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ORIGINAL ARTICLE

Usefulness of the thromboelastogram in children: correlation with habitual coagulation tests

Utilidad del tromboelastograma en pediatría: correlación con pruebas habituales de la coagulación

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Abstract

Introduction: Usual coagulation tests partially evaluate different elements of hemostasis, and do not translate cell interactions, which is an especially sensitive issue in critically ill patients. Viscoelastic measurement techniques, such as thromboelastogram (TEG) show the complete coagulation process and are being evaluated as global coagulation tests. **Objective:** To determine the correlation of the usual coagulation tests with the TEG values, in children treated in an intensive care unit (ICU). **Patients and Method:** We reviewed 238 TEGs of patients under 18 years of age, with evidence of clinical and/or laboratory coagulation alterations, who were hospitalized in the ICU. The TEG parameter values were correlated with each of the usual coagulation test values. The tests were obtained according to the protocol, using a 4.5 ml blood sample for TEG with TEG® 5000 Thrombelastograph Hemostasis System, through an electromagnetic transducer that allows the measurement of resistance during the clot formation and lysis. Platelet count was obtained using an automated method or phase-contrast microscopy, and fibrinogen levels, prothrombin time, and partial thromboplastin time activated by nephelometric methods. **Results:** 201 TEGs corresponding to 59 patients were reviewed. A moderate to low correlation was observed in all the measured parameters. No correlation was found between the percentages of clot lysis or clot firmness. **Conclusions:** There is a low correlation between the information provided by TEG and the usual coagulation tests. This suggests that the TEG provides different information about the coagulation status of the evaluated critical patients.

Keywords:
Thromboelastography;
Coagulopathy;
TEG;
Children

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Introduction

The cell-based model of coagulation, described by Maureane Hoffman in 2003, has determined a very important change in the understanding of the coagulation phenomenon. Among its contributions, a relevant point is the participation of cells and their membranes in the activation and modulation of coagulation[1]. Based on this new premise, the usual coagulation tests, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and platelet count, turn out to be only partial views of a complex and dynamic global phenomenon[2]. Therefore, the current trend is to look for 'global coagulation tests', which somehow manage to show the final result of the multiple interactions between plasma proteins, cell membranes, and inflammatory factors[3].

It is in this context that the viscoelastic measurement techniques reappear, described in 1948 in Germany. There are currently two types of techniques, RoTEM® and TEG®, both are performed on whole blood and measure the viscoelastic properties variation of the blood during the coagulation process, detailing from the clot formation to fibrinolysis[4] (Figure 1).

The following are the described variables[5]:

- **Reaction time (R):** it allows the evaluation of the time elapsed since the first fibrin bands begin to form. It mainly represents the quantity and function of coagulation factors.
- **Coagulation time (K):** it records the time from the beginning of fibrin formation until the clot reaches a certain firmness, in other words, it evaluates the time of clot formation. It represents the action of coagulation factors, platelets, and fibrinogen.
- **Alpha angle (α):** it reflects the clot formation speed, which decreases, for example, in the presence of antiplatelet agents.
- **Maximal Amplitude (MA):** it evaluates when the clot reaches its maximum strength, depending on the interaction between the fibrin and the number and function of the platelets. It increases in states of hypercoagulability and decreases in platelet dysfunction, thrombocytopenia or hypofibrinogenemia.
- **Clot lysis (LY30):** It is the measure in percentage of the clot lysis in a determined time (30 minutes). It reflects the clot stability, and it increases in processes where there is an increase in fibrinolysis (hyperfibrinolysis).
- **Clot firmness (G):** it measures the clot firmness globally, its value is expressed in absolute numbers and is very sensitive to changes of maximal amplitude.
- **Coagulation index (CI):** it measures globally the patient's coagulation status, i.e. hypocoagulability or hypercoagulability.

Until now, their use as a point of care has been the most widespread and validated, especially as a blood transfusion guideline in cardiac surgery[6], liver transplantation[7], postpartum hemorrhage[8], and trauma[9].

Their usefulness in the coagulation evaluation in the critical patient, especially adult, is being assessed in different scenarios, mainly because of the ability to deliver a global coagulation view. Even, unlike most of the available test, they give us the ability to evaluate patients on treatment with heparin (a drug widely used in critical care), due to the possibility of blocking the heparin effect by adding heparinase in the sample[10].

The Clinical Hospital of the UC CHRISTUS Health Network began using the TEG in 2013. Unlike other centers, which use one equipment in each critical unit, we have only two equipment for the entire hospital (located in the emergency laboratory), thus the sam-

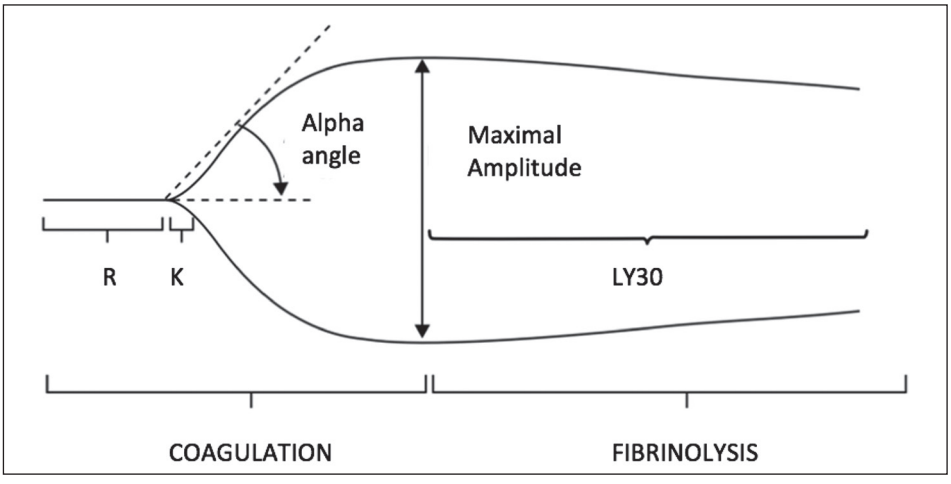

Figure 1. Schematic representation of normal thromboelastogram. Extracted from Gempeler et al.[5].

ples are taken and derived quickly, transmitting their processing directly through terminals and monitors in different critical areas.

The objective of this study is to determine the correlation between the usual coagulation tests and the values of the different thromboelastogram phases in the coagulopathies evaluation of patients hospitalized in the pediatric intensive care units at the Clinical Hospital of the UC CHRISTUS Health Network.

Patients and Method

Study design

Descriptive, retrospective, correlational study carried out with information collected from the database of thromboelastograms in a period of 2 years and 6 months (from June 2015 to December 2017).

Samples were selected through convenience sampling from pediatric patients who presented clinical and/or laboratory coagulation alteration and were hospitalized in the intensive care unit.

Strict criteria for admission to the study were established, selecting the TEGs, which were requested simultaneously with usual coagulation tests, obtained from the same blood sample of the patient. Those TEGs that had a delay in sampling time regarding the rest of the tests or that did not have a complete usual coagulation study were excluded.

This study received approval and informed consent from the Ethics Committee of the Pontifical Catholic University of Chile on January 02, 2018.

Tests and selection processes from a database

The database of pediatric patients evaluated with TEG was analyzed, including the record of thromboelastograms, associated pathologies, and conventional coagulation tests performed.

We reviewed 238 thromboelastograms and 201 of those were selected, which had PT, aPTT, and platelets count and fibrinogen performed simultaneously. 37 TEGs were excluded due to the lack of regular tests carried out all at ones and/or incomplete regular tests.

Procedures and data collection

Test results were obtained via the thromboelastogram database record performed at the Clinical Hospital of the UC CHRISTUS Health Network.

The tests were performed according to the institutional protocol, using a 4.5 ml blood sample to carry out the thromboelastogram with the TEG® 5000 Thrombelastograph Hemostasis System, through an electromagnetic transducer that allows measuring the resistance during the formation and lysis of the clot.

In addition, platelet results were obtained using the automated method (hematology analyzer) or phase-contrast microscopy (Neubauer counting chamber), fibrinogen with Nephelometry method (ACL 9000), and prothrombin time and aPTT using Nephelometry method (ACL 9000, ACL TOP).

Variables Analyzed

A clinical records review of the patients was conducted and the following variables were collected: age, sex, pathologies, platelet count, fibrinogen, PT, aPTT, and TEG.

Statistical analysis

The statistical analysis was performed using the IBM SPSS Statistics 20 software. The values of the different parameters of thromboelastography were correlated with each of the values of the regular coagulation tests performed routinely.

Continuous quantitative variables were analyzed using Pearson's correlation coefficient, and the measurement variability levels using the Bland-Altman method, calculating 95% confidence intervals. In addition, scatter plots were made for the analyzed variables and the determination coefficient was calculated.

Results

201 TEGs of 59 patients with different pathologies were reviewed. The median age of the patients was 11 months, ranging from 2 days to 17 years.

Out of the total number of thromboelastograms performed, 85 (42.3%) corresponded to female patients and 116 (57.7%) to male ones.

Among the different pathologies that were analyzed using thromboelastograms to evaluate coagulopathies were the following (Table 1): patients with extracorpo-

Table 1. Pathologies and number of thromboelastograms performed

Pathologies	N° of TEGs
Respiratory / cardiac pathologies in ECMO	61
Liver transplant	43
Cardiomyopathy in ventricular assistance	23
Operated Heart Disease	20
Hemorrhagic diathesis	18
Liver failure	16
Multiple Organic Dysfunction	12
Trauma surgery	4
Acute leukemia with coagulopathy	4
Total	201

ECMO: extracorporeal membrane oxygenation; TEGs: thromboelastograms.

real membrane oxygenation (ECMO), liver transplantation, cardiomyopathy requiring ventricular assist device, surgeries for complex heart diseases, bleeding diathesis, liver failure, multiple organ dysfunction, trauma surgery, and acute leukemias with associated coagulopathies.

The correlation (r) between the different continuous quantitative laboratory variables was calculated with the values of the different thromboelastogram phases (n = 201) (table 2).

Reaction time (R) with platelets, fibrinogen, PT, and aPTT

A moderate correlation with aPTT with r = 0.45 ($p < 0.01$) was considered significant, showing that aPTT prolongation is directly proportional to R time prolongation; no significant correlation was found with the rest of the variables analyzed.

Coagulation time (K) with platelets, fibrinogen, PT, and aPTT

A moderate correlation with PT was considered significant, with r = -0.398 ($p<0.01$), inversely proportional, therefore, the lower the PT percentage, the longer the K time extension; low correlation with platelets and fibrinogen since the latter are found in small quantities and were associated with a longer K time extension; there was no significant correlation with aPTT.

Alpha angle (α) with platelets, fibrinogen, PT, and aPTT

A moderate correlation with fibrinogen was considered significant, with r = 0.493 ($p<0.01$), low correlation with platelets, with r = 0.370 ($p<0.01$), in other words, a higher platelet count and fibrinogen were associated with a higher alpha angle; without significant correlation with PT or aPTT.

Maximal amplitude (MA) with platelets, fibrinogen, PT, and aPTT

A moderate correlation with platelets with r = 0.519 ($p < 0.01$) was considered significant, and moderate correlation with fibrinogen, with r = 0.496 ($p < 0.01$), therefore, the platelets count and fibrinogen were directly associated with the maximal amplitude reached; with no significant correlation with PT or aPTT.

Clot lysis (LY30) with platelets, fibrinogen, PT, and aPTT

There was no significant correlation with the analyzed variables.

Clot firmness (G) with platelets, fibrinogen, PT, and aPTT

There was no significant correlation with the analyzed variables.

Coagulation index (CI) with platelets, fibrinogen, PT, and aPTT

Low correlations with platelets r = 0.278 ($p < 0.01$), PT r = 0.255 ($p < 0.01$), aPTT r = - 0.328 ($p < 0.01$), and fibrinogen r = 0.316 ($p < 0.01$). Therefore, when the analyzed variables were found in small quantities, they were associated with hypocoagulability, and in contrast, when they were found in higher quantity, they were associated with hypercoagulability.

Discussion

Our study suggests a moderate to low correlation between the regular coagulation tests with the different TEG phases.

This confirms our appreciation since we have ob-

Table 2. Phase correlation of thromboelastogram with conventional coagulation tests (n = 201 TEGs)

	Pearson correlation coefficient (r)			
Phases of the TEG	Conventional coagulation tests			
	Platelets (x 10^3/mm3)	PT(%)	aPTT (seconds)	Fibrinogen (mg/dL)
Reaction time (minutes)	-0.150	0.261	**0.450 ***	-0.088
K time (minutes)	-0.349*	**-0.398***	0.240	**-0.376***
Alpha angle (α)	**0.370***	0.245	-0.221	**0.493***
Maximal Amplitude (millimeters):	**0.519***	0.242	-0.079	**0.496***
Ly30:% clot lysis (%)	0.052	-0.092	0.127	-0.099
G: clot firmness (dynes / cm2)	0.260	-0.068	-0.004	0.467
IC: Coagulation Index	**0.278***	**0.255***	**-0.328***	**0.316***

* $p < 0.05$. PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

served that although PT and aPTT reflect the concentration of coagulation factors, this is often not evident in the corresponding R or K time. Something similar occurs with platelet count and fibrinogen regarding the MA, despite that in both cases we found a correlation, it was lower than expected[11]. This could be explained by the fact that PT, aPTT, and fibrinogen are performed in plasma obtained from centrifugation, isolating cellular components[12]. In addition, the platelet count considers the number of platelets, but not their function or state of activation and interaction with other humoral or cellular components[13].

Our study also highlights the moderate correlation between R with aPTT and K with PT; perhaps this suggests that R reflects the integrity of the intrinsic system, and K would translate the action of extrinsic pathway factors, given by the formation of the TF/FVII complex, responsible for initiating clot formation and 'thrombin burst', a key event for clot formation.

Another important point is that there was no correlation between any of the usual coagulation tests and the fibrinolysis degree (LY30), which is an important contribution of these viscoelastic techniques since patients with hyperfibrinolysis can be treated with antifibrinolytic drugs (Tranexamic Acid or Aminocaproic Acid)[14].

We believe that adding viscoelastic techniques in the evaluation of critical patients, in addition to the use as a point of care to guide transfusion therapy, would contribute to a better understanding of the coagulation state in these patients, especially in those with altered regular coagulation tests, as occurs in various pathologies (e.g. liver or kidney failure, inflammatory and infectious states, or drugs), but may not be translated in the same way in global coagulation, or in contrast, conditions or pathologies in which routine tests are normal, or slightly altered, and are not capable of translating coagulation alterations (Figure 2).

Our study has the limitations of a descriptive, correlational study, establishing only associations in a group with heterogeneous patients.

Conclusions

We believe that the TEG provides us with additional and/or complementary information to the regular coagulation tests, which allows us to better unders-

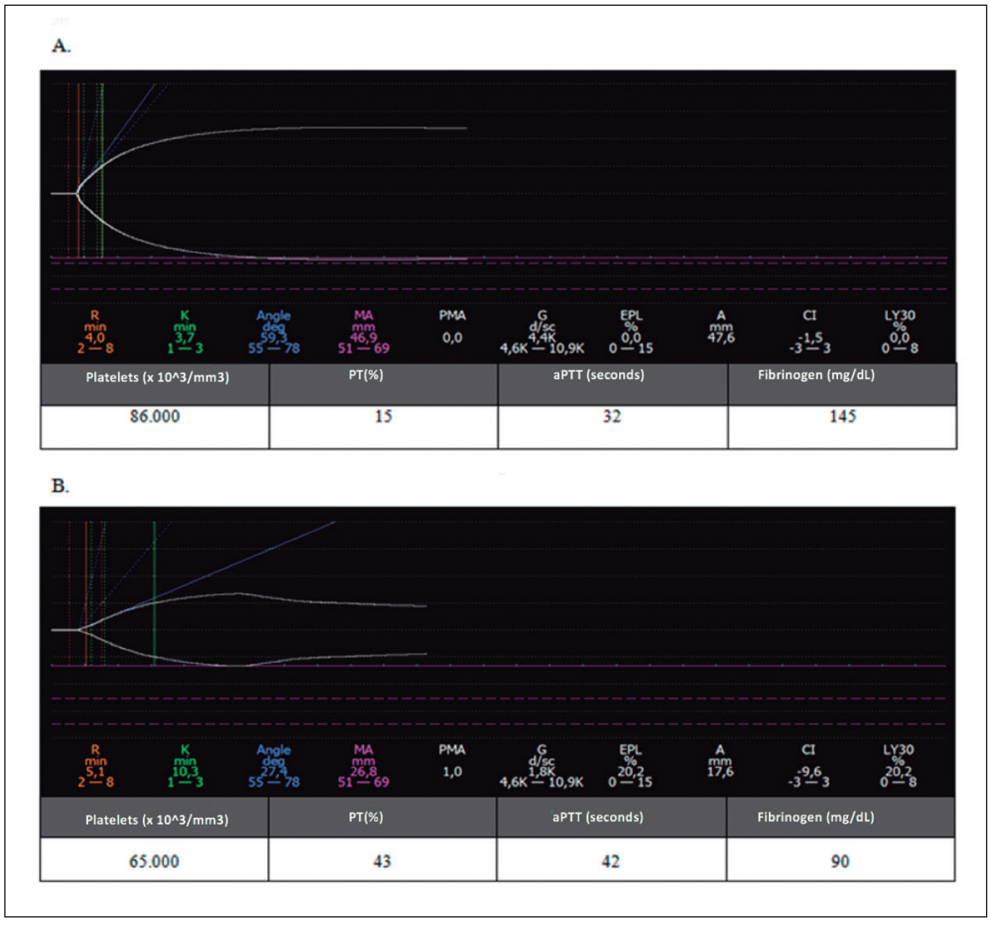

Figure 2. Examples of thromboelastograms that show little correlation with usual coagulation tests. **(A)** Patient with chronic liver damage prior to liver transplantation, with alterations in usual coagulation tests, but with hemostatic rebalance characteristic of the underlying pathology. **(B)** Patient with multiple organic dysfunction, with clear evidence of hyperfibrinolysis (LY30: 20.2%), impossible to identify with conventional tests.

tand the evolution of the coagulation state in critical patients. However, it still remains to be assessed how it influences the morbidity and mortality of pediatric patients.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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