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This technology review (mini-HTA) is prepared to assist health care decision-makers and health care professionals in making well-informed decisions related to the use of health technology in health care system, which draws on restricted review from analysis of best pertinent literature available at the time of development. This technology review has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Other relevant scientific findings may have been reported since the completion of this technology review. MaHTAS is not responsible for any errors, injury, loss or damage arising or relating to the use (or misuse) of any information, statement or content of this document or any of the source materials.

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

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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

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.

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.

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.