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TECHNOLOGY REVIEW (MINI-HTA)

VISCOELASTIC HAEMOSTATIC ASSAY FOR NON-CARDIAC SURGERY

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
012/2021

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EXECUTIVE SUMMARY

Background

Bleeding remains a serious condition related to trauma, surgery, invasive procedures and childbirth. Major haemorrhage is an important cause of morbidity and mortality, affecting up to 40% of all trauma patients. Uncontrolled bleeding remains the leading preventable cause of death, mainly attributed by dysfunctional haemostasis. If bleeding becomes life-threatening and if factors such as hypothermia and hypocalcaemia are not controlled, the risk increases for developing severe consumptious coagulopathy, disseminated intravascular coagulation and hyperfibrinolysis, which may lead to increase mortality.

Detection and correction of coagulopathy is therefore important in the management of severe haemorrhage. Diagnosis of major bleeding is often made using clinical measures which can be insensitive. Clinical sign of coagulopathy, such as oozing is a late sign, hence accurate management of massive transfusion is often challenged as there is no simple and reliable diagnostic coagulation test available. Monitoring dynamic haemostatic changes by performing viscoelastic haemostatic assay (VHA) test is thought to enable clinician in distinguishing between surgical cause of bleeding or coagulopathy, in diagnosing specific type of coagulopathy and in guiding choice of haemostatic treatment. Transfusion can be guided by clinical judgement, standard laboratory tests (SLT), VHA or a combination of these in a transfusion algorithm.

Traditionally, SLT was used in the assessment of haemostasis measuring activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), platelet count and plasma fibrinogen. These SLT tests provide a quantitative snapshot of isolated component in a complex clotting cascade, however were limited by lack of real-time monitoring, slow turnaround times, inability to identify coagulation factor deficiency, lack of correlation with bleeding and hypercoagulability, and no rapid assessment of fibrinolysis, platelet dysfunction or haemostatic response to injury or surgery.

Viscoelastic testing (VET) or VHA are point of care test, emerged as an alternative that measures qualitative aspect of the clotting process in whole blood from clot formation, propagation, maximum clot strength, and clot dissolution with results generated faster. They were said to have the advantage of being easy to use by non-laboratory personnel as a point-of-care assay in the emergency and peri-operative setting, produce rapid graphic and numerical result of haemostatic status, able to detect the anticoagulant effect of acidosis, hypo or hyperthermia, and able to detect and quantify the underlying cause of coagulopathy such as thrombocytopenia, factor deficiency, heparin effect, hypofibrinogenaemia and hyperfibrinolysis. They add value in the investigation of coagulopathies and goal-directed management of bleeding.

While the use of this point-of-care system in patients undergoing cardiovascular surgery has been extensively evaluated, there has been less experience in other clinical setting and its effectiveness in this setting is still debated. As of now, VHA is not available yet in the Emergency Department, HKL. The availability of VHA will assist in guiding resuscitation and management of patients with severe bleeding. Currently, SLT is being used in haemostatic assay analysis which requires approximately 45 to 60 minutes, and the result did not provide

detail information on stages of haemostasis. Hence, this technology review was conducted following a request from Emergency Physician, Hospital Kuala Lumpur, to provide the best scientific evidence on VHA in the management of patients with bleeding in non-cardiac surgery.

Objective/ aim

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of VHA for the management of patients with bleeding in non cardiac surgery.

Results and conclusion

The review included sixteen studies which were consisted of systematic review (three), randomised controlled trials (three), non-randomised trial (one), pre-post intervention study (two), cohort studies (five), case control (one) and cost effectiveness analysis (one).The included articles were published between 2009 and 2021. The studies were conducted in US, Austria, Germany, UK, China, Israel and Russia. This review included a total of 7,087 participants enrolled from all the studies. Sample size for each of the included studies ranged from 60 to 396 participants (primary studies), and from 229 to 2,835 participants (systematic review). The longest period of the included study was up to three years. The intervention commonly being studied is either TEG or ROTEM. Most of the study participants were patients with trauma either blunt or penetrating with varying haemorrage management protocol, followed by patients with liver transplant, post-partum hemorrhage and patients underwent microsurgery.

Effectiveness

Based on the above review, there was sufficient fair level of evidences on VHA to be used in the management of patients with trauma. Evidence demonstrated that the VHA-guided haemostatic therapy was effective in guiding transfusion, with fewer consumption of blood products, avoidance of allogenic transfusion and reduction of blood wastage, compared to conventional coagulation test in patients with trauma. No difference in hospital length of stay or quality of life following VHA-guided therapy compared to control, and its effectiveness in terms of mortality was inconclusive.

Evidence on the reported thresholds of VHA (ROTEM) parameters in diagnosing coagulopathy, predicting or guiding transfusion and predicting mortality in trauma patients showed parameters such as abnormal EXTEM and FIBTEM CA or MCF or lysis index.

- Parameters identified for diagnosis of coagulopathy were EXTEM-Clot Amplitude (CA)5, CA10, CA15 (correlated with PT and INR). The cut-off values varied from 5 mm in CA5 to 35 mm in CA15. AUC of the parameters ranged from 0.77 to 1.00, the highest AUC was for EXTEM MCF ≤ 18mm.
- Parameters identified for prediction of transfusion needs were EXTEM CA5 ≤35 mm and FIBTEM-MCF ≤7 mm. AUC of the parameters ranged from 0.75 to 0.84, with the highest AUC was for FIBTEM MCF ≤ 7mm.
- Parameters identified for prediction of mortality include FIBTEM < 7 mm/ <9 mm/<9.5 mm, EXTEM-MCF < 45 mm; shorter EXTEM-CT, INTEM-CT, EXTEM-CFT and INTEM-CFT; higher EXTEM-MCF, INTEM-MCF. AUC of the parameters ranged from 0.77 to 1.00, with the highest AUC was for EXTEM MCF ≤ 18mm.

There was limited evidence on VHA-guided therapy in the management of patients with PPH, demonstrating combination of TEG assessment of coagulation, early surgical haemostasis and intrauterine balloon tamponade were effective in reducing rate of peripartum hysterectomies, reducing blood loss and FFP transfusion in these patients. The highest predictive ability for PPH was TEG-Maximum Amplitude parameter (AUC 0.9).

There was sufficient fair level of evidences on VHA to be used in the management of patients with liver transplant. The VHA-guided therapy was effective in guiding transfusion with less consumption of blood products, increase avoidance of allogenic transfusion, and reduce postoperative mortality in patients with liver transplant despite no difference in ICU or hospital length of stay.

There was very limited evidence on VHA-guided therapy for microsurgery patients, with predictive parameter identified for flap thrombosis was parameter relating to clot strength (maximal clot strength and fibrinogen-to-platelet ratio).

Safety

TEG 5000 and ROTEM delta had obtained USFDA approval for adult population. The USFDA approved TEG 6S for adults with cardiac indication, while Hemosonics Quantra has been approved for adults with cardiac or orthopedic indication. Following VHA, lower complications namely re-operation due to bleeding, re-transplantation, acute kidney injury demonstrated, however more neurological complication and viral infection were reported in patients with liver transplant.

Cost-effectiveness

The TEG 6S Haemonetics USA cost is approximately RM170,000 to RM180,000 per device while each cartridge costs about RM500 to RM520. In UK, the total cost of testing per trauma patient for the four technologies was £203 for ROTEM, £170 for TEG, £130 for SLTs, and £73 for Sonoclot. For patients with trauma, the use of VHA was estimated to generate cost saving, amounting to per patient saving of £688 for ROTEM compared with conventional coagulation tests, £721 for TEG, and £818 for Sonoclot, in a CEA conducted in UK.

Organisational

Staff should be trained and have good pipetting technique for non-cartridge-based methods. Internal Quality Control should be performed daily or weekly depending on volume of use, and participation in an accredited external quality assurance programme is recommended. Reference ranges should be determined locally and re-established when a new machine is introduced. The diagnostic thresholds for various VHA parameters are assay, institution, or algorithm specific.

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2020), EBM Reviews-Cochrane Central Register of Controlled Trials (September 2021), EBM Reviews – Database of Abstracts of Review of Effects (3rd Quarter 2021), EBM Reviews-Health Technology Assessment (3rd Quarter 2021), EBM Reviews-NHS Economic Evaluation Database (3rd Quarter 2021). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits

were applied to the search. The last search was run on 30 September 2021. Additional articles were identified from reviewing the references of retrieved articles. Among the tools used to assess the risk of bias and methodological quality of the articles retrieved is the Cochrane risk of bias tool and Critical Appraisal Skills Programme (CASP) checklist. All full text articles were then graded based on guidelines from the US/Canadian Preventive Services Task Force.

TABLE OF CONTENT

ABBREVIATION

ADR	Adverse dug reaction
AUC	Area under curve
CA	Clot amplitude
CCT	Conventional coagulation test
CI	Confidence Interval
CrI	Credible Interval
CT	Clotting time,
CFT	Clot formation time
ExTEM	Extrinsically activated ROTEM
FC	Fibrinogen concentrate
FFP	Fresh frozen plasma
HR	Hazard Ratio
HRQOL	Health related quality of life
INR	international normalized ratio
IQR	Interquartile Range
ISS	Injury Severity Score
LI30	Lysis index at 30 min
LY	Life years
MA	Maximal amplitude
MCF	Maximum clot firmness
MOH	Ministry of Health
MT	massive transfusion
MTP	massive treatment protocol
PCT	prothrombin complex concentrate
POC	Point-of-care
PPH	Post partum hemorrhage
PT	prothrombin time
QALY	Quality adjusted life years
QOL	Quality of Life
RCT	Randomised controlled trial
ROTEM	Rotational thromboelastometry
RR	Relative risk
SADR	Serious Adverse Drug Reaction
SE	Standard error
SR	Systematic review
SLT	Standard laboratory test
TEG	Thromboelastography
vs	Versus
VHA	Viscoelastic hemostatic assay
VET	Viscoelastic testing
WMD	Weighted mean difference

1.0 BACKGROUND

Major haemorrhage is an important cause of morbidity and mortality, affecting up to 40% of all trauma patients.[1] Uncontrolled bleeding remains the leading preventable cause of death, mainly attributed by dysfunctional haemostasis. In up to 35% of patients with severe injury, this trauma induced coagulopathy is already present upon arrival to the Emergency Department.[2,3]

Bleeding remains a serious condition related to trauma, surgery, invasive procedures and childbirth. Severe bleeding and coagulopathy are serious clinical condition associated with high mortality. Ongoing severe bleeding is associated with increased morbidity and mortality, and may prompt the need for additional surgery.[4] If bleeding becomes life-threatening with development of hypovolaemic shock with acidosis, and if factors such as hypothermia and hypocalcaemia are not controlled, the risk increases for developing severe consumptious coagulopathy, disseminated intravascular coagulation and hyperfibrinolysis, which may lead to increase mortality.[5,6]

Diagnosis of major bleeding is difficult and is often made using clinical measures but these measures can be insensitive, particularly in younger patients in whom blood loss can be masked and haemodynamic stability preserved, or in elderly patients on cardiovascular modulating medication. Detection and correction of coagulopathy is therefore important in the management of severe haemorrhage.[1]

Coagulopathy, as a result of uncontrolled bleeding and massive transfusion leads to defect in clot firmness due to fibrinogen, coagulation factor and platelet deficiency, decreased clot stability due to hyperfibrinolysis and factor VIII deficiency, and prolonged clot generation due to various coagulation factor deficiencies. [7] Clinical sign of coagulopathy, such as oozing is a late sign, hence accurate management of massive transfusion is often challenged as there is no simple and reliable diagnostic coagulation test available.[8] Monitoring dynamic haemostatic changes by performing viscoelastic haemostatic assay (VHA) test is thought to enable clinician in distinguishing between surgical cause of bleeding or coagulopathy, in diagnosing specific type of coagulopathy and in guiding choice of haemostatic treatment.[4]

Transfusion can be guided by clinical judgement, available predictive scoring system commonly ABC score or TASH score, standard laboratory tests (SLT), VHA or a combination of these in a transfusion algorithm.[9,10] Component therapy was thought to be better for resource utilization and reduction of infection risk associated with transfusion.[11] Blood product is valuable resources, due to its scarcity and cost, and carry not-insignificant risk of transfusion related morbidity such as transfusion associated circulatory overload, infection and recipient immunomodulation.[12] Algorithm was commonly constructed as a mean of guiding haemostatic therapy in bleeding patients to facilitate individualized goal-directed therapy, with intended improvements to reduce transfusion of allogeneic blood products, adverse outcomes, mortality and increase cost-effectiveness.[13]

Traditionally, assessment of haemostasis was done with conventional coagulation assay (CCA) or standard laboratory test (SLT) using activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), platelet count and plasma fibrinogen.[9] These SLT tests provide only a quantitative snapshot of isolated components in a

complex clotting cascade, and were limited by lack of real-time monitoring, slow turnaround times, inability to identify coagulation factor deficiency, lack of correlation with bleeding and hypercoagulability, and no rapid assessment of fibrinolysis, platelet dysfunction or haemostatic response to injury or surgery. [9,14,15]

Viscoelastic testing (VET) or VHA has emerged as a promising alternative that measures qualitative aspects of the clotting process from clot formation, propagation, maximum clot strength, and clot dissolution with results generated faster, in as little as 10 minutes. [16] VET refers to several commercially available point-of-care test that use blood sample to derive various parameters pertaining to the quality of clot formed. They have been introduced into trauma care as a single assay that characterize the life-span of a clot; from time to initial fibrin cross-linking, maximal clot strength incorporating platelets and red blood cells, to clot breakdown by fibrinolysis.[17] Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are VHA that provide graphical evaluation of the kinetics of all stages of clot formation (initiation, propagation, strength and dissolution) in whole blood. [9,18] The VHA add value in the investigation of coagulopathies and goal-directed management of bleeding by providing complete picture of clot formation, strength, and lysis in whole blood.[14] In recent years, TEG and ROTEM have been used to evaluate global clotting function, monitor and guide haemostatic treatment and allogenic blood transfusion requirements in conditions characterized by excessive bleeding, including major surgery, liver transplantation, obstetric haemorrhage and trauma.[19]

The TEG and ROTEM were said to have the advantage of being easy to use by non-laboratory personnel as a point-of-care assay in the emergency and peri-operative setting; produce rapid graphic and numerical result of haemostatic status; able to detect the anticoagulant effect of acidosis, hypo or hyperthermia; and able to detect and quantify the underlying cause of coagulopathy such as thrombocytopenia, factor deficiency, heparin effect, hypofibrinogenaemia and hyperfibrinolysis.[20]

While the use of this point-of-care system in patients undergoing cardiovascular surgery has been extensively evaluated, there has been less experience in other clinical setting and its effectiveness in this setting is still debated.[21] As of now, VHA is not available yet in the Emergency Department, HKL. The availability of VHA will assist in guiding resuscitation and haemostatic therapy in patients with bleeding. Currently, SLT is being used in haemostasis assessment which requires about 45 to 60 minutes, and the result only provide snapshot of isolated component in the clotting cascade. Hence, this technology review was conducted following a request from Emergency Physician, Hospital Kuala Lumpur, to provide the best scientific evidence on VHA in the management of patients with bleeding in non-cardiac surgery.

2.0 OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of VHA in the management of patients with bleeding in non-cardiac surgery.

3.0 TECHNICAL FEATURES

The TEG assay was first described in 1948 by Dr. Helmut Hartert in Germany. As blood clots, the fluid becomes less viscous and more elastic in nature. Computerised, commercially available, automated systems (TEG and ROTEM) dynamically evaluate clot formation and fibrinolysis, by continuously measuring and graphically displaying the kinetics of all stages of clot formation (initiation, propagation, strength and dissolution).[22]The two predominant commercially available VET system are TEG and ROTEM, whereas Sonoclot has been studied less. The TEG and ROTEM assess clot formation, strength, and dissolution by measuring the effect of a continuously applied rotational force on whole blood that is transmitted to an electromechanical transduction system (TEG) or optical detection system (ROTEM), with results displayed as a graph. This allows the quantitative and qualitative measurement of the function of almost all components of clot formation and lysis, including platelets, other blood cellular components, fibrinogen, microvesicles, and soluble factors. The TEG device has a pin suspended from a torsion wire immersed in a cup of whole blood. The cup is held in a heating block and continually oscillates. Changes in viscoelastic clot strength are directly transmitted to the torsion wire and detected by an electromechanical transducer. The ROTEM device has a cup, which remains fixed in a heating block with whole blood, while a pin suspended on a ball bearing mechanism oscillates.The subsequent rotation of the pin is inversely related to the viscoelastic clot strength and is detected optically.(Figure 1).[14]

Thromboelastography (TEG) is a VHA analyser that provides an evaluation of the kinetics of all stages of clot initiation, formation, stability, strength and dissolution in whole blood. The speed and pattern of changes in strength and elasticity in the clot are measured by a computer and depicted as a graph. In the reagent-modified ROTEM, the sensor shaft rotates rather than the cup rotating as in TEG.[9]

ROTEM uses almost identical graphical result display compared to TEG, and measure similar parameters on the graphic, but uses different names. (Table 1). While the measurement and graphic of TEG and ROTEM are akin conceptually, because of test reagent differences, their value cannot be directly compared. ROTEM also market multiple assays for analysis of various aspect of coagulation cascade, including EXTEM measuring extrinsic pathway, INTEM for the intrinsic pathway, FIBTEM for evaluating fibrinogen contribution to clot formation, HEPTEM and APTEM for evaluating heparin effect or thrombolysis reversal.[12]

Common devices in use currently are the TEG 5000 (Figure 2A) and ROTEM Delta (Figure 2B). The TEG 6s (Figure 2C) and the ROTEM Sigma (Figure 2D), are newer version of these analyzers, using cartridge-based systems with dry reagents designed to improve both usability at point of care by non-laboratory trained personnel and interoperator reproducibility. The result of TEG and ROTEM is not interchangeable although both assess clot kinetics, strength and lysis (Figure 2E). Comparison of TEG 5000 and ROTEM Delta parameter and their interpretation is highlighted in Table 1.[14]

Although the mechanical principles of TEG and ROTEM are similar, the variability in hardware and reagents results in different output values and reference ranges; consequently, the generated results cannot be used interchangeably. There are potential advantages to VHA-guided evaluation of coagulopathy. Due to use of whole blood instead of plasma,

actionable data may be available within 10 to 20 minutes as compared with 45–60 minutes for CCTs.[23]

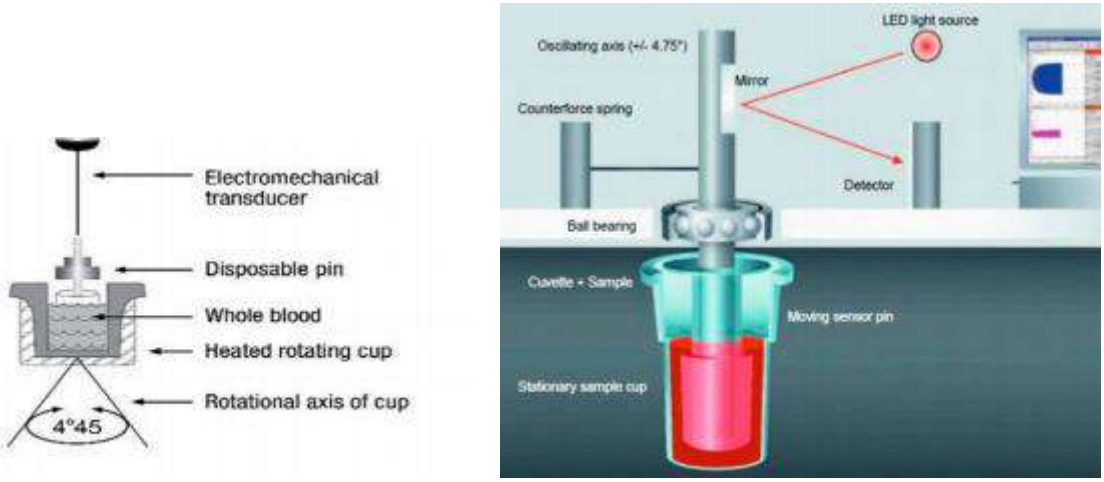

Figure 1: TEG principle (left), and ROTEM principle (right)
Source: Selby R 2020

Figure 2A-D: The VHA device; TEG 5000 (A), ROTEM Delta (B), TEG 6S (C) and ROTEM Sigma (D)

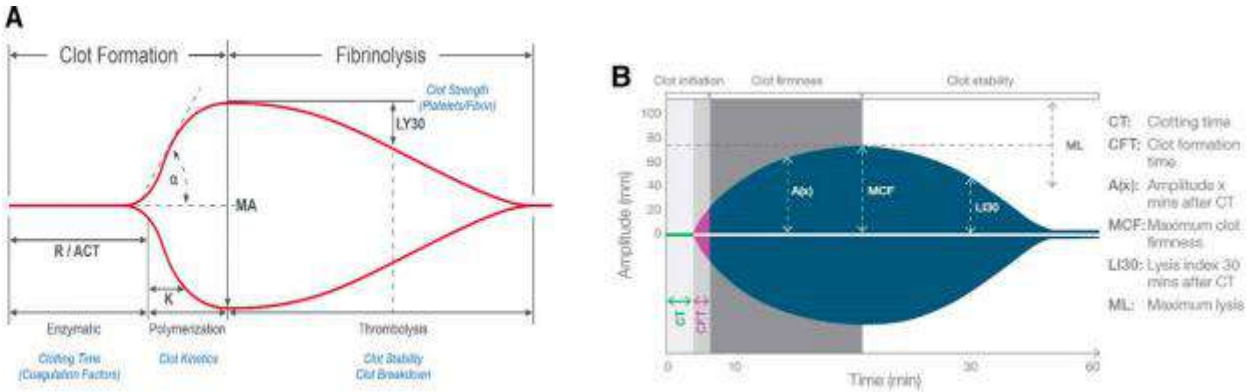

Figure 2E: Thromboelastography (A) output and ROTEM (B) output demonstrating kinetics of all stages of clot formation (clot initiation, propagation, strength, and lysis)
Source: Selby R 2020

Table 1: Comparison of TEG 5000 and ROTEM Delta parameter, interpretation and physiological correlation to hemostasis

Parameters		Interpretation	Physiological correlation to phase of hemostasis
TEG 5000 (units)	**ROTEM Delta (units)**		
Reaction rate (R) (min)	Clotting time (CT) (s)	Time for the trace to reach an amplitude of 2 mm	Activation of coagulation, thrombin generation, time to initial clot formation, and influence of anticoagulants
Kinetics time (K) (min)	Clot formation time (CFT) (s)	Time for the clot amplitude to reach from 2 mm to 20 mm	Fibrin activation and polymerization (ie, speed of clot propagation)
Angle (α) (degrees)	Angle (α) (degrees)	Angle created by drawing a tangent line from the point of clot initiation (R or CT) to the slope of the developing curve	Fibrin activation and polymerization (ie, speed of clot propagation)
N/A	A10 (mm)	Amplitude reached 10 min after CT	Fibrinogen and platelet contribution to the strength of the clot
Maximum amplitude (MA) (mm)	Maximum clot firmness (MCF) (mm)	Peak amplitude or strength of the clot	Fibrinogen and platelet contribution to the strength of the clot
Lysis 30 (LY 30) (%)	Lysis index 30 (LI 30) (%)	TEG: Percentage reduction in the area under the TEG curve (assuming MA remains constant) that occurs 30 min after MA is reached ROTEM: Percentage clot remaining (compared with MCF) when amplitude is measured 30 min after CT is detected	Fibrinolysis
Lysis 60 (LY 60) (%)	N/A	Percentage reduction in the area under the TEG curve (assuming MA remains constant) that occurs 60 min after MA is reached	Fibrinolysis
N/A	Maximum lysis (ML) (%)	Degree of fibrinolysis relative to MCF achieved during the measurement (percentage clot firmness lost). It is not calculated at a fixed time.	Fibrinolysis

Several different assays can be performed on both TEG and ROTEM analyzers using various activators or inhibitors. In both systems, contact activation using ellagic acid or kaolin can provide information similar to the aPTT. Tissue factor activation can provide information similar to the PT. Neutralization of heparin using lyophilized heparinase, blocking platelet contribution to clot formation by using platelet inhibitors, or inhibiting fibrinolysis with antifibrinolytics can help assess various aspects of coagulation. These assays can be customized for use in algorithms depending on the information needed for decision-making. The diagnostic thresholds for various parameters are assay, institution, or algorithm specific.[14]

4.0 METHODS

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Registered of Controlled Trials – September 2021
- EBM Reviews – Database of Abstracts of Review of Effects – 3rd Quarter 2021
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to September 2021
- EBM Reviews – Health Technology Assessment – 3rd Quarter 2021
- EBM Reviews - NHS Economic Evaluation Database – 3rd Quarter 2021

Other databases:

- PubMed
- Horizon Scanning database (National Instutute of Health research (NIHR) Innovation Observatory, Euroscan International Network)
- Other websites: US FDA, INAHTA, MHRA

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on human. No limitation in the study design. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on the 1 September 2021.

4.2 SELECTION

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients (adults and children) with bleeding
Interventions	VHA (TEG, ROTEM, TEG6S, ROTEM Sigma or Sonoclot)
Comparators	Standard laboratory test (SLT), conventional coagulation assay (CCA), clinical judgement, no testing or other VHA test
Outcomes	Mortality, bleeding events, blood loss, proportion of patients needing transfusion, amount of blood products (red blood cells, platelet concentrates, fresh frozen plasma) transfused, blood wastage, transfusion avoided, incidence of surgical intervention, length of stay (ICU or hospital stay), complications (such as infection, thrombosis, allergic)
Study design	Systematic reviews (SR), randomised control trials (RCTs), cohort study, case control study
Type of publication	English, full text articles

Exclusion criteria

Study design	Case report, survey, anecdotal, animal studies
Type of publication	Non-English
Setting	Studies evaluating VHA in cardiovascular surgery/setting

4.3 RISK OF BIAS ASSESSMENT

Relevant articles were critically appraised according to the study design. Randomised controlled trial was appraised using ROB-2, and cohort studies were appraised using Critical Appraisal Skills Programme (CASP) checklist and evidences were graded according to the US/Canadian Preventive Services Task Force (See Appendix 2). Data were extracted from included studies using a pre-designed data extraction form (evidence table as shown in Appendix 6) and presented qualitatively in narrative summaries. No meta-analysis was conducted for this review.

5.0 RESULTS

A total of 836 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to September 2021), EBM Reviews-Cochrane Central Register of Controlled Trials (September 2021), EBM Reviews-Database of Abstracts of Review of Effects (3rd Quarter 2021), EBM Reviews-Health Technology Assessment (3rd Quarter 2021), EBM Reviews-NHS Economic Evaluation Database (3rd Quarter 2021) and PubMed.

Thirty-eight articles were identified from references of retrieved articles. After removal of 38 duplicates, 798 titles were screened. A total of 232 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 770 abstracts were found to be irrelevant. Twenty-eight potentially relevant abstracts were retrieved in full text. After applying the inclusion and exclusion criteria and critical appraisal to the 28 full text articles, 16 full text articles were included and 8 full text articles were excluded. (Figure 3). The review included sixteen studies which were consisted of systematic review (three), randomised controlled trials (three), non-randomised trial (one), pre-post intervention study (two), cohort studies (five), case control (one) and cost effectiveness analysis (one).

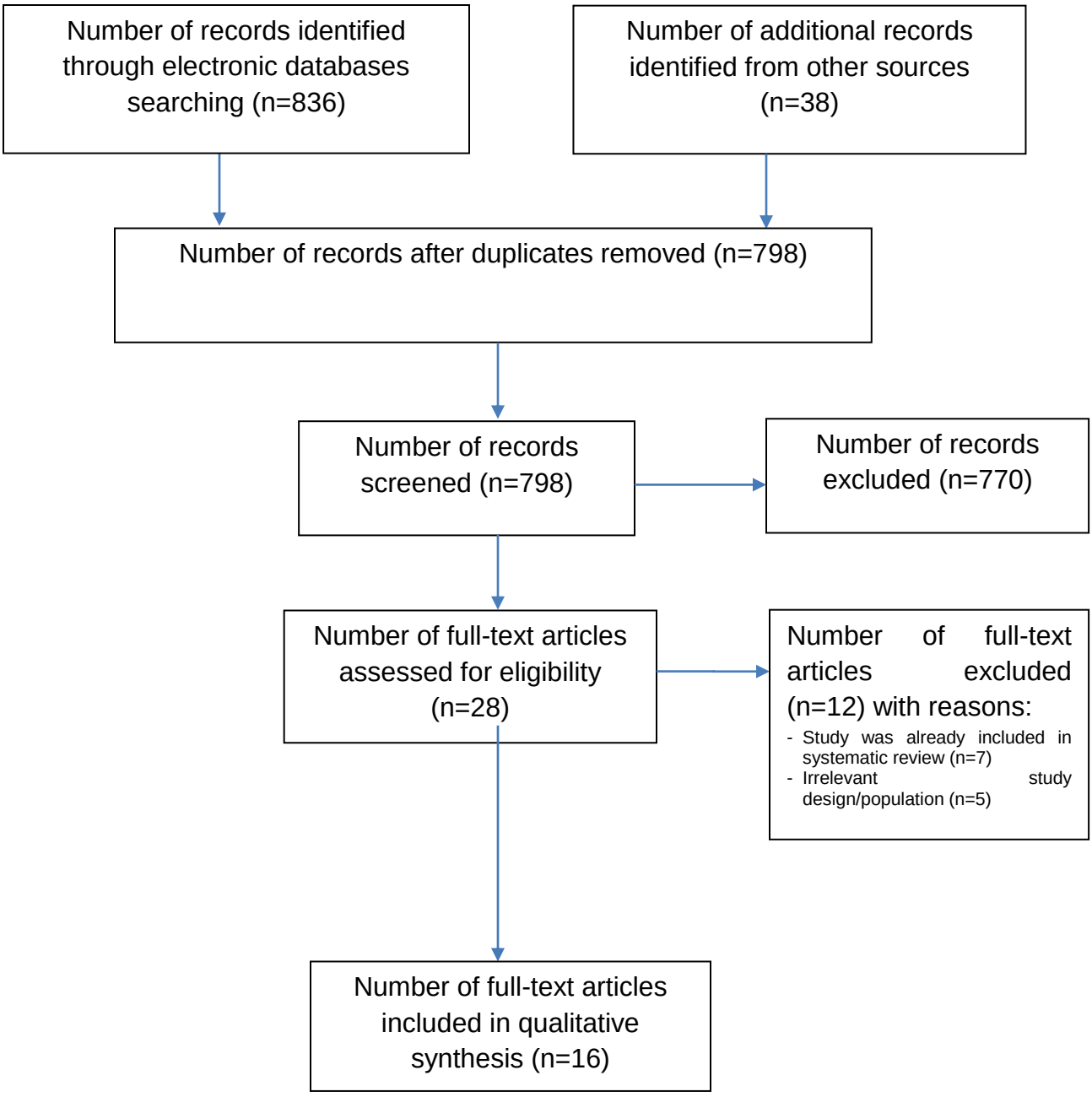

Figure 3: Flow chart of study selection in the review according to the PRISMA guidelines

Of the 16 included articles in this review, mostly were included in the effectiveness section, one study was in the safety and two studies were in the cost-effectiveness section. The included articles were published between 2009 and 2021. The studies were conducted in US, Austria, Germany, UK, China, Israel and Russia. This review included a total of 7,087 participants enrolled from all the studies. Sample size for each of the included studies ranged from 60 to 396 participants (primary studies), and from 229 to 2,835 participants

(systematic review). The longest period of the included study was up to 90 days. The intervention commonly being studied is either TEG or ROTEM. Most of the study participants were patients with trauma either blunt or penetrating with varying haemorrage management protocol, followed by patients with liver transplant, post-partum hemorrhage and patients underwent microsurgery.

5.1 RISK OF BIAS OF INCLUDED STUDIES

Risk of bias of the studies included in this review was evaluated independently by two reviewers, RS and RAR on specified domain based on CASP checklist, except for RCT where Cochrane Risk of Bias 2 (RoB2) was used. Any disagreements were resolved through discussion until consensus was reached. For RCT, the risk of bias was evaluated in accordance with the method recommended by the Cochrane Handbook for Systematic Review of Interventions. The content of the assessment consisted mainly of the following items; random sequence generation, allocation concealment, blinding of participants and researcher, blinding of outcome assessment, incomplete outcome data, selective reporting and overall risk of bias. Trials having three or more high risk of bias were considered as having poor methodological quality. The plot of the domain-level judgements for each individual result was generated using robvis, a web app designed for visualizing risk-of-bias assessments. [24] The results were illustrated in the figure as below.(Figure 5).

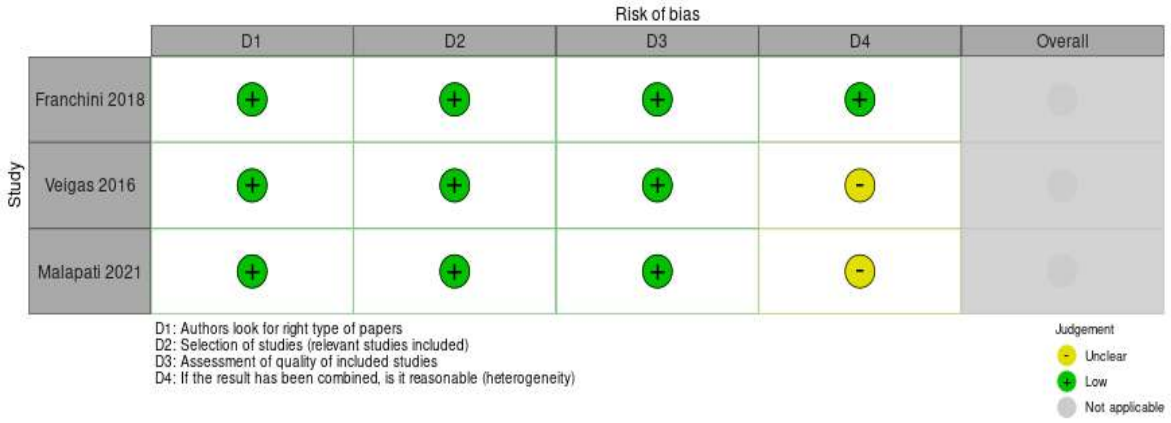

Figure 4a: Assessment of risk of bias of systematic review (CASP)

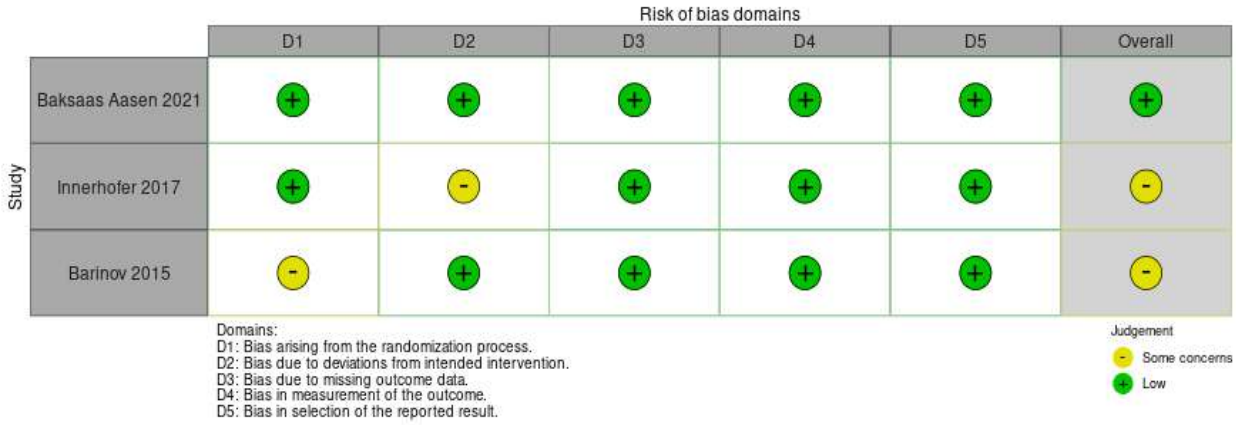

Figure 4b: Assessment of risk of bias of RCT (Cochrane)

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Park MS et al.2009	+	+	+	?	?
Tapia NM et al.2013	+	+	+	+	+
Yin J et al. 2014	+	+	+	?	?
Schochl H et al.2011	+	+	+	?	?
Kaufner L et al.2016	+	+	+	+	?

Figure 4c: Quality assessment of cohort studies (CASP)

Criteria assessed	Whiting et al. 2015
A well-define question posed?	+
Comprehensive description of competing alternative given?	+
Effectiveness established?	+
Effects of intervention identified, measured and valued appropriately?	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	+
Costs and consequences adjusted for different times at which they occurred (discounting)?	?
Results of the evaluation?	+
Incremental analysis of the consequences and costs of alternatives performed?	+
Sensitivity analysis performed?	+

Figure 4d: Assessment of risk of bias of economic evaluation (CASP)

5.2 EFFECTIVENESS

There were thirteen studies retrieved on the effectiveness of VHA in the non-cardiac surgical setting consisted of three systematic review, three RCTs, one non-randomized trial, one pre-post intervention studies and five cohort studies.

5.2.1 Patients with trauma

Mortality

Franchini M et al. (2018) in a systematic review of RCT evaluated the usefulness of VHA tests (TEG and ROTEM) in bleeding patients outside the cardiac surgical setting (burn trauma, injured adult, cirrhosis patients undergoing invasive procedure and patients undergoing liver transplant). In this review, search was done from The Cochrane Library, MEDLINE, EMBASE and SCOPUS database as well as clinical trial registries for ongoing and unpublished studies. Only RCTs published in full in English between January 1970 and November 2017 were included in this review. RCTs evaluating the use of TEG/ROTEM in cardiovascular surgery were excluded since they have been extensively reviewed. The primary outcome was mortality, evaluated through meta-analytical pooling as the Risk Ratio (RR) between VHA monitoring (treatment group) vs standard of care (control group). Secondary

outcomes were related to blood product use, including red blood cells (RBC), platelet concentrates (PC), and fresh frozen plasma (FFP) transfusion. The risk of bias of included study was assessed independently following the domain-based evaluation described in the Cochrane Handbook for SR of Interventions, addressing six domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting, and other issues relating to bias. Principle of GRADE system was used to assess the quality of the body of evidence associated with specific outcomes. Overall grading of evidence defines certainty of body of evidence which includes consideration of methodological quality, directness, heterogeneity, precision and risk of publication bias. The SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guideline. Four RCTs included in this review that met their inclusion criteria with a total of 229 participants. The sample size was small (from 28 to 111 patients) and the follow-up periods very heterogenous (from 4 weeks to 3 years). No study assessed as being at low risk of bias. All the included studies were at high risk of bias for one or more domains, and three studies were at unclear risk of bias for three domains.

The review found pooled data from the 3 trials reporting on mortality (199 participants) do not show any effect of the use of TEG on reducing mortality as compared to standard monitoring (based on the average treatment effect from a fixed-effects model): Risk Ratio (RR) 0.71 (95% Confidence Interval (CI): 0.44 to 1.15).The evidence on mortality and other outcomes was uncertain (very low-certainty evidence, down-graded due to risk of biases, imprecision, and inconsistency). [21 level I]

In the RCT by Baksaas Aasen et al. (2021) found 50/201 (25%) of patients in the VHA arm (TEG 6s or ROTEM Sigma) and 55/194 (28%) patients in the CCT arm died in the analysis of mortality at 28 days, with OR of 0.84, (95% CI 0.54 to 1.31). [25 level I]

In a pre-post intervention study by Cochrane C et al (2020), mortality at both 24 hours and 30 days was significantly lower in the post-TEG group compared to the pre-TEG group. Only 5% (n = 8/175) of patients in the post-TEG group died within 24 h, compared to 13% (n = 17/126) in the pre-TEG group (p=0.006). Mortality at day 30 in the pre-TEG group was more than double that of the post-TEG group (25% [n=32/126] compared to 11% [n= 20/175]; p=0.002). [26 level II-2]

Yin et al. (2014) in a retrospective cohort study involving patients with abdominal trauma evaluating goal-directed transfusion protocol based on standard TEG (goal directed group) compared to control, found no differences in mortality at 28 days between the two groups. [27 level II-2]

Schochl et al. (2011) in another retrospective cohort study observed mortality was comparable between both groups following TEM-guided therapy, 7.5% in the fibrinogen-PCC group and 10.0% in the FFP group (p=0.69). [28 level II-2]

Tapia et al. (2013) evaluated outcome of TEG-directed resuscitation compared to massive treatment protocol (MTP) resuscitation in trauma patients in Texas, US. In this study, they performed TEG earlier in guiding resuscitation. Following consensus recommendations for massive treatment protocol (MTP), they implemented MTP in 2009 with 1:1:1 ratio of blood (red blood cells [RBC]), plasma (fresh-frozen plasma [FFP]), and platelets for patients. They found in patients who received 10U or more RBC, the mortality increased from 54.1% for MTP compared to 33.3% preMTP (p=0.04), as well as early death (death less than 24 hours) increased to 16% (MTP) from 14% (preMTP). (Table 2). MTP therapy worsened mortality in penetrating MOI patients receiving 10U or more RBC, indicating a continued need for TEG-directed therapy.[11 level II-2]

Table 2: Mortality rate comparing preMTP and MTP in blunt and penetrating MOI

	Blunt MOI			Penetrating MOI, %		
	PreMTP, %	MTP, %	*p*	PreMTP, %	MTP, %	*p*
30-Day mortality						
≥6U RBC	30	25	0.59	23	31	0.24
≥10U RBC	41	39	0.91	33	54	0.04*
Early death†						
≥6U RBC	12	7	0.20	19	18	0.13
≥10U RBC	11	5	0.24	14	16	0.01*
Delayed death‡						
≥6U RBC	1	7	0.06	9	4	0.76
≥10U RBC	1	6	0.04*	3	4	0.24

Guiding transfusion and haemostatic therapy

Franchini M et al. (2018) in the SR of RCT likewise found the pooled data on the use of VHA (TEG) does not reduce the need for red blood cells [mean difference (MD) –0.64 (95% CI: –1.51 to 0.23) (four trials, n=299)], platelet concentrates [MD –1.12; (95% CI: –3.25 to 1.02), three trials, n=199], and fresh frozen plasma [MD –0.91 (95% CI: –2.02 to 0.19), three trials, n=199] transfusion. (Table 3). However, overall, the certainty of the evidence provided by the trials was too low to be certain of the benefits and harms of VHA as compared to standard monitoring in bleeding patients outside the cardiac surgical settings. They suggested for more larger, and better-designed RCTs to be carried out in this area to better clarify the exact role of VHA in the management of acquired bleeding condition. [21 level I]

Table 3: TEG compared to standard laboratory measures for patients with coagulopathy in non-cardiac surgical setting (SR by Franchini M 2018)

Outcomes	Relative effect (95%CI)	No. of participants (studies)
Mortality	RR 0.71 (0.43 to 1.16)	199 (3 studies)
RBC transfusion	MD -0.64(-1.51 to 0.23)	229 (4 studies)
Platelet concentrate transfusion	MD -1.12 (-3.25 to 1.02)	199 (3 studies)
FFP	MD -0.91(-2.02 to 0.19)	199 (3 studies)

Innerhofer et al. (2017) in the RCT conducted using ROTEM in identifying plasma coagulopathy involving 100 patients (FFP, n=48) and (Coagulation Factor Concentrates, CFC, n=52) found an increase need for massive transfusion following FFP, (13 [30%] patients compared to six [12%] in the CFC group; OR 3.04 (95%CI 0.95 to 10.87).[29 level I]

Yin et al. (2014) in a retrospective cohort study involving patients with abdominal trauma evaluating goal-directed transfusion protocol based on standard TEG found administration of total blood products at 24 h appeared to be fewer in the goal-directed group than the control group (10.2 [7.0-43.1]Unit vs 14.8 [8.3-37.6]Unit, p = 0.28), but this was not statistically significant. Subgroup analysis including patients with ISS ≥16 showed that patients in the goal-directed group had significantly fewer consumption of total blood products than patients in the control group (7[6.1-47.0]Unit vs 37.6[14.5- 89.9]Unit, p = 0.015). [27 level I]

Baksaas-Aasen K et al (2021) in the RCT conducted aimed to determine whether augmenting major haemorrhage protocols (MHPs) with Viscoelastic Haemostatic Assays (VHA) would improve outcomes compared to Conventional Coagulation Tests (CCTs). The 'Implementing Treatment Algorithms for the Correction of Trauma-Induced Coagulopathy' (ITACTIC) trial was a pragmatic, multi-centre RCT involving injured patients who were suspected of having haemorrhage and who required at least one RBC transfusion. The trial compared outcomes in patients who received an empiric MHP supplemented by haemostatic therapy guided by either CCTs (CCT group) or by VHAs (VHA group). The VHA device used at each study site (Thromboelastography TEG 6S Haemostasis Analyzer, or ROTEM® Sigma) was determined by existing familiarity with a specific device appliance and to ensure a balanced use of the devices across the study. Adult trauma patients were enrolled if they presented with clinical signs of bleeding activating the local MHP and if RBC transfusion had been initiated. They were randomised using block randomisation and group allocation concealment by sealed envelope. The trial was unblinded to the treating clinical teams, while research personnel collecting subsequent safety and outcome data were blinded to group allocation. Primary outcome was proportion of subjects who, at 24 h after injury, were alive and free of massive transfusion. Massive transfusion was defined as the administration of ten or more units of RBCs in the first 24 h after injury. Secondary endpoints were all-cause mortality at 6 h, 24 h, 28 days, and 90 days post-admission; total blood components; 28-day ventilator-free, and intensive care unit (ICU)-free days; total hospital length-of-stay; and the proportion of patients with symptomatic thromboembolic events, with multiple organ dysfunction, and with serious adverse events. The trial involved 396 patients (201 VHA, 195 CCT). Median age was 43 (28–59) years in CCT group versus VHA 40 (26–54) years. According to gender, male sex CCT 159/194 (82%) versus VHA 145/198 (73%). Baseline characteristics were comparable between treatment groups with two-thirds of the intention-to-treat cohort had sustained blunt trauma alone, and the overall median Injury Severity Score

(ISS) was 26, interquartile range (IQR) 17 to 36,with score over 15 indicating severe trauma.

They found at 24 h, there was no difference in the proportion of patients who were alive and free of massive transfusion (VHA: 67% versus CCT: 64%), OR 1.15 (95% CI 0.76 to 1.73). (Figure 5) [25] level I

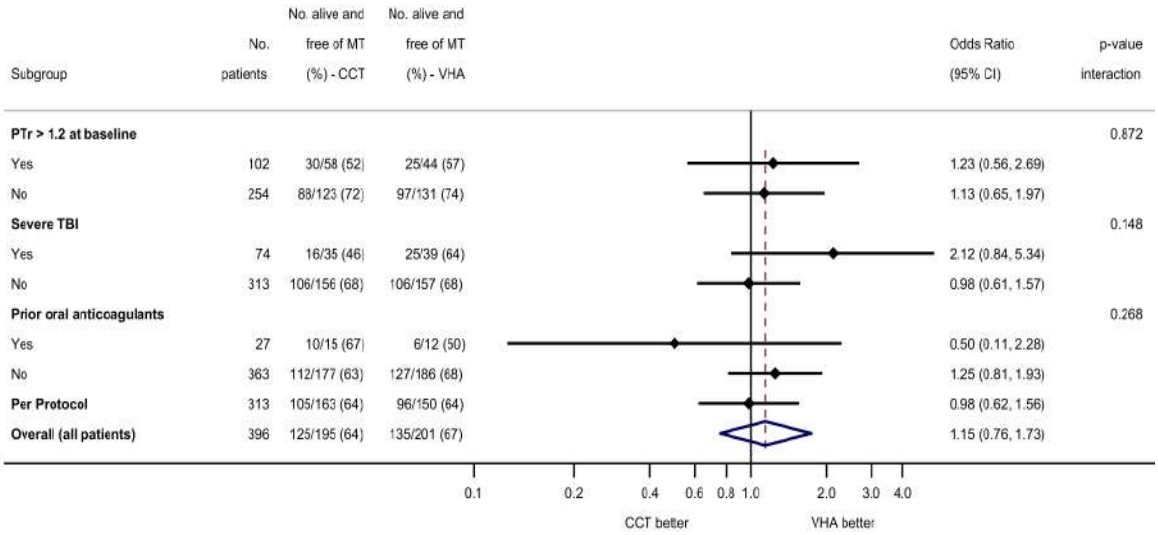

Figure 5 : Primary outcome (alive and free of massive transfusion at 24 hour)

Transfusion avoided

Schochl et. al. (2011), evaluated TEM-guided haemostatic therapy with fibrinogen concentrate and prothrombin complex concentrate (PCC) compared to fresh frozen plasma (FFP)-based therapy in major trauma patients. This retrospective analysis of transfusion parameters involved patients from the Salzburg Trauma Centre, Austria treated with fibrinogen concentrate and/or PCC, but no FFP (fibrinogen-PCC group, n = 80), compared to patients from the trauma registry of the German Society for Trauma Surgery (TR-DGU), which includes 161 trauma hospitals mostly in Germany, receiving ≥ 2 units of FFP (FFP group, n = 601). Inclusion criteria were age 18 to 70 years, base deficit at admission ≥2 mmol/L, injury severity score (ISS) ≥16, abbreviated injury scale for thorax and/or abdomen and/or extremity ≥3, and for head/neck < 5. Coagulation management of patients in the FFP group was dictated by clinical practice at each trauma department and was therefore not standardized. In the fibrinogen-PCC group, coagulation management was guided by TEM analysis, haemostatic therapy comprised of administration of 2 to 4 g of fibrinogen concentrate, and administration of 1,000 to 1,500 U of PCC, for patients showing prolonged clotting time in the thromboelastometry EXTEM test (> 1.5 times normal). Mean age of patients was 37.3±14.5 years (fibrinogen-PCC group) and 39.1±14.5 9 (FFP group).

They found for haemostatic therapy in the emergency room and during surgery, the FFP group (ISS 35.5 ± 10.5) received a median of 6 units of FFP (range: 2,

51), while the fibrinogen-PCC group (ISS 35.2 ± 12.5) received medians of 6 g of fibrinogen concentrate (range: 0, 15) and 1200 U of PCC (range: 0, 6600). RBC transfusion was avoided in 29% of patients in the fibrinogen-PCC group compared with only 3% in the FFP group (p< 0.001). Transfusion of platelet concentrate was avoided in 91% of patients in the fibrinogen-PCC group, compared with 56% in the FFP group (p< 0.001). The authors concluded TEM-guided haemostatic therapy with fibrinogen concentrate and PCC reduced the exposure of trauma patients to allogeneic blood products.[28 level II-2]

Blood product wastage

Cochrane C et al. (2020) in a pre- and post- intervention study investigated whether thromboelastography (TEG®) goal-directed transfusion improved blood utilization, reduced mortality, and was cost-effective. Data were prospectively collected in a UK level 1 trauma center in patients who activated the major hemorrhage protocol one year pre- and one year post-implementation of a TEG 6s-driven transfusion algorithm into the center's code red resuscitation protocol. They used retrospective control group. Inclusion criteria: major haemorrhage protocol activation, code red trauma call, code amber trauma call with suspicion of significant active bleeding, and blood transfusion commenced in a trauma patient. Data were collected on age, gender, mechanism, site of injury, injury severity score (ISS), shock index (SI), blood products used and wasted, outcomes at 24 h, and TEG results. Cost was defined as overall blood product usage and TEG cartridge cost within initial 24 h and wastage of blood products requested but not transfused and not re-issued by blood bank. Analyses compared the pre- and post TEG groups in terms of demographic, the units of blood product transfused, the cost of blood product transfused and total hospital length of stay. The study involved 126 patients (pre-TEG group) and 175 patients (post-TEG group). The intervention was TEG 6s Hemostasis Analyzer (Haemonetics Corp., Boston, MA, USA). Patients were followed up to one month. They found there was no statistical difference between the groups for ISS, SI, injury site, and mechanism, excluding gender (the post-TEG group had fewer females, p < 0.05). No difference in the number or ratio of blood products transfused pre- TEG 6.7 ± 7.5 versus post-TEG 7.5 ± 8.8; p=0.094). Blood product wastage was significantly lower in the post-TEG group (pre- TEG 1.8 ± 2.1 versus post-TEG 1.1 ± 2.0; p = 0.002). A mean of 1.1 units was wasted per patient in the post-TEG group, compared to 1.8 units in the pre-TEG group. More post-TEG patients had no transfusion, as the MTP was stood down prior to transfusion. [26 level II-1]

Volume of transfusion

Tapia et al. (2013) in a retrospective comparative study evaluated outcome of TEG-directed resuscitation compared to massive treatment protocol (MTP) resuscitation in massively transfused penetrating trauma patients. The center performed TEG earlier to analyze coagulation profiles in guiding resuscitation. Following consensus recommendations for MTP, they implemented MTP in 2009 with 1:1:1 ratio of blood (red blood cells [RBC]), plasma (fresh-frozen plasma [FFP]), and platelets. Severely injured trauma patients may require

massive transfusion which was often defined as requiring greater than 10 units (U) of packed RBCs in a 24-hour period. In this study, all patients receiving 6 units (U) or more of RBC in the first 24 hours for 21 months before and after MTP initiation in an urban level I trauma center in Ben Taub General Hospital, Texas were examined. Although the most commonly used definition of massive transfusion is a requirement of 10U or more RBC, this study include patients with 6U RBC. The trauma database was retrospectively analysed after defining two cohort groups: (1) patients before protocol implementation (preMTP patients) and (2) patients after protocol implementation (MTP patients). Demographics, mechanism of injury (MOI), Injury Severity Score (ISS), 24-hour volume of RBC, FFP, platelets, crystalloid, and 30-day mortality were compared, excluding patients with traumatic brain injuries and patients less than 15 years old. Mean age of patients were 35 years, predominantly male. A total of 165 patients from the preMTP group, and 124 patients in the MTP group were analysed. There were no significant differences in ISS, age, or sex. PreMTP patients with 6U or more RBC had significantly more penetrating MOI ($p = 0.017$), whereas preMTP patients with 10U or more RBC had similar MOIs.

All patients (blunt and penetrating, >6U and >10U) received less crystalloid after MTP adoption ($p<0.001$) (Table 4). There was no difference in volume of blood products or mortality in patients receiving 6U or more RBC.

Blunt trauma patients who received 10U or more RBC received more FFP after MTP ($p=0.02$), with no change in 30-day mortality. Penetrating trauma patients who received 10U or more RBC received a similar volume of FFP). (Table 2a).

For all patients, there was no significant difference in **number of days on a ventilator** or of ICU days after implementation of MTP.[11 level II-2]

Table 4: Transfusion volume and ratio comparing preMTP and MTP in blunt and penetrating MOI

Blunt	**≥6U RBC**			**≥10U RBC**		
Volume, mL	**PreMTP (n = 47)**	**MTP (n = 52)**	***p***	**PreMTP (n = 32)**	**MTP (n = 28)**	***p***
RBC	3,542 ± 1,933	3,462 ± 2,402	0.33	4,390 ± 1,785	4,892 ± 2,496	0.83
FFP	1,040 ± 1,121	1,561 ± 1,630	0.08	1,396 ± 1,180	2,315 ± 1,861	0.04*
Platelets	271 ± 408	338 ± 421	0.31	334 ± 456	512 ± 490	0.10
Total blood products	4,854 ± 3,102	5,361 ± 4,137	0.92	6,121 ± 2,988	7,719 ± 4,389	0.20
Crystalloid	6,742 ± 3,841	4,697 ± 3,536	0.01*	7,548 ± 4,039	5,085 ± 3,764	0.02*
Penetrating	**≥6U RBC**			**≥10U RBC**		
Volume, mL	**PreMTP (n = 118)**	**MTP (n = 72)**	***p***	**PreMTP (n = 66)**	**MTP (n = 37)**	***p***
RBC	3,659 ± 2,344	3,960 ± 3,460	0.85	5,100 ± 2,245	5,918 ± 3,928	0.83
FFP	1,546 ± 1,478	1,874 ± 2,759	0.64	2,256 ± 1,580	2,935 ± 3,506	0.04
Platelets	372 ± 437	436 ± 981	0.55	561 ± 470	663 ± 1310	0.10
Total blood products	5,577 ± 3,906	5,271 ± 6,790	0.76	7,918 ± 3,764	9,516 ± 8,241	0.20
Crystalloid	6,475 ± 4,275	4,234 ± 2,522	0.001*	7,388 ± 4,844	3,974 ± 2,642	0.02*

Parameter for diagnosis of coagulopathy

Veigas PV et al. (2016) in a SR of cohort studies summarized the reported Rotational thromboelastometry (ROTEM®) parameters and their thresholds for the presence of coagulopathy, to predict bleeding, guide the hemostatic resuscitation and predict mortality. Systematic search was conducted on MEDLINE, EMBASE and EBM Reviews (Cochrane Data-base of Systematic Reviews) from 1946 to March 2016. The SR was reported accordance to the PRISMA guidelines. The review included observational studies and RCTs in trauma where cut off values of ROTEM® parameters were reported in: (1) diagnosing coagulopathy; (2) predicting or guiding transfusion; and, (3) predicting mortality, however no RCT found from the search. Selection, data extraction, and risk of bias assessment was conducted by two reviewers. Methodological quality of the studies was assessed using the Newcastle-Ottawa Scale and Quality Assessment of Diagnostic Accuracy Studies-2 tool (QUADAS-2). The SR outcome were accuracy in diagnosing coagulopathy, predicting massive transfusion, diminishing exposure to allogeneic blood products and predicting mortality. The SR included 13 studies (2835 patients) comprised of nine prospective cohort and four retrospective cohort studies. Median age of the study population ranged from 21 to 47 years. In this review, ROTEM was compared to standard coagulation test (SCT). There were ten studies addressing ROTEM® thresholds for diagnosis of coagulopathy in this review. However, definition of coagulopathy by SCTs was not standardized. The ROTEM threshold used and comparator varied in the included studies. Most common parameters used were EXTEM-CA5, CA10, CA15 (correlated with PT and INR). The cut-off values varied from 5 mm in CA5 to 35 mm in CA15. AUC of the parameters ranged from 0.77 to 1.00, the highest AUC was for EXTEM MCF ≤ 18mm.[30 level II-2]

Prediction parameter for transfusion

In the SR by Veigas et al (2016), six studies addressed the thresholds for prediction or guidance of transfusion. The ROTEM threshold used and comparator varied in the included studies. For prediction of transfusion, one study established EXTEM-CA5 ≤35 mm using INR as control. Values outside the reference range for EXTEM and INTEM CT,CFT, CA at 10, 20 and 30 min, as well as reduced MCF were more likely in patients who required a MT, as compared to patients who did not. Other parameters used were EXTEM CA5 ≤35 mm and FIBTEM-MCF ≤7 mm that were also associated with the need for MT. In transfusion guidance, FIBTEM MCF < 10 mm and EXTEM CT > 1.5 times normal were used to guide administration of FC and PCC, respectively, with a reduction of the number of RBC units used in the FC/PCC group, compared to fresh frozen plasma (FFP) group ($p < 0.001$). AUC of the parameters ranged from 0.75 to 0.84, with the highest AUC was for FIBTEM MCF ≤ 7mm. [30 level II-2]

Prediction parameter for mortality

Veigas et al. (2016) in the SR found, six studies were addressing prediction of mortality. The ROTEM threshold used and comparator varied in the included studies. Overall, an association between hyperfibrinolysis and mortality was demonstrated (maximum lysis of 100 %, defined using (ELT as control). Multiple parameters were found to be associated with mortality, including: FIBTEM < 7 mm/ <9 mm/<9.5 mm, EXTEM-MCF < 45 mm; shorter EXTEM-CT, INTEM-CT, EXTEM-CFT and INTEM-CFT; higher EXTEM-MCF, INTEM-MCF. AUC of the parameters ranged from 0.77 to 1.00, with the highest AUC was for EXTEM MCF ≤ 18mm. [30 level II-2]

Length of stay, Quality of life

Baakses-Aasen et al. (2020) in the ITACTIC trial found hospital length-of-stay was similar in both groups, VHA and CCT group and so were the quality-of-life (EQ-5D) scores at both discharge/28 days and 90 days (Table 5). [25 level I]

Table 5: Summary of secondary outcomes in Baakses-Aasen et al (2020) ITACTIC trial

	CCT ($n=195$)	VHA ($n=201$)	Odds ratio (95% CI)	p value
Mortality at 6 h—no. (%)	22/195 (11%)	22/201 (11%)	0.97 (0.52–1.80)	0.915
Mortality at 24 h—no. (%)	33/195 (17%)	29/201 (14%)	0.83 (0.48–1.42)	0.495
Mortality at 28 days—no. (%)	55/194 (28%)	50/201 (25%)	0.84 (0.54–1.31)	0.435
Mortality at 90 days—no. (%)	56/177 (31%)	53/179 (29%)	0.91 (0.58–1.42)	0.678
Death from exsanguination—no. (%)	17/56 (30%)	13/51 (25%)	0.78 (0.34–1.82)	0.576
Died before haemostasis—no. (%)	24/54 (44%)	19/50 (38%)	0.77 (0.35–1.67)	0.505
Median time to haemostasis^ (IQR)—mins	122 (80–185), $n=170$	125 (77–185), $n=176$		0.929
PTr > 1.2 at haemostasis^—no. (%)	17/151 (11%)	21/142 (15%)	1.37 (0.70–2.69)	0.369
Massive transfusion at 24 h—no. (%)	55/195 (28%)	53/201 (26%)	0.91 (0.59–1.42)	0.682
Patients with symptomatic TE^^—no. (%)	27/195 (14%)	17/201 (9%)	0.57 (0.31–1.08)	0.088
Patients with MODS^^^—no. (%)	134/159 (84%)	141/164 (86%)	1.14 (0.62–2.10)	0.668
Median 28-day ventilator-free days (IQR)	20 (0–26), $n=192$	17 (0–25), $n=198$		0.422
Median 28-day ICU-free days (IQR)	15 (0–23), $n=192$	13 (0–23), $n=198$		0.691
Median hospital LOS in survivors (IQR)	24 (10–42), $n=138$	29 (13–49), $n=147$		0.147
Median EQ-5D^^^^ index at discharge/28 days (IQR)	49 (25–60), $n=86$	40 (28–60), $n=$ $n=92$		0.672
Median EQ-5D^^^^ index at 90 days (IQR)	60 (40–70), $n=75$	53 (40–70), $n=72$		0.718

MODS – Multiple Organ Dysfunction Syndrome

Cochrane C et al. (2020) in a pre-post intervention study evaluating TEG-directed transfusion in UK trauma patients found total hospital LOS was significantly greater in the post-TEG group (p<0.001) with a median LOS of 14 days, compared to a median of 9 days for the pre-TEG group in line with survival bias (Table 6). [26 level I]

Table 6: Length of stay and mortality

Outcome	Pre-TEG (n= 126)	Post-TEG (n= 175)	p-value
Total hospital LOS	9 [3, 19]	14 [6, 27]	<0.001
24 h mortality	17 (13%)	8 (5%)	0.006
30 day mortality	32 (25%)	20 (11%)	0.002

Yin et al. (2014) in a retrospective cohort study involving patients with abdominal trauma aimed to determine if goal-directed transfusion protocol based on standard TEG is feasible and beneficial in these patients. This study analyzed the abdominal trauma database, involving data collected between 2008 and 2012 of patients with abdominal trauma at Department of General Surgery, Jinling Hospital, Nanjing, China. Inclusion criteria were age older than 18 years, abdominal abbreviated injury scale ≥2, and requirement of two or more units of RBC transfusion within 24 hours of Emergency Department (ED) admission. In this study, 60 adult patients with abdominal trauma who received 2 or more units of RBC transfusion within 24 hours of admission were involved. Patients managed with goal-directed transfusion protocol based on TEG (goal-directed group) were compared to patients admitted before utilization of the protocol who received conventional transfusion management (control group). Patients who received conventional transfusion management between November 2008 and October 2010, were assigned to the control group, whereas patients who were managed with the goal-directed transfusion protocol between November 2010 and October 2012, were assigned to the goal-directed group. Patients in the control group received conventional transfusion management, based on individual experience and interpretation of conventional coagulation testing results, RBC and FFP were delivered at a ratio of 1:1 to 1:2. Patients in the goal-directed group were managed with goal-directed transfusion protocol based on TEG result. Data of all included patients from ED, Surgical Intensive Care Unit (SICU), operation room, blood bank, and laboratory were linked. TEG parameters (R value, α angle, and MA value) of the first TEG test and the follow-up one between 24 to 48 hours after the first one was collected from patients in the goal-directed group. In addition, mortality at 28d, length of stay in ICU and hospital were noted. There were 29 patients in the goal-directed group and 31 in the control group. Baseline parameters were similar. They found no difference in length of stay in intensive care unit and hospital between the two groups. [27 level II-2]

Schochl et al. (2011) in the evaluation of TEM-guided haemostatic therapy with fibrinogen concentrate and prothrombin complex concentrate compared to FFP in major trauma patients, also measured the length of stay in ICU and hospital. Median length of stay (LOS) in the ICU was comparable in the two groups: 14.5 days (IQR: 8.5, 21) in the fibrinogen-PCC group and 14 days (IQR: 6, 23) in the FFP group (p=0.95). In contrast, the median LOS in the hospital was significantly different between the two groups: 23 days (IQR: 14.5, 40.5) in the fibrinogen-PCC group and 32 days (IQR: 20, 49) in the FFP group (p= 0.005). The median duration of postoperative intubation was 9.5 days (IQR: 3.5, 14) in

the fibrinogen-PCC group, significantly longer than the 7 days (IQR: 2, 16) in the FFP group (p= 0.005).[28 level II-2]

Multiple organ dysfunction, incidence of thromboembolic event

Baakses-Aasen et al (2020) in the multicentre RCT (ITACTIC trial) found no statistically significant differences in other secondary outcomes between the two study groups, the CCT and VHA group, including the rate of multiple organ dysfunction, the incidence of symptomatic thromboembolic events, and a number of ventilator-free days or ICU-free days at day 28. (Table 5). [25 level I]

Innerhofer et al. (2017) in the RCT evaluating ROTEM-guided first line haemostatic therapy using FFP compared to coagulation factor concentrate in patients with trauma demonstrated higher multiple organ failure following FFP, reported in 29 (66%) patients, compared to 25 (50%) patients in the CFC group, OR 1.92 (95% CI 0.78 to 4.86), however it was not significant. [29 level I]

Reversal of coagulopathy, frequency of immediate surgery

Innerhofer et al. (2017) conducted RCT using ROTEM in identifying plasma coagulopathy, to compare the efficacy of first-line therapy using fresh frozen plasma (FFP) or coagulation factor concentrates (CFC), for the reversal of trauma-induced coagulopathy, the arising transfusion requirements, and the development of multiple organ failure. This trial was a single-centre, parallel-group, open-label, randomised trial, done at the Level 1 Trauma Center in Innsbruck Medical University Hospital (Innsbruck, Austria). Patients with major blunt trauma aged 18 to 80 years, with trauma exhibiting an Injury Severity Score (ISS) greater than 15, bleeding signs, and plasmatic coagulopathy identified by abnormal fibrin polymerisation or prolonged coagulation time using ROTEM were eligible. Risk of substantial haemorrhage were screened for trauma-induced coagulopathy, which was defined as abnormally low fibrin polymerization, measured with bedside ROTEM using the FibTEM assay (10-minute value of fibrinogen polymerisation [FibA10] <9 mm) or prolonged initiation of coagulation in the extrinsically activated ROTEM (ExTEM) assay (coagulation time of ExTEM assay [ExCT] >90 s). The ROTEM assay visualizes the entire coagulation process, from initiation to final clot stability. Bleeding score was devised as, (0: no substantial bleeding; 1: injury-related normal bleeding with visible clots; 2: diffuse microvascular bleeding from wound and catheter insertion sites; 3: massive bleeding with transfusion of >3 U red blood cells [RBC] per hour) to aid assessment of blood loss. Before therapy, all patients received tranexamic acid (20 mg/kg of bodyweight). These patients were excluded; those with injuries that were judged incompatible with survival, cardiopulmonary resuscitation on the scene, isolated brain injury, burn injury, avalanche injury, or prehospital coagulation therapy other than tranexamic acid. A computer-generated randomisation list was used, stratified for brain injury and ISS, and random allocation (1:1) of patients to treatment with FFP (15 mL/kg of bodyweight) or CFC (primarily fibrinogen concentrate [50 mg/kg of bodyweight]) was done using closed opaque envelopes. Bleeding management began immediately after randomisation and continued until 24 hours after

admission to the intensive care unit. The primary endpoint was multiple organ failure as assessed by the daily Sequential Organ Failure Assessment (SOFA) score, with a score of three or more in at least two organ systems defined as multiple organ failure. Reversal of coagulopathy and need for massive transfusions were secondary endpoints, that was looked for deciding the trial continuation or termination. Massive transfusion was defined as transfusion of more than 10 RBC during the first 24 hour. Successful reversal of trauma-induced coagulopathy was defined as just normalised FibA10 (FibA10 >8 mm) ExCT (ExCT <78 seconds) measured after completed single-dose or double dose study drug administration, and absence of diffuse or massive bleeding (bleeding score 0 to 1). Patients were followed up until hospital discharge or day 30, whichever occurred first. Between March 2012, and February 2016, 100 out of 292 screened patients were included and randomly allocated to FFP (n=48) and CFC (n=52). Six patients (four in the FFP group and two in the CFC group) discontinued treatment due to overlooked exclusion criteria or a major protocol deviation with loss of follow-up. A total of 44 patients in the FFP group and 50 patients in the CFC group were included in the final analysis.

Patients had a median age of 43 years (IQR 26 to 54), an ISS of 34 (IQR 26 to 43), and nearly 50% had concomitant brain injury. Demographics, pre-hospital treatment, haemodynamic, and laboratory parameters on arrival at the emergency department were balanced between groups. The study was terminated early due to futility and safety reason as high proportion of patients in the FFP group required rescue therapy compared with those in the CFC group (23 [52%] in the FFP group compared to two [4%] in the CFC group; odds ratio [OR] 25.34 (95% CI 5.47 to 240.03).

The odds in favour of successful reversal of coagulopathy after single-dose study drug was higher for CFC than for FFP, OR 8.22 (95% CI 3.06 to 23.78). The number needed to treat for reversal of coagulopathy with CFC only was 2.07 (95% CI 1.6 to 3.1). Frequency of immediate surgery was similar for both groups (40 [88%] in the FFP group, 36 [82%] in the CFC group; OR 0.62 (95% CI 0.16 to 2.24). [29 level I]

Detection of hypercogulability

Park MS et al. (2009) investigated the hemostatic status of critically ill, nonbleeding trauma patients, aimed to determine coagulation changes during the first seven days in critically injured, nonbleeding, burned or nonburn trauma patients. The patients were stratified by burn status, and findings from plasma-clotting assays (PT and aPTT) and whole-blood clotting test (TEG) were compared. Trauma patients admitted to the ICU within 24 hours after injury were enrolled. Inclusion criteria were; age 18 years or older, admitted within 24 hours after injury, and an anticipated stay of at least 72 hours at the US Army Institute of Surgical Research Burn Center or Trauma ICU of Brooke Army Medical Center. A total of 20 healthy volunteers were recruited and their laboratory data were used as a reference. Blood samples were drawn on days 0 through 7. Laboratory tests included prothrombin time (PT), activated partial thromboplastin time (aPTT), levels of activated factor XI, D-dimer, protein C

percent activity, antithrombin III percent activity, and thromboelastography (TEG). Definition for hypercoagulable state was the presence of at least two of the following: shortened R time, increased α angle, and increased maximal amplitude (MA). Clinical data were collected from subjects during their ICU stay for up to 30 days or until the patient was transferred out of the ICU. Deep vein thrombosis (DVT) and pulmonary embolism diagnoses were made on the basis of a duplex scan of the legs and a computed tomographic scan of the chest if clinically indicated. Sixty-one patients were enrolled from April 1, 2004, to May 31, 2005, and included nonburn trauma patients (n=33), burned patients (n=25) with 20 healthy subjects (control). They found despite aggressive thromboprophylaxis, three subjects (two burned and one nonburn trauma patients [6%]) had pulmonary embolism during hospitalization. Compared with controls, all patients had prolonged PT and aPTT ($p<0.05$). The rate of clot formation (α angle) and maximal clot strength were higher for patients compared with those of controls ($p<0.05$), indicating a hypercoagulable state. Injured patients also had lower protein C and antithrombin III percent activities and higher fibrinogen levels ($p<0.05$ for all). Activated factor XI was elevated in 38% of patients (control subjects had undetectable levels). They highlighted the TEG analysis of whole blood demonstrated that patients were in a hypercoagulable state; and this was not detected by plasma PT or aPTT.[31 level II-2]

5.2.2 Postpartum haemorrhage (PPH)

Blood loss, volume of transfusion

Barinov SV et al. (2015) in a randomised trial evaluated the performance of a combined strategy of PPH management, based upon TEG assessment of coagulation, early surgical haemostasis and mechanical compression of the uterine wall combined with uterine cavity draining via intrauterine balloon tamponade (BT). They carried out an open controlled trial, involving 119 women with obstetric haemorrhage (intervention group, n=90; control group using conventional strategy, n=29). Inclusion criteria was gestational age between 28 and 42 weeks, labour or post-partum period. The combined strategy comprised of three components: early surgical haemostasis, mechanical pressure of the uterine wall and draining of the uterine cavity via BT, and treatment of blood coagulation disorders identified via TEG. Surgical hemostasis was performed in the intervention group if the blood loss exceeded 1,000 ml (early surgical hemostasis), included ligation of the descending uterine arteries branches, ligation of bleeding vessels of the placental site, and positioning of an external uterine haemostatic supraplacental assembly suture. During BT, a modified obstetric uterine balloon catheter (Zhukovski double-balloon obstetric catheter) was inserted into the uterine cavity.The balloon was filled to achieve mechanical compression of the placental site and left in uterus for three to six hours, after which it was emptied and removed. Meanwhile, conventional management of haemorrhage consisted of uterine massage, manual uterus examination, transfusion of FFP, RBC, platelet concentrate, protease inhibitors, and surgical haemostasis (performed conventional time point when the blood loss exceeded 2,000 ml). The rate of peripartum hysterectomies was the primary outcome. Secondary outcomes included total blood loss volume, rate of

blood loss >2,000 ml, and total volumes of infusion therapy, FFP, RBC and platelet concentrate use.

They found from 2012 to 2014, there were 9,721 deliveries in the centre, among which 4,259 (46.5%) were caesarean sections. The mean age of participants was 28.5±5.4 years. The combined haemorrhage management strategy resulted in significantly lower number of peripartum hysterectomies compared to standard management (4.44% versus 31.03%, respectively, p=0.02). Blood loss of >2,000 ml occurred significantly less common in the main group compared to the control group (16.2% versus 27.6%, respectively, p=0.03). Mean total blood loss after combined management was significantly lower than after the standard approach (2,502 ± 203 ml versus 1,836 ± 108 ml, p=0.04). Significantly higher total volume of infusion therapy and FFP was required in control group compared to the main group (infusion: 4,441 ± 907 ml versus 2,437 ± 730 ml, p = 0.041; and FFP: 2,498 ± 503 ml versus 1,196 ± 415 ml, p = 0.034) respectively. The rate of peripartum hysterectomies was reduced by almost eight-fold, blood loss by 1.5 fold, and FFP transfusion by two-fold.

The highest ability for prediction of major obstetric haemorrhage was observed for fibrin clot density, Maximum Amplitude [AUC = 0.9 (95% CI 0.83 to 0.95). Transfusion of blood coagulation factors (Protromblex 600, Coagyl), FFP, cryoprecipitate and platelet concentrate were done simultaneously with the surgical haemostasis, with choice of transfused product was driven by the TEG result. There were six participants experienced haemorrhage after three to six hours from the removal of the intrauterine balloon, justifying re-laparotomy, in which four underwent hysterectomy. [32 level I]

Kaufner L, et. al. (2016) in a prospective observational pilot study assessed whether prepartum TEM-derived parameters and fibrinogen levels really predict postpartum hemorrhage (PPH). The study included 217 healthy pregnant women in a single centre observational study conducted in Berlin, Germany. Inclusion criteria were age >18 years, sufficient German language skills, good mental health, and a Class II–III physical status according to the American Society of Anesthesiologists classification, enrolled between 2012 and 2013. Maximum clot firmness (FIBTEM-MCF), fibrinogen levels and standard coagulation parameters were measured upon admission to the delivery room for labor and within one hour after vaginal delivery. ROTEM® derived parameters were measured using ROTEM® delta (TEM International GmbH, Munich, Germany). Blood loss was measured with a calibrated transparent collecting drape during the third stage of labor. The PPH was defined as blood loss ≥500 ml occurring within 24 h irrespective of the mode of delivery. Primary outcome was correlation of prepartum ROTEM parameters (FIBTEM, MCF, EXTEM A10) and fibrinogen level, and measured post partum blood loss. Predictors for bleeding were identified via receiver operating characteristic analyses and multivariate regression analyses. Mean age of patients was 29(±6) years old. Seventy-one (71%) participants underwent vaginal delivery, 17% were having urgent caeserian section and 12% did instrumental delivery.They found women with and without PPH did not differ in median FIBTEM-MCF [23 mm (25th percentile 20 mm, 75th percentile 26 mm) vs

23 mm (19 mm, 26 mm), respectively; p=0.710] or mean Fibrinogen$_{pre}$ (4.57 ± 0.77 g/L vs. 4.45 ± 0.86 g/L, respectively; p=0.431).

Blood loss and prepartum coagulation parameters were not correlated (FIBTEM-MCF, r_s =−0.055, p=0.431; Fibrinogen$_{pre}$, r_s =−0.017, p=0.810), as in Figure 5. Neither prepartum ROTEM parameter nor fibrinogen level showed a correlation with postpartum blood loss. The areas under the curves (predictive power for PPH) for FIBTEM-MCF and Fibrinogen$_{pre}$ were 0.52 (95%CI 0.41 to 0.64) and 0.53 (95%CI 0.40 to 0.65), respectively. Neither FIBTEM-MCF nor Finbrinogen$_{pre}$ was associated with PPH. However, primiparity (adjusted OR 4.27, 95% CI 1.32 to 13.80) and urgent cesarean section (adjusted OR 2.77, 95%CI 1.00 to 7.67) were independent predictors of PPH. [33] level II-2

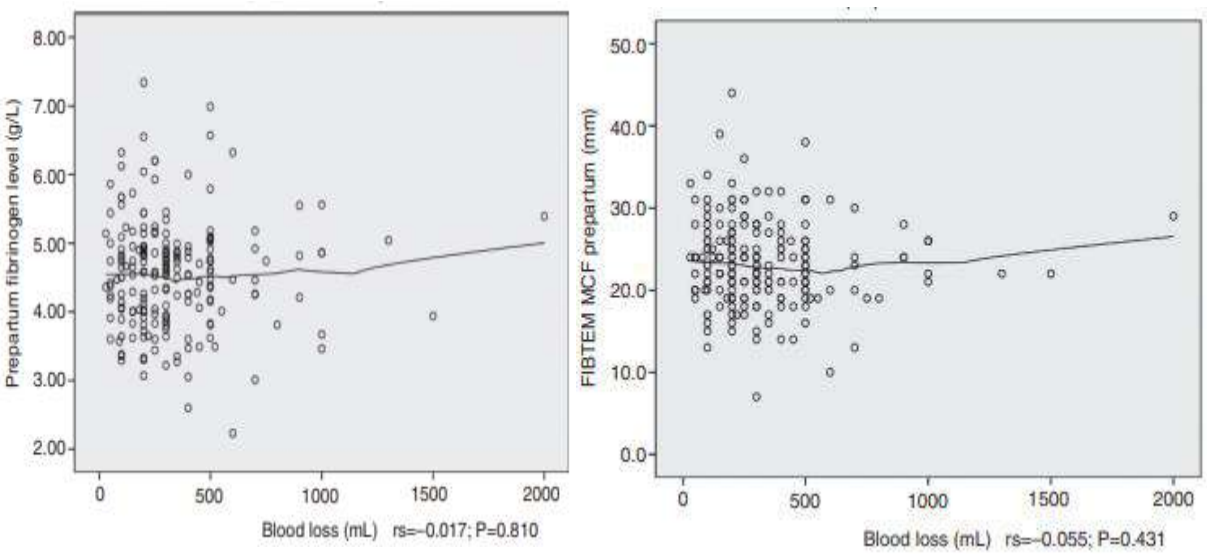

Figure 5: Correlation between blood loss and prepartum fibrinogen (left) and FIBTEM MCF (right)

5.2.3 Liver transplant

Guiding transfusion and haemostatic therapy

Leon Justel A et al. (2019) in a non-randomised trial evaluated the impact on transfusion requirements and evaluated the impact in adverse patient outcomes, defined as the rate of occurrence of immediate postoperative complications. They involved 200 orthotopic liver-transplantation (OLT) patients (100 intervention, 100 control) in the evaluation of impact in transfusion requirement and patient outcomes of the new approach for haemostasis and transfusion management based in point of care (POC) monitoring in comparison with the current standard procedure based in routine testing performed in the main laboratory. The primary study outcome were transfusion requirements (numbers of units of blood product given per patient intraoperatively, the proportion of patients who completely avoided blood product transfusion (total avoidance), and the proportion of patients who

received massive transfusion (defined as the transfusion of more than 10 RBC units). Secondary outcome was rate of immediate postoperative complications. In the intervention group, POC group, haemostasis and transfusion management was decided according to a specific algorithm based in mobile laboratory-unit (MLU) results, whereas in the standard care group, haemostasis and transfusion management was supported by routine laboratory testing performed at the main laboratory.

Transfusion requirements were reduced in the POC group. There was reduction in median and IQR for:

- Red-blood-cells (RBC) transfusion units from 5 [2–8] to 3 [0–5] ($p<0.001$),
- Plasma from 2 [0–4] to 0 ($p<0.001$)
- Platelets from 1 [0–4] to 0 [0–1] ($p<0.001$),

Fibrinogen transfusion was higher in POCG, 1.13 ± 1.44 g per patient vs 0.48 ± 1.28 in SCG. There was increased incidence of transfusion avoidance, 5% vs. 24% ($p<0.001$) and reduced incidence of massive transfusion (defined as the transfusion of more than 10 RBC units), 13% vs. 2% ($p=0.005$) in the POC compared to SCG. A relationship between RBC transfusion requirements and preoperative haemoglobin, and between platelet transfusion and preoperative fibrinogen levels were observed. [34 level II-1]

Zamper RPC et al. (2018) in a pre- and post-intervention study assessed whether viscoelastic tests-guided therapy with the use of synthetic factor concentrates impact transfusion rates of haemocomponents in adult patients undergoing liver transplantation. Study protocol was approved by the local ethics committee of Hospital Israelita Albert Einstein. Inclusion criteria was all patients undergoing deceased donor liver transplantation for chronic liver disease. In the control phase this study involved patients undergoing liver transplantation operated between 2007 and 2009. While in the intervention phase, they involved patients undergoing liver transplantation operated during a 10-month period after the implementation (January 2015 to October 2015). Clinical coagulopathy with bleeding, and management was based on a POC-VET algorithm. Primary outcome was need of any transfusion of blood product during surgery and in the first 48 h in the postoperative (RBC, FFP, cryoprecipitate, platelets) and secondary outcomes were: 1) use of synthetic factor concentrates or antifibrinolytic; 2) clinical complications related to the procedure; 3) postoperative duration of ventilation in days; 4) ICU and hospital length of stay in days; and 5) in-hospital mortality. The study population consisted of unmatched cohort =237 (54 intervention, 183 control), with matched cohort =135 (46 intervention, 89 control). Matched cohort was adjusted by age, Child-Pugh, MELD, presence of HCC and pre-op Hb. The intervention was POC-VET (ROTEM).

They found proportion of patients receiving any transfusion of blood product components was significantly lower, 35.2% in the intervention phase and 56.3% in the control phase ($p= 0.006$). After propensity score matching, the proportion of patients receiving any transfusion of hemocomponents was lower in the intervention phase [37.0% vs 58.4%; OR 0.42 (95% CI: 0.20 to 0.87); $p = 0.019$]. Patients in the intervention phase received less RBC [30.2% vs 52.5%;

OR 0.21(95% CI: 0.08 to 0.56); p=0.019]. Patients in the intervention phase received less FFP [5.7% vs 27.3%; OR 0.11 (95% CI: 0.03 to 0.43); p =0.002]. There was no difference on cryoprecipitate and platelets transfusion. Secondary outcome found the use of haemoderivates was higher in the intervention phase (35.2 vs 0.0%; p< 0.001) and the use of antifibrinolytic agents was lower [14.8% vs 42.3%; p<0.001; adjusted OR 0.33 (95% CI: 0.13 to 0.80); p= 0.015].

There was no difference regarding complications related to the procedure, duration of mechanical ventilation, ICU length of stay and hospital mortality among the two groups. After propensity score matching, there was only a trend toward decreased hospital length of stay in survivors in the intervention phase (11.6 ± 7.5 vs 15.1 ± 11.4 days; p= 0.066](Table 7).[35 level II-1]

Table 7: Clinical outcomes after transplantation in Zamper et al. (2018)

Table 4 Clinical outcomes after transplantation

	Unmatched Cohort (n = 237)			Matched Cohort (n = 135)[b]	
	Intervention (n = 54)	Control (n = 183)	p value[a]	Intervention (n = 46)	Control (n = 89)
Related to the procedure					
2003Any complication	25 / 53 (47.2)	99 / 183 (54.1)	0.373	21 / 45 (46.7)	44 / 89 (49.4)
Upper digestive hemorrhage	10 / 53 (18.9)	54 / 174 (31.0)	0.084	10 / 45 (22.2)	27 / 84 (32.1)
Arterial thrombosis	1 / 53 (1.9)	6 / 172 (3.5)	0.557	1 / 45 (2.2)	2 / 82 (2.4)
General					
Duration of mechanical ventilation	0.5 ± 1.1	1.1 ± 3.9	0.242	0.5 ± 1.2	0.9 ± 1.4
Survivors	0.4 ± 1.1	0.8 ± 1.2	0.052	0.4 ± 1.1	0.8 ± 1.4
ICU length of stay	3.2 ± 4.0	4.2 ± 6.6	0.290	3.4 ± 4.3	3.6 ± 4.6
Survivors	2.8 ± 2.7	3.6 ± 5.3	0.306	2.9 ± 2.9	3.5 ± 4.6
Hospital length of stay	12.1 ± 8.9	17.2 ± 15.4	0.022	12.4 ± 9.5	16.1 ± 16.6
Survivors	11.3 ± 7.2	16.3 ± 12.7	0.007	11.6 ± 7.5	15.1 ± 11.4
In-hospital mortality	1 / 53 (1.9)	11 / 182 (6.0)	0.226	1 / 45 (2.2)	5 / 89 (5.6)

ICU: intensive care unit
Data presented as mean ± standard deviation or number / total (percentage)
[a]Comparison of differences between the two groups using the t test for continuous variables and the $\chi 2$ test for categorical variables
[b]Adjusted by age, Child, MELD, presence of HCC and pre-transplantation hemoglobin

Alamo JM et al. (2013) in a case-control study aimed to estimate the influence of orTEM on graft survival and patient morbidity and mortality after liver transplant compared with classic laboratory tests (non-orTEM) and identify differences in transfusion requirements. The study involved 303 consecutive patients underwent liver transplant with or without thromboelasometry (TEM) located within the operating room performed at the Virgen del Rocío Hospital. Outcomes were morbidity, mortality and transfusion requirements. The study involved 303 patients (135 in the orTEM and 168 in the non-orTEM group). One hundred-twenty three patients had a preoperative risk (MELD score ≥ 21 and patients undergoing retransplantation), of which 66 were in the non-orTEM, and 57 in the orTEM group. Among patients who received ≥ 5 RBC units during the liver transplant, 80 were non-orTEM patients and 32 orTEM patients. They found significant decrease in the number of blood products used in the orTEM group (p<0.05; Figure 6). More patients required ≥ 5 units of RBC in the non-orTEM group than in the orTEM group (33.9% vs 23.7%; p<0.05)

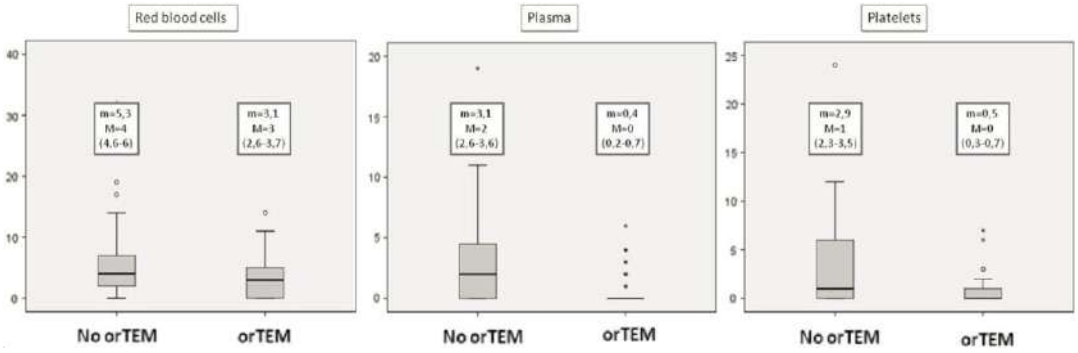

Figure 6: Blood requirements in the orTEM and non-orTEM groups (m=average,M=median)

Lower survival was observed in the non-orTEM group compared to the orTEM group, although the differences were not significant [p=0.76 in non- orTEM and p=0.68 in orTEM (Figure 7)].

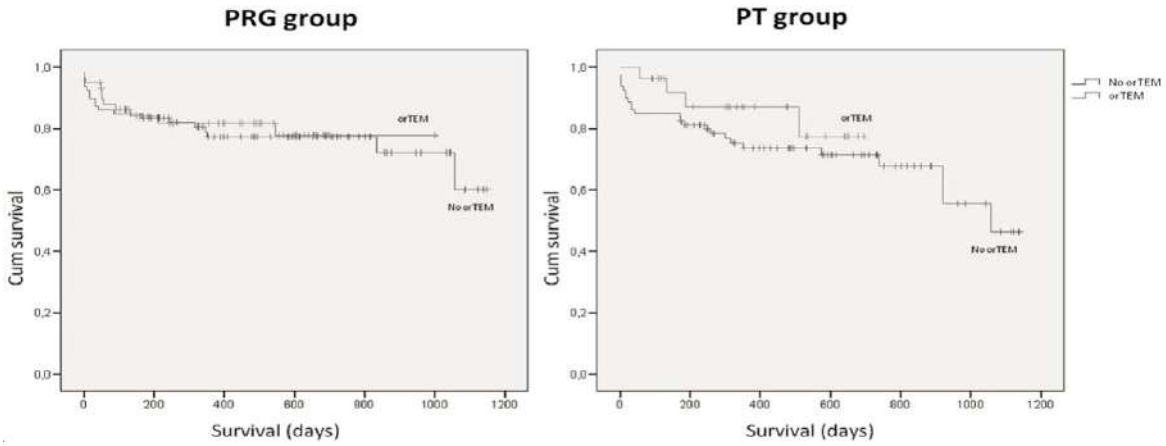

Figure 7: Patient survival in PRG and PT groups (p<0.05)

In addition, use of orTEM was associated with a lower rate of postoperative mortality (p<0.05), in patients who required ≥5 unit of RBC during the liver transplant. (Data not shown) [36 level II-2]

5.2.4 Patients underwent microsurgery

Malapati H et. al. (2021) conducted a systematic review to evaluate the efficacy of viscoelastic testing (VET) to predict microvascular thrombotic complications and flap failure. Flap thrombosis is a rare but devastating complication in microsurgery. Preoperative identification of patients at increased risk for microvascular thrombosis remains challenging. Systematic review was performed in accordance with the PRISMA guidelines. Systematic search was conducted through PubMed, Embase, Cochrane Library, Web of Science and Scopus databases on May 2020. Information on patient characteristics, timing and features of viscoelastic tests, and outcomes were collected using a standardized data collection form. Review articles, letters to the editor,

abstracts, and case reports were excluded. A total of six studies were included (two prospective cohort, two retrospective cohort, two retrospective case series). The review involved 596 patients and 328 were in free flaps. Significant heterogeneity was noted in study design, interventions, and outcome data reporting, precluding a meta-analysis. Four studies found a statistically significant relationship between viscoelastic testing results and flap thrombosis or flap loss. The maximum clot strength and the fibrinogen-to-platelet ratio (FPR) were key viscoelastic parameters in these studies, both representing a measure of maximal clot strength. An elevated FPR (>42%) generated a sensitivity and specificity for flap loss ranging from 57% to 75% and 60% to 82%, respectively. Negative predictive value for flap failure with a normal preoperative FPR was greater than 90% in all studies reporting a correlation. The remaining two studies reported no predictive value for VET with respect to flap failure or pedicle thrombosis. Studies included were presented as in Table 8. The author's concluded that the results of this review suggest that VET, particularly parameters relating to clot strength, may help clinicians identify patients at risk for flap thrombosis.

Table 8: Included studies in SR by Malapati et al. (2021)

Study	Population	VET	AC protocol	Flap loss	Pedicle thrombosis	Conclusion	Notes
Parker et al. Retrospective cohort	Patients: 29 free flaps: 35	TEG: FPR	Not standardized	4 (11.4%)	9 (26%) Arterial (2), Vein (7)	FPR ≥ 42% was associated with increased risk of flap thrombosis (P = 0.003)	Sensitivity 89%, specificity 75%
Kolbenschlag et al. Retrospective cohort	Patients: 181 Free flaps: 181 Indication: varied	ROTEM: MCF, FPR	Not standardized. Heparin 15,000U/d or LMWH BID postoperatively	14 (7.7%)	28 (15%) Arterial (6), Vein (15), both (7)	Elevated MCF and FPR >43 was associated with flap thrombosis (P = 0.036 and 0.003, respectively)	Odds ratio for flap failure: Elevated MCF, OR = 3.75 FPR >43, OR = 7.9
Vanags et al. Prospective cohort	Patients: 103 Indication: trauma	ROTEM: CT, CFT, MCF, FPR	Enoxaparin 40 mg daily		16 (15.5%)	FPR ≥ 42 was associated with flap thrombosis (P = 0.003) in the delayed reconstruction cohort only	The acute reconstruction cohort was underpowered
Zavlin et al30 Retrospective cohort	Patients: 171 Indication: breast reconstruction	TEG	Dosing based on TEG-G. Intraoperative: IV heparin Postoperative: LMWH	2 (1.2%)	5 (2.9%) Arterial (1), Vein (4)	TEG-G > 10,900 was associated with flap thrombosis (P = 0.049)	Elevated preoperative TEGs were prophylactically treated with higher dose heparin
Ekin et al. Retrospective Case series	Patients: 77 Free flaps: 77 Indication: varied	TEG	Not standardized	3 (3.9%)	5 (6.5%)	TEG was not associated with flap thrombosis or flap complications	No hypercoagulable patients were included in the study
Wikner et al. Prospective cohort	Patients: 35 Free flaps: 35 Indication:	ROTEM: INTEM CT,	Intraoperative IV heparin,	3 (8.6%)	5 (14.3%)	ROTEM values did not correlate with flap	ROTEM exhibited a dose response to IV

	H&N cancer	EXTEM CT	adjustment based on pTT			thrombosis or loss	heparin

AC, anticoagulation; AUC, area under the curve; BID, twice a day; CT, clotting time; gtt, drops; EXTEM, extrinsic pathway ROTEM parameter; HN, head & neck; INTEM, intrinsic pathway ROTEM parameter; IV, intravenous; POD, postoperative day; pTT, partial thromboplastin time; RTE, rotational thromboelastometry; SIEV, superficial inferior epigastric vein; TEG-G,thromboelastography log-derivation of maximum amplitude parameter; TEG-K, thromboelastography kinetics parameter; TEG-R, thromboelastography reaction parameter; TEG-SP, thromboelastography split point parameter.

5.3 SAFETY

There were three studies retrieved on the safety of VHA in the management of non cardiac surgery setting, consisted of one RCT, one non randomized trial and another one was case-control study.

5.3.1 Trauma

Baksaas-Aasen et al. (2020) in the ITACTIC trial found safety and cause-of-death profiles were similar across the VHA and CCT groups.[25 level II-1]

5.3.2 Liver transplant

Leon-Justel et al. (2019) in a non-randomised trial involving 200 orthotopic liver-transplantation (OLT) patients found there were differences in the rates of various complications, with a significant reduction in the POC group: re-operation due to bleeding (p=0.048), postoperative hemodynamic instability (p =0.028), re-transplantation (p=0.033); acute kidney injury (AKI) (p<0.001); pantocytopenia (p=0.029). (Table 1) In contrast, neurological complications (p = 0.023) and viral infections (p = 0.007) were significantly increased in the POC group. (Table 9)

Table 9: Complications in OLT patients in Leon Justel et al.(2019)

Complication type	**SCG**	**POC**	**p Value**
Neurological complication	14	27	0.023
Haemodynamic instability	29	16	0.028
Viral infection	7	20	0.007
Re-operation for bleeding	13	5	0.048
Reoperation for retransplant	10	2	0.033
Acute kidney injury	17	2	<0.001

Alamo JL et al. (2013) The patient with preoperative risk group (PRG) had a lower rate of complications when orTEM was used during liver transplant (p <0.05), decreasing the incidence of postoperative renal failure, surgical complications, postoperative bleeding, hematopenia, primary graft dysfunction, and retransplantation. However, a greater number of viral infections (cytomegalovirus [CMV]) and ascites in the orTEM group were detected (data not shown). Fewer complications in the patients requiring ≥ 5 units of red blood cells (PT group) were reported when liver transplant was performed with orTEM, with significant (p<0.05) differences in reperfusion syndrome, primary dysfunction, biliary complications, renal failure, surgical complications, bleeding, reoperations, and re-transplant.[36 level II-2]

The two leading VHA instruments that directly assess shear modulus, the rotational TEG (TEG 5000; Haemonetics, Braintree, MA (FDA 510(k) no. K002177]), and rotational thromboelastometry (ROTEM delta; Instrumentation Laboratory, Bedford, MA) (FDA 510(k) no. K083842) has obtained USFDA approval.(Table 10). [26,38] ROTEM and TEG devices have been shown to meet the USFDA standards of accuracy, precision, interference, reagent stability, and reference ranges, as well as software validation.[23]

Table 10. USFDA-approved viscoelastic testing

Instrument	Manufacturer	FDA approved patient population
Rotational clot measurement		
TEG 5000	Haemonetics	Adults
ROTEM delta	Instrumentation Laboratory	Adults
Harmonic resonance clot measurement		
TEG 6S	Haemonetics	Adults with cardiac indications (global hemostasis cartridge, TEG-PM cartridge) or trauma (trauma cartridge)
Hemosonics Quantra	Stago	Adults with cardiac or orthopedic indications

The Quantra system (HemoSonics, Charlottesville, VA) was recently approved by USFDA, that uses SEER ultrasound technology to monitor the evolving shear modulus of a developing clot. The HemoSonics Quantra QPlus system is categorized as moderate complexity under clinical laboratory improvement amendment (CLIA). The FDA-approved TEG 6S instrument is categorized as moderate complexity under CLIA, uses a disposable microfluidics cartridge-based system that requires simple transfer pipetting.[38]

ROTEM sigma is a cartridge-based harmonic VET instrument which is not yet approved by the USFDA. Analogously to the TEG 6S and Quantra systems, it is fully automated, without need for manual pipetting, and uses test cartridges with lyophilized reagent, while still using pin and cup technology.[39]

Several TEG 6S cartridges have obtained the USFDA approval, including:

- Global hemostasis cartridge: including kaolin, kaolin with heparinase, rapid TEG, and CFF. Approved for use in adults undergoing cardiac surgery on citrated blood samples. This cartridge does not allow for assessment of fibrinolysis, based on FDA-approved software limitations.

- Trauma cartridge: including kaolin, rapid TEG, and CFF. Approved for use in adults with trauma. This cartridge allows for assessment of fibrinolysis.
- TEG 6S Platelet Mapping cartridges allow for assessment of platelet function, similar to that described using the TEG 5000 platform, but with substantially increased ease of use. There are both ADP and arachidonic acid channels. This cartridge is approved for adult patients undergoing cardiovascular surgery or cardiology procedures, to assess hemorrhagic or thrombotic conditions. [38]

5.4 ECONOMIC EVALUATION / COST-EFFECTIVENESS ANALYSIS

There was one cost-effectiveness analysis (CEA) from a Health Technology Assessment report and one cost descriptive analysis retrieved on VHA in the management of haemostasis in non-cardiac surgery patients from the databases.

A CEA was conducted by Whiting et al. (2015) from the National Centre of Clinical Excellence (NICE), UK. This assessment aimed to assess the clinical effectiveness and cost-effectiveness of VE devices to assist with the diagnosis, management and monitoring of haemostasis disorders during and after cardiac surgery, trauma-induced coagulopathy and post-partum haemorrhage (PPH). The health-economic analysis considered the costs and quality-adjusted life-years (QALY) of ROTEM, TEG and Sonoclot compared with SLTs in cardiac surgery and trauma patients. A decision tree was used to consider short-term complications and longer-term side effects from transfusion. The model assumed a 1-year time horizon. There were insufficient data from the clinical effectiveness review to construct a model to assess the cost-effectiveness of VE devices in women with PPH. There were no data on the clinical effectiveness of Sonoclot, hence therefore they assumed that the TEG- and ROTEM-based estimates used in the model would also be applicable to Sonoclot. For the calculation of QALYs, they explored trauma-specific utilities. Similar to the model in cardiac surgery patients, the trauma model also considered short (one month) and long-term (one year) costs. Short-term costs included the following four groups: (1) peritrauma costs of transfusion; (2) costs of blood components; (3) test costs for the identification of patients at risk of bleeding during or after transfusion; and (4) costs related to complications due to surgery and blood loss, transfusion-related complications and infection due to bacterial contamination. Long-term costs included those related to the other transfusion-transmitted infections (i.e. vCJD, HAV, malaria, HTLV, HIV, HBV and HCV).(Table 11)

Table 11: Comparison of cost for ROTEM, TEG and Sonoclot basic test (trauma patients)

Basic test	Cost (£)
ROTEM INTEM	1.13
ROTEM EXTEM	1.22
ROTEM FIBTEM	2.22
Cup and pin (×3)	3.15 × 3
Equipment cost	26.67
Total cost ROTEM test	**40.69**
Rapid TEG	11.25
Plain cup and pin	5.45
Equipment cost	17.33
Total cost TEG test	**34.03**
gbACT	2.20
Equipment cost	12.33
Total cost Sonoclot test	**14.53**

The assumptions of the models used were ROTEM, TEG and Sonoclot were equally effective. Complications related to surgery and/or transfusion, transfusion-related complications and infection caused by bacterial contamination were assumed to occur during the hospitalisation period. For the transfusion-transmitted infections (except bacterial contamination), 1-month mortality was assumed to be zero, as these infections were assumed to manifest themselves after the hospitalisation period. Patients were assumed to die in the middle of the period where death occurred. We assumed that four-channel VE devices were used. Only those extra items that were available (and comparable) for the three devices, were included in the acquisition costs. After-care and training costs were also included. They assumed 3 years of machine usage. Further assumption were on average, 500 tests were performed per machine per year, and equal average length of hospital stay for the VE and SLTs groups. For HAV, HBV, HCV and HIV, they assumed two acute hospitalisations and three outpatient visits during the first 12 months after surgery whereas for malaria and HTLV they assumed two acute hospitalisations with no outpatient visits.

The base-case results from the analysis reported as LYs, QALYs and costs per technology for patients with coagulopathy induced by trauma are summarised in Table 12. All of the VE technologies dominated SLTs. They found VE testing was cost-saving and more effective than SLTs. For the cardiac surgery model, the cost-saving was £43 for ROTEM, £79 for TEG and £132 for Sonoclot. For the trauma population, the cost-savings owing to VE testing were more substantial, amounting to per-patient savings of £688 for ROTEM compared with SLTs, £721 for TEG, and £818 for Sonoclot. This finding was entirely dependent on material costs, which are slightly higher for ROTEM. A comparison of the most expensive technology, ROTEM, with SLTs found a cost-effectiveness probability equal to 0.96 for ROTEM for a ceiling ratio of £0.

As the ceiling ratio increased, this probability converged on 0.87. The increased cost savings observed for the trauma compared with the cardiac population were primarily due to the higher blood volumes that are transfused in the trauma patients.

VE testing remained cost-saving following various scenario analyses to assess the impact of various parameters. (Tables 13 and 14) The total cost of testing per trauma patient for the four technologies was £203 for ROTEM, £170 for TEG, £130 for SLTs, and £73 for Sonoclot (£84). The PSA confirmed that SLTs was the strategy with the lowest probability of being cost-effective (0.022 at most).(Figure 8) They concluded VE testing is cost-saving and more effective than SLTs, in both patients undergoing cardiac surgery and trauma patients. [40]

Table 12: Trauma model output (base case)

Outcome	SLTs	ROTEM	TEG	Sonoclot
LY	0.8343	0.8425	0.8425	0.8425
QALY	0.5644	0.5713	0.5713	0.5713
Cost (£)	7661	6973	6940	6842
Incremental QALYs vs. SLTs		0.0069	0.0069	0.0069
ICs vs. SLTs (£)		–688	–721	–818

IC, incremental cost.

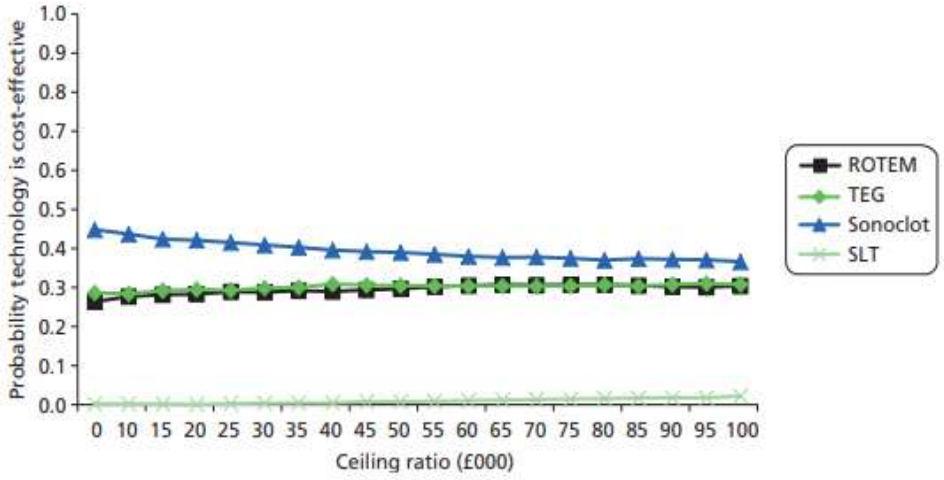

Figure 8: Cost effectiveness acceptability curve for all technologies in trauma population

Table 13: Trauma model output (scenario)

Scenario	ROTEM			SLTs			Incremental QALY	IC	ICER
	LYs	QALYs	Cost (£)	LYs	QALYs	Cost (£)			
Base case	0.8425	0.5713	6973	0.8343	0.5644	7661	0.0069	–688	Dominance
5 years' machine usage	0.8425	0.5713	6929	0.8343	0.5644	7661	0.0069	–731	
200 tests per year	0.8425	0.5713	7173	0.8343	0.5644	7661	0.0069	–488	
No. of tests per patient decreased (2, no transfusion; 3 transfusion)	0.8425	0.5713	6862	0.8343	0.5644	7591	0.0069	–729	
VE testing add-on to SLT	0.8425	0.5713	7103	0.8343	0.5644	7661	0.0069	–558	
RR transfusion = 0.80 (lower limit)	0.8480	0.5759	6668	0.8343	0.5644	7661	0.0115	–993	
RR transfusion = 0.96 (upper limit)	0.8370	0.5667	7278	0.8343	0.5644	7661	0.0023	–383	
Lower probability of transfusion SLTs group (0.209)	0.8636	0.5889	5802	0.8582	0.5844	6224	0.0045	–422	
Higher probability of transfusion SLTs group (0.444)	0.8194	0.5520	8259	0.8080	0.5425	9238	0.0095	–979	
Equal volumes of blood components transfused	0.8425	0.5713	7240	0.8343	0.5644	7661	0.0069	–421	
Probability experiencing ARDS (0.0775) and MOF (0.15)	0.8420	0.5731	5814	0.8337	0.5665	6344	0.0066	–530	
Probability experiencing ARDS (0.2325) and MOF (0.45)	0.8430	0.5695	8132	0.8349	0.5624	8977	0.0071	–846	
Calibrated 1-month mortality (0.1483)	0.8823	0.5969	7144	0.8794	0.5935	7855	0.0034	–711	
Calibrated 1-month mortality (0.4450)	0.8028	0.5457	6801	0.7891	0.5354	7466	0.0104	–664	

IC, incremental cost.

Table 14: Trauma model output: assay scenario

Additional scenarios trauma patients	Technology	LYs	QALYs	Cost (£)	Incremental QALY vs. SLT	IC (£) vs. SLT	ICER vs. SLT
Base case	ROTEM	0.8425	0.5713	6973	0.0069	–688	Dominance
	TEG	0.8425	0.5713	6940	0.0069	–721	
	Sonoclot	0.8425	0.5713	6842	0.0069	–818	
	SLTs	0.8343	0.5644	7661			
Assay scenario 1: five sets of test performed – first time, four assays; next, four tests, two assays	ROTEM	0.8425	0.5713	6961	0.0069	–699	Dominance
	TEG	0.8425	0.5713	6970	0.0069	–690	
	Sonoclot	0.8425	0.5713	6842	0.0069	–818	
	SLTs	0.8343	0.5644	7661	0.8343		
Assay scenario 2: five sets of test performed, each time two assays	ROTEM	0.8425	0.5713	6925	0.0069	–736	Dominance
	TEG	0.8425	0.5713	6912	0.0069	–748	
	Sonoclot	0.8425	0.5713	6842	0.0069	–818	
	SLTs	0.8343	0.5644	7661	0.8343		
Assay scenario 3: three sets of test performed, each time two assays	ROTEM	0.8425	0.5713	6863	0.0069	–746	Dominance
	TEG	0.8425	0.5713	6855	0.0069	–753	
	Sonoclot	0.8425	0.5713	6813	0.0069	–796	
	SLTs	0.8343	0.5644	7609	0.8343		

Cochrane C et al. (2020) in a pre- and post- intervention study investigated whether TEG goal-directed transfusion improved blood utilization, reduced mortality, and was cost-effective. Data were prospectively collected in a UK level 1 trauma center in patients who activated the major hemorrhage protocol one year pre- and one year post-implementation of a TEG 6s-driven transfusion algorithm into the center's code red resuscitation protocol. They used retrospective control group. Inclusion criteria were major haemorrhage protocol activation, code red trauma call, code amber trauma call with suspicion of significant active bleeding, and blood transfusion commenced in a trauma patient.Data were collected on age, gender, mechanism, site of injury, injury severity score (ISS), shock index (SI), blood products used and wasted, outcomes at 24 h, and TEG results. Cost was defined as overall blood product usage and TEG cartridge cost within initial 24 h and wastage of blood products requested but not transfused and not re-issued by blood bank. The cost of blood products transfused was compared between groups, for individual products and in total. The costs of TEG cartridges and standard coagulation tests were also considered. The cost of hospital length of stay was not included as this is likely to be affected by multiple factors. For the subgroup of patients with wastage data, the cost of wasted blood products was also factored into the analysis. As with blood product usage, data on the cost of transfused units were available for all patients. However, costs of wasted products were not available for all patients, and hence fewer patients were included in the analyses

involving this information. Analyses compared the pre- and post TEG groups in terms of demographic, the units of blood product transfused, the cost of blood product transfused and total hospital length of stay. The study involved 126 patients (pre-TEG group) and 175 patients (post-TEG group), with TEG 6s as the intervention.

They found cost of blood products transfused was comparable, with the exception of platelets (average £38 higher post-TEG). Results suggest that there was a significantly higher cost of platelets in the post-TEG group than in the pre-TEG group (41 ± 90 pre-TEG; 79 ± 152 post-TEG; p = 0.008), on average by £38. However, the overall cost of transfusions did not significantly vary between the groups (625 ± 655 pre-TEG; 678 ± 786 post-TEG; p=0.52). When the total cost, including the cost of TEG cartridges was considered, patients in the post-TEG group had a mean cost of £127 per patient more than the pre-TEG patients (625 ± 655 pre-TEG; 753 ± 828 post-TEG; p=0.14); however, this difference was not significant (Table 4).

Wastage of blood products overall was significantly lower in the post-TEG group (127 ± 146 pre-TEG; 74 ± 133 post-TEG; p=0.002), by a mean of £53. In particular, wastage of FFP/Octaplas was significantly higher in the pre-TEG group (99 ± 128 pre-TEG; 57 ± 112; p = 0.004), by a mean of £42 per patient.

When the data on blood product utilization, wastage, and the costs of TEG cartridges is considered, the results showed no significant difference between the overall cost in the two groups over the initial 24 h (753 ± 651 pre-TEG; 830 ± 847 post-TEG; p = 0.41; Table 15).[26 level II-2]

Table 15: Cost outcomes in study by Cochrane C et al (2020)

Outcome	Pre-TEG Mean ± SD (n = 126)	Post-TEG Mean ± SD (n = 175)	Difference [1] Mean (95% CI)	p-Value
Units transfused				
RBC	432 ± 401	472 ± 480	40 (−54, 133)	0.42
FFP/Octaplas	142 ± 196	111 ± 191	−30 (−67, 17)	0.18
Platelets	41 ± 90	79 ± 152	38 (10, 68)	**0.008**
Cryoprecipitate	10 ± 32	15 ± 36	5 (−3, 11)	0.24
All products combined	625 ± 655	678 ± 786	53 (−91, 227)	0.52
TEG cartridges	-	74 ± 59		-
Total cost 1 [2]	625 ± 655	753 ± 828	127 (−22, 308)	0.14
Units wasted				
RBC	26 ± 80	10 ± 60	−15 (−33, 1)	0.07
FFP/Octaplas	99 ± 128	57 ± 112	−42 (−69, −14)	**0.004**
Platelets	2 ± 17	3 ± 24	1 (−3, 7)	0.57
Cryoprecipitate	1 ± 8	3 ± 14	2 (0, 5)	0.09
All products combined	127 ± 146	74 ± 133	−53 (−91, −17)	**0.002**
Total cost 2 [3]	753 ± 651	830 ± 847	78 (−88, 304)	0.41

1 Difference calculated as post=TEC minus pre-TEG 2 Cost calculated as cost of total units transfused plus TEG cartridges
3 Cost calculated as cost of total units transfused, total units wasted plus TEG cartridges

The TEG 6S Haemonetics USA cartridge costs approximately RM500 to RM520 each. No evidence retrieved from the scientific databases on the cost of the device or other VHA. It was reported that the typical hospital charge for BasicTEG is about $USD250 and for TEG with PlateletMapping is about $USD550. These are the list prices and the actual reimbursed costs are said to be lower.[41]

Meanwhile, in Malaysia, cost per test of conventional coagulation assay, PT, aPTT or INR in MOH facilities ranged from RM2 to RM3, hence the total cost per profile of PT, aPTT and INR ranged from RM6 to RM9. However, there is scarcity of local data with regard to utility of the interventions (VHA), as well as the utility of the comparator namely SLT, CCT or clinical judgement, hence limiting the possibility of estimating its cost-effectiveness.

5.5 ORGANISATIONAL

The use of viscoelastic tests to characterize coagulopathy and guide haemostatic therapy is endorsed in guidelines for managing trauma, postpartum haemorrhage and severe perioperative bleeding. [42-45]

The Trauma Quality Improvement Project of the American College of Surgeons suggests that all level I and II trauma centers have TEG available.[46] Similarly, the European Trauma Guidelines suggest that ROTEM be performed to assist in the characterization of the coagulopathy and in guiding hemostatic therapy.[47] The updated European guidelines on the management of bleeding trauma patients published in 2016 recommend that suspected or detected plasmatic coagulopathy should be corrected by transfusion of FFP or CFC, or both. [29]

In 2014, the National Institute for Health and Care Excellence (NICE) guidance recommended the use of ROTEM and TEG to monitor blood clotting during and after cardiac surgery, but not for obstetric or trauma haemorrhage. The guidance reported that there is insufficient evidence to recommend the routine adoption of viscoelastometric point-of-care testing (ROTEM, TEG and Sonoclot systems) in the NHS to help detect, manage and monitor haemostasis in the emergency control of bleeding after trauma and during PPH. Research is recommended into the clinical benefits and cost effectiveness of using viscoelastometric testing to help in the emergency control of bleeding after trauma or during PPH because of uncertainty as to how much benefit they provide in these settings.[48] The HTA conducted by Whiting et. al (2015) in UK on the assessment of VHA tests concluded that they are more effective than standard laboratory tests and cost saving.[40]

The British Society of Hematology guideline (2018) recognises the limited available evidence but aims to provide pragmatic advice as to how to interpret and use VHA results during the management of major bleeding in these scenarios; obstetric haemorrhage, liver disease and trauma haemorrhage.[1]

For managing major haemorrhage using VHA, the BSH recommended few practice points: [1]

- Transfusion algorithms should be adapted according to local normal ranges and locally validated.
- Normal VHA parameters are a useful indicator that bleeding due to coagulopathy is unlikely and transfusion of blood components is unlikely to be needed.
- An abnormal VHA result is relatively poor at predicting patients who will bleed and changes in serial measurements may be more valuable.
- When blood component transfusion is necessary, the use of VHA to guide and monitor replacement has generally been found to reduce the volumes required and improve other measures of outcome.

For patients with trauma, the BSH recommended:- [1]

- Normal VHA results confer a high negative predictive value for transfusion need, enabling the clinical team to monitor the patient closely without immediate activation of the major haemorrhage protocol.
- Low clot strength measures on TEG and ROTEM and lysis of greater than 3% on TEG may be used as an indicator that a trauma patient is at higher risk of requiring RBC and blood components.
- VHA, particularly TEG, may reduce mortality and reduce transfusion exposure and, if available, may be considered for transfusion guidance in trauma haemorrhage.
- Tranexamic acid should not be withheld based on the TEG or ROTEM parameters.

For obstetric and postpartum bleeding, the BSH recommended:- [1]

- Viscoelastic haemostatic assays (VHA) are not usually helpful for predicting post-partum haemorrhage when taken during labour in a non-bleeding pregnant woman.
- VHA may be used as part of an agreed algorithm to manage postpartum haemorrhage when the local institution's major obstetric haemorrhage protocol is activated.
- During ongoing major postpartum haemorrhage, if the FIBTEM A5 is >12 mm fibrinogen replacement is unlikely to improve clinical haemostasis.
- During major postpartum haemorrhage, if FIBTEM A5 is <7 mm, or <12 mm with ongoing bleeding, fibrinogen replacement may improve clinical haemostasis. [1]

For liver disease and liver surgery patient, the BSH recommended:- [1]

- Prothrombin time (PT)/International Normalised Ratio (INR) does not reliably predict bleeding risk in patients with liver disease.
- In bleeding patients, VHA (FIBTEM, TEG ff) should be used to guide fibrinogen replacement.
- VHA can be used in liver transplant patients to reduce overall transfusion requirement (a normal VHA trace has a 95% negative predictive value for transfusion requirement).

The BSH recommended several practice points on the use of VHA:- [1]

- Reference ranges should be determined locally and re-established when a new machine is introduced.
- For non-cartridge-based methods, staff should be trained and have good pipetting technique. Training and competency should be documented.
- Anticoagulated samples should be tested within four hours; no resting period is required.
- Internal Quality Control (IQC) should be performed daily for high volume usage or weekly if low volume usage.
- The TEG and ROTEM measures must not be used interchangeably.
- Participation in an accredited external quality assurance (EQA) programme is recommended.

Calibration is necessary to ensure the accuracy of devices providing quantitative information. It is also a consideration with the ROTEM and TEG devices but, because viscoelastic methods are semi-quantitative, formal calibration such as proficiency testing or inter-laboratory comparison is not a prerequisite. TEG 5000 devices are calibrated twice a year using biological controls, and this could be considered as an alternative assessment protocol in line with practices recommended by the Clinical and Laboratory Standards Institute.[49,50] ROTEM devices are calibrated during manufacture, and subsequent calibration procedures are not considered by the manufacturer to be required.[51]

One of the drawbacks of VHA test was the need for users to be trained in basic pipetting, the TEG5000 and Sonoclot operate with manual pipetting, the ROTEM delta with automated pipetting. In response to this, the manufacturers have developed cartridge-based techniques designed to improve ease of use and precision (the TEG6s and the ROTEM sigma).[1] Device-specific limitations may influence the preference of VHA type. While the standard ROTEM is automated and capable of analysing four samples simultaneously, the TEG is limited to two samples at a time. The TEG 5000 system requires frequent quality controls. ROTEM and TEG are both device dependent; serial studies from the same patient should be run on the same machine. Robust correlations between VHAs and CCTs have been reported, such as between FIBTEM MCF and plasma fibrinogen level and between TEG MA and platelet count. However, since ROTEM and TEG tests use whole blood and not plasma, they do not concur with plasma-based reference standards, for example, the FIBTEM assay and plasma fibrinogen concentration tests measure different physical properties. Therefore, neither the USFDA nor the European Medicines Agency (EMA) require that SLT be used as a reference method for ROTEM or TEG tests. [52]

5.6 LIMITATION

Our review has several limitations. Although there was no restriction in language during the search, only English full text articles were included in the report. Very few RCT and head-to-head comparison trial available assessing the effectiveness of VHA outside cardiac surgery patients, with various outcome measures were inconsistently reported. Many of the studies were observational

in nature and heterogeneity exist in these studies limiting quantitative summary of results. There is lack of longer-term data on the measure of effectiveness in the included studies. There was variation in the VHA being studied, with most used device was either TEG or ROTEM and variation in the haemorrhage management protocol or algorithm implemented in the included studies. Included studies which had a high risk of bias may affect methodological quality of this review. Lack of local data on cost and utility of the interventions and comparator in the population of interest prohibit the generation of local cost-utility analysis.

6.0 CONCLUSION

Based on the above review, there was sufficient fair level of evidences on VHA to be used in the management of patients with trauma to demonstrate that the VHA-guided haemostatic therapy was effective in guiding transfusion, with fewer consumption of blood products, avoidance of allogenic transfusion and reduction of blood wastage, compared to conventional coagulation test in patients with trauma. There was no difference in hospital length of stay or quality of life following VHA-guided therapy compared to control, and its effectiveness in terms of mortality was inconclusive in these patients.

VHA (ROTEM) demonstrated benefit in identifying parameters for diagnosis of coagulopathy, predict transfusion and mortality such as abnormal EXTEM and FIBTEM CA or MCF or lysis index.

There was limited evidence on VHA-guided therapy in patients with PPH, demonstrating combination of TEG assessment of coagulation, early surgical haemostasis and intrauterine balloon tamponade were effective in reducing rate of peripartum hysterectomies, reducing blood loss and FFP transfusion in these patients.

There was sufficient fair level of evidence on VHA to be used in the management of patients with liver transplant. The VHA-guided therapy appeared effective in guiding transfusion with less consumption of blood products, increase avoidance of allogenic transfusion, and reduce postoperative mortality in patients with liver transplant despite no difference in ICU or hospital length of stay.

There was very limited evidence on VHA-guided therapy for microsurgery patients, with predictive parameter identified for flap thrombosis was parameter relating to clot strength (maximal clot strength and fibrinogen-to-platelet ratio).

TEG 5000 and ROTEM delta had obtained USFDA approval for adult population. The USFDA approved TEG 6S for adults with cardiac indication, and Hemosonics Quantra was approved for adults with cardiac or orthopedic indication. Following VHA, lower complications namely re-operation due to bleeding, re-transplantation, acute kidney injury demonstrated, however more

neurological complication and viral infection were reported in patients with liver transplant.

The TEG 6S Haemonetics USA cost is approximately RM170,000 to RM180,000 per device while each cartridge costs RM500 to RM520. The total cost of testing per trauma patient for the four technologies was £203 for ROTEM, £170 for TEG, £130 for SLTs, and £73 for Sonoclot. For patients with trauma, the use of VHA was estimated to generate cost saving, amounting to per patient saving of £688 for ROTEM compared with conventional coagulation tests, £721 for TEG, and £818 for Sonoclot, in a CEA conducted in UK. Staff should be trained and have good pipetting technique for non-cartridge-based methods in VHA. Internal Quality Control should be performed daily or weekly depending on volume of use, and participation in an accredited external quality assurance programme is recommended. Reference ranges should be determined locally and re-established when a new machine is introduced. The diagnostic thresholds for various VHA parameters are assay, institution, or algorithm specific.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present

1	(Viscoelastic testing).tw.
2	Viscoelastic hemostatic assay.tw.
3	ROTEM.tw
4	Rotational thromboelastometry.tw
5	TEG.tw
6	Sonoclot.tw
7	ROTEM Sigma.tw
8	TEG 6000.tw
9	Point of care haemostatic assay.tw
10	Bleeding.tw.
11	Coagulopathy.tw.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
13	10 or 11
14	limit 16 to (english language and humans and english)(836)

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Similar MeSH, keywords, limits used as per MEDLINE search
INAHTA	
US FDA	

APPENDIX 3: EVIDENCE TABLE

Only available upon request.

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