

# Evaluation of Thromboelastometry in Sepsis in Correlation With Bleeding During Invasive Procedures

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## Abstract

Prolongation of prothrombin time (PT) is often encountered in patients with sepsis. On the other hand, thromboelastometry as a global coagulation test might yield normal results. The aim of our study was to evaluate whether prolonged PT in the presence of normal thromboelastometry parameters is associated with severe bleeding in patients with sepsis undergoing invasive procedures. In patients with sepsis undergoing low-risk bleeding invasive procedures (central venous catheter placement, dialysis catheter insertion, drain insertion, and so on) or high-risk bleeding invasive procedures (surgical tracheostomy, surgical laparotomy, thoracotomy, and so on), coagulation was assessed by thromboelastometry using EXTEM test (test for evaluation of the extrinsic pathway of coagulation, contains activator of extrinsic pathway) and with PT. For period of years 2013 to 2016, we assessed occurrence of severe bleeding during those procedures and 24 hours later in patients with prolonged PT and normal thromboelastometry results. This retrospective study was performed at Department of Anaesthesiology and Intensive Care Medicine of Motol University Hospital in Prague. Data from 76 patients with sepsis were analyzed. Median value of international normalized ratio (INR) was 1.59 (min—1.3 and max—2.56), and median value of prothrombin ratio (PR) was 1.5 (min—1.23 and max—2.55) with normal thromboelastometry finding. Despite prolonged INR/PR, no severe bleeding was observed during invasive procedures. Our data show that sepsis may be accompanied by normal thromboelastometry results, despite prolonged values of PT, and invasive procedures were performed without severe bleeding. This approach to coagulation assessment in sepsis may reduce administration of fresh frozen plasma to the patients. The study was registered at Clinical Trials.gov with assigned number NCT02971111.

## Keywords

EXTEM, invasive procedure, prothrombin time, sepsis, thromboelastometry

## Introduction

Evaluation of extrinsic coagulation pathway using prothrombin time (PT) with its derived measures of prothrombin ratio (PR) and international normalized ratio (INR) is routinely used for coagulation assessment before invasive procedures in intensive care unit (ICU) patients. Because they do not reflect global coagulation profile (they do not consider effect of platelets and other blood substances), they are being replaced by rotational thromboelastometry (ROTEM) in perioperative assessment of coagulation during liver transplant surgery, general surgery, pediatric surgery, and trauma resuscitation.<sup>1-4</sup>

Thromboelastometry is a method that evaluates coagulation profile of the whole blood (containing platelets, red blood cells, and so on) and takes into account the principle of cell-based model of coagulation where platelets play critical role in coagulation.<sup>5</sup> This method is increasingly used in monitoring of

coagulation profile mainly in surgical situations, especially in cardiothoracic and other surgeries,<sup>3,4</sup> but also for coagulation assessment in nonsurgical situation such as obstetric bleeding in pregnant women and patients with sepsis.<sup>6-8</sup> Sepsis is often accompanied by normal or hypercoagulable thromboelastometry results, despite prolonged values of INR.<sup>6,9,10</sup> Additionally, in other medical fields such as hepatology, De Pietri et al used

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thromboelastography to assess coagulation profile before invasive procedure in patients with cirrhosis and found normal coagulation profile, despite prolonged INR.<sup>11</sup> Thromboelastometry seems to better correlate with clinical situation than standard coagulation tests,<sup>3</sup> and it is imperative to look for a coagulation test that would assess coagulation profile in patients with sepsis better than INR. Normal or hypercoagulable thromboelastometry results prevent administration of fresh frozen plasma (FFP) or other clotting factors such as prothrombin complex concentrate (PCC) which would have been administered to the patient to correct pathologic INR in order to prevent severe bleeding. Recently, we have published a small prospective study in ICU patients who had surgical tracheostomy performed without severe bleeding with normal ROTEM results, despite prolonged INR values.<sup>12</sup> We decided to do a retrospective study, where we assessed coagulation profile of patients with sepsis by thromboelastometry and INR/PR in patients undergoing invasive procedures. We also evaluated whether procedures were accompanied by severe bleeding.

## Methods

The study was approved by the Ethics Committee for Multi-Centric Clinical Trials of the University Hospital Motol, V Uvalu 84, Prague, on December 7, 2016, with reference no: EK-1555/16. Data were extracted retrospectively from patients hospitalized at our ICU during the period March 2013 to October 2016. Patients with septic shock undergoing low-risk bleeding invasive procedures (central venous catheter placement, dialysis catheter insertion, drain insertion, and so on) or high-risk bleeding invasive procedures (surgical tracheostomy, surgical laparotomy, thoracotomy, and so on) were included in the study. Coagulation was assessed by thromboelastometry using EXTEM test (test for evaluation of the extrinsic pathway of coagulation, contains activator of extrinsic pathway) and with PT using INR. Septic shock was defined using the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) of Singer et al, where patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level >2 mmol/L (>18 mg/dL) in the absence of hypovolemia.<sup>13</sup> Patients with septic shock who underwent invasive procedures with prolonged value of INR  $\geq 1.3$  (normal range 0.8-1.2) and normal EXTEM results were included in the study, and the presence of severe bleeding was evaluated. We also evaluated coagulation status and the presence of disseminated intravascular coagulation (DIC) using International Society of Thrombosis and Haemostasis score (ISTH score), and patients were classified as having or not having overt or non-overt DIC.<sup>14</sup> This included platelet count (platelet count >100/nL = 0; <100/nL = 1; and <50/nL = 2), prolonged PT (PT <3 seconds = 0; >3 but <6 seconds = 1; >6 seconds = 2), fibrinogen level (>1.0 g/L = 0; <1.0 g/L = 1), and D-dimer level (no increase = 0; moderate increase = 2; and strong increase = 3). If the ISTH score was calculated as 5 or more, it would be

compatible with overt DIC. If the score was <5, it would be suggestive (not affirmative) for nonovert DIC.

## Exclusion Criteria

Patients taking antiplatelet drugs or anticoagulant therapy (heparin, vitamin K antagonists, and so on) and patients with cirrhosis were excluded.

The following EXTEM parameters were evaluated: coagulation time (CT), time from the start of the sample run to the first detectable clot formation (amplitude = 2 mm); clot formation time (CFT), time from CT to the clot amplitude of 20 mm (to specify the kinetics of the clot development);  $\alpha$  angle, angle between the trace and the x-axis; maximum clot firmness (MCF); and Lysis Index (LI30 and LI60), percentage of fibrinolysis at 30 and 60 minutes after CT. Bleeding was assessed during the procedure and postoperatively for up to 24 hours. The following 3 conditions were considered as severe bleeding: (1) surgeon performing procedure assessed the bleeding as major—nonstandard, (2) surgical revision was necessary to stop the bleeding, or (3) decrease in hemoglobin levels during 24-hour postoperative period by more than 10 g/L because of bleeding.

Analysis of PT was done by the ACL TOP 700 Automated Haemostasis Testing System manufactured by Instrumentation Laboratory, Bedford, Massachusetts. Reagents were provided by the device manufacturer (PT-PT RecombiPlas-tin, Bedford, Massachusetts). For thromboelastometry, EXTEM test was used (TEM International GmbH delta, Munich, Germany; test containing tissue factor for activation of extrinsic pathway of coagulation).

## Statistical Analysis

For data analysis, GraphPad Prism 6.0 statistics program was used. Descriptive statistics was used to determine median, minimal, and maximal values of INR/PR and EXTEM parameters CT, CFT,  $\alpha$  angle, MCF, LI30, and LI60 (data were not normally distributed according to the D'Agostino & Pearson omnibus normality test).

## Results

Seventy-six patients were included in our study, and there was no severe bleeding in any of the patient with normal thromboelastometry results, despite prolonged values of INR/PR, neither during the procedure nor postoperatively for up to 24 hours. No fresh frozen plasma or other clotting factors such as PCC were administered before intervention to correct INR before the procedure. Types of invasive procedures performed are specified in Table 1, and characteristics of the patients and the source of infection are described in Table 2. Median value of INR was 1.59 (min—1.3 and max—2.56), median value of PR was 1.5 (min—1.23 and max—2.55), and median value of DIC score was calculated as 4 (min—1 and max—6). All these parameters are described

**Table 1.** Characteristics of Invasive Procedures.

| Type of Low-Risk Bleeding Invasive Procedure   | n  | Type of High-Risk Bleeding Invasive Procedure | n  |
|--|----|---|----|
| central venous and arterial catheter insertion | 26 | Surgical tracheostomy                         | 12 |
| Dialysis catheter insertion                    | 7  | Surgical laparotomy                           | 12 |
| Abdominal and thoracic drain insertion         | 14 | surgical thoracotomy                          | 3  |
| Lumbar puncture                                | 1  | Total number                                  | 76 |
| Percutaneous endoscopic gastrostomy            | 1  |   |    |

**Table 2.** Characteristics of the Study Population.

|   |            |
|---|------------|
| Age, years, median, min-max   | 64, 24-89  |
| Sex, men/women  | 43/33      |
| SOFA score, median, min-max   | 9.75, 4-17 |
| Source of infection   |            |
| Lungs (pneumonia)   | 13         |
| Mediastinum (mediastinitis)   | 12         |
| Abdomen (peritonitis, cholangitis, cholecystitis, and pancreatitis) | 38         |
| Spine (spondylodiscitis)  | 2          |
| Hip (coxitis)   | 2          |
| Knee (gonitis)  | 1          |
| Leg gangrene  | 5          |
| Central nervous system (meningitis)                                 | 1          |
| Unknown   | 2          |

Abbreviations: max, maximum; Min, minimum; SOFA, Sequential Organ Failure Assessment Score.

together with other coagulation and thromboelastometry parameters in Table 3.

## Discussion

In our group of 76 patients with sepsis who had normal values of EXTEM, despite prolonged INR/PR invasive procedures were performed without severe bleeding. Also, Müller and Li in their studies<sup>15,16</sup> describe that patients with sepsis did not bleed during invasive procedures, despite prolonged values of INR. This phenomenon may be explained by the fact that whole blood has different coagulation profile than pure plasma (when measuring INR/PR) and that blood cells such as platelets play critical role in coagulation as described in the cell-based model of coagulation.<sup>5</sup> Li et al described similar finding and detected isolated decreased level of FVII<sup>16</sup> prolonging only INR in patients with acute appendicitis, while thromboelastometric results were normal. In the current study, findings are also similar to a randomized controlled trial published by De Pietri et al who showed that invasive procedures can be done without severe bleeding in patients with cirrhosis and INR >1.8.<sup>11</sup>

**Table 3.** Values of Laboratory Coagulation Parameters, DIC Score, and EXTEM (Rotational Thromboelastometry) Parameters.<sup>a</sup>

|                       | Median | Min-Max    |
|-----------------------|--------|------------|
| Coagulation parameter |        |            |
| INR                   | 1.59   | 1.3-2.56   |
| PR                    | 1.5    | 1.23-2.55  |
| PT, seconds           | 17     | 13-32      |
| Platelets, × 1000/μL  | 259    | 32-893     |
| Fibrinogen, g/L       | 4.93   | 1.42-8.9   |
| D-dimers, ng/mL       | 1782   | 240-15 000 |
| ISTH DIC score        | 4      | 1-6        |
| EXTEM parameter       |        |            |
| CT, seconds           | 62     | 30-79      |
| CFT, seconds          | 66     | 28-153     |
| α angle, °            | 77     | 65-85      |
| MCF, mm               | 70     | 51-97      |
| LI30, %               | 99     | 97-100     |
| LI60, %               | 95     | 89-100     |

Abbreviations: INR, international normalized ratio; PR, prothrombin ratio; PT, prothrombin time; ISTH DIC score, International Society on Thrombosis and Haemostasis Disseminated Intravascular Coagulation; CT, coagulation time, time from the start of the sample run to the first detectable clot formation (amplitude = 2 mm); CFT, clot formation time, time from CT to the clot amplitude of 20 mm (to specify the kinetics of the clot development); α angle, angle between the trace and the x-axis; MCF, maximum clot firmness; LI30 and LI60, Lysis Index at time 30 and 60 minutes after CT; min-max, minimal value-maximal value.

<sup>a</sup>Normal values of EXTEM parameters: CT 38-79 seconds, CFT 34-159 seconds, α angle 63-83°, MCF 50-72 mm, LI 30 94%-100%, LI 60 85%-100%.

The coagulation system is commonly activated in sepsis as a result of cross-reactions with inflammatory system.<sup>17</sup> Daudel et al in his study proved it by measuring low level of factor VII (FVII) and factor II (FII) which explained prolonged PT and APTT value. However, fibrinogen was increased with normal values of factor V (FV), factor X (FX), and platelet count which explained normal results of ROTEM giving complex information of whole blood coagulation.<sup>18</sup> Similarly, Collins et al found a patient with sepsis with low levels of FII, FV, FVII, FX, FXI, FXII, antithrombin, and protein C, while FVIII and fibrinogen level was increased together with MCF of low-dose-tissue factor activated ROTEM (LD-TFA ROTEM).<sup>19</sup> He also described prolonged CT of LD-TFA ROTEM and concluded that initiation phase may be delayed but once initiated clot formation is normal or increased. It means that coagulation in sepsis is not constant and can change in the time dynamically. This phenomenon may be responsible for the fact that even thromboelastometry results can be influenced by many factors, and results of different studies are not consistent. Therefore, according to Levi et al, only in cardiac surgery field there is an adequate evidence to show that use of thromboelastography leads to better clinical outcomes, such as reduction in bleeding-related morbidity and mortality and cost-effectiveness, and he says that more research is required in other areas.<sup>20</sup>

In our group of patients with sepsis, median DIC score was calculated as 4 (Table 3), which indicates that these patients might have been going through nonovert DIC. Despite maximum calculated score of 6, which would mean the presence

of overt DIC, no increased bleeding was observed in any patient, thus disapproving the presence of overt DIC. Whether detected coagulopathy in our patients was result of increased consumption or decreased production of coagulation factors is not clear. However, sepsis coagulopathy is often described as very complex, both by standard coagulations tests and by thromboelastometry, which is accompanied with hypercoagulation status at the beginning, leading to consumption of coagulation factors and subsequently to hypocoagulation status characterized by diffuse bleeding.<sup>21-23</sup> Referring to the mentioned article, we believe that our patients were somewhere at the beginning of sepsis coagulopathy process accompanied by nonovert DIC. In those cases, thromboelastometry seemed to be helpful in assessment of sepsis coagulopathy before invasive procedures and if normal, procedures were performed without increased bleeding.

In the current study, thromboelastometry EXTEM test was preferably analyzed in this study because extrinsic pathway of coagulation plays the most critical role in coagulation in vivo as Mackman et al<sup>24</sup> have documented in their article, and it is critical for clotting based on the cell-based model of coagulation.<sup>5</sup> Our results indirectly support this statement, as there was no severe bleeding recorded in all procedures when EXTEM finding was normal. In addition, EXTEM test was also used by Hagemo in patients with trauma, and he found it to be a valid marker of acute traumatic coagulopathy.<sup>25</sup>

Using thromboelastometry for evaluation of coagulation in patients with sepsis before interventions also prevented transfusion of FFP or PCC which would have been administered to the patient to correct pathologic INR/PR, and procedures could have been done without delay. As it is well known that unnecessary administration of FFP may lead to many complications and is even associated with higher mortality,<sup>26</sup> we believe that thromboelastometry may be the more appropriate test for coagulation assessment than INR/PR in patients with sepsis undergoing invasive procedures.

The limitation of the study is that it only describes a cohort of patients with normal thromboelastometry results and prolonged values of INR/PR. There were no data found describing the case of abnormal thromboelastometry results and performed invasive procedure. The most probable reason is that no doctor would put the patient to such risk of bleeding complication. Nevertheless, we believe that these findings will be helpful for clinicians in the assessment and management of septic coagulopathy in daily practice.

## Conclusions

In conclusion, our data describe that sepsis may be accompanied by normal thromboelastometry results, despite prolonged values of INR/PR. When EXTEM results were within normal range, invasive procedures were performed without severe bleeding and without administration of fresh frozen plasma or other clotting factors, despite prolonged value of INR/PR. This approach in coagulation assessment of sepsis (using thromboelastometry) might reduce unnecessary FFP or PCC

administration in daily practice and can shorten the time needed to prepare the patient for an invasive procedure.

## Authors' Note

Pavel Lukáš designed the study, conducted the study, collected data, analysed data and prepared the manuscript. Miroslav Durila, designed the study design, conducted the study, collected data, and prepared the manuscript. Jakub Jonáš, collected data and helped to prepare the manuscript. Tomáš Vymazal collected data and helped to prepare the manuscript.

**Information about registration at clinicaltrial.gov:** <https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0006PTL&selectaction=Edit&uid=U000352I&ts=8&cx=52k6lv> Unique Protocol ID: 1318514. ClinicalTrial.gov ID: NCT02971111

## Declaration of Conflicting Interests

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