Peertechz

Medical Group

Journal of Cardiovascular Medicine and Cardiology

DOI:http://dx.doi.org/10.17352/jcmc

ISSN: 2455-2976

CC By

Kornhall L[1], Wikander D[1], Strandberg K[2], Berntorp E[3] and Schött U[4]*

[1]Medical Graduate, Medical Faculty, Lund University, Sweden

[2]Associate Professor, Faculty of Medicine, Lund University and Coagulation Laboratory, Department of Clinical Chemistry, Division of Laboratory Medicine, Skåne University Hospital, Sweden

[3]Professor, Clinical research Unit, Lund University, skåne university Hospital, Malmö, Sweden

[4]Department of Anesthesia and Intensive Care, Skåne University Hospital, Lund, S-22185 Sweden and Institution of Clinical Sciences, Medical faculty, Lund University, Lund, Sweden

Received: 25 February, 2019
Accepted: 15 March, 2019
Published: 18 March, 2019

***Corresponding author:** Ulf Schött, Department of Anesthesia and Intensive Care, Skåne University Hospital, Lund, S-22185 Sweden and Institution of Clinical Sciences, Medical faculty, Lund University, Lund, Sweden, Tel: 46-(0)46-171319 alt 171000; Fax: 46-(0)46-176050; E-mail: ulf.schott@skane.se

https://www.peertechz.com

Check for updates

Research Article

ROTEM and vitro reversal of warfarin with APCC

Abstract

Background: Warfarin-treated patients with a prolonged Prothrombin Time (PT) can have a normal rotational thromboelastometry (ROTEM) clotting time (CT). A previous in vitro study found that activated prothrombin complex concentrates (APCC) could reverse an albumin-induced coagulopathy monitored with ROTEM, but that prothrombin complex concentrates (PCC) could not. The aim of this study was to investigate the ability of ROTEM to monitor the in vitro reversal of warfarin-induced coagulopathy using APCC and to define an APCC dose response.

Method: During the routine control of PT in 27 patients treated with warfarin, one extra 4.5 ml test tube of citrated whole blood was retrieved. Two concentrations of tissue factor ROTEM tissue factor (TF) activating reagents were used: a standard ROTEM ExTEM and a diluted 1:19000 concentration. The effects of two separate doses of APCC added in vitro corresponding to in vivo doses of 50 IE or 100 IE/kg were then studied on the ROTEM.

Results: The ROTEM EXTEM CT was prolonged beyond the upper normal range of 68 s in patients with PT >3.0, with a correlation coefficient of 0.88 to PT. ROTEM with the ExTEM reagent alongside high and low doses of APCC resulted in a significant shortening of median CT, both compared to baseline (100 s) and after low (65 s) and high doses (57 s). This was most evident in patients with PT >2.0. ROTEM signals of clot propagation to clot formation time (CFT) and α angle had the reverse pattern. There was no effect on maximal clot strength with APCC. With the diluted TF no CT shortening was found with APCC.

Conclusion: A clear dose response of APCC added in vitro to correct the effects of warfarin on ROTEM EXTEM CT was verified. ROTEM CT should be tested with non-activated PCC for in vivo reversal of warfarin in patients along with verification of a normalised PT. Further studies are needed to verify if a ROTEM CT in the lower normal range of <57-65 s, as found in our in vitro APCC-spiked warfarin blood, is safe for invasive procedures.

Introduction

Warfarin is a commonly prescribed anticoagulant which inhibits the enzyme vitamin K reductase and thus prevents the γ-carboxylation of the vitamin K dependent procoagulant factors FII, FV, FIX and FX as well as the anticoagulant proteins C, S and Z [1]. This suppresses the binding of calcium to these factors, which is necessary for their activation. Patients on warfarin need to be monitored regularly to guide the anticoagulative treatment. This is routinely done with Owren PT-INR (Prothrombin Time-International Normalized Ratio), which represents the formation of fibrin from fibrinogen, catalysed by thrombin [2]. By adding tissue factor (TF) to citrated plasma, the PT-INR measures the extrinsic and common pathways of coagulation. Together with FVII, TF activates the FX/FV complex, which drives the cleaving of prothrombin (FII) to thrombin [3]. The prothrombin time is standardized internationally to eliminate inter-laboratory differences. Owren PT-INR is the standard method in Scandinavia, the Netherlands and Japan, while Quick PT-INR, which also takes concentrations of fibrinogen and FV into account, is used in the rest of the world [2].

Newer methods are increasingly employed alongside PT-INR in surgical and emergency settings to guide coagulative treatment and transfusions. One such method is rotational thromboelastometry (ROTEM), which is a Viscoelastic Haemostatic Assay (VHA). ROTEM measures the resistance against a rotating pin during forced oscillation and provides information regarding clot formation, clot strength and fibrinolysis in whole blood [4-7]. The ROTEM can give an overview of the different steps in coagulation with the initiation, amplification and propagation phases, but also clot structure, platelet function and fibrinolysis [8]. The corresponding whole blood POC PT devices in the market only reflect clot initiation, amplification and propagation phases and also give rapid

Citation: Kornhall L, Wikander D, Strandberg K, Berntorp E, Schött U (2019) ROTEM and vitro reversal of warfarin with APCC. J Cardiovasc Med Cardiol 6(1): 006-011. DOI: http://doi.org/10.17352/2455-2976.000081

test results as compared to standard laboratory plasma based coagulation analyses such as he PT tests.

The ability of ROTEM to detect warfarin-induced coagulopathies has been proposed, but is an area in need of further study [7,8]. Treatment of bleeding in warfarin-treated patients often requires a reversal of the anticoagulative effect. This is commonly done with vitamin K or, in critical situations, with PCC (Prothrombin Complex Concentrate), which contains high concentrations of factors II, VII, IX and X. Using VHA to guide this reversal has not been thoroughly evaluated but the possibility has been suggested [9]. APCC (Activated Prothrombin Complex Concentrate) such as FEIBA (Factor Eight Inhibitor Bypassing Activity) is commonly used to control bleeding in haemophilic patients with inhibitors to factor eight (FVIII), but has also been proposed as an alternative anticoagulation reversal agent [10,11]. Non-activated PCC contains anticoagulants like protein C/S and heparin (to counteract the procoagulant factors, especially factor II/IIa [prothrombin/thrombin]) [12] and leads to ROTEM artefacts even if protamine or heparinase is used to block the heparin. APCC not containing any anticoagulants is therefore better for in vitro dose response studies than PCC [12].

Previous studies have showed normal ROTEM graphs/parameters even at high PT-INRs [7,8]. However, the range for ROTEM normal values are quite wide reflecting individual variations - and it would be interesting to study in vitro APCC effects in warfarin treated patients to see if some of the patient's moves to the lower normal range or even become hypercoagulant.

The aim of this study is to investigate the ability of ROTEM in monitoring in vitro reversal of a warfarin-induced coagulopathy using APCC. A secondary aim is to examine the effect of different dosages of APCC added in vitro to warfarin-treated blood. A hypothesis was formulated that the reversal of warfarin-induced coagulopathies could be monitored using ROTEM

Methods and Materials

Ethics

This study was approved by the Regional Ethical Review Board of Lund, Sweden (registration numbers DNR 2010/482 and DNR 2015/406). Twenty-seven patients treated with warfarin gave signed consent to participate over a 2 week study period. Inclusion criteria were warfarin treatment and an age above 18 years. No exclusion criteria were used.

Sampling

Warfarin-treated patients attending the University hospital-based anticoagulation clinic for routine INR monitoring were included in the study. One extra blood sample was taken from each patient using a 4.5 mL tube (Becton Dickinson [BD] Vacutainer Coagulation Tube) with 0.109 M buffered sodium citrate, which was then placed in a heating block (37°C). After 30-40 minutes of heating, ROTEM analyses can decrease the variation coefficients of ROTEM parameters [13,14]. Citrated samples are stable for up to eight hours after sampling [15].

Prothrombin time

Owren PT-INR (international normalized ratio) was performed using a combined thromboplastin reagent (Owren PT, Medirox, Nyköping, Sweden). Plasma analyses were performed on a Sysmex CA-5100 automated coagulation analyser (Siemens Healthcare AB, Upplands Väsby, Sweden). The PT-INR assay was calibrated using reference plasma samples with certified INR from Equalis (Uppsala, Sweden), and the normal reference range for this PT-INR was set at 0.9-1.2, with a coefficient of variation of <5%.

Viscoelastic haemostatic assays

ROTEM analysis (TEM International GmbH, Munich, Germany) was performed according to the manufacturer's instructions with ExTEM (tissue factor extrinsic activation). Blood was added to a cuvette and placed in a pre-heated container (37°C) while a rotating pin immersed in the blood created a forced oscillation. Increased resistance as the blood started to coagulate was detected and used to determine several variables. This study focused on clotting time (CT), clot formation time (CFT), the alpha angle (α) and maximum clot firmness (MCF). The reference intervals for the EXTEM protocol were set according to the manufacturer and Lang et al: CT 38-79 s, CFT 34-159 s, α angle 63-83° and MCF 50-72 mm [15]. ROTEM EXTEM coefficients of variation have been reported to be 3-12% for CT, 3-12% for CFT, 1-5% for α angle and 1-5% for MCF [4,16].

This study used the standard commercial ExTEM reagent, which is a high dose TF reagent (exact concentration not given by the manufacturer). The use of a diluted TF reagent to improve the detection of coagulation defects has previously been suggested [12]. Therefore, a commercial TF reagent (Innovin, Siemens Healthcare AB) was diluted to 1:19000, in line with recommendations from the Coagulation Laboratory, Region Skåne, Malmö, Sweden. Four mL of distilled water was added to the Innovin, then the solution was further diluted by titrating 10 µL of the solution with 112 mL of 0.9% NaCl. This diluted TF (DTF) reagent was then used as a substitute for the standard EXTEM reagent provided by TEM International.

APCC *in vitro* titration

In this experiment, two different doses of APCC (FEIBA 50 IU/mL, Baxter, Vienna, Austria) were used on 27 samples of warfarin-treated blood. These concentrations are equivalent to clinical doses of 50 IU/kg and 100 IU/kg in a male weighing 70 kg with a blood volume of 5000 mL [14]. Each blood sample was analysed in vitro with a high dose of APCC (1.4 IU/mL), a low dose of APCC (0.7 IU/mL) and a baseline control using the standard ExTEM reagent. The first 10 patients were also analysed with the DTF reagent. This resulted in six ROTEM channels per sample in the first 10 samples and 3 ROTEM channels per sample in the following 17.

Statistical analysis

Statistical analysis was performed using the Graph Pad

Citation: Kornhall L, Wikander D, Strandberg K, Berntorp E, Schött U (2019) ROTEM and vitro reversal of warfarin with APCC. J Cardiovasc Med Cardiol 6(1): 006-0011. DOI: http://doi.org/10.17352/2455-2976.000081

Prism software. Non-parametric tests were chosen, as all data was not normally distributed. P-values were calculated using the Wilcoxon signed-rank test. Linear and non-linear correlations between PT-INR and EXTEM CT in warfarin blood treated with the standard EXTEM reagent were calculated with Spearman's rank correlation. To minimize the risk of type 1 errors, statistical significance was set to $p<0.01$.

Results

Study population

Twenty-seven patients were included in the study. Three patients were excluded due to insufficient test tube sampling volume. The median age was 69 years (range 46-99 years). The median PT-INR was 2.4 (range 1.3-3.2), 11 patients had a PT-INR <2.0 and four patients had a PT-INR >3.0. One patient was incorrectly sampled and PT-INR could not be analysed. The remaining 11 patients had PT-INR values within the common therapeutic interval 2-3.

Effects of APCC on warfarin-treated blood

ROTEM analysis with the standard ExTEM reagent alongside high and low doses of APCC resulted in a significant shortening of CT, both compared to the baseline and between low and high doses ($p<0.0001$, Figure 1). Additionally, a high dose of APCC significantly prolonged CFT and reduced the α angle ($p<0.01$) compared to the baseline. No other significant results were found using the standard ExTEM reagent ($p>0.01$). The DTF reagent yielded no significant results ($p>0.01$, Figure 2).

The difference between high and low dose APCC was limited to samples with higher control CT values when separating the patients after PT-INR into groups of ranges 2-2.9 and ≥ 3 (Figure 3).

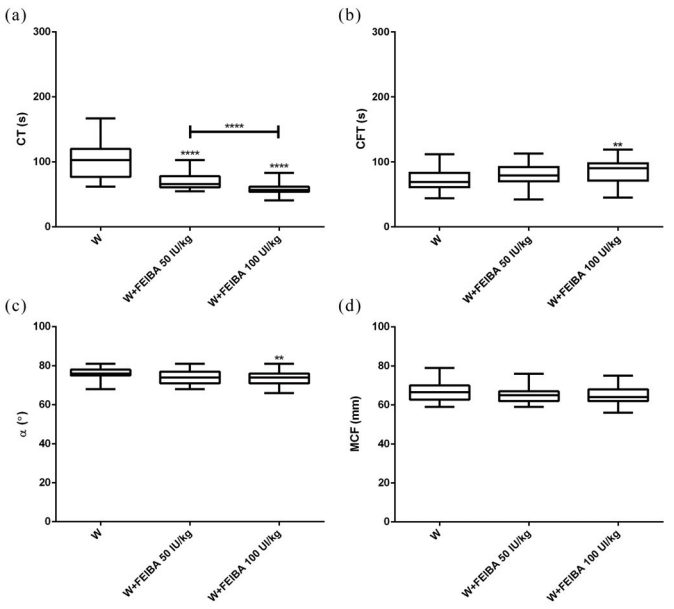

Figure 1: ROTEM analysis of warfarin blood (W) and APCC using standard ExTEM reagent: (a) Clotting Time, (b) Clot Formation Time, (c) Alpha angle and (d) Maximum Clot Firmness. Significance is expressed in comparison to the untreated warfarin control (****$p<0.0001$, **$p<0.01$).

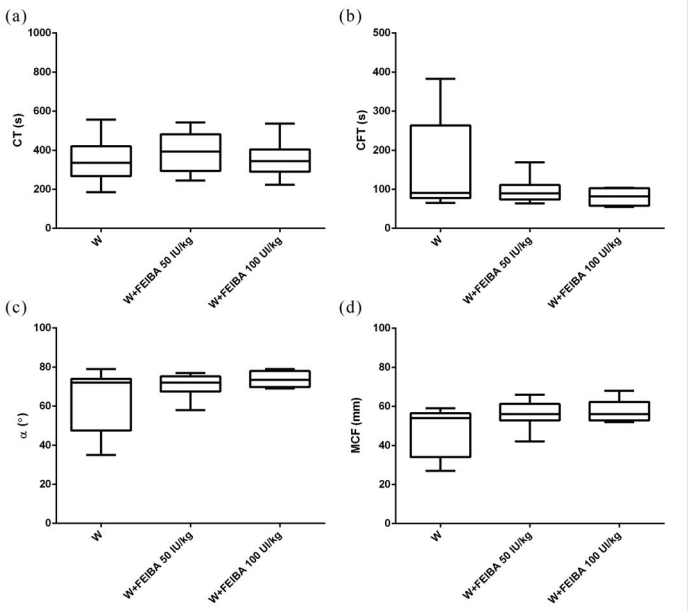

Figure 2: ROTEM analysis of warfarin blood (W) and APCC using the DTF reagent: (a) Clotting Time, (b) Clot Formation Time, (c) Alpha angle and (d) Maximum Clot Firmness.

EXTEM CT correlation to Owren PT-INR

Statistical analysis with Spearman's rank correlation test showed a significant linear correlation between elevated PT-INR and increased EXTEM CT (rho 0.88; $p<0.0001$, Figure 4).

Discussion

In this study, tissue factor-activated ROTEM monitoring of in vitro reversal of warfarin-induced coagulopathies with APCC was studied. We hypothesized that ROTEM could monitor this reversal and detect a dose response effect with both low and high doses of APCC. Only with the standard high-concentration tissue factor ExTEM reagent was the time until initial clot formation (CT) significantly reduced by in vitro administration of APCC to warfarin blood. There was an additional effect of high-dose APCC compared to low-dose APCC, further significantly shortening CT. The reduction in CT was greater with higher control CTs linked to PT-INRs > 2. Therefore, the hypotheses are supported.

ROTEM EXTEM and PT

Schmidt et al. found a strong correlation (rho=0.87) between ROTEM EXTEM CT and PT-INR in a recent study on warfarin-treated patients [7]. Nilsson el al. only found a moderate 0.66 correlation between EXTEM CT and PT-INR, but a better 0.76 between EXTEM CT and Quick-PT [8]. INTEM and FIBTEM CT had lower correlations in both studies. Our study demonstrated a similar high correlation as in the Schmidt study between PT-INR and ROTEM EXTEM CT, as seen in Figure 4 (rho=0.88). This is likely because both tests were activated by high concentration tissue factor reagents [7], stimulating the extrinsic pathway. This correlation indicates that a reduction in EXTEM CT by administering APCC may equate to a corresponding reduction in PT-INR, but this subject needs to be studied further (see below).

Citation: Kornhall L, Wikander D, Strandberg K, Berntorp E, Schött U (2019) ROTEM and vitro reversal of warfarin with APCC. J Cardiovasc Med Cardiol 6(1): 006-0011. DOI: http://doi.org/10.17352/2455-2976.000081

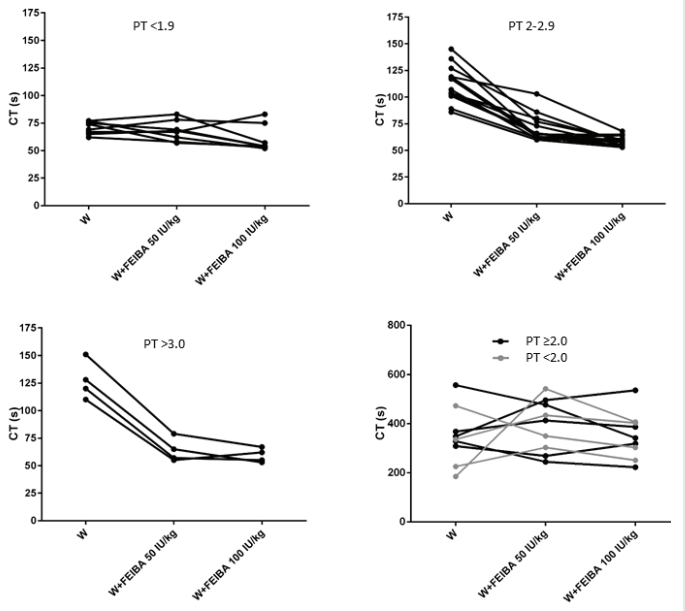

Figure 3: The effect of APCC on EXTEM CT of individual warfarin treated patients when separated by PT-INR and TF reagent: (a) Standard ExTEM reagent and PT-INR<2.0, (b) Standard ExTEM reagent and PT-INR 2.0-3.0, (c) Standard ExTEM reagent and PT-INR>3, (d) DTF reagent, PT-INR≥2.0 (black) and PT-INR<2.0 (grey).

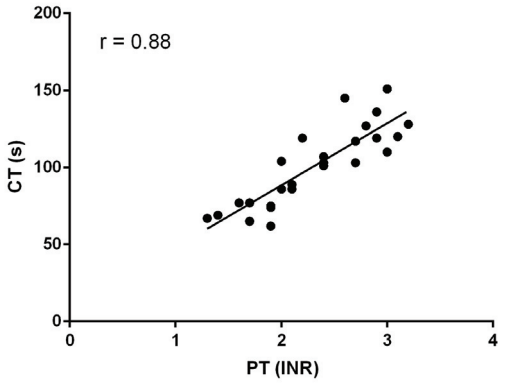

Figure 4: Scatterplot of PT-INR against ROTEM EXTEM CT in warfarin treated patients.

Schmidt et al. so also described a significant but small increase in ROTEM EXTEM MCF in warfarin-treated patients compared to healthy controls; there were no differences in ROTEM EXTEM α angles. ROTEM EXTEM CFT, α angle and MCF ranges in our study are similar to the ranges described by Schmidt et al [7]. We did not measure fibrinogen plasma levels. Increased fibrinogen measured with the Clauss method has been found to correlate positively with ROTEM MCF levels (rho=0.70) [17]. Many patients on warfarin have atherosclerosis, which can be linked to an inflammatory process with higher fibrinogen plasma levels [18]. Haematocrit and platelet count and function can also affect MCF [19]. In a recent study on stent implantation in superficial femoral arteries, only a short ROTEM CT predicted late in-stent restenosis, whereas calibrated automated thrombography, activated partial thromboplastin time, platelet aggregation, platelet adhesion, fibrinogen, and microparticles' procoagulant activity failed [20].

However, Gudmundsdottir et al. found a discrepancy between PT-INR and ROTEM variables in warfarin-anticoagulated, platelet-poor plasma activated with highly diluted (1:17000) thromboplastin, that is internal coagulation pathway activation (corresponding to ROTEM INTEM) in a study from 2012 [21]. PT-INR has a high sensitivity to changes in FVII plasma levels and activity and FVII has a shorter half-life than the other vitamin K dependent coagulation factors, such as FII and FX. ROTEM did not show this correlation with FVII but instead correlated with FX and less so with FII, indicating that these factors play a more predominant role than factor VII on global coagulation as seen in vitro using ROTEM [21].

The use of ROTEM for analysing warfarin coagulopathies has the benefit of being a point-of-care method and can be performed using whole blood. The standard plasma-based PT-INR is not a point-of-care method. However, there are several point-of-care whole blood PT methods [22], and some of these can monitor both high and low PTs in warfarin-treated patients [23].

Diluted Innovin

It has been suggested that the standard commercial ROTEM EXTEM reagent causes too strong activation of the extrinsic pathway due to high concentrations of TF, resulting in the possibility that mild coagulopathies are overridden by the massive activation [12,21]. In contrast to this, our study produced no significant results with the heavily diluted (1:19000) TF reagent (Innovin). As seen in Figure 2, the variation of the different ROTEM parameters with the DTF reagent was considerably higher than those of the corresponding standard EXTEM reagent, especially before adding APCC. The CTs obtained with the DTF reagent were markedly higher than their standard EXTEM reagent CT counterparts; however, no major differences were seen in CFT, α or MCF. Comparing our DTF CT values to a previous study, Elvstam et al. [12], using the NATEM protocol (no TF, only recalcification of citrated blood), our CT was lower while still within NATEM protocol range (300-1000s), which indicates that the dilution can be compared to studies using no TF [12]. Additionally, with the DTF reagent, CT values after adding APCC were higher than those of the previously mentioned study on albumin-diluted blood with the same doses of APCC [12]. Based on our findings and previous results, we argue that the recommended 1:19000 TF dilution is too extensive, while the standard EXTEM TF reagent might have a too high concentration. This could produce unreliable results in both instances. Therefore, a TF concentration somewhere between the standard ExTEM reagent and the diluted Innovin used in this study should be considered.

APCC for *in vitro* reversal of warfarin

APCC resulted in a significant shortening of median CT, both compared to the baseline (100 s) and after low (65 s) and high doses (57 s). This was most evident in patients with PT-INR >2.0 (Figure 3). In patients with PT-INR <2.0, the APCC effects were not clear. This is interesting, as patients with PT-INRs in this range represent elective or emergency patients after 2-3 days of warfarin withdrawal, after PCC or intravenous

Citation: Kornhall L, Wikander D, Strandberg K, Berntorp E, Schött U (2019) ROTEM and vitro reversal of warfarin with APCC. J Cardiovasc Med Cardiol 6(1): 006-0011. DOI: http://doi.org/10.17352/2455-2976.000081

vitamin K treatment. In surgical patients with normal or slightly prolonged PT-INR (and on no warfarin medication), correlations between ROTEM CT/the alternative system thromboelastography (TEG) reaction time (TEG R) are low [24, 25]. Current guidelines do not address whether a low ROTEM CT combined with a slightly prolonged PT-INR >1.2-1.5 or higher (still below 2.0) allows the anaesthesiologist to perform a regional anaesthesia in patients with warfarin medication.

A previous study has found that APCC can correct (and in the case of CT, overcorrect) an albumin-induced coagulopathy, but PCC cannot [12]. This failure of PCC is probably an effect of the heparin content or protein C/S added to 4-factor PCC to counteract its strong pro-coagulative effects [12,26]. APCC has no heparin; also, its content of activated VII (fVIIa) can exaggerate the reversal effect of APCC in vitro and in vivo. Still, we did not find ROTEM CT in the very low range (around 38 s) [12, 16] after APCC correction of the warfarin blood. Perhaps an even higher APCC in vitro dose would have accomplished this.

APCC has previously been shown to revert the effects of rivaroxaban in vitro [27] and experimentally in pigs [28]. APCC also reversed the effects of the in vitro albumin-induced coagulopathy [12], on clot amplification and clot propagation parameters CFT, α and MCF. With the warfarin-induced coagulopathy, we did not detect any effect of APCC on these parameters with the ExTEM reagent. However, with the DTF reagent the boxplot confidence intervals markedly decreased (Figure 2).

Counteractively, our results showed that CFT was prolonged and the α angle was decreased with the high-dose APCC as compared to the baseline EXTEM CFT. This implies impaired clot propagation. Similar results were recently reported by Peng et al. when in vitro-administered TF caused a reduction in CT and an increase in CFT [29]. The authors speculated that a decrease in clot formation kinetics may be the result of excessive activation of the extrinsic tenase pathway (FVII–TF). This mechanism could also explain the decrease in α angle by the high-dose APCC in this study.

APCC should not be used to reverse warfarin in patients. It is an antibody-bypassing agent in haemophilia patients used to treat bleeding. TEG has been used to titrate the optimal dose of APCC as an antibody-bypassing agent in haemophilia patients [30], but also used for monitoring the reversal of NOAC [31], with the TEG parameter reaction time (R) corresponding to ROTEM CT. No comparison of ROTEM and TEG with TF activating reagents has been performed, but monitoring warfarin reversal with PCC has been suggested in an in vitro study using ROTEM EXTEM CT [9] and in patients with intracranial bleeding using TEG R and TEG MA (maximal amplitude corresponding to ROTEM MCF) [32]. Schmidt el al found ROTEM EXTEM CT to correlate more than TEG R with PT-INR in warfarin-treated patients [7].

Limitations

This study was limited by the absence of healthy controls. In addition, we did not analyse variables other than PT-INR at baseline, so variations in haematocrit, fibrinogen and platelet count, which may interfere with coagulation and ROTEM, are unaccounted for. Also the study period was limited, including more patients at the different PT-INR levels defined in Figure 3 would have strenghtened our results. ROTEM has high coefficients of variation (CV) for the different test parameters [8] – so repetetive testing of the same sample before and after reversal would detect a change of CVs. In an ongoing study we have found lower CVs for ROTEM test parameters in the lower normal range when testing at 8 simultaneous ROTEM channels. There are also indications that with the fully automated ROTEM-Sigma®, CVs are lower than with the previous ROTEM models using digital pipetting of activating reagents as in our study.

Conclusion

This study demonstrates that a tissue factor-activated ROTEM analysis can be used to monitor the reversal of warfarin-induced coagulopathies with APCC in vitro. However, this effect was limited to patients with PT-INR >2 when looking at individuals. Further studies are needed to study in vivo warfarin reversal monitored with ROTEM and to find the optimal individual PCC and/or vitamin K in vivo dosages for elective and emergency patients.

Acknowledgements

We'd like to thank the biomedical scientists at the Department of Laboratory Medicine, Region Skåne, Lund for their aid in providing information to the patients, collecting the signed consents and sampling the blood.

References

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, et al. (2008) American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133: 160-198. Link: https://goo.gl/BQ9zZ9

2. Horsti J (2002) Comparison of quick and owren prothrombin time with regard to the harmonisation of the International Normalised Ratio (INR) system. Clin Chem Lab Med 40: 399-403. Link: https://goo.gl/Ur6rsm

3. Vine AK (2009) Recent advances in haemostasis and thrombosis. Retina 29: 1-7. Link: https://goo.gl/gECKVs

4. Ganter MT, Hofer CK (2008) Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesth Analg 106: 1366-1375. Link: https://goo.gl/kXxE3A

5. Whiting D, DiNardo JA (2014) TEG and ROTEM: technology and clinical applications. Am J Hematol 89: 228-232. Link: https://goo.gl/4XTG7o

6. Larsson A, Tynngård N, Kander T, Bonnevier J, Schött U (2015) Comparison of point-of-care hemostatic assays, routine coagulation tests, and outcome scores in critically ill patients. J Crit Care 30: 1032-1038. Link: https://goo.gl/9L3PPC

7. Schmidt DE, Holmström M, Majeed A, Näslin D, Wallén H, Ågren, et al. (2015) Detection of elevated INR by thromboelastometry and thromboelastography in warfarin treated patients and healthy controls. Thromb Res 135: 1007-1011. Link: https://goo.gl/km4b71

8. Nilsson CU, Strandberg K, Reinstrup P (2018) Warfarin monitoring with viscoelastic haemostatic assays, thrombin generation, coagulation factors and correlations to Owren and Quick prothrombin time. Scand J Clin Lab Invest 78: 358-364. Link: https://goo.gl/EbPmAe

Citation: Kornhall L, Wikander D, Strandberg K, Berntorp E, Schött U (2019) ROTEM and vitro reversal of warfarin with APCC. J Cardiovasc Med Cardiol 6(1): 006-011. DOI: http://doi.org/10.17352/2455-2976.000081

9. Rumph B, Bollinger D, Narang N, Molinaro RJ, Levy JH, et al. (2010) *In vitro* comparative study of hemostatic components in warfarin-treated and fibrinogen-deficient plasma. J Cardiothorac Vasc Anesth 24: 408-412. Link: https://goo.gl/Q2NUAp

10. Wojcik C, Schymik ML, Cure EG (2009) Activated prothrombin complex concentrate factor VIII inhibitor bypassing activity (FEIBA) for the reversal of warfarin-induced coagulopathy. Int J Emerg Med 2: 217–225. Link: https://goo.gl/MCxjMv

11. Turecek PL, Varadi K, Gritsch H, Schwarz HP (2004) FEIBA: mode of action. Haemophilia 10: 3-9. Link: https://goo.gl/iZ7QX5

12. Elvstam O, Berntorp E, Schött U (2016) ROTEM monitoring of activated and non-activated prothrombin complex concentrate correction of dilutional coagulopathy. Scand J Clin Lab Invest 76: 202-207. Link: https://goo.gl/xwT2zf

13. Bowbrick VA, Mikhailidis DP, Stansby G (2000) The use of citrated whole blood in thromboelastography. Anesth Analg 90: 1086-1088. Link: https://goo.gl/mKUy5b

14. Camenzind V, Bombeli T, Seifert B, Jamnicki M, Popovic D, et al. (2000) Citrate storage affects Thrombelastograph analysis. Anesthesiology 92: 1242–1249. Link: https://goo.gl/no64mN

15. Sørensen B, Fenger-Eriksen C, Christiansen K, Larsen OH, Ingerslev J (2010) Evaluation of coagulation kinetics using thromboelastometry-methodologic influence of activator and test medium. Ann. Hematol 89: 1155-1161. Link: https://goo.gl/iV9A4H

16. Lang T, Bauters A, Braun SL, Poetzsch B, von Pape KW, et al. (2005) Multi-centre investigation on reference ranges for ROTEM thromboelastometry. Blood Coagul Fibrinolysis 16: 301-310. Link: https://goo.gl/JJ3HRP

17. Winstedt D, Solomon C, Hillarp A, Lundahl T, Schött U (2016) Intraoperative Hydroxyethyl Starch and its Effects on Different Fibrinogen Measurements. Clin Appl Thromb Hemost 22: 641-647. Link: https://goo.gl/8QAjE1

18. Buljubasic N, Akkerhuis KM, Cheng JM, Oemrawsingh RM, Garcia-Garcia HM, et al. (2017) Fibrinogen in relation to degree and composition of coronary plaque on intravascular ultrasound in patients undergoing coronary angiography. Coron Artery Dis 28: 23-32. Link: https://goo.gl/zsQ1gQ

19. Spiezia L, Radu C, Marchioro P, Bertini D, Rossetto V, et al. (2008) Peculiar whole blood rotation thromboelastometry profile in 40 sideropenic anaemia patients. Thromb Haemost 100: 1106-1110. Link: https://goo.gl/eDbRbK

20. Cvirn G, Hoerl G, Schlagenhauf A, Tafeit E, Brodmann M, et al. (2012) Stent implantation in the superficial femoral artery: short thrombelastometry-derived coagulation times identify patients with late in-stent restenosis. Thromb Res 130: 485-490. Link: https://goo.gl/tykhjR

21. Gudmundsdottir BR, Francis CW, Bjornsdottir AM, Nellbring M, Onudarson PT (2012) Critical role of factors II and X during coumarin anticoagulation and their combined measurement with a new Fiix-prothrombin time. Thromb Res 130: 674-681. Link: https://goo.gl/977Mnn

22. Schött U (2014) Prehospital coagulation monitoring of resuscitation with point-of-care devices. Shock 41: 26-29. Link: https://goo.gl/xnBbB1

23. Meneghelo ZM, Barroso CM, Liporace IL, Cora AP (2015) Comparison of the international normalized ratio levels obtained by portable coagulometer and laboratory in a clinic specializing in oral anticoagulation. Int J Lab Hematol 37: 536-543. Link: https://goo.gl/C1amZx

24. Theusinger OM, Schröder CM, Eismon J, Emmert MY, Seifert B, et al. (2013) The influence of laboratory coagulation tests and clotting factor levels on Rotation Thromboelastometry (ROTEM(R)) during major surgery with hemorrhage. Anesth Analg 117: 314-321. Link: https://goo.gl/RvUwGi

25. Ågren A, Wikman AT, Holmström M, Östlund A, Edgren G (2013) Thromboelastography (TEG®) compared to conventional coagulation tests in surgical patients - a laboratory evaluation. Scand J Clin Lab Invest 73: 214-220. Link: https://goo.gl/McfWpo

26. Sørensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R (2011) Clinical review: Prothrombin complex concentrates--evaluation of safety and thrombogenicity. Crit Care 15: 201. Link: https://goo.gl/NChXwc

27. Schenk B, Würtinger P, Streif W, Sturm W, Fries D, et al. (2016) *Ex vivo* reversal of effects of rivaroxaban evaluated using thromboelastometry and thrombin generation assay. Br J Anaesth 117: 583-591. Link: https://goo.gl/MAA7Pw

28. Honickel M, Maron B, van Ryn J, Braunschweig T, ten Cate H, et al. (2016) Therapy with activated prothrombin complex concentrate is effective in reducing dabigatran-associated blood loss in a porcine polytrauma model. Thromb Haemost 115: 271-284. Link: https://goo.gl/s9xfdJ

29. Peng HT, Grodecki R, Rizoli S, Shek PN (2016) A comparative study of tissue factor and kaolin on blood coagulation assays using rotational thromboelastometry and thromboelastography. Blood Coagul Fibrinolysis 27: 31-41. Link: https://goo.gl/xKuuwG

30. Young G, Blain R, Nakagawa P, Nugent DJ (2006) Individualization of bypassing agent treatment for haemophilic patients with inhibitors utilizing thromboelastography. Haemophilia 12: 598-604. Link: https://goo.gl/d2sjdN

31. Solbeck S, Ostrowski SR, Stensballe J, Johansson PI (2016) Thrombelastography detects dabigatran at therapeutic concentrations in vitro to the same extent as gold-standard tests. Int J Cardiol 208: 14-18. Link: https://goo.gl/XS7co6

32. Voils SA, Martin EJ, Mohammed BM, Bayrlee A, Brophy DF (2015) Laboratory assessment of warfarin reversal with global coagulation tests versus international normalized ratio in patients with intracranial bleeding. Blood Coagul Fibrinolysis 26: 443-447. Link: https://goo.gl/aGLFdh

Citation: Kornhall L, Wikander D, Strandberg K, Berntorp E, Schött U (2019) ROTEM and vitro reversal of warfarin with APCC. J Cardiovasc Med Cardiol 6(1): 006-011. DOI: http://doi.org/10.17352/2455-2976.000081