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Burn Patients with TBSA ≤ 30% Display Whole Blood Hypercoagulablility 14 days' Post Trauma

Christian Lyngsaa Lang[1]*, Jais Oliver Berg[1], Sisse Rye Ostrowski[2], PärIngemar Johanson[2], and Liselotte Sabroe Ebbesen[1]

[1]*Department of Plastic Surgery, Copenhagen University Hospital Rigshospitalet, Denmark*

[2]*Section for Transfusion Medicine 2032, Copenhagen University Hospital Rigshospitalet, Denmark*

***Corresponding author**

Christian Lyngsaa Lang, Department of Plastic Surgery, Copenhagen University Hospital Rigshospitalet, Sankt Petersborg Plads 2, 3th, 2150 Nordhavn, Denmark, Tel: 0045-40930858; Email: c.lyngsaa@gail.com

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Keywords

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Abstract

Introduction: The aim of this study was to investigate baseline and 14 days prospective changes in viscoelastic whole blood coagulation by thromboelastography (TEG) in patients with moderate and severe burns corresponding to ≥ 10 % total body surface area (TBSA).

Methods: 13 patients with burns ≥ 10% were included in the study. TEG analysis and standard coagulation parameters as APTT, INR, platelet count, and fibrinogen were carried out at admission and the following 14 days.

Results: Most TEG variables changed in a hypercoagulable direction the first 2 weeks following burn injury. α values increased ($p<0.0004$) from post burn day one 54 degrees to 69 degrees' day seven. MA increased ($p<0.05$) from 62 mm at day one to 73 mm at day five. K values decreased ($p<0.03$) from 2.9 minutes at day one to 1.9 minutes at post burn day three. MTG ($p<0.005$) started at 15994 mm*100/sec at day one and increased to 30549 mm*100/sec at post burn day eight. All remained significant until day 14. R, Ly-30 and TMG did not change in the observation period.

In contrast APTT increased ($p<0.05$) from 25.8 sec. to 30.2 sec. in six days. Fibrinogen increased from 11.55mmol/L to 20.37 mmol/L day six ($p<0.05$) and INR decreased from 1.17 to 1.05 day five ($p< 0.02$).

Conclusion: Burn patients with TBSA ≤ 30% and who are not subject to surgical intervention are in a hypercoagulable state detected by whole blood viscoelastic haemostatic assays TEG that extended 2 weeks post injury.

ABBREVIATIONS

TEG: Thromboelastography; TBSA: Total Body Surface Area; R: Reaction Time; K: kinetics; α: Angle; APTT: Activated Partial Thromboplastin Time; INR: International Normalised Ratio; MA: Maximum Amplitude; LY30: Lysis After 30 Minutes; MTG: Maximal Thrombin Generation Time; TMG: Time to MTG; VTE: Venous Thrombo Embolism; IH: Inhalation Injury; ATIII: Anithrombin III; VIIa: Activated Factor VII; ICU: Intensive Care Unit

INTRODUCTION

Patients with non-thermal trauma have varying degrees of acute coagulopathy [1]. The type of trauma acquired coagulopathy seems to be related to the degree of tissue injury and circulatory shock [2]. As a sub population, there is relatively little data regarding haemostatic changes in burn injury patients. Previous studies in burn patients have focused on single factor test, split products of coagulation and other plasma-based standard coagulation test. These studies indicate that in the first week following severe burn injury, burned patients are in a hypercoagulable and hyper fibrinolytic state [3-5]. Few studies have examined whole blood coagulation and in these studies, study subjects were only evaluated on admission and after one week with a limited number of patients who all received early burn wound surgery [6,7]. Moreover, it is not clear whether this coagulopathy extends beyond the first 7 days, nor has the natural course of haemostatic changes in burn patients previously been described. Burn injury associated coagulopathy is of interest as burn patients face opposite directed challenges associated with the haemostatic changes; the heightened thrombogenecity enhances the risk of venous thromboembolism (VTE) [8]. Furthermore, patients with large burns often require large amounts of blood transfusions during escharectomy all of which may result in increased mortality and morbidity.

Understanding the haemostatic changes in burn patients might help to plan an individualised treatment hereby preventing VTE and excessive bleeding during escharectomy. Given the limited data on the haemostatic changes that occurs following burn injury, the aim of this study was to investigate baseline

and 14 days' prospective changes in viscoelastic whole blood coagulation by thromboelastography (TEG) in patients with moderate and severe burns corresponding to ≥ 10 % total body surface area (TBSA).

MATERIALS AND METHODS

Study design

A prospective, explorative study of whole blood coagulation in burn patients evaluated by TEG during the first 14 days of admission at a burn unit in a national referral university hospital (Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark). The study was approved by the regional ethics committee (H-C-2008-075) and the Danish Data Protection Agency and conducted in accordance with the Helsinki II declaration.

Inclusion criteria

Adult patients (age > 18 years) with 2nd and 3rd degree burns ≥ 10 % TBSA, with no need of acute burn surgery, who were referred within the first 10 hours after thermal trauma and who were able to give informed consent were included at admission. Exclusion criteria were: primary need for palliative or intensive care, lack of informed consent, pregnancy, chronic uraemia, hepatic insufficiency, known hematologic disease or participation in other scientific studies.

Blood samples

Blood samples were collected by venepuncture on a daily basis in the first 14 days of the post burn period. After the samples were drawn they were analysed by TEG and routine assessment of international normalized ratio (INR), activated partial thromboplastin time (APTT), D-dimer, Anti-thrombin, Fibrinogen and platelets. The samples for TEG analyses were collected in 3.0 mL glass container with citrate and the analyses were conducted within 30 minutes after sampling. Kaolin was used as activator. The following parameters were evaluated with TEG: Reaction time (R), kinetics (K), angle (α), maximal amplitude (MA), and percent of lysis after 30 minutes (LY30), maximal thrombin generation time (MTG) and time to MTG (TMG).

End-points

Clinical endpoints: TBSA%, burn depth, inhalation injury (IH) defined as bronchoscopic finding of soot or Adult Respiratory Distress Syndrome, pre- and postburn co-morbidities, pre-traumatic use of medication, sepsis, DIC and VTE complications.

Data extraction and statistical methods

Data were acquired from medical charts and blood charts and were double typed in a database. Statistical analysis was performed using SAS 9.1.3 SP4 (SAS Institute Inc., Cary, NC, US) and SPSS 19 (IBM Corporation, New York, US). Changes over time in the hemostatic variables were investigated by repeated measures analyses with Tukey-adjusted post-hoc tests. Only significant changes from baseline were reported. P-values ≤ 0.05 were considered statistically significant. Data are presented as means with standard error (SE) unless otherwise stated.

Treatment

Most patients with extensive burns or IH are referred to the national burn centre by the primary care giver in a sedated and intubated state. Due to national health legislation, only patients with ability to give informed written consent could be enrolled in this study. Initial resuscitation and stabilisation included anti-shock fluid therapy with Lactated Ringer's solution guided by the Parkland formula: 4 ml/kg/%TBSA/first 24 hours for adult patients with ≥ 15% TBSA. All patients received Tinzaparin adjusted according to body weight. The study cohort was treated according to a standard protocol; in which early escharectomy was postponed if the patients had large mainly 2nd degree burns. A conservative approach was acceptable unless patients developed sepsis or had extended 3rd or 4th degree burns with an early need of surgery.

RESULTS

Patient characteristics

Between December 1st 2008 and of March 31st 2011, 14 burn patients who met the inclusion criteria were consecutively included in the study (Table 1). None had additional traumatic

Table 1: Patient demographics.

Age (years; mean, range)	46,7 (25,5-66,5)
Sex ratio (M:F)	11:2
No. of patients with pre burn co-morbidities	4 (27%)
Co-morbidities, total of cohort	7
- mental depression	3
- diabetes	1
- arterial hypertension	2
- dyslipidemia	1
Pre-traumatic use of anticoagulant medicine	0
Tobacco smoking	7 (54 %)
Alcohol abuse	1 (8 %)
Mechanism of thermal trauma	
- direct flame	3 (23 %)
- flash burn/explosion	9 (69 %)
- scalds	1 (8%)
TBSA, mean (range)	15,7 (8-30)
- 3rd grade TBSA, mean (range)	3,4 (0-12)
Inhalation injury*	0
Anti-shock fluid therapy no. (pct)	6 (46 %)
No. days w fluid-therapy, mean (range)	1,5 (0-5)
Antibiotics administered no. (pct)	11 (78,6 %)
Anti-thrombotic prophylaxis	14 (100%)
Infection, total no (pct)	6 (46%)
- wound infection, no. (pct)	4 (36%)
- Pneumonia, no. (pct)	0
- Urinary tract infection, no. (pct)	1 (8%)
- other infections, no. (pct)	1 (8%)
Sepsis no (pct)	1 (8%)
DIC, VTE, PE	0
Escharectomy performed No. (pct)	11 (85%)
Escharectomy on postburn day, mean (range)	15,3 (13-21)
Escharectomy %TBSA (deep dermal and sub dermal burns), mean (range)	7 (2-20)

Time from injury to hospital admission, hours mean (range)	1,25 (0,25-2,75)
Completion rates for daily blood samples between day 1-14	
- routine plasma-based tests, Mean (Range); percent	11,07 (6-14); 79,1 %
- TEG (CK-cup), Mean (Range); percent	10,69 (7-13); 76,4 %
LOS (length of stay)	30 (12-49)
LOS at ICU, days cumulative	0,5
Ventilator support	0,5
Pressure support	0
Hemodialysis	0
30-day mortality	0

Abbreviations: TBSA: Total Body Surface Area; DIC: Dissiminated Intravacular Coagulation; VT: Venous Tromboembolism; LOS: Length of Stay; PE: Pulmonary Embolism; ICU: Intensive Care Unit

injuries. One patient with 18% TBSA 3rd and 4th degree burns and sepsis was operated on day 3 and hence excluded. The remaining 13 patients all had postponed early escharectomy to mean day 15 (range 13-21). All patients received daily injections of Tinzaparin (Innohep® mean IE/day, range 3500-6500IE/day).The mean completion rates of blood sampling and analysis post burn day 1-14 were 76.4% for TEG and 79.1% for routine based plasma test.

Trombelastographic results from whole blood

Most TEG variables changed in a hypercoagulable direction throughout the 2 weeks following burn injury. R (Figure 1a) did not change significantly during the fourteen days. α values (Figure 1b) increased throughout the 14 days, and reached a significant level from post burn day seven 69 degrees compared with day one 54 degrees ($p<0.0004$). MA (Figure 1C) also increased throughout the 14 days, and was found significant from day five 73mm compared to day one 62mm ($p<0.05$). LY-30 (Figure 1d) did not change significantly during the fourteen days (Figure 1d). K values (Figure 2a) decreased from day one today fourteen, and was significant from post burn day three 1.9 minutes ($p<0.03$) compared with day one 2.9 minutes. MTG (Figure 2b) increased throughout the 14 days and reached a significant level from day eight 30549 mm*100/sec ($p<0.005$) compared with day one 15994 mm*100/sec. TMG did not change in the observation period.

Routine Tests and Plasma Based Coagulation Tests

Hemoglobin (Hgb) levels decreased ($p<0.016$) from mean 9.65 mmol/L day one to a significant level 8.76 mmol/L at day four and until day fourteen. Platelets increased ($p<0.0005$) throughout the 14 days starting at mean 218 billion/L day one, reaching a significant level at 384 billion/L at day nine to fourteen. APTT increased ($p<0.05$) from 25.8s day 1 reaching 30.2s day 6 (Figure 3a). INR declined ($p<0.02$) from 1.17 day one to 1.05 day five (Figure 3b), and remained significant until day fourteen. Fibrinogen increased ($p<0.05$) from 11.55 mmol/L day 1 to 20.37 mmol/L day 6 and also remained significant until day 14. Leukocytes, antitrombin and d-dimer did not show any significant changes during the fourteen days.

DISCUSSION

This is the first study to describe the natural course of haemostatic changes during the first 14 post burn days without any surgical intervention evaluated by TEG and conventional coagulation tests. The main result of this study is that TEG was able to detect a significant hypercoagulable state extending 2 weeks' post injury. TEG is a whole blood viscoelastic haemostatic assay that is increasingly appreciated as a method of real-time assessment of haemostatic changes after injury and in patients with bleeding complications [9]. TEG measures the velocity at which whole blood coagulates and the structure, the stability and the dissolution of the blood clot [1]. Standard parameters include R, K, α, MA and ly30. R denotes the time from the blood is placed in the cup until cloth formation. Similar to R, K reflects the time from the blood is placed in the cup but until predefined cloth firmness. α represents the increase in cloth strength, MA describes the maximal cloth strength and LY-30 reflects the cloth lysis [10]. Whole blood analysis provides information of the cellular haemostatic elements in contrast to conventional plasma based coagulation tests [2].

In the present study we observed that the speed of clot formation (α), the time to elapse a certain level of predefined firmness of the clot (K), the maximum thrombus generation time (MTG) and the maximal strength of clots (MA) were peaking post-burn day 7, 3, 8 and 5 respectively. These significant findings

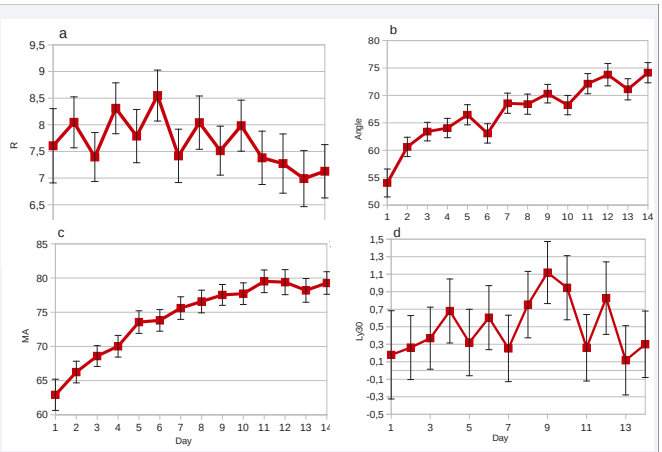

Figure 1 Changes in standard TEG parameters during the 14 days study period. (a): R ($p>0.05$). (b): MA significant at day 7 ($p<0.001$). (c): Angle significant at day 5 ($p<0.005$). (d): Ly-30 ($p>0.05$).

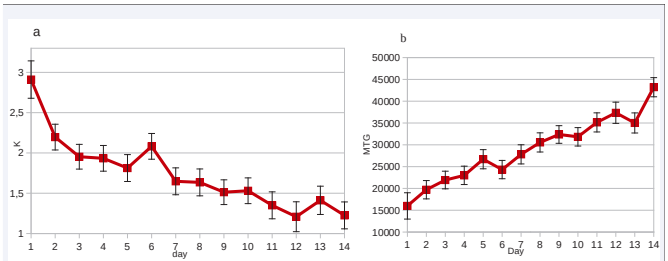

Figure 2 Changes in additional TEG parameters during the 14 days study period. (a): K significant at day 3 ($p<0.001$). (b): MTG significant at day eight ($p<0.001$).

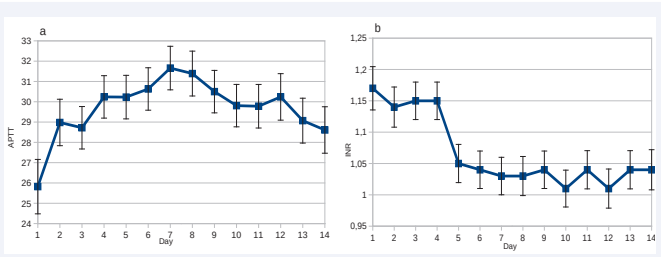

Figure 3 Changes in APTT and INR during the 14 days study period. (a): APTT significant at day 6 (p<0.02). (b): INR significant at day five (p<0.001).

indicate that the clot formation and the clot strength are stronger post-burn day 3-8, compared to the immediate and early post-burn period. The finding of consistent hypercoagulability after post burn day 5 is in concordance with other studies with a study period of 7 days [6,7] which also showed an increase in α and MA. No severe coagulopathies or VTE were found in the present study, which is somewhat in contrast to what might be expected in a burn patient cohort. It may be attributed to the study cohort characteristics with TBSA ≤ 30% or the administration of Tinzaparin. On the other hand, Van Haren et al., found no differences in TEG values or the risk of VTE between groups of major (<50%) and non-major burns (>50%)(7). Surgery is known to promote a hypercoagulable state [11]. Though our cohort did not receive surgery during the 14 days' study period all patients showed a transition to a hypercoagulable state.

Previous studies [6,7] show that burn patients who receive surgery tends to become more hypercoagulable during recovery, this is also the case in our cohort which did not received surgery. Coagulopathy in burn patients has traditionally been monitored by conventional plasma-based coagulation tests such as APTT, pro-thrombin time (PT), INR, and platelet count. These conventional plasma tests have not revealed any acute traumatic coagulopathy in burn patients at admission [12]. However, some studies argue that a coagulopathy does exist in major thermal injuries [4]. Measurements of additional coagulation products such as anithrombin III (ATIII), Protein C, Protein S, fibrinogen, D-dimer and activated factor VII (VIIa) also suggest that burn patients with TBSA>30% does present a hypercoagulable state [5].

In our study INR and APTT changed during the two weeks of evaluation. Although INR was within local reference values, it decreased significantly from day five compared with day one and APPT showed a significant increase between day six and nine. However these plasma based tests are non-specific, and may reflect either consumption of single coagulation factors [6] or a dilution effect by the treatment offered. The effects on APTT and INR were not measurable on the R-time values on whole blood coagulation and therefore, the clinical relevance of the changes in the plasma based parameters (APTT and INR) remains subject for discussion. As a consequence, we are reluctant to draw any conclusions on their changes.

Platelet count increased from day five and throughout the study period with a significant difference day nine compared with day one. Fibrinogen was above local reference values and increased during the first days and was significant from day six compared with day one. The increase in Platelets and Fibrinogen could be reactive due to the trauma [13]. The observed increase in platelets and fibrinogen after the first days are in accordance with several other studies [7,14,15]. The increase in both platelets and fibrinogen could both reflect the increase in MTG and MA. Moreover, multi-plate analysis was performed on a few patients, and showed a tendency towards an increase in platelet function which also would affect MTG and MA towards a hypercoagulable state or it might reflect an increase in coagulation factors. The increase in platelet count and/or platelet function is not selectively evaluated by TEG, hence the increase in MTG and MA must be classified as multifactorial.

Bleeding during excision of burn wounds remains a surgical challenge. Early excision have been reported to decrease bleeding [16], as has postponing surgery [17,18]. This discrepancy might reflect different techniques, measurement difficulties, depth of tissue excision and haemostatic competence prior to surgery. Transfusions in burn patients, especially in those with comorbidities, are known to increase mortality [19]. Recent data suggest that a perioperative transfusion algorithm guided by TEG reduces allogenic blood product requirements [20]. Our results show, that the haemostatic state is in a more hypercoagulable direction post-burn day 3-8 than in the immediate post burn period. These findings support the use of TEG in burn wound management compared to conventional plasma-based coagulation tests.TBSA was estimated to 15,7% day 1 (Table 1). During surgical intervention 14 days' post trauma only 7% TBSA was removed during escharectomy. The conservative standard approach that made this study possible reduced the TBSA which needed surgical intervention. This finding raises the question whether a conservative approach would lessen the need of surgery and furthermore the need of blood transfusions.

The study had several limitations. The cohort was small and from a single centre. The cohort was highly selected (i.e. awake, non-intubated patients with no need of intensive care) and characterized by moderate extent of burn injury, no IH, moderate median age, predominantly male cohort and moderate co-morbidity. The occurrence of haemostatic effects in a severe burn population may be underestimated in this cohort. The total number of blood samples collected and analysed were not 100 % due to local challenges in logistics, and intermediate short admissions to the ICU for stabilisation.

CONCLUSION

Despite these limitations, TEG was able to detect a significant hypercoagulable state during the first 2 weeks' post injury in burn patients with TBSA ≤ 30%. The findings of this study support that TEG analyses has a central role in monitoring coagulopathies in the burned patient population. Further prospective studies of whole blood coagulation assays with TEG and platelet function tests in patients with extensive burns and inhalation injury are warranted in order to develop an individualised TEG-guided burn patient treatment.

CONFLICT OF INTEREST

Conflicts of Interest and Source of Funding: All of the authors have read "Guide for Authors" and accept the

conditionsposed. All the authors have seen and agreed on the submitted version of the paper, and bearresponsibility for it. All contributors have agreedthat the material is original; and that it has beenneitherpublishedelsewhere nor submitted for publicationsimultaneously. Westatethat non of the authors have receivedanyfounding nor have anyconflicts of interest.

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