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Rotational Thrombo Elastometry and Standard Coagulation Tests for Hepatic Patients undergoing Major Liver Resection

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Abstract

Background: Coagulopathy can associate right hepatotomy in cirrhotic patients.

Methods: 20 cirrhotic patients were prospectively studied for 10 days with rotational thromboelastometry (ROTEM) and standard coagulation tests (SCTs). EXTEM and INTEM of ROTEM represent extrinsic and intrinsic coagulation pathways respectively. FIBTEM (ROTEM) represents fibrinogen activity. SCTS include Prothrombin time (PT), activated partial thromboplastin time (aPPT), fibrinogen and platelets.

Results: Age and body mass index were 55.9 ± 6.9 years and 23.7 ± 3.1 Kg/m^2. Males: Female (11:9). ROTEM parameters were normal except for a prolonged clotting time (CT) on day 1 and 3, associated with a normal clotting formation time (CFT). CT and PT were maximum on day 1 (86.25+15.7 mm and 17.2 ± 2.2 sec, $p<0.05$, respectively). CT and CFT (EXTEM) were not in correlation with PT (r=-0.29, r=-0.01, $p>0.05$ respectively). CT and CFT of (INTEM) were also not in correlation with aPTT (r=0.16, r=0.21, $p>0.05$ respectively). Fibrinogen correlated with maximum clot firmness (MCF) of FIBTEM (r=0.5, $p<0.05$). No correlation between Platetets count and MCF (EXTEM) or (INTEM) (-0.18, -0.22, $p>0.05$). Model of end stage liver disease (MELD) score correlated with preoperative CFT and MCF (EXTEM) (r=0.47, r=-0.48, $p<0.05$) respectively.

Conclusion: Despite prolonged PT and CT, other ROTEM parameters reflected normal blood coagulation. ROTEM parameters correlated insignificantly with SCTs. MELD and ROTEM inter-relationship invites further studies.

Keywords: Coagulation; Cirrhosis; Hepatectomy; Rotational thromboelastometry

Introduction

Removal of a considerable hepatic mass during right hepatotomy could reduce the hepatic synthesis of clotting factors resulting in a hypocoagulable state or alternatively hypercoagulable from the diminished synthesis of anticoagulants, extensive tissue trauma and acute phase response [1].

During major liver surgery, different coagulation problems often appear. This may be due to the procedure itself, or to the associated liver dysfunction, which causes both qualitative and quantitative alterations in pro-coagulants, anticoagulants and platelets [2-4].

Liver failure can complicate major hepatic resection, in which residual liver volume may not be able to maintain an effective liver function and normal coagulation [5].

Postoperative coagulopathy is currently diagnosed by abnormalities in standard coagulation tests (SCT) such as the prothrombin time (PT), partial thromboplastin time (PTT) and low platletes count [6].

The introduction of thrombelastographic studies (TEG) as a point of care coagulation test can enable a complete evaluation of the whole process of clot initiation, formation and stability, using whole blood with all its components in patients subjected to hepatectomy [7]. Rotational thromboelastometry is a development of TEG coagulation monitoring device that is based also on the viscoelastic properties of the whole blood and currently used to monitor coagulation in various clinical scenarios [8].

This study aims to investigate the immediate and late perioperative coagulation profile changes up to day 10 in hepatic patients classified as Child-Pugh A during and after right hepatectomy with the use of both rotational thrombelastometry analyser (ROTEM) and standard coagulation tests (SCT), as well as to study the correlations between them.

Patients and Methods

Ethical approval for this study (Ethic committee Nº MD13) was provided by the local ethics committee of the Liver Institute, Menoufiya University, Shebeen El Kom city, Egypt (Chairperson Prof. Magdy Kamal) on 12 November 2010.

After informed consent, 20 consecutive hepatic patients Child-Pugh classification A (Child A) with cirrhosis undergoing right hepatotomy for hepatic tumors at the Liver Institute, Menoufiya University, Egypt were included in this study. Age ranges between 40 to 65 years. Clinical laboratory and ultrasound evidence were used to diagnose cirrhosis.

Exclusion criteria include Child B or C and the presence of known haemorrhagic or thrombotic diseases or other conditions known to alter the haemostatic balance.

On admission to the operating room and after standard basic monitoring, a thoracic epidural catheter was placed between T6 and T11 preoperatively with patient consent. General anesthesia was induced

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with Propofol (2 mg/kg), Rocuronium (0.6 mg/kg) and Fentanyl (2 µg/kg), followed by an endotracheal intubation. General anaethesia was maintained with a mixture of air/oxygen and sevoflurane at low flow circuit.

The surgical team was the same for all the procedures; an ultrasonic dissector was used to divide the liver parenchyma. No Pringle maneuver was performed. The middle hepatic vein was preserved. Measures to reduce intraoperative bleeding included: maintaining a low positive central venous pressure during the process of resection, careful parenchymal transection with Cavitron Ultrasonic Surgical Aspirator (CUSA), bipolar elctrocautery and harmonic scalpel.

Low-molecular-weight heparin (40 mg of enoxaparin) was given subcutaneously once daily for all patients from the second postoperative day until hospital discharge but was repeatedly revised with coagulation studies. Any blood products given were reported. The epidural catheter removed when the international normalized ratio (INR) was less than 1.4 and the platelet count was greater than $100x10^9$ /l, 12 hours after last dose of low-molecular-weight heparin.

The ROTEM analysis (Pentapharm, Munich, Germany) was performed for each patient: before the skin incision baseline (Pre-Op), during surgery, on postoperative day 1 (POD1; 24 hours after surgery) and during postoperative days 3, 5, 10 (POD3, POD5, POD10). The standard coagulation tests (SCT) (PT, INR, PTT, platelets) were also measured at the same time points. Postoperatively sampling was done before next low-molecular weight heparin dose in all patients.

The following ROTEM tests were performed for each sample: intrinsically activated thromboelastometry (INTEM), which evaluates the formerly known intrinsic pathway; extrinsically activated thromboelastometry (EXTEM), which evaluates the extrinsic pathway and (FIBTEM), which measures the fibrinogen activity. The following parameters were measured in the curves generated by INTEM and EXTEM assays: the coagulation time (CT), which is the time (seconds) that the blood takes to form first fibrin strands; the clot formation time (CFT), which is the time (in seconds) until a definite clot is formed (defined as an amplitude of 20 mm); the α-angle measured between the midline of the tracing and a straight line drawn from the 1-mm point tangential to the curve, indicates the rate of fibrin polymerization; and the maximum clot firmness (MCF; given in millimeters), which measures the clot strength and depends primarily on platelet and fibrinogen function. The maximum lysis (ML) represents the maximum fibrinolysis detected during the analysis. It is defined as the ratio of the lowest amplitude after reaching of the MCF and the MCF. Normal reference value for each parameter is depicted in Table 1 [8,9].

Quantitative analysis of ROTEM tracings is commonly based on 4 main parameters: CT, CFT, a-angle, and MCF. Hypocoagulability or hypercoagulability was defined when at least 2 or more parameters were altered.

PT, aPTT and fibrinogen were measured with a semi-automated technique using fibrin timer (Siemens, Behring, Marburg, Germany) [10,11].

Test name	CT (sec)	CFT (sec)	Angle α	MCF (mm)	ML (%)
EXTEM	38-79	34-159	63-83	50-72	<15
INTEM	100-240	30-110	70-83	50-72	<15
FIBTEM		MCF <9 mm a sign of decreased Fibrinogen level MCF >25 mm is a sign of elevated Fibrinogen level			

Table 1: ROTEM parameters of Extrinsically Activated Thromboelastometry test (EXTEM), Intrinsically Activated Thromboelastometry test (INTEM) and Fibrinogen Thromboelastometry test (FIBTEM) with normal reference range in a normal volunteer preoperatively [9].

Statistical Analysis

All data were tested with Kolmogorov- Smirnov Z test and most of them were found normally distributed and so presented with mean ± SD in tables. Both parametric and non parametric testes were used for associations or correlations as appropriate. Expected frequency of liver resection cases in the year is 50 cases. Percent of liver resection in cirrhotic cases is 20.0%. Confidence interval was estimated to be 95.0% and power of the study is 80.0%. Relative risk for liver resection in cirrhotic cases is 0.2 and sample size equals 20.

Data was statistically analyzed using SPSS (statistical package for social science) program version 13 for windows and for all the analysis a ($p<0.05$) was considered statistically significant. Repeated measures ANOVA test and Friedman test were performed to differentiate changes in different follow up results. Spearman correlation coefficient between ROTEM parameters and standard coagulation tests was used.

Results

Twenty three patients were involved in the study scheduled for right hepatotomy, three were not allowed to proceed for resection and were not included in the study, two were treated with intraoperative radiofrequency and one was aborted due to peritoneal metastasis. Patients had a mean age of 55.9 ± 6.9 years with a range from 42 years to 67 years, body mass index 23.7 ± 3.1 Kg/m^2, 17 patients diagnosed with hepatitis C and 3 with Hepatitis B. Eleven males and nine females underwent right hepatectomy to eradicate a focal tumour. Mean operation time was 4.19 ± 1.1 hour, and mean hospital stay was 13.04 ± 2.3 days (range 7-21 days). The median resident time for epidural catheters was 4 ± 1.5 days (range 3-5 days). No patient included in this study developed any clinically manifested thrombotic or haemorrhagic events. Mean blood products transfusion required 4 ± 1.1 units of packed red blood cells. Two demanded fresh frozen plasma units to normalize high INR before catheter removal. All patients received crystalloids in the form of Ringer Acetate mean 4.6 ± 1.1 liters and colloids as hydroxyethystarch (HES) 130/0.4 of a mean 1 ± 0.3 liters.

The ROTEM analysis all over the measuring points was normal and within normal reference ranges except on day 1 and 3 postoperatively were signs of hypocoagulability was demonstrated in the prolonged CT measurements of EXTEM. No signs of hypercogulability were detected at any stage (Tables 2 and 3).

SCT results demonstrated a statistical significant increase in both PT, INR in comparison to the basal values denoting a tendency towards hypocoagulability with a peak during postoperative day 1 (POD 1), decreasing later to normal value on POD 5. The basal value of PT was 12.34 ± 0.17, INR was 1.2 ± 0.21 and the highest mean significant increase on POD 1 for PT was 17.6 ± 2.1 and for INR was 1.49 ± 0.18. The aPTT values showed a significant increase intraoperatively and on POD 1 in comparison to the basal values, but these changes were still in normal range. The highest increase was in POD 1 (41.55 ± 4.16) sec, $p<0.05$.

Correlation between ROTEM parameters and SCTs were variable. Fibrinogen blood levels and maximum clot firmness (MCF) of FIBTEM demonstrated significant correlation ($r=0.51$, $p<0.05$), while CT and CFT (EXTEM) were not in correlation with PT ($r=-0.29$, $r=-0.01$, $p>0.05$) respectively. CT and CFT of (INTEM) were also not in correlation with aPTT ($r=0.16$, $r=0.21$, $p>0.05$) respectively.

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Parameter	Pre-Op	Intra-Op	Post-Op	D-1	D-3	D-5	D-10	p
CT (Sec)	74.6 ± 10.5	73.0 ± 11.00	76.3 ± 10.5	86.2 ± 15.7	82.7 ± 13.8	79.2 ± 11.3	71.9 ± 10.4	<0.01
CFT (Sec)	111.4 ± 29.7	117.4 ± 28.30	120.0 ± 30.1	149.7 ± 25.2	143.8 ± 24.8	129.3 ± 03.0	105.8 ± 03.0	<0.01
MCF (mm)	57.8 ± 04.8	53.9 ± 04.30	52.9 ± 04.7	54.9 ± 04.7	57.8 ± 04.4	59.1 ± 04.9	61.6 ± 05.5	<0.01
A10 (mm)	51.8 ± 06.6	47.7 ± 05.30	46.6 ± 04.7	48.4 ± 05.2	51.9 ± 04.8	53.1 ± 05.6	55.2 ± 05.3	<0.01
MI %	3.9 ± 03.6	7.2 ± 04.40	12.4 ± 05.9	11.3 ± 06.6	6.6 ± 04.4	4.4 ± 03.2	2.1 ± 02.4	>0.05#
α (deg)	66.0 ± 07.2	61.5 ± 06.78**	59.4 ± 7.50**	62.8 ± 7.00**	67.4 ± 07.2	68.8 ± 07.5	68.8 ± 08.4	<0.01

Table 2: Extrinsically Activated Thromboelastometry test (EXTEM) at different measuring pointsa.

Parameters	Pre-Op	Intra-Op	Post-Op	D-1	D-3	D-5	D-10	p
CT (Sec)	148.7 ± 23.9	151.2 ± 23.6	158.6 ± 20.2	163.9 ± 26.1	158.1 ± 10.0	149.7 ± 23.0	152.6 ± 20.7	<0.01
CFT (Sec)	100.4 ± 22.3	104.3 ± 23.7	109.1 ± 02.0	103.3 ± 21.3	95.1 ± 21.7	89.2 ± 21.4	91.6 ± 21.0	<0.01
MCF(mm)	60.7 ± 06.4	55.5 ± 05.1	55.6 ± 07.6	57.6 ± 06.1	60.1 ± 07.5	61.4 ± 06.4	63.2 ± 07.8	<0.01
A10 (mm)	54.0 ± 06.3	50.0 ± 05.0	50.9 ± 07.7	52.3 ± 05.8	54.7 ± 06.8	55.7 ± 06.3	57.5 ± 07.2	<0.01
MI %	3.6 ± 03.8	6.4 ± 03.5	9.1 ± 04.2	7.6 ± 02.9	5.5 ± 02.8	4.5 ± 03.0	3.7 ± 02.8	>0.05#
α (deg)	65.7 ± 04.6	62.6 ± 06.3	61.9 ± 07.0	65.8 ± 06.4	66.9 ± 05.9	69.1 ± 06.0	69.6 ± 05.7	<0.01

Table 3: Intrinsically activated thromboelastometry test (INTEM) at different measuring points.

Parameters	Pre-Op	Intra-Op	Post-Op	POD-1	POD-3	POD-5	POD-10	p
PT sec	14.4 ± 1.3	15.8 ± 01.4	15.2 ± 01.3	17.20 ± 02.2	17.2 ± 01.90	14.5 ± 01.3	14.6 ± 01.2	<0.01
INR	1.2 ± 0.2	1.2 ± 00.1	1.2 ± 00.1	1.49 ± 00.1	01.4 ± 00.17	01.3 ± 00.1	1.28 ± 00.1	<0.01
HB g/dl	12.1 ± 1.1	11.6 ± 00.9	11.5 ± 01.3	11.40 ± 03.6	10.3 ± 01.10	10.2 ± 00.2	10.2 ± 01.1*	<0.01
Platelets109/l	207.0 ± 43.0	199.0 ± 42.0	193.0 ± 42.0	176.00 ± 44.0	177.0 ± 43.00	184.0 ± 00.4	198.0 ± 42.0	<0.01
aPTT (sec)	34.8 ± 4.8	37.2 ± 04.7	39.8 ± 04.7	41.50 ± 04.1	37.9 ± 03.00	34.9 ± 00.3	33.2 ± 03.8	<0.01#
Fib (mg/dl)	293.5 ± 51.0	270.3 ± 48.1	263.3 ± 49.7	279.70 ± 52.9	316.5 ± 49.90	308.2 ± 49.6	298.6 ± 04.0	<0.01

Table 4: Different coagulation parameters at different measuring points.

Variabe	Pre-Op	IIntra-Op	D-1	D-3	D-5	D-10	D-30	p
A10 (mm)	11.2 ± 1.8	11.0 ± 2.04	12.1 ± 3.2	15.4 ± 2.0	15.9 ± 2.0	16.9 ± 1.0	12.8 ± 2.9	<0.01
MCF (mm)	12.0 ± 3.1	12.1 ± 1.20	12.9 ± 4.6	17.9 ± 4.0	17.8 ± 2.0	19.6 ± 2.0	15.2 ± 3.3	<0.01

Table 5: Fibrinogen Thromboelastometry test (FIBTEM) at different measuring points. A10, Clot formation thickness at 10 mins; MCF, Maximum Clot Formation thickness; D, postoperative day; repeated measured ANOVA (ANOVA).

Platelet counts showed a gradual decrease, 199 ± 42, 176 ± 44, and 177 ± 43×109/l, intraoperatively and on Day 1, and Day 3 respectively (Table 4). The decrease in platelets count was statistically significant, without any clinical implications. No significant correlation was observed between the platelets count and both the MCF (EXTEM) (r=0-0.18, p>0.05) and MCF (INTEM) (r=-0.22, p>0.05).

Preoperative Model of end stage liver disease (MELD) score (11.35 ± 3.66) demonstrated a significant correlation with preoperative values of CFT (EXTEM), MCF (EXTEM) and CFT (INTEM), r= 0.47, r=-0.45, r=-0.48 and r=0.45, p<0.05, respectively.

Maximum clot firmness at 10 minutes (A10) (EXTEM) and INTEM were also found to be in statistically significant correlation with MELD score r=-0.49 and -0.32, p<0.05, respectively.

Surgical complications reported in one patient included an injury to the left hepatic duct with intraoperative reconstruction and stent placement. Bile leak was reported and treated with endoscopic retrograde cholangiopancreatography (ERCP) and stent insertion in three patients.

Discussion

ROTEM is widely used in clinical settings and is now introduced as a laboratory technology in a wider range. 12Several studies with particular interest in hepatic patients subjected to liver surgery were able to present an activation of the coagulation cascade reaching some times to a hypercoagulable state due to the sustained up regulation of the coagulation process itself [13]. Standard coagulation tests in these situations could give false impression of a state of hypocoagulability when instead the patient would indeed need prophylactic anti-coagulation measures to manage the undiagnosed hypercoagulable status [2-4,14].

Our study results presented mostly normal coagulation findings and were unable to demonstrate signs of hypercoagulability as suggested by other studies probably to the limited number of patients included in the study, but definitely the reported clinical case studies of embolism do present a potential perioperative threat that requires monitoring. A prophylactic anticoagulation regime would be recommended and should not be denied for cirrhotic patients despite the mild coagulopathy that could be observed postoperatively in SCTs.

ROTEM as a bed side point of care coagulation device is gaining grounds as an important coagulation monitor than the routinely used traditional laboratory test used for many decades and would be of help in specialized liver centers to help monitoring the frequent changes in coagulation for hepatic patients undergoing surgery that can vary from a patient to another.

SCTs have their own pitfalls and miss leads that can give false impression about coagulation in hepatic patients. The PT determines the speed of thrombin generation, but not the stability of the clot as ROTEM. Chowdhury et al. study observed that a high percentage of patients with an abnormal coagulation test had enough coagulation factor levels for adequate thrombus generation [15].

Prothrombin time (PT) and activated partial thromboplastin time (PTT) were developed to monitor certain coagulation factors and not

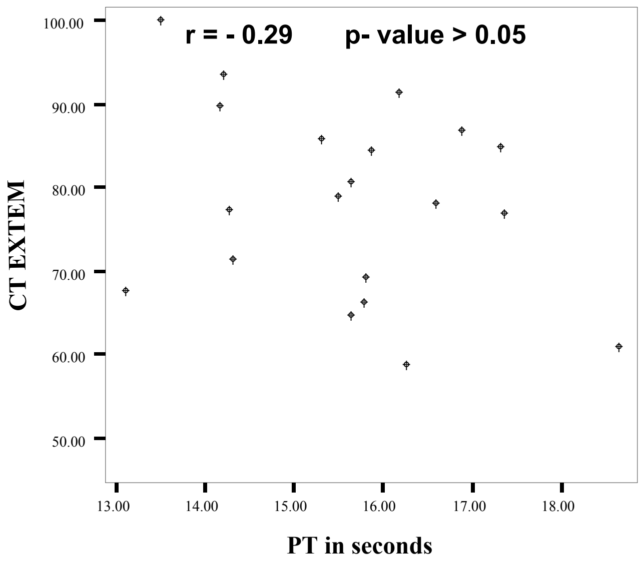

Figure 1: Correlation between Clot time (CT) in millimeter and Prothrombin time in seconds.

to assess bleeding tendency. Lack of correlation between prolonged standard coagulation tests and reduced post surgical bleeding tendency or lower need for blood administration was observed by several studies [16-19] and was recently confirmed in a meta-analysis by Segal and colleagues [20].

De Pietri et al demonstrated a discrepancy between laboratory and thromboelastographic variables in patients undergoing major liver resections [2-4].

Patients with prolonged standard coagulation tests as PT were able to coagulate normally when assessed by different methods which rely on both procoagulant and natural anticoagulants as ROTEM. Clinically and during surgery many patients with high INR do not bleed even when no blood transfusion products are infused. Herbstreit et al. demonstrated also that clot formation time of thrombelastometry and the standard coagulation tests as PT and aPTT showed poor correlation similar to our study [14]. The poor presence of blood cellular structures as endothelial cells and platelets during most of the standard conventional tests could explain the lack of a significant correlation between these tests and the ROTEM parameters due to the difference in methodology of measurement. ROTEM in comparison to standard coagulation tests provides information about the coagulation initiation, stability and fibrinolysis which involves all blood cellular structures and provides final blood clot product. SCTs such as prothrombin time reflect the blood level and activity of few clotting factors at a certain portion of the blood cascade. The clinical impact of ROTEM was in presenting a normal coagulation process despite prolonged INR and CT results postoperatively. Associated prolonged SCTs looks at the coagulation cascade from a limited portion, while ROTEM presents the overall coagulation process and its final end product. Epidural catheter insertion in this group of cirrhotic patients undergoing a major liver resection could be considered as not the favourable plan for postoperative pain management and some anaethesist would prefer to use an alternative technique. ROTEM results in this study presented assurance that despite the prolonged postoperative SCTs and CT of ROTEM the overall coagulation process compensates for any defects during the process of the coagulation to provide in the end a well formed coagulation end product. May be in a future study, criteria for epidural catheter insertion and removal could be revisited and redesigned according to ROTEM guided parameters and a protocol could be developed.

Other studies not involving liver resection presented different results such as the study by Stancheva et al. [21] which looked into the correlation between ROTEM and SCTs during and after liver transplantation and found in contrast to our study a significant correlation between PT and CFT of EXTEM and also between aPTT and CFT of INTEM, but only during the preoperative period only, this correlation later was reduced to insignificance.

This current study interestingly also showed a significant correlation between the Model of end-stage liver disease (MELD) score and both ROTEM parameters; CFT (INTEM) and MCF (EXTEM) suggesting a role in risk assessment. PT-INR already vary from a laboratory to another, this could affect calculations of the MELD score. The correlations between both CFT (EXTEM) and MCF (EXTEM) with MELD score were found in our results to be statistically significant and close to the correlation between INR and MELD score, 0.47 (direct), -0.48 (inverse) *vs*. 0.67 respectively. Maximum clot firmness after 10 minutes (A10) for both EXTEM and INTEM demonstrated also significant correlation with the classical MELD score. A10 is measured faster and could help in early diagnosis and faster follow up of hepatic patients as it only needs 10 minutes. Further studies could be designed to help develop a new risk assessment for cirrhotic patients using ROTEM parameters particularly to help identify those at risk of liver failure post-resection. A similar observation to the current study was also observed by Tripodi A et al. study [3] which found that Prothrombin time (PT) correlated with CFT and MCF (unlike our study).They used Child-Pugh score instead of the MELD in correlation studies and suggested MCF again as a suitable index to assess disease severity.

The sample size of the patients sample used in the study can be considered as one of the limitations of the study despite the calculated sample size in the statistics, may be due to the strict inclusion criteria which include only right hepatectomy in cirrhotic patients of Child A. Right hepatotomy would be considered a more severe surgery than a limited liver resection.

One of the limitations observed in this current study also is the inability of both EXTEM and INTEM parameters of ROTEM to detect the coagulation effect of low molecular weight heparin used in the study perioperatively.

Another limitation is the significant correlations reported in the current study between ROTEM parameters and MELD scores were only studied preoperatively, a perioperative follow up study would help indentify changes in both ROTEM and MELD score perioperatively.

In conclusion, despite the prolonged PT and CT post-operatively, all other ROTEM parameters reflected normal blood formation and stability with no hypercoagulability [22] or hypocoagulability after right hepatoctomy up to 10 days post resection. Most ROTEM parameters were not in agreement with the standard coagulation tests statistically, both SCTs and ROTEM should be available for perioperative coagulation monitoring to diagnose and manage any deviation from the normal coagulation pattern post resection.

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