrinsic or extrinsic pathways of the coagulation cascade. These tests are often used as a starting place when investigating the cause of bleeding. Tests, such as prothrombin time (PT), activated partial thromboplastin time (APTT) and platelet count, have limited capacities to reveal a patient's risk of bleeding and do not provide information on the patient's risk for thrombosis. Routine tests do not provide specific data about clot quality or stability.[6,7]

The thromboelastograph (TEG) haemostasis analyser system can objectively reflect the blood clotting, fibrinogen/fibrin/platelet interactions, and the formation, development and dissolution of thrombus processes in the body.[8-12] The TEG is intended to provide a complete analysis to help determine the right blood product or therapy at the right time to manage the patient's risk for haemorrhage or thrombosis. In addition, the TEG has played an important role in the diagnosis and management of coagulation disorders in paediatric patients and neonates.[13-15]

While the coagulation status of neonates is different from adults, the reference range of coagulation-related indexes is also significantly different from adults.[16-18] Therefore, it is necessary to establish a biological reference range related to coagulation for the neonatal period, which can help clinicians become acquainted with the coagulation status of newborns over time. However, there is no published reference range for TEG parameters in the neonatal period thus far. Data about the standard range of TEG parameters for newborns are limited.[16,19,20] In addition, because of the differences in research designs, reagents and methods, the establishment of reference ranges is more complicated.[21-24]

The aim of our study was to establish the reference range of TEG parameters for healthy full-term infants in the neonatal period. The results of this study have been significant in assessing the coagulation status and diagnosing the blood coagulation disorder in neonates. This study is conducive to the clinical diagnosis and management of neonatal coagulation-related diseases.

2 | MATERIALS AND METHODS

2.1 | Study population and design

A retrospective study was conducted on neonates born at the Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology, from January 2016 to December 2017. A total of 371 full-term infants in the neonatal period were recruited as study subjects. This study has been approved by the Hospital Ethics Committee of our hospital. Because the participants were neonates, this study obtained the informed consent signed by their guardians.

All the neonates were selected based on gestational age ≥37 weeks, appropriate birthweight (2.5-3.9 kg), and not given Vitamin K postpartum. Neonates with significant bleeding events and platelets, fresh frozen plasma or cryoprecipitate infusion history were excluded from this study. Significant bleeding events were defined as any clinical bleeding in the mucous, clinical bleeding in respiratory, gastrointestinal, or urinary tract, haemoglobin levels decreasing to more than 20 g/L within 24 hours, needing emergency surgery and transfusing blood, platelets, fresh frozen plasma or cryoprecipitate. Neonates who had a family history of bleeding were also excluded from the study. Neonates who were suspected to have major chromosomal abnormalities, septicaemia, perinatal loss of blood, birth asphyxia or perinatal stress were also excluded from this study. All newborns were delivered by normal vaginal delivery or caesarean section (LSC), but neonates delivered by emergency caesarean section were excluded from the study. In addition, all newborns hospitalized in the ICU were excluded from this study. The infants were divided into three groups according to age as follows: 1, 2-7 and 8-28 days. Infant data, including gestational weeks, birthweight, gender, mode of delivery and age, were recorded. Clinical data, including maternal diseases, drugs and complications during pregnancy, were also recorded.

2.2 | Biochemical analysis

We collected 2 mL peripheral blood with 0.109 mol/L sodium citrate anticoagulation. All the samples were detected by a TEG 5000 Thrombelastograph Hemostasis Analyzer System (Haemonetics Corporation) with associated coagulant activators (kaolin, mixed phospholipid and $CaCl_2$) according to standardized procedures. Five main parameters were obtained as follows: *R*, Angle, *K*, MA and LY30. Stop detection, if *R* was up to 60 minutes, indicated *R* was beyond the upper limits of detection.

Routine coagulation tests, PT, APTT, Fib and TT, were detected by the SYSMEX Automated Coagulation Analyzer CA-7000 (Sysmex Corporation) with matching agents, PT, APTT, Fib and TT. The PLT count data were obtained through a laboratory information system. Both the TEG tests and routine coagulation tests were performed within 2 hours after blood collection.

2.3 | Statistical analysis

For each group of TEG parameters, we used the 2.5th and 97.5th percentiles to establish a reference range, according to the NCCRS guide.[25] The distribution of the group was evaluated by Q-Q plots and Shapiro-Wilk tests, and almost all tests showed significant deviations from normality. Therefore, nonparametric methods were used for analysis; McNemar's test was used for the analysis between the reference range provided by our study and manufacturers. The Mann-Whitney *U* test was used among two groups. The Kruskal-Wallis one-way ANOVA test (*k* samples) was used among groups, and the Spearman correlation was used for the correlation analysis among the parameters. All statistical

analyses were performed using SPSS 22 software. All *P*-values were two-tailed values. For all tests, a *P*-value <0.05 indicated statistical significance.

3 | RESULTS

3.1 | Characteristics of the study population, TEG reference interval of neonates, coagulation test reference interval of neonates

The study population consists of 371 full-term (≥37 weeks of gestation) healthy infants. Demographic and clinical data and the parameters of the standard TEG and coagulation tests are presented in Table 1.

3.2 | Comparing the differences of TEG parameters reference range provided by this study and manufacturers in evaluating neonatal coagulation

The McNemar test was used for the analysis between the reference ranges provided by our study and manufacturers. The results presented in Table 2 show that there were significant differences in *R*, Angle, *K* and MA values between the two methods.

3.3 | The effects of patient characteristics on TEG values

To analyse the influences of patient characteristics on TEG values, nonparametric methods were utilized for TEG values and gestational age, birthweight and age at examination. According to Spearman's correlation coefficient, there were significant negative correlations between age and *K* value ($\rho = -0.601$, $P < 0.001$) and significant positive correlations between age and Angle ($\rho = 0.592$, $P < 0.001$), age and MA ($\rho = 0.614$, $P < 0.001$), age and LY30 ($\rho = 0.288$, $P = 0.012$), and MA and birthweight ($\rho = 0.130$, $P = 0.012$). The Mann-Whitney *U* test was used to analyse the TEG results of different genders and modes of delivery in newborns. Except for the *R* value, there were no significant differences in the Angle, *K*, MA and LY30 parameters according to gender and mode of delivery. The *R* value of females was higher than that of males ($P = 0.001$), and the *R* value of caesarean section was higher than that of spontaneous delivery ($P = 0.044$).

3.4 | TEG parameters for different age groups

Newborns were divided into 3 groups according to age as follows: 1, 2-7 and 8-28 days. The nonparametric method of Kruskal-Wallis one-way ANOVA test (*k* samples) was used to analyse the differences among the three groups. The Mann-Whitney *U* test was used for statistical comparisons between two groups. The results shown in Table 3 indicate that there were significant differences in Angle, *K* and MA values between every age group. With the increase in the age, Angle, MA and LY30 values increased and the *K* value decreased.

TABLE 1 Characteristics and experimental results of the study population

Parameter	Data (n = 371)
Gestational age, wk	39.05 ± 2.31
1 d	50/371 (13.5%)
2-7 d	105/371 (28.3%)
8-28 d	216/371 (58.2%)
Body weight, g	3280 ± 459
Gender (female)	135/371 (36.4%)
Spontaneous partum	158/371 (42.6%)
Caesarean section	213/371 (57.4%)
R	4.80 (2.80-7.17)
Angle	69.90 (44.73-78.88)
K	1.40 (0.80-4.57)
MA	63.30 (43.92-74.65)
LY30	0.10 (0.10-6.94)
TT	19.60 (16.43-25.40)
APTT	49.80 (32.68-86.75)
PT	13.10 (10.60-18.27)
Fib	2.21 (1.05-5.12)
PLT	321.00 (120.50-623.70)

Note: Demographic and clinical data were expressed as the mean ± standard deviation, or no. (%). Data of TEG parameters and coagulation test parameters are presented as medians and reference ranges (2.5th and 97.5th percentiles). *R* (s), *K* (s), Angle (α), maximum amplitude (MA, mm), and lysis at 30 min (LY30, %), thromboplastin time (TT, s), activated partial thromboplastin time (APTT, s), prothrombin time (PT, s), and fibrinogen (Fib, g/L), platelet count (PLT, 10^9/L).

3.5 | Correlation analysis between TEG parameters, coagulation test parameters and platelet count

To analyse the correlations between TEG parameters and coagulation test parameters, nonparametric methods were utilized. According to Spearman's correlation coefficient, Angle, MA and LY30 values were negatively correlated with routine coagulation tests for TT, APTT and PT and positively correlated with Fib and platelet count tests. However, the correlations between the *K* value and coagulation test parameters were negative. In addition, the *R* value was only positively correlated with the APTT test. Please refer to Table 4 for all correlation results.

4 | DISCUSSION

The normal reference range of neonatal coagulation-related indicators is significantly different from that of adults.[4,5,19,26] The level of coagulation factors in neonates is only 50% of that in adults, and the level of these factors does not reach the adult level until an infant is 6 months old.[19] In addition, thrombin and its precursors in newborns are also at low level, which eventually leads to an increase in APTT and PT and a decrease in Fib. It has been reported that neonatal

TABLE 2 Comparing the differences in the reference ranges of TEG parameters determined in this study and provided by manufacturers in evaluating neonatal coagulation

Parameter	This study	Manufacturer provided	N/N	N/A	A/N	A/A
R	2.80-7.17**	5.00-10.00	162	195	4	10
Angle	44.73-78.88**	53.00-72.00	199	155	0	17
K	0.80-4.57**	1.00-3.00	277	87	0	7
MA	43.92-74.65**	50.00-70.00	262	91	0	18
LY30	0.10-6.94	0.00-8.00	363	0	2	6

Note: The McNemar test was used for the analysis between the reference ranges determined in our study and provided by manufacturers. *R* (s), *K* (s), Angle (α), maximum amplitude (MA, mm) and lysis at 30 min (LY30, %).
Abbreviation(s): A/A, abnormal data evaluated by both methods; A/N, abnormal data evaluated by this study, normal data evaluated by manufacturers; N/A, normal data evaluated by this study, abnormal data evaluated by manufacturers; N/N, normal data evaluated by both methods; TEG, thromboelastograph.
**$P < 0.01$.

blood is maintained in a state of low coagulation and hyperfibrinolysis. The smaller the gestational age is, the more significant the difference. This is part of the pathophysiological reasons for premature infants with intracranial haemorrhage, pulmonary haemorrhage, gastrointestinal bleeding and DIC.[1,20] Therefore, it is necessary to monitor neonatal coagulation function, which is conducive to the clinical diagnosis and management of neonatal coagulation-related diseases.

In recent years, the TEG has attracted much attention in assessing blood coagulation function and guiding blood transfusion in the preoperative period. Compared with routine coagulation function tests, a TEG can reflect clinical bleeding more sensitively and can also reflect the first and second stages of haemostasis and fibrinolysis.[27-29] The TEG can be more effective and comprehensive in evaluating the coagulation status in the body.[19]

However, the usefulness of the TEG is limited in paediatric populations, especially neonates, mainly owing to the lack of reference ranges and standardization. Currently, the normal reference range of neonatal TEG parameters is mostly based on the biological reference range of adults provided by reagent manufacturers.[30] Approximately 8.5% of the healthy neonates were diagnosed with coagulation abnormalities according to the reference range provided by the manufacturers for TEG determination.[31] The results may mislead clinicians in the diagnosis and treatment and cause adverse events.[8-12] To acquaint clinicians with the coagulation status of neonates over time and to give intervention and treatment actively in neonates, it is necessary to determine the TEG biological reference range for newborns.[32] Reference range for newborns would also help to avoid misdiagnosis and to reduce neonatal mortality.

Based on the statistical analysis of TEG parameters of 371 healthy newborns, we preliminarily established a normal reference range for each TEG parameter during the neonatal period. Moreover, the normal reference range of TEG parameters in the neonatal period is different from the technical parameters provided by manufacturers. In addition, we also analysed the correlation between neonatal patient characteristics, routine blood coagulation test results and platelet count results with TEG test results. Through correlation analyses of TEG parameters and general clinical data, we found that the detection age of a newborn has the maximum effect on TEG parameters. It positively correlated with the *R*, Angle, MA and LY30 values and negatively correlated with the *K* value. With the increase in age, the Angle, MA and LY30 values increased and the *K* value decreased. Results showed that the younger the neonate is, the higher the risk of bleeding, and healthy newborns showed a positive correlation with the speed of starting coagulation, which was consistent with previous

TABLE 3 Thromboelastograph (TEG) parameters for different age groups

	R	Angle	*K*	MA	LY30
1 d (n = 50)	4.80 (2.22-6.50)	57.75 (36.90-73.49)**,‡	2.75 (1.20-6.43)**,‡	50.25 (36.75-67.05)**,‡	0.10 (0.10-0.87)*,‡
2-7 d (n = 105)	4.80 (2.50-7.88)	65.10 (42.20-76.30)‡	1.80 (0.90-5.14)‡	58.50 (44.53-70.72)‡	0.10 (0.07-3.41)‡
8-28 d (n = 216)	4.90 (2.80-7.17)	73.60 (54.80-79.60)	1.20 (0.80-2.82)	66.7 (52.57-75.57)	0.10 (0.10-8.66)
P	0.521	0.000	0.000	0.000	0.000

Note: Data are presented as medians and reference ranges (2.5th and 97.5th percentiles). *R* (s), *K* (s), Angle (α), maximum amplitude (MA, mm) and lysis at 30 min (LY30, %). The Kruskal-Wallis one-way ANOVA test (*k* samples) was used for statistical comparisons among groups. The Mann-Whitney *U* test was used for statistical comparisons between two groups.
Compared with the 2-7 d group,
Compared with the 8-28 d group,
*$P < 0.05$.
**$P < 0.01$.
‡$P < 0.01$.

TABLE 4 Correlation between TEG parameters and coagulation test parameters

	TT		APTT		PT		Fib		PLT	
	ρ	*P*-value	*ρ*	*P*-value	*ρ*	*P*-value	*ρ*	*P*-value	*ρ*	*P*-value
R	0.079	0.131	0.225**	0.000	−0.073	0.160	−0.045	0.387	0.031	0.552
Angle	−0.413**	0.000	−0.527**	0.000	−0.505**	0.000	0.486**	0.000	0.541**	0.000
K	0.417**	0.000	0.520**	0.000	0.520**	0.000	−0.481**	0.000	−0.551**	0.000
MA	−0.404**	0.000	−0.518**	0.000	−0.515**	0.000	0.594**	0.000	0.572**	0.000
LY30	−0.130*	0.012	−0.188**	0.000	−0.236**	0.000	0.131*	0.012	0.364**	0.000

Abbreviation(s): APTT, activated partial thromboplastin time; Fib, fibrinogen; LY30, lysis at 30 min; MA, maximum amplitude; PLT, platelet count; PT, prothrombin time; TEG, thromboelastograph; TT, thromboplastin time.
Spearman correlation was used for the correlation analysis among the parameters. Spearman correlation coefficient (ρ),
*$P < 0.05$.
**$P < 0.01$.

reports.[15,20,33] In addition, the *R* value was more prolonged in newborns delivered by caesarean section, indicating a probable higher risk of bleeding by caesarean section. According to the statistical results, we found that the *R* value was also related to gender, the *R* value was more prolonged in girls and they may be at higher risk of bleeding.

We analysed the correlation between TEG parameters and blood coagulation parameters and platelet counts, which was discussed in the results section. The *R* value was only positively correlated with the APTT test. The TEG test in this study used kaolin; thus, it initiated coagulation activation through the intrinsic pathway, which is the same pathway as the APTT test.[34]

Thus far, there are still few studies on neonatal TEG parameters, the detection methods are diverse, and the sources of the specimens are different. Sources for specimens are peripheral blood, umbilical blood and arterial blood samples.[16,19,20] All these factors have resulted in the diversity of laboratory results. The Pediatric/Neonatal Thrombosis and Hemostasis Scientific and Standardization Committee (SCC) of the International Society on Thrombosis and Haemostasis consistently publishes updated recommendations for the results of laboratory reports for paediatric haemostasis tests and recommends that all diagnostic laboratories use age, analyser and reagent-appropriate reference ranges when processing paediatric samples.[32] Therefore, this study provided a reference value for the detection of coagulation-related indicators in neonates with similar TEG analysers and reagents. However, our research has some limitations. Due to the difficulty in collecting whole blood samples from newborns and recruiting healthy newborns, the number of healthy patients in this study was relatively small. The number of neonates in delivery mode, gender and age was different. There were different amounts of neonates in each group, with more patients with ages between 8 and 28 days than in other age groups. All the above parameters should be further studied.

5 | CONCLUSION

It is necessary to consider the differences in the normal values of the blood coagulation-related tests between neonates and adults when evaluating the blood coagulation function of newborns. The laboratory should establish a suitable biological reference range for newborns according to the instruments and reagents used. In this study, we preliminarily established the reference range for TEG parameters, which might contribute to the management of haemostasis in newborns and the assessment of the status of neonatal bleeding. The results of this study are helpful for the diagnosis and treatment of clinically related diseases and for guiding clinical transfusions of neonates.

ACKNOWLEDGEMENTS

This work was supported by grants from the Science and Technology Project of Zhejiang Province (Grant No. 2018C37008) and the Wuhan Scientific Research Projects (Grant No. WX15C22). In addition, the authors would like to thank the staff of the Department of Blood Transfusion and Clinical Laboratory, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology.

CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTION

Hongbing Hu designed the research study. Xin Chen and Zhunhui Ke performed the research. Qin Liu and Jia Wang analysed the data. Qin Liu and Chunfeng Xu wrote the paper.

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How to cite this article: Liu Q, Xu C, Chen X, Wang J, Ke Z, Hu H. Establishing a reference range for thromboelastograph parameters in the neonatal period. *Int J Lab Hematol*. 2019;41:530–535. https://doi.org/10.1111/ijlh.13043