THE USE OF A THROMBOELASTOGRAM (TEG®) PROTOCOL TO DECREASE THE USAGE OF BLOOD PRODUCTS IN ADULT PATIENTS UNDERGOING CARDIAC SURGERY AT UNIVERSITAS ACADEMIC HOSPITAL, BLOEMFONTEIN, FREE STATE, SOUTH ARICA

BY

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30 NOVEMBER 2020

DECLARATION OF AUTHORSHIP

I hereby declare that the work for the master's degree mini-dissertation and interrelated publishable article that I submit for the degree in MMed (Anaesthesiology) at the University of the Free State is my own work and that I have not previously submitted it for qualification at any other institution of higher education. I have acknowledged all helped appropriately.

I hereby declare that I am aware that copyright of this mini dissertation is vested in the University of the Free State.

I hereby declare that all the royalties in relation to intellectual property that was developed during and/or in connection with the study at the University of the Free State will accrue to the University.

DR JB MOGOROSI: 

DATE: 30 November 2020

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ABSTRACT

Background: Blood transfusion during cardiac surgery carries potential complications like transfusion reactions, increased length of hospital stays and financial costs[1-4]. Efforts through research of Point of Care (POC) strategies like the Thromboelastogram (TEG®) that provide health care practitioners with rapid, predictive and outcome based POC coagulation testing algorithms[5,6] to guide perioperative blood transfusions are underway.

Objectives: There is currently no POC protocol to guide blood product use at Universitas Academic Hospital in Bloemfontein, South Africa.

Aim: The primary aim of the study was to establish whether the use of a TEG® protocol versus physician decision will reduce blood product usage in adult patients undergoing elective cardiac surgery at Universitas Academic Hospital in Bloemfontein, Free State, RSA.

Methods: A comparative, descriptive study using:

A. The **physician decision group** consisting of a retrospective file review of the usual clinical practice, using clinical notes from Meditech® (an integrated software system that provides solutions to healthcare organisations throughout Africa) and the National Health Laboratory System (NHLS) Lab Trak® (an inter-systems results portal), 25 June to 30 September 2019, and
B. The **TEG® protocol group** consisting of a prospective cohort of patients using the usual clinical practice with the addition of TEG®-based protocol, 25 June to September 2020.

Results: The COVID pandemic markedly reduced elective theatre lists owing to the small prospective study population. Average cell saver volume (276ml, $p < 0.0001$) and FFP (2 units, $p = 0.05$) were statistically significant. There was no statistical significance in the average volume of RCC (1 unit, $p = 0.6679$), Platelets (1 unit, $p = 0.2329$) or Cryoprecipitate (1 unit, $p = 0.6382$) saved between the two groups.

Conclusion: Cell saved blood and FFP transfusion were statistically and clinically significantly reduced in the **TEG® protocol group**. While red blood cell, platelet, cryoprecipitate, and total blood product transfusion had reduced trends in the **TEG® protocol group** though not of statistical significance.

We suggest that this preliminary report be considered for future MMed or PhD research because it was a first in our institution and there is great potential to improve patient outcomes and contribute to best practice regarding patient blood management in the perioperative period.

KEYWORDS

thromboelastogram, rotational thromboelastometry, point of care, cardiac surgery, cardiopulmonary bypass, coagulation

LIST OF ABBREVIATIONS

ABG:	Arterial Blood Gas
ACT:	Activated Clotting Time
AR:	Aortic Valve Regurgitation
AS:	Aortic Valve Stenosis
AVR:	Aortic Valve Repair/Replacement
BIS:	Bispectral Index
BMI:	Body Mass Index
CABG:	Coronary Artery Bypass Graft
CPB:	Cardiopulmonary Bypass
FFP:	Fresh Frozen Plasma
HB:	Haemoglobin
HCT:	Haematocrit
INR:	International Normalized Ratio
MR:	Mitral Valve Regurgitation
MS:	Mitral Valve Stenosis
MVR:	Mitral Valve Repair/Replacement
NHLS:	National Health Laboratory Services
POC:	Point of Care
PS:	Pulmonary Valve Stenosis
PR:	Pulmonary Valve Regurgitation
PT:	Prothrombin Time
PTT:	Partial Thromboplastin Time
PVR:	Pulmonary Valve Repair/Replacement
RBC:	Red Blood Cell
ROTEM:	Rotational Elastometry
SLT:	Standard Laboratory Tests
TEG:	Thromboelastogram
TR:	Tricuspid Valve Regurgitation
TS:	Tricuspid Valve Stenosis
TVR:	Tricuspid Valve Repair/Replacement
UAH:	Universitas Academic Hospital

LIST OF DEFINITIONS

Alpha angle: The tangent of the curve made as the K value is reached and offers similar information to the K value.

Anaesthesiologist: A specialist doctor who cares for patients' perioperative needs including putting patients to sleep and rendering them pain free for surgery to be performed.

Coronary artery bypass graft (CABG): Coronary Artery Bypass Graft is a type of cardiac surgery performed in patients to restore coronary blood flow.

Cardiopulmonary bypass (CPB): A technique in which a machine temporarily takes over the function of the heart and lungs during surgery. It maintains the circulation of blood and oxygen to the patient's body. It is often referred to as the heart lung machine or "the pump". It is operated by perfusionists.

Current clinical practice: Entails clinical observation of the operative field by the surgeon for bleeding post op prior to wound closure. Ordering of blood and blood products is then done after discussion with anaesthesiologist on which products may likely be needed for adequate coagulation.

K value: Represents the speed of clot formation. It is the time from the end of the R time until clot reaches 20mm.

LY 30: Represents the percentage of clot lysis at 30 minutes.

MA: Maximum amplitude reflects clot strength.

Perfusionist: A healthcare professional who operates the cardiopulmonary bypass machine during cardiac surgery and other surgeries that require cardiopulmonary bypass to manage a patient's physiological status.

POC: Point of Care is performance of medical diagnostic testing at or near the point of care, i.e., at the time and place of patient care.

ROTEM: Rotational thromboelastometry (ROTEM) evolved from TEG® technology and both devices generate output by transducing changes in the viscoelastic strength of a small sample of clotting blood (300 ml) to which a constant rotational force is applied (Whiting & Di Nardo 2013 AJH). Here the sensor shaft rather than the cup rotates.

R time: Reaction time represents the time until the first evidence of clot is detected.

SLT: Standard Laboratory Tests is the historical pattern in which diagnostic testing entails sending off patient specimens to a medical laboratory.

TEG®: Thromboelastogram is a device that measures the efficiency of blood coagulation. It is mainly used in surgery and anaesthesiology; however, its use is increasing in emergency departments, intensive care units, labour, and delivery units. A small sample of whole blood from a patient is rotated gently six times a minute to imitate venous flow and activate coagulation. The speed of clot formation till breakdown of the clot is analysed by computer mechanics. This produces a characteristic pattern depicting the function of various blood components within the coagulation cascade within a matter of minutes.

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CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Blood transfusion during cardiac surgery is known to carry a whole range of potential complications like transfusion reactions, increased length of hospital stays and increased financial costs.[1-4] Increased efforts are made worldwide through research to reduce the rate of transfusions. Examples of this work is the use of point of care (POC) strategies like the thromboelastogram (TEG®) that provide health care practitioners with rapid, outcome based POC coagulation testing algorithms[5,6] to guide perioperative blood transfusions. Transfusion medicine is a strategically placed integral part of the multidisciplinary team setup.

Cardiac surgery uses a significant portion of an institutions financial budget in the form of replacement devices, complexity of the surgical techniques and the use of blood and blood products.[1-4] Extreme care surrounding transfusion practices and potential patient harm cannot be over emphasised. The Society of Anaesthesiologists of South Africa published guidelines recently surrounding patient blood management (PBM)[15] wherein patient safety is advocated with every decision that may influence their transfusion requirements. Within these guidelines are targeted goals at various aspects of a patients care: Optimise haemopoiesis (pre-operatively), Minimise blood loss and bleeding (intra-operatively), Harness and optimise physiological tolerance of anaemia[15] (intra-and post-operatively)

1.1.1 Social value (relevance)

Any medical condition a patient presents with has significant implications on his or her life. Within the health fraternity, we as physicians are concerned with patient's

baseline physical functioning from the first time they present to our facilities and post treatment outcome when they are discharged. Being diagnosed with a health condition that requires a surgical intervention is even more distressing to patients and their families. Cardiothoracic surgery is one of the most complex surgical disciplines known to us and when patients need open heart surgery a multitude of complications (bleeding, infections and even death) are possible. Transfusion of blood, fresh frozen plasma (FFP), and platelets are associated with increased patient morbidity and mortality.[1] The multidisciplinary team actively seeks benefits like reduced transfusion needs, less complications, shorter length of ICU and hospital stay, better survival and reduced treatment costs[4] to contribute positively to a patient's healthcare experience. It is understandable that patients may often only remember experiencing a complication and forget the success of the entire perioperative period. This places the anaesthesiologist, who is frequently involved in decisions regarding the management of haemorrhagic conditions and blood transfusions[15] in an invaluable position towards counselling and settling the anxiety of patients.

Consent issues surrounding transfusions include in general, age of the patient, mental capacity, neurological assessment at the time of the need to transfuse, religious reasons.[15] Informed refusal should always be born in mind and patients' rights to refuse ought to be respected by all healthcare workers. Ethical distribution of hospital resources, including blood and blood products can only be judged as justifiable[15] if done fairly and equitably.

Loss of time from work and loss of income due to physical incapacity are true social ills that patients face. Interpersonal relationships suffer strain. This is true for all patients especially those in low- and middle-income countries like South Africa. The emotional strain on a family when a parent has been admitted to hospital is known to all but sadly not quantifiable. Hospital and health department costs may potentially influence the quality of patient care as seen by Spalding GJ, et al.[9] If a hospitals budget is under strain, those responsible for procuring medical or surgical products are constantly facing the pressure to balance satifactory patient outcome on the one hand and economically sound decision making on the other.

Since bleeding is a feared complication during surgery and the administration of blood products is not without side effects various means are in place to minimise unnecessary transfusion. Patients who are at higher risk of requiring blood transfusion before surgery, including advanced age, decreased blood cell volume or small body size, those who suffer from anaemia before or during the procedure, patients treated with anticoagulants, severe renal insufficiency, haematological diseases, hereditary deficiencies in platelet function and those who are being treated for emergent or complex procedures[12,14,15] are more likely to require blood products. These are all high-risk patients whose management becomes complex requiring strict multidisciplinary teamwork. Communication is at the core of this teamwork to ensure patients come to minimal harm when transfusions are administered.

The relevance of this study was to investigate the role a Thromboelastogram (TEG®) has on the incidence of blood transfusions in cardiac surgery with the intension to introduce a point of care (POC) protocol to the current clinical practice which depends on the physician experience in deciding when to transfuse based on clinical grounds (hypotension, tachycardia) and evaluation of the operative field (continuous bleeding from surgical wound).

1.1.2 Scientific value (originality of this study, knowledge gap)

Interruption of the normal clotting mechanism (haemostasis), results in coagulopathy (impaired blood clotting). The normal clotting process begins with platelets which form a temporary clot, then clotting proteins which strengthen the clot, and finally fibrin which forms a solid fibrin clot.[6] Activation of the coagulation cascade during Cardiopulmonary bypass (CPB) is attributed to by the systemic inflammatory syndrome, hypothermia, acidosis, residual heparin anticoagulation, and hyperfibrinolysis.[1] Platelets and coagulation factors are consumed[6] resulting in bleeding post cardiac surgery. This explains the high transfusion incidence in cardiac surgery and is well placed to study potential methods that promise to reduce the need for transfusions.

As part of the continued research surrounding coagulation abnormalities during the perioperative period clinicians have asked what the ideal method is to mitigate the

effects of CPB on platelets and coagulation factors. Knowing when to transfuse allogeneic platelets for instance is beneficial to the clinician as concluded by Ereth MH, et al. The activated clotting time (ACT) is a bedside monitor that assess anticoagulation during CPB.[10] It is by no means a complete assessment of the coagulation cascade. The use of standard laboratory tests (SLT) [examples: haemoglobin, platelet function test, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalised ratio (INR)] in evaluating coagulation have stood the test of time and may not easily be replaced by novel modalities. Standard laboratory tests are validated for use during cardiac surgery and have formed part of numerous conventional protocols for blood product use.[11]

One modality that has been of much interest with regards to blood product use in cardiac surgery is the Thromboelastogram (TEG®) or Rotational thromboelastometry (ROTEM®). These visco-elastometric tests have shown some valuable trends in reducing the need for allogeneic transfusions as reported by Avidan et al who compared TEG® to laboratory-based algorithm and found blood product use more in the laboratory group.[11] However due the fact that these are not yet widely validated, reports and guidance on their use varies inter-institutionally. The Society of Thoracic Surgeons (STS) transfusion guidelines demonstrated this wide variation with RBC transfusions (27-92%) and coagulation factor transfusion (0-36%) with the introduction of visco-elastometric testing.[14] Shore-Lesserson's two randomised controlled trials[11] compared mediastinal tube drainage and blood product use between TEG® group and the conventional group. Combining standard laboratory tests with POC strategies[15] appears to be a rational approach to improve patient outcomes instead of implementing these strategies in isolation of each other. Literature done in Europe and America has shown superiority of POC haemostasis practice over standard laboratory testing.[9-12] Trends in Africa, and South Africa are still under investigation. This supports the relevance of this study done locally.

The gap in this area of clinical practice is evident and needs to be explored further by the middle to high income populations where these complex procedures and challenging complications pose crippling effects to the health care system. Until we can confidently state that we have found the ideal visco-elastometric method, transfusion medicine will continue to be a field of great opportunity to make a difference in training and development. We in South Africa are fortunate to have

various societies that follow worldly trends and make sacrificial efforts to maintain current evidence-based clinical practice. The Society of Anaesthesiologists of South Africa (SASA) has adopted the monitoring of bleeding patients through POC and regular laboratory tests for coagulation, fibrinogen and platelet counts or function.[15] This society has also taken a strong stance on the use of cell salvage[15] in routine practice whenever bleeding more than 500ml is to be expected to prevent transfusions of allogeneic blood products.

1.1.3 Conceptual framework (theoretical basis of the research)

TEG® (thromboelastogram) is a POC device that evaluates various aspects of the coagulation cascade like clot formation, clot strength and fibrinolysis.[1, 3, 6-8] Adding a TEG® guided algorithm to current clinical practice provides an additional focussed assessment, which may possibly reduce blood product use and potentially contribute to good patient outcome and financial cost saving to this institution and the Free State at large owing to the scarcity[15] and high costs of blood products.

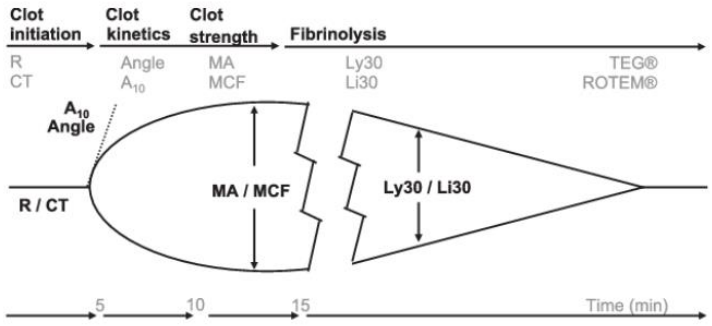

Fig 1. TEG® machine in use at NHLS haematology is the TEG® thromboelastograph Haemostasis Analyzer system, 400 Wood Rd, Braintree, MA.

Schematic TEG â /ROTEM â trace, including the most frequently used variables: reaction time (R)/clotting time (CT), clot formation time (K, CFT), alpha angle (a), maximum amplitude (MA)/ maximum clot firmness (MCF) and lysis (Ly)/clot lysis (CL). The R-value/ CT is the time from the start of the test to the initial fibrin formation. The K value is the clot formation time to reach a specific level of clot strength. The alpha angle represents the acceleration (kinetics) of fibrin build up and cross-linking (clot strengthening). The MA/MCF reflects the ultimate strength of the clot, which depends on the number and function of platelets and their interaction with fibrin. Lysis or clot lysis can be indicated to a certain time, e.g. 30 min, and represents the lysis index at 30 min after MA. Ly is increased with fibrinolysis.

(Taken from Johansson PI, et al. Current management of massive hemorrhage in trauma. Scand J Trauma Resusc Emerg Med. 2012;20:1–10.)

Figure 1. TEG® machine in use at NHLS haematology

The theoretical basis of the research that has been described thus far seeks to provide us with an understanding that perioperative patient outcomes depend on multifactorial components throughout the hospital stay. Following the pre-, intra-, and post-operative strategy gives a clear working plan and enables us to set goals for each period of a patients care. With reference to the TEG® (also ROTEM®) point of care protocol, time to detection of a coagulopathy is critically important during cardiac surgery owing to the extensive transfusion load in this patient group. Within 5 to 10 minutes elements of coagulation become evident as compared to the standard laboratory analyses which consistently showed turnaround times of 60 minutes or more.[4] The fibrinolytic system within the coagulation cascade also gets evaluated by the POC methods in 30 minutes[4] of a blood specimen drawn for assessment, a function that is lacking in standard laboratory tests. Point of care machinery also boasts another benefit in that they are generally small, compact, affordable, and easily moveable within confined spaces in a hospital setting. Many of them have been used in emergency departments, intensive care units and the theatre complex. The National Health Laboratory Systems (NHLS) standard laboratory testing equipment on the other hand is generally big, immoveable, and expensive.

Arguments against POC infrastructure development and routine use is usually the daily running costs of disposable cartridges, maintenance costs and lack of validation studies to prove the quality of the results and those of the tried and tested standard laboratory tests.[4,11] Short comings in the scientific evidence in support of validating these POC machinery are the vast heterogeneity of the trials done in disciplines like trauma, obstetrics, and cardiac surgery. Counter arguments for their use enjoy attention towards the rationale that shorter timescale to provide results[6] and the inherent ability to provide additional information on the clotting process[4] will inevitably lead to earlier diagnosis of coagulopathy, targeted administration of blood products and minimise the risks associated with unnecessary transfusions. Theatre turnaround time may become less, hospital and intensive care unit stay potentially gets reduced[6]. The cumulative need for blood products may also be reduced markedly thereby easing the continuous burden on the National Blood Services, and minimising patient exposure to allogenic blood products[15] with their potential and costly early and late onset complications.

This led us to the construction our research question: The use of a thromboelastogram TEG® protocol to reduce the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital (UAH), Bloemfontein, Free State, South Africa. Work towards answering this research question started with the appreciation of the current clinical practice at this institution in 2019 and 2020. Patient population demographics, type of cardiac surgeries done and the workflow from presentation of a patient to cardiothoracic surgery until discharge from intensive care unit were evaluated. Only a summary of this workflow has been included in this report.

1.1.4 Current clinical practice

The patient enters theatre for his/her cardiac surgery. Monitors such as blood pressure, pulse oximetry and electrocardiogram are attached by the anaesthesiologist with the assistance of the nursing staff. The peripheral venous cannula sited. The patient is induced with general anaesthesia (GA) using intravenous anaesthetic agents indicated according to a patient's haemodynamic profile. These commonly include but are not limited to:

- *Opioid/analgesics:* Fentanyl, Remifentanil, Sufentanil, Morphine;
- *Induction agent:* Propofol, Etomidate or Ketamine;
- *Muscle relaxant:* Suxamethonium and Rocuronium, Atracurium or Cisatracurium;
- *Anticoagulant:* Heparin; and
- *Reversal of anticoagulant:* Protamine.

Once successfully intubated, the patient is mechanically ventilated and anaesthesia is maintained with a volatile anaesthetic agent (Sevoflurane, Isoflurane) or a Total Intravenous Anaesthetic (TIVA) technique with Propofol is used. An arterial and central venous cannula are then sited using ultrasound guidance. The first blood samples for an arterial blood gas (ABG) and activated clotting time (ACT) are drawn from the arterial line by one of the clinical perfusionists for testing. It is at this point that a sample for a baseline thromboelastogram (TEG®), prior to the administration of heparin for anticoagulation, was drawn.

The rest of the monitors are applied, Bispectral Index monitoring (BIS), Near Infrared Spectroscopy (NIRS), temperature and urinary catheter. The participant is then positioned for disinfection and cleaning of the surgical site. Sterile drapes are applied. The surgeon and his/her assistant scrub and don sterile gowns and gloves proceed with the indicated surgical procedure. During the operation arterial blood gasses are frequently drawn by either anaesthesiologist or a perfusionist to monitor the participant's physiological status every thirty (30) minutes or more frequently if indicated. Once the surgery has been concluded and before the closure of the sternum and wound, about five minutes after protamine administration (given to reverse the anticoagulant effects of heparin) or as close after that time point as possible, a second TEG® sample was drawn for analysis. Together with the post-operative TEG® a Platelet Function Assay (PFA 100) and Fibrinogen level was drawn for each patient for complete assessment of the coagulation profile. These results were used to direct the decision to order blood and blood products in conjunction with the surgeon's observation and assessment of the surgical field for bleeding. Patients are usually transferred to the cardiothoracic intensive care unit (ICU) intubated and ventilated post operatively for further monitoring and management. Blood and blood product usage was evaluated up to six (6) hours post operatively for inclusion in the study.

1.1.5 Ordering of blood products

The usual practice regarding the ordering of blood and blood products happens during the pre-operative period the day before the scheduled surgery. Informed consent for the surgery and blood transfusion are taken by the surgical team and confirmed by the anaesthesia team. A blood sample is sent to the South African National Blood Services (SANBS) with a form stating the possible need for blood and blood products on the day of the surgery, together with the complete pre-operative biochemical workup as indicated by the patient's comorbidities. A request is made to have the patient's sample cross matched and products kept on standby for ease of access once needed, unless a patient is at high risk of needing blood products at the beginning of the procedure or for priming of the Cardiopulmonary bypass (CPB) circuit, in which case blood is then issued earlier.

1.1.6 Concern in the current clinical practice

The decision to transfuse is currently based on physician discernment of the operative field, experience, and limited Standard Laboratory Tests (SLT) available.[2,4,5] There is currently no clear point of care (POC) protocol in place to guide blood product use in cardiac surgery at Universitas Academic hospital, possibly one of very few academic hospitals in South Africa that performs similar cardiac procedures without POC protocols. There is thus a lack of accurate scientific evidence of managing coagulopathic patterns during cardiac surgery at our institution.

1.2 AIM AND OBJECTIVES

The aim of the study was to establish whether the use of a TEG® protocol versus physician decision reduces blood product usage in adult patients undergoing open-heart surgery at Universitas Academic Hospital in Bloemfontein, Free State. Universitas Academic Hospital (UAH) is the only public hospital in the Free State that provides cardiac surgery for the Free State population. Patients from the Northern Cape and Lesotho are also accepted for surgery at this Free State Department of Health facility. The motivation of doing this study was because it has never been done in our institution and it is our duty to research novel ways to improve patient outcomes in everything we do as clinicians. Evidence based quality service delivery, education and research are cornerstones in clinical medicine.

All patients aged 18 years and older who underwent first time elective cardiac surgery during June to September 2019 were included in the retrospective file review group (Group A), clinical notes from Meditech® (Medical Information Technology Inc. A Massachusetts-based software and service company selling information systems for health care organisations, Pappalardo N, et al.) and the National Health Laboratory System (NHLS) Lab Trak® (A laboratory information system, results portal Ltd 1996), 25 June to 30 September 2019, and those who presented during June to September 2020 were prospectively allocated to the TEG® protocol group (Group B). No re-do or emergency surgery was included in this study. Re-do surgery bleeds more and blood usage is inevitably increased.[12,14,15]

The secondary aims of the study were to evaluate trends regarding the cardiac surgical procedures that are conducted commonly at our institution as well as giving a description of the common medical conditions and treatment of these that may influence coagulation profiles of patients. Baseline laboratory data (haemoglobin, platelets, prothrombin time, activated partial thromboplastin time and international normalised ratio) were described. We also provide commentary on the haemostatic effects of known pharmaceutical agents like tranexamic acid, heparin, protamine, and bio-plasma as over the counter non-therapeutics like garlic, ginger, turmeric, vitamin E and common remedies in which cayenne pepper may be found.

1.2.1 Hypothesis

The hypothesis of the study was that the use of a POC viscoelastic TEG® protocol reduces the usage of blood and blood products during cardiac surgery in adult patients undergoing cardiac surgery in Universitas Academic Hospital, Bloemfontein, Free State, South Africa.

1.2.2 Ethics

UFS-HSD2019/0184/2807

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CHAPTER 2

PUBLISHABLE MANUSCRIPT

The publishable manuscript was compiled according to the author guidelines for possible submission to the *Southern African Journal of Anaesthesia and Analgesia (SAJAA).*

THE USE OF A THROMBOELASTOGRAM (TEG®) PROTOCOL TO DECREASE THE USAGE OF BLOOD PRODUCTS IN ADULT PATIENTS UNDERGOING CARDIAC SURGERY AT UNIVERSITAS ACADEMIC HOSPITAL, BLOEMFONTEIN, FREE STATE, SOUTH AFRICA

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ABSTRACT

Introduction: Blood transfusion during cardiac surgery is known to carry a whole range of potential complications like transfusion reactions, increased length of hospital stays and increased financial costs[1-4] Increased efforts are made worldwide through evidence-based medicine to reduce the rate of transfusions. Examples of this work is the use of Point of Care (POC) strategies like the thromboelastogram (TEG®) that provide health care practitioners with rapid, outcome based POC coagulation testing algorithms[5, 6] to guide perioperative blood transfusions. There is currently no clear POC protocol in place to guide blood product use at Universitas Academic Hospital in Bloemfontein, South Africa. Therefor the decision regarding the need for blood transfusion at this unit is currently based on physician discernment of the operative field, experience, and limited Standard Laboratory Tests (SLT) available[2, 4, 5] The aim of this study was to establish whether the use of a TEG® protocol versus physician decision will reduce blood product usage in adult patients undergoing open heart surgery at Universitas Academic Hospital in Bloemfontein, Free State, South Africa.

Methods: A comparative, descriptive study was performed at Universitas Academic Hospital using:

A. The **physician decision group** which consisted of a retrospective file review of the usual clinical practice, and
B. The **TEG® protocol group** which consisted of a prospective cohort of patients using the usual clinical practice with the addition of TEG®-based protocol.

Universitas Academic Hospital is a tertiary training public hospital in the Free State province of South Africa. All patients aged 18 years and older who presented for first time elective cardiac surgery during June to September 2019 were included in group A and those who presented during June to September 2020 in group B.

Data from 33 patient files were retrospectively included in group A and 14 prospectively included in group B.

Results: The COVID pandemic markedly reduced elective theatre lists owing to the small prospective study population. Average cell saver volume saved (276ml, $p < 0.0001$), FFP (2 units, $p = 0.05$) were statistically significant. There was no statistical significance in the average volume of RCC (1 unit, $p = 0.6679$), Platelets (1 unit, $p = 0.2329$) or Cryoprecipitate (1 unit $p = 0.6382$) saved between the two goups.

Conclusion: Cell saved blood and FFP transfusion were statistically and clinically significantly reduced in the **TEG® protocol group**. While red blood cell, platelet, cryoprecipitate, and total blood product transfusion had reduced trends in the **TEG® protocol group** though not of statistical significance.

We suggest that this preliminary report be considered for future MMed or PhD research because it was a first in our institution and there is great potential to improve patient outcomes and contribute to best practice regarding patient blood management in the perioperative period.

Keywords: thromboelastogram, rotational thromboelastometry, point of care, cardiac surgery, cardiopulmonary bypass, coagulation

Introduction

Background

Blood transfusion during cardiac surgery is known to carry a whole range of potential complications like transfusion reactions, increased length of hospital stays and increased financial costs.[1-4] Increased efforts are made worldwide through research to reduce the rate of transfusions. Examples of this work is the use of point of care (POC) strategies like the thromboelastogram (TEG®) that provide health care practitioners with rapid, outcome based POC coagulation testing algorithms[5, 6] to guide perioperative blood transfusions. Transfusion medicine is a strategically placed integral part of the multidisciplinary team setup.

Cardiac surgery uses a significant portion of an institutions financial budget in the form of replacement devices, complexity of the surgical techniques and the use of blood and blood products.[1-4] Extreme care surrounding transfusion practices and potential patient harm cannot be over emphasised. The Society of Anaesthesiologists of South Africa published guidelines recently surrounding patient blood management (PBM)[15] wherein patient safety is advocated with every decision that may influence their transfusion requirements. Within these guidelines are targeted goals at various aspects of a patients care: Optimise haemopoiesis (pre-operatively), Minimise blood loss and bleeding (intra-operatively), Harness and optimise physiological tolerance of anaemia[15] (intra-and post-operatively)

Social value (relevance)

Any medical condition a patient presents with has significant implications on his or her life. Within the health fraternity, we as physicians are concerned with patient's baseline physical functioning from the first time they present to our facilities and post treatment outcome when they are discharged. Being diagnosed with a health condition that requires a surgical intervention is even more distressing to patients and their families. Cardiothoracic surgery is one of the complex surgical disciplines known to us and when patients need open heart surgery a multitude of complications (bleeding, infections and even death) are a possibility. Transfusion of blood, fresh frozen plasma (FFP), and platelets are associated with increased patient morbidity and mortality.[1] The multidisciplinary team actively seeks benefits

like reduced transfusion needs, less complications, shorter length of ICU and hospital stay, better survival and reduced treatment costs[4] to contribute positively to a patient's healthcare experience. It is understandable that patients may often only remember experiencing a complication and forget the success of the entire perioperative period. This places the anaesthesiologist, who is frequently involved in decisions regarding the management of haemorrhagic conditions and blood transfusions[15] in an invaluable position towards counselling and settling the anxiety of patients.

Consent issues surrounding transfusions include in general, age of the patient, mental capacity, neurological assessment at the time of the need to transfuse, religious reasons.[15] Informed refusal should always be born in mind and patients' rights to refuse ought to be respected by all healthcare workers. Ethical distribution of hospital resources, including blood and blood products can only be judged as justifiable[15] if done fairly and equitably.

Loss of time from work and loss of income due to physical incapacity are true social ills that patients face. Interpersonal relationships suffer strain. This is true for all patients especially those in low- and middle-income countries like South Africa. The emotional strain on a family when a parent has been admitted to hospital is known to all but sadly not quantifiable. Hospital and health department costs may potentially influence the quality of patient care as seen by Spalding GJ, et al.[9] If a hospitals budget is under strain, those responsible for procuring medical or surgical products are constantly facing the pressure to balance satifactory patient outcome on the one hand and economically sound decision making on the other.

Since bleeding is a feared complication during surgery and the administration of blood products is not without side effects various means are in place to minimise unnecessary transfusion. Patients who are at higher risk of requiring blood transfusion before surgery, including advanced age, decreased blood cell volume or small body size, those who suffer from anaemia before or during the procedure, patients treated with anticoagulants, severe renal insufficiency, haematological diseases, hereditary deficiencies in platelet function and those who are being treated for emergent or complex procedures[12,14,15] are more likely to require blood products. These are all high-risk patients whose management becomes complex requiring strict multidisciplinary teamwork. Communication is at the core of this

teamwork to ensure patients come to minimal harm when transfusions are administered.

The relevance of this study was to investigate the role a Thromboelastogram (TEG®) has on the incidence of blood transfusions in cardiac surgery with the intension to introduce a point of care (POC) protocol to the current clinical practice which depends on the physician experience in deciding when to transfuse based on clinical grounds (hypotension, tachycardia) and evaluation of the operative field (continuous bleeding from surgical wound).

Scientific value (originality of this study, knowledge gap)

Interruption of the normal clotting mechanism (haemostasis), results in coagulopathy (impaired blood clotting). The normal clotting process begins with platelets which form a temporary clot, then clotting proteins which strengthen the clot, and finally fibrin which forms a solid fibrin clot.[6] Activation of the coagulation cascade during Cardiopulmonary bypass (CPB) is attributed to by the systemic inflammatory syndrome, hypothermia, acidosis, residual heparin anticoagulation, and hyperfibrinolysis.[1] Platelets and coagulation factors are consumed[6] resulting in bleeding post cardiac surgery. This explains the high transfusion incidence in cardiac surgery and is well placed to study potential methods that promise to reduce the need for transfusions.

As part of the continued research surrounding coagulation abnormalities during the perioperative period clinicians have asked what the ideal method is to mitigate the effects of CPB on platelets and coagulation factors. Knowing when to transfuse allogeneic platelets for instance is beneficial to the clinician as concluded by Ereth MH, et al. The activated clotting time (ACT) is a bedside monitor that assess anticoagulation during CPB.[10] It is by no means a complete assessment of the coagulation cascade. The use of standard laboratory tests (SLT) [examples: haemoglobin, platelet function test, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalised ratio (INR)] in evaluating coagulation have stood the test of time and may not easily be replaced by novel modalities. Standard laboratory tests are validated for use during cardiac surgery and have formed part of numerous conventional protocols for blood product use.[11]

One modality that has been of much interest with regards to blood product use in cardiac surgery is the Thromboelastogram (TEG®) or Rotational thromboelastometry (ROTEM®). These visco-elastometric tests have shown some valuable trends in reducing the need for allogeneic transfusions as reported by Avidan et al who compared TEG® to laboratory-based algorithm and found blood product use more in the laboratory group.[11] However due the fact that these are not yet widely validated, reports and guidance on their use varies inter-institutionally. The Society of Thoracic Surgeons (STS) transfusion guidelines demonstrated this wide variation with RBC transfusions (27-92%) and coagulation factor transfusion (0-36%) with the introduction of visco-elastometric testing.[14] Shore-Lesserson's two randomised controlled trials[11] compared mediastinal tube drainage and blood product use between TEG® group and the conventional group. Combining standard laboratory tests with POC strategies[15] appears to be a rational approach to improve patient outcomes instead of implementing these strategies in isolation of each other. Literature done in Europe and America has shown superiority of POC haemostasis practice over standard laboratory testing.[9-12] Trends in Africa, and South Africa are still under investigation. This supports the relevance of this study done locally.

The gap in this area of clinical practice is evident and needs to be explored further by the middle to high income populations where these complex procedures and challenging complications pose crippling effects to the health care system. Until we can confidently state that we have found the ideal visco-elastometric method, transfusion medicine will continue to be a field of great opportunity to make a difference in training and development. We in South Africa are fortunate to have various societies that follow worldly trends and make sacrificial efforts to maintain current evidence-based clinical practice. The Society of Anaesthesiologists of South Africa (SASA) has adopted the monitoring of bleeding patients through POC and regular laboratory tests for coagulation, fibrinogen and platelet counts or function.[15] This society has also taken a strong stance on the use of cell salvage[15] in routine practice whenever bleeding more than 500ml is to be expected to prevent transfusions of allogeneic blood products.

Conceptual framework (theoretical basis of the research)

TEG® (thromboelastogram) is a POC device that evaluates various aspects of the coagulation cascade like clot formation, clot strength and fibrinolysis.[1, 3, 6-8] Adding

a TEG® guided algorithm to current clinical practice provides an additional focussed assessment, which may possibly reduce blood product use and potentially contribute to good patient outcome and financial cost saving to this institution and the Free State at large owing to the scarcity[15] and high costs of blood products.

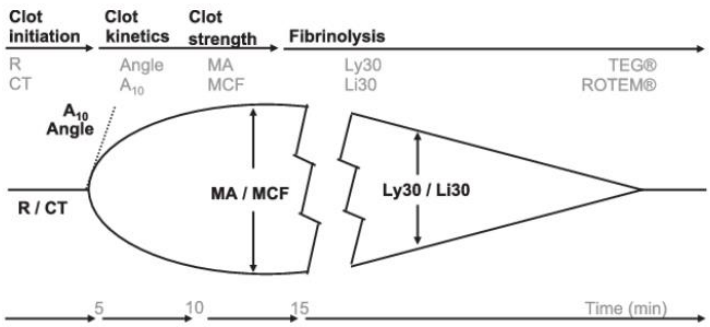

Fig 1. TEG® machine in use at NHLS haematology is the TEG® thromboelastograph Haemostasis Analyzer system, 400 Wood Rd, Braintree, MA.

Schematic TEG â /ROTEM â trace, including the most frequently used variables: reaction time (R)/clotting time (CT), clot formation time (K, CFT), alpha angle (a), maximum amplitude (MA)/ maximum clot firmness (MCF) and lysis (Ly)/clot lysis (CL). The R-value/ CT is the time from the start of the test to the initial fibrin formation. The K value is the clot formation time to reach a specific level of clot strength. The alpha angle represents the acceleration (kinetics) of fibrin build up and cross-linking (clot strengthening). The MA/MCF reflects the ultimate strength of the clot, which depends on the number and function of platelets and their interaction with fibrin. Lysis or clot lysis can be indicated to a certain time, e.g. 30 min, and represents the lysis index at 30 min after MA. Ly is increased with fibrinolysis.

(Taken from Johansson PI, et al. Current management of massive hemorrhage in trauma. Scand J Trauma Resusc Emerg Med. 2012;20:1–10.)

Figure 1. TEG® machine in use at NHLS haematology

The theoretical basis of the research that has been described thus far seeks to provide us with an understanding that perioperative patient outcomes depend on multifactorial components throughout the hospital stay. Following the pre-, intra-, and post-operative strategy gives a clear working plan and enables us to set goals for each period of a patients care. With reference to the TEG® (also ROTEM®) point of care protocol, time to detection of a coagulopathy is critically important during cardiac surgery owing to the extensive transfusion load in this patient group. Within 5 to 10 minutes elements of coagulation become evident as compared to the standard laboratory analyses which consistently showed turnaround times of 60 minutes or more.[4] The fibrinolytic system within the coagulation cascade also gets evaluated by the POC methods in 30 minutes[4] of a blood specimen drawn for assessment, a function that is lacking in standard laboratory tests. Point of care machinery also boasts another benefit in that they are generally small, compact,

affordable, and easily moveable within confined spaces in a hospital setting. Many of them have been used in emergency departments, intensive care units and the theatre complex. The National Health Laboratory Systems (NHLS) standard laboratory testing equipment on the other hand is generally big, immoveable, and expensive.

Arguments against POC infrastructure development and routine use is usually the daily running costs of disposable cartridges, maintenance costs and lack of validation studies to prove the quality of the results and those of the tried and tested standard laboratory tests.[4,11] Short comings in the scientific evidence in support of validating these POC machinery are the vast heterogeneity of the trials done in disciplines like trauma, obstetrics, and cardiac surgery. Counter arguments for their use enjoy attention towards the rationale that shorter timescale to provide results[6] and the inherent ability to provide additional information on the clotting process[4] will inevitably lead to earlier diagnosis of coagulopathy, targeted administration of blood products and minimise the risks associated with unnecessary transfusions. Theatre turnaround time may become less, hospital and intensive care unit stay potentially gets reduced[6]. The cumulative need for blood products may also be reduced markedly thereby easing the continuous burden on the National Blood Services, and minimising patient exposure to allogenic blood products[15] with their potential and costly early and late onset complications.

This led us to the construction our research question: The use of a thromboelastogram TEG® protocol to reduce the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital (UAH), Bloemfontein, Free State, South Africa. Work towards answering this research question started with the appreciation of the current clinical practice at this institution in 2019 and 2020. Patient population demographics, type of cardiac surgeries done and the workflow from presentation of a patient to cardiothoracic surgery until discharge from intensive care unit were evaluated. Only a summary of this workflow has been included in this report.

Current clinical practice

The patient enters theatre for his/her cardiac surgery. Monitors such as blood pressure, pulse oximetry and electrocardiogram are attached by the

anaesthesiologist with the assistance of the nursing staff. The peripheral venous cannula sited. The patient is induced with general anaesthesia (GA) using intravenous anaesthetic agents indicated according to a patient's haemodynamic profile. These commonly include but are not limited to:

- *Opioid/analgesics:* Fentanyl, Remifentanil, Sufentanil, Morphine;
- *Induction agent:* Propofol, Etomidate or Ketamine;
- *Muscle relaxant:* Suxamethonium and Rocuronium, Atracurium or Cisatracurium;
- *Anticoagulant:* Heparin; and
- *Reversal of anticoagulant:* Protamine.

Once successfully intubated, the patient is mechanically ventilated, and anaesthesia is maintained with a volatile anaesthetic agent (Sevoflurane, Isoflurane) or a Total Intravenous Anaesthetic (TIVA) technique with Propofol is used. An arterial and central venous cannula are then sited using ultrasound guidance. The first blood samples for an arterial blood gas (ABG) and activated clotting time (ACT) are drawn from the arterial line by one of the clinical perfusionists for testing. It is at this point that a sample for a baseline thromboelastogram (TEG®), prior to the administration of heparin for anticoagulation, was drawn.

The rest of the monitors are applied, Bispectral Index monitoring (BIS), Near Infrared Spectroscopy (NIRS), temperature and urinary catheter. The participant is then positioned for disinfection and cleaning of the surgical site. Sterile drapes are applied. The surgeon and his/her assistant scrub and don sterile gowns and gloves proceed with the indicated surgical procedure. During the operation arterial blood gasses are frequently drawn by either anaesthesiologist or a perfusionist to monitor the participant's physiological status every thirty (30) minutes or more frequently if indicated. Once the surgery has been concluded and before the closure of the sternum and wound, about five minutes after protamine administration (given to reverse the anticoagulant effects of heparin) or as close after that time point as possible, a second TEG® sample was drawn for analysis. Together with the post-operative TEG® a Platelet Function Assay (PFA 100) and Fibrinogen level was drawn for each patient for complete assessment of the coagulation profile. These results were used to direct the decision to order blood and blood products in

conjunction with the surgeon's observation and assessment of the surgical field for bleeding. Patients are usually transferred to the cardiothoracic intensive care unit (ICU) intubated and ventilated post operatively for further monitoring and management. Blood and blood product usage was evaluated up to six (6) hours post operatively for inclusion in the study.

Ordering of blood products

The usual practice regarding the ordering of blood and blood products happens during the pre-operative period the day before the scheduled surgery. Informed consent for the surgery and blood transfusion are taken by the surgical team and confirmed by the anaesthesia team. A blood sample is sent to the South African National Blood Services (SANBS) with a form stating the possible need for blood and blood products on the day of the surgery, together with the complete pre-operative biochemical workup as indicated by the patient's comorbidities. A request is made to have the patient's sample crossmatched and products kept on standby for ease of access once needed, unless a patient is at high risk of needing blood products at the beginning of the procedure or for priming of the Cardiopulmonary bypass (CPB) circuit, in which case blood is then issued earlier.

Concern in the current clinical practice

The decision to transfuse is currently based on physician discernment of the operative field, experience, and limited Standard Laboratory Tests (SLT) available.[2,4,5] There is currently no clear point of care (POC) protocol in place to guide blood product use in cardiac surgery at Universitas Academic hospital, possibly one of very few academic hospitals in South Africa that performs similar cardiac procedures without POC protocols. There is thus a lack of accurate scientific evidence of managing coagulopathic patterns during cardiac surgery at our institution.

Aim and Objectives

The aim of the study was to establish whether the use of a TEG® protocol versus physician decision reduces blood product usage in adult patients undergoing open heart surgery at Universitas Academic Hospital in Bloemfontein, Free State. Universitas Academic Hospital (UAH) is the only public hospital in the Free State

that provides cardiac surgery for the Free State population. Patients from the Northern Cape and Lesotho are also accepted for surgery at this Free State Department of Health facility. The motivation of doing this study was because it has never been done in our institution and it is our duty to research novel ways to improve patient outcomes in everything we do as clinicians. Evidence based quality service delivery, education and research are cornerstones in clinical medicine.

All patients aged 18 years and older who underwent first time elective cardiac surgery during June to September 2019 were included in the retrospective file review group (Group A), clinical notes from Meditech® (Medical Information Technology Inc. A Massachusetts-based software and service company selling information systems for health care organisations, Pappalardo N, et al.) and the National Health Laboratory System (NHLS) Lab Trak® (A laboratory information system, results portal Ltd 1996), 25 June to 30 September 2019, and those who presented during June to September 2020 were prospectively allocated to the TEG® protocol group (Group B). No re-do or emergency surgery was included in this study. Re-do surgery bleeds more and blood usage is inevitably increased.[12,14,15]

The secondary aims of the study were to evaluate trends regarding the cardiac surgical procedures that are conducted commonly at our institution as well as giving a description of the common medical conditions and treatment of these that may influence coagulation profiles of patients. Baseline laboratory data (haemoglobin, platelets, prothrombin time, activated partial thromboplastin time and international normalised ratio) were described. We also provide commentary on the haemostatic effects of known pharmaceutical agents like tranexamic acid, heparin, protamine, and bio-plasma as over the counter non-therapeutics like garlic, ginger, turmeric, vitamin E and common remedies in which cayenne pepper may be found.

Hypothesis

The hypothesis of the study was that the use of a POC viscoelastic TEG® protocol reduces the usage of blood and blood products during cardiac surgery in adult patients undergoing cardiac surgery in Universitas Academic Hospital, Bloemfontein, Free State, South Africa.

Methods

The study was approved by the research ethics committee of the University of the Free State, HSREC: UFS-HSD2019/0184/2807 on 25 June 2020.
Comparative, descriptive study was performed immediately after ethics approval using:

A. The **physician decision group** consisting of a retrospective file review of the usual clinical practice, using clinical notes from Meditech (an integrated software system that provides solutions to healthcare organisations throughout Africa) and the National Health Laboratory System (NHLS) Lab Trak (an inter-systems results portal), 25 June to 30 September 2019, and
B. The **TEG® protocol group** consisting of a prospective cohort of patients using the usual clinical practice with the addition of TEG®-based protocol, 25 June to September 2020.

The study was conducted at Universitas Academic Hospital, Bloemfontein. This is a tertiary training public hospital in the Free State, South Africa which serves the whole Free State province, great parts of the Northern Cape province as well as Lesotho. All patients aged 18 years and older who presented for first time elective cardiac surgery during the set times were included in the study. During the retrospective review patient files were requested from the hospitals patient data management system department and a diligent search was done of these in addition to the institution's medic-tech surgical and anaesthetic clinical records, nursing records up to six hours postoperatively by the principal researcher.

The prospective part of the study was conducted during the COVID pandemic by the principal researcher with the help of anaesthesiology registrars and consultants working in the cardiothoracic theatres at the time. This proved to be a challenging time for all non-COVID related research in our institution as reflected in the low study population of 14 included in the prospective arm and 33 in the retrospective arm. The estimated samples size for a three (3) month period was 30 to 35. Data was collected and entered in a Research Electronic Data Capture (RedCap®) data form, a metadata-driven software for clinical and translational research databases, for

both retrospective and prospective parts. A **TEG® protocol** was set up from examples from the Cochrane database systematic review of 2011.

Inclusion criteria included age 18 years and older, elective cardiac surgery on cardiopulmonary bypass, signed informed consent, no known coagulopathy. Patients excluded from the study were children below 18 years, emergency or re-do cardiac surgery, known coagulopathy, informed refusal to participate. *Figure 2* below outlines the process for patient selection.

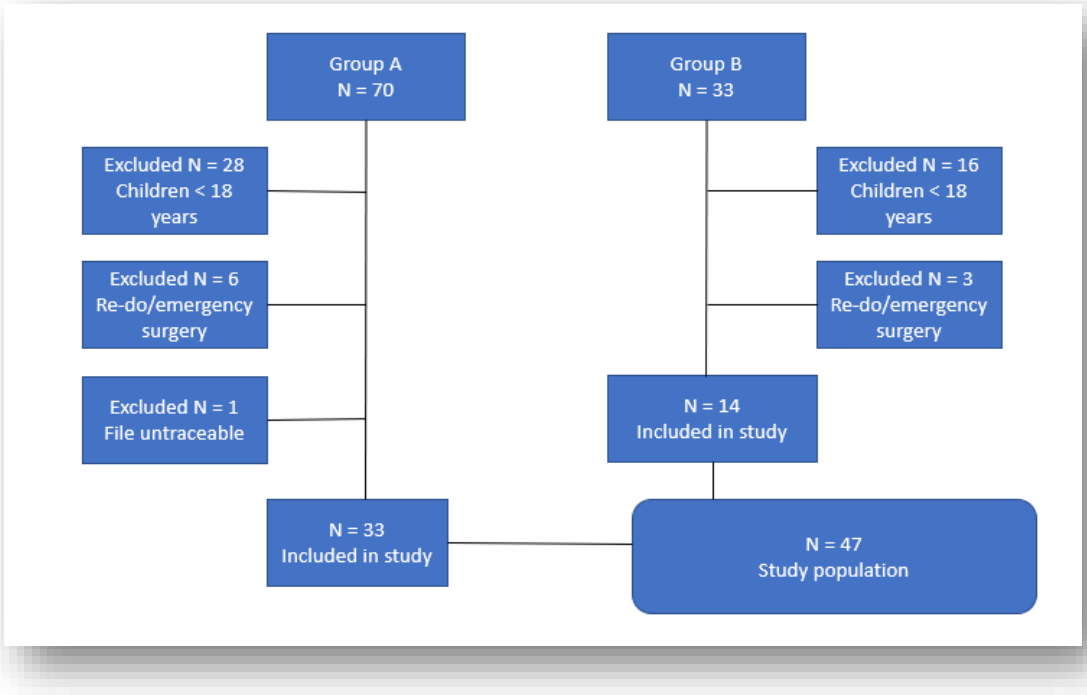

Figure 2. Patient selection process

Statistical analysis

Age (years), BMI (kg/m^2), Cell saved blood transfused (ml), RCC, FFP, Cryoprecipitate and Platelets (all in units) are displayed as median and interquartile range because of their non-parametric distribution. The categorical variables are sex, medication, medical conditions, and surgical procedures. Statistical significance was tested using the Kruskal Wallis paired test. A $p < 0.05$ was considered statistically significant.

Results

From the sample size of 47, 12 (26%) were female and 35 (74%) were male. These findings were in keeping with the different time periods, i.e., Group A (2019)

presented 9/33 (27%) females and 24/33 (73%) males. While Group B (2020) had 3/14 (21%) females and 11/14 (79%) males.

Table 1 below provides a collated representation of 2019 and 2020 data. The BMI for the two groups were comparable (2019: minimum 19, maximum 41, IQR: 24-28 and 2020: minimum 17, maximum 39, IQR: 22-30).

Table 1: Patient demographics, preoperative laboratory tests and intraoperative ACT (2019 and 2020 combined)

Variable	n total (%)	n 2019 (%)	n 2020 (%)	Average 2019	Average 2020	p-value
A. Patient demographic						
Age (years)	47	33	34	54	54	0.8890
BMI (kg/m2)	47	33	34	25	27	0.7801
Sex	47	33	34	-	-	0.6743
Female	12 (26)	9 (27)	3 (21)	-	-	-
Male	35 (74)	24 (73)	11 (79)	-	-	-
B. Pre-operative laboratory tests						
Hb (g/dL)	47	33	14	14	14	0.6583
Hct (%)	47	33	14	472	42	0.5766
INR	47	33	14	1.1	1.0	0.1397
aPTT (seconds)	47	33	14	28	29	0.8283
PT (seconds)	47	33	14	13	12	0.0924
C. Intra-operative ACT (seconds)						
Pre-haparin	47	33	14	166	173	0.0826
Post-protamine	47	33	14	142	137	0.1723

BMI: Body mass index, Hb: Haemoglobin, Hct: Haematocrit, INR: International normalized ratio, aPTT: Activated partial thromboplastin time, PT: Prothrombin time, ACT: Activated clotting time

Table 2: Blood product use reported via Wilcoxon Scores (Rank Sums)

Year	Average transfused	P-value
1. CSB		<0.0001
2019	844ml	
2020	568ml	
2. RCC		0.6679
2019	3 units	
2020	2 units	
3. FFP		0.05
2019	4 units	
2020	2 units	
4. Platelets		**0.2329**
2019	2 units	

2020	1 unit	
5. Platelets		0.2329
2019	2 units	
2020	1 unit	
6. Cryoprecipitate		0.6383
2019	2 units	
2020	1 unit	

RCC: Red cell concentrate, FFP: Fresh frozen plasma, CSB: Cell saved blood

Table 2 above, depicts the statistical significance in the transfusion of cell saved blood and FFP's with the introduction of the **TEG® protocol group.** There was no difference in terms of RCC, platelet and cryoprecipitate transfusion but a statistical trend towards reduced use with the **TEG® protocol.** The introduction of the **TEG® protocol** in the 2020 leg yielded the following results illustrated in Table 3. No worrisome intra- or early postoperative bleeding (up to six hours follow up in Intensive care) was observed.

Table 3: Post-operative TEG®, PFA 100 and Fibrinogen

Variable	Number	IQR	Normal values
Baseline/pre-heparinisation TEG			
R Time (min)	14	5.9-10	< 4
K time (min)	14	1.8-4	1-4
Alpha angle (degrees)	14	41-67	> 45
MA	14	66-73	45-73
LY30 (%)	14	0	0-8
Post-operative/post protamine TEG, PFA100 and Fibrinogen			
R time (min)	14	3.8-5.9	< 4
K time (min)	14	1-2	1-4
Alpha angle (degrees)	14	64-73	> 45
MA	14	60-70	45-73
LY30 (%)	14	0	0-8
PFA: Col/Epi (seconds)	12	159-197	84-160
PFA: Col/ADP (seconds)	12	102-155	68-121
Fibrinogen (g/L)	12	1.75-2.55	2-4

R: reaction time, K: Clot formation time, MA: Maximum amplitude, LY30: Lysis at 30 minutes, PFA: Platelet function analysis, Epi: Epinephrine, ADP: Adenosine diphosphate, IQR: Inter quartile range

Additional data collected

Of the three common chronic cardiovascular diseases that contribute to the morbidity of the metabolic syndrome, hypertension was by far the most common at 83% (39/47), followed by hypercholesterolaemia at 53% (25/47) and diabetes mellitus at 26% (12/47). Only one patient in the study population had asthma. No thyroid diseases were recorded for the duration of study and HIV was the commonest “other comorbid” condition, 21% (10/47), see Fig 3.

The most common type of surgery performed (Fig 5) was CABG (23/47, 49%, LR: 0.168, p = 0.2124), followed by MVR (15/47, 32%, LR: 0.315, p = 0.4957), AVR (12/47, 26%, LR: 0.04, p = 0.0768) and TVR (4/47, 9%, LR: 0.824, p = 1.0000).

Dual therapy in the form of Aspirin and Clopidogrel was found to be prevalent in this study population. *Fig 5* describes the individual drug use as percentages of the total study population of 47, i.e., 2019 and 2020 combined.

Of the over-the-counter therapeutics and home remedies that may influence coagulation it was found that two patients (2/47, 4.2%, p = 0.0842) consumed ginger and one (1/47, 2.1%, p = 0.2979) garlic in the **TEG® protocol group.** In none of the groups was ginseng, turmeric, cayenne peppers or vitamin E recorded.

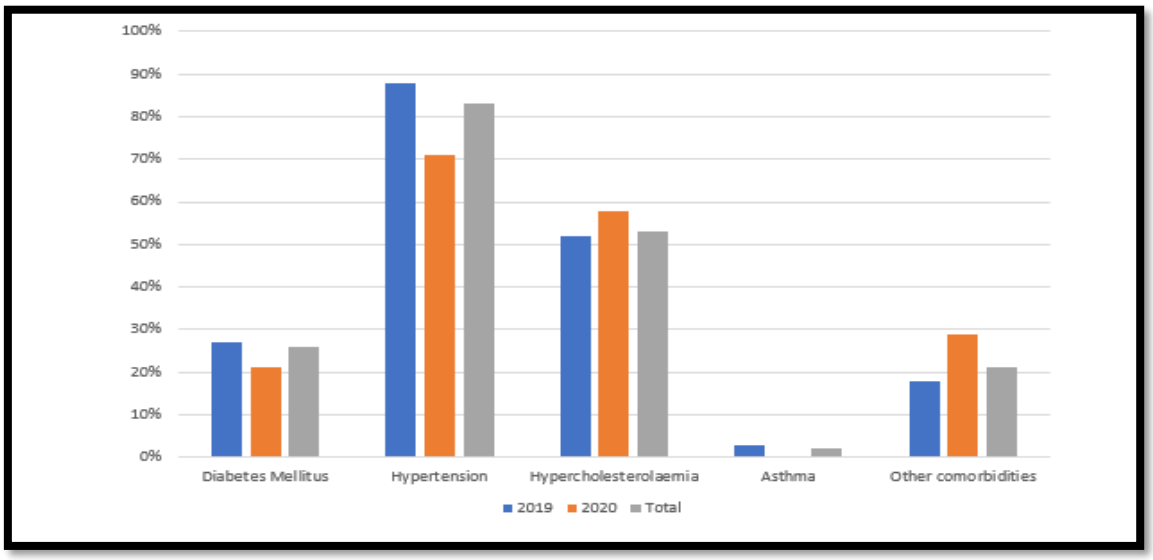

Figure 3: Medical conditions

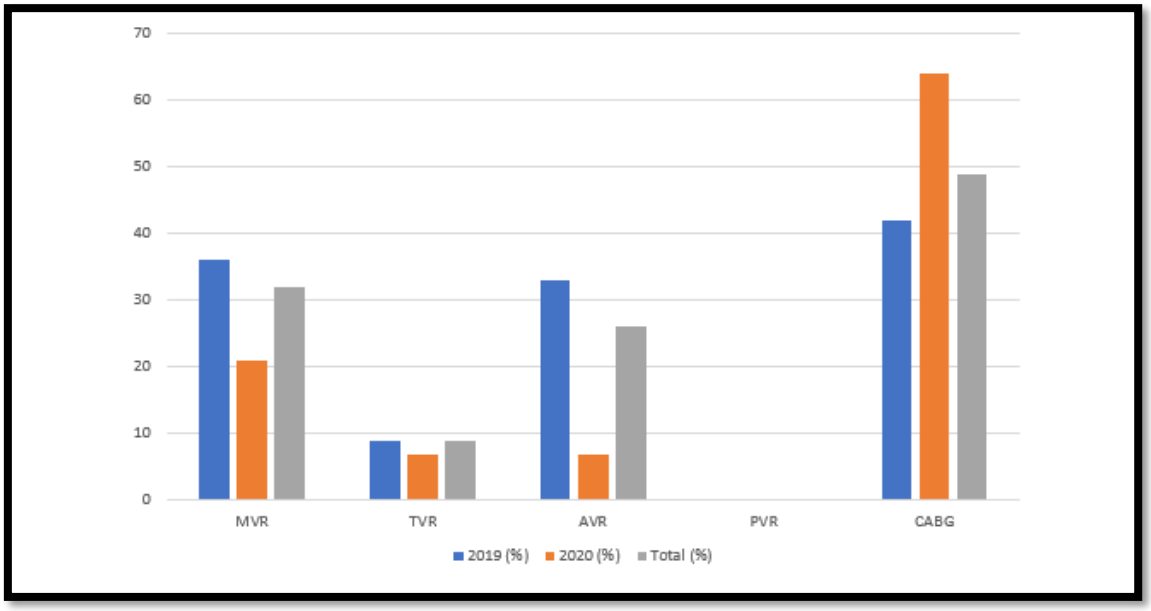

Figure 4. Surgical procedures performed (MVR: Mitral valve repair/replacement, TVR: Tricuspid valve repair/replacement, AVR: Aortic valve repair/replacement, PVR: Pulmonary valve repair/replacement, CABG: Coronary artery bypass graft)

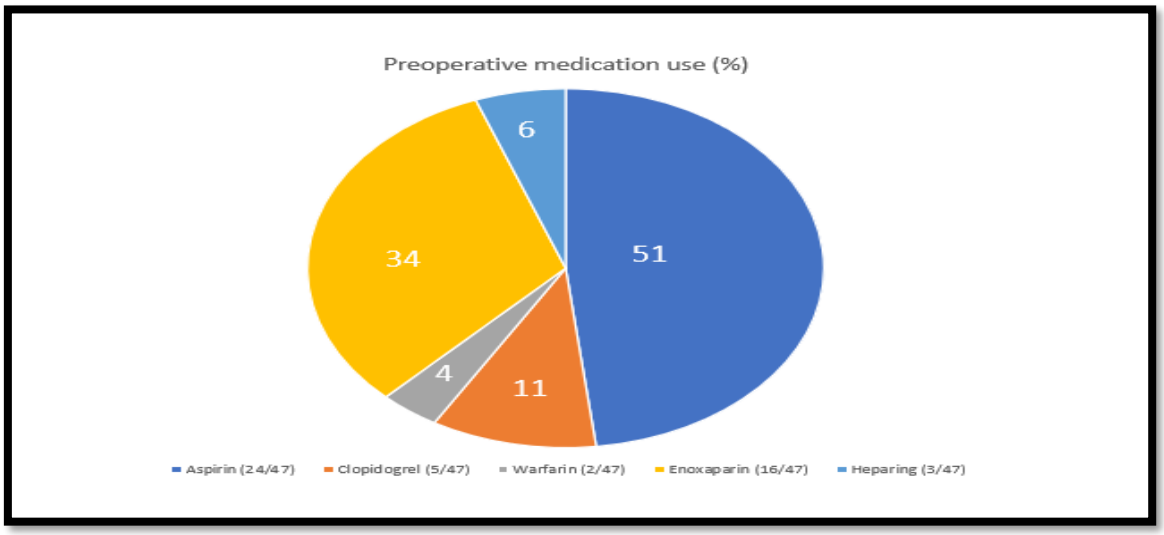

Figure 5: Pre-operative medication use

Discussion

Our primary outcome defined as blood and blood products used intra and early postoperatively was proven to be reduced with the introduction of the **TEG® protocol**. Cell saved blood, FFP, and platelet transfusion had reduced trends statistically and clinically in the **TEG® protocol group** which is in keeping with the findings of Sharma AD et al. Furthermore mean units of red blood cells, plasma, and cryoprecipitate were significantly reduced after TEG® was implemented (all, $p <$ .0001)[12] according to Flemming K, et al. who also demonstrated that the mean units

of all blood products in the perioperative period were reduced by approximately 40% (both, $p < .0001$).[12]

NICE guidelines published in 2014 revealed similar findings where RBC, FFP and Cryoprecipitate transfusion indicated a decreased trend post-TEG®, Platelets showed no significant difference while total number of units decreased post TEG®[13] Higher CTO (Chest Tube Output) at 8hr was associated with advanced age, male patients, patients who received pre-operative clopidogrel for 5 or 10 days and patients who were transfused with larger amounts of intraoperative CSB (cell saver blood).[1] Meta-analysis shows exposure to allogeneic blood products was lower in the point of care (POC) group (49.6%) than in the conventional group (60.2%)[15] TEG®-guided transfusion algorithms during cardiac surgery have resulted in a reduced administration of blood products. When implemented in cardiac surgery, POC coagulation testing resulted 50% reduction of blood/blood product transfusions[1] Post-TEG®: significantly lower blood product use perioperatively (OR and 24 hours postoperatively) regarding RBC, FFP and cryoprecipitate. Platelet use was reduced by 5% but did not reach statistical significance[12]

Preoperative anaemia is an independent risk factor for perioperative blood transfusions. The median preoperative haemoglobin recorded for the 2019 group was 13 g/dl while that for the 2020 group was 14 g/dl with the minimum recording of 9.9 g/dl and 10.8 g/dl, respectively. This slight difference may potentially have contributed to the higher trend towards RCC in the 2019 group. TEG results do not directly guide the use of RBC.[13] The increased incidence of Coronary artery bypass graft (CABG) surgery in male patients was to be expected due to the higher rate of atherosclerotic disease in the stated population group[1] which also confirmed our trends locally to those in other parts of the world. The complex surgical cardiac patient population is typically older, sicker, and more prone to haemostatic disorders.[12]

An interesting finding regarding the ACT results is that the median intraoperative Heparin dose in 2019 was 35000U vs 31000U in 2020 even though the median BMI was slightly higher in 2020, 26 kg/m^2 compared to 25 kg/m^2 in 2019. Heparin dose typically ranged between 300-400U/kg with bolus top ups as indicated to maintain

ACT above 480 seconds for full anticoagulation. Protamine reversal of Heparin was typically done in a 1:1 ratio (1mg per 100U Heparin). This was also slightly different, 2019 median = 310 mg vs 2020 median 325 mg. This trend was unexpected since cell saved blood contains residual heparain and transfusion of cell saved blood was significantly more in the 2019 goup. One patient who presented with a history of a garlic and ginger homemade remedy the week prior to surgery had aplatelet count of 179. He had an inadequate haemostasis clinically and was successfully managed with DDAVPA potential limiting factor to the findings of the over the counter/non-therapeutics in the retrospective **Physician decision group** may be that these variables are not always specifically asked for in the history taking of any discipline, cardiothoracic surgery being no exception to the rule. Other medications that potentially may affect coagulation like Rivaroxaban and Dabigatran were not recorded in any of the patients in the study population.

Another patient had a markedly deranged baseline TEG® which led to early consultation with haematology. It was noticed to have been a laboratory error as a new intern clinical technologist had omitted an important step in the preparation of the blood sample after running a control sample for machine readiness. This illustrated the importance of the multidisciplinary communication throughout the study to ensure patient safety. Platelet function testing according to the SASA guidelines[15] is considered to guide the timing of cardiac surgery. Benefit to the routine use of platelet function assay is yet to be proven unless patients have taken P2Y12 receptor inhibitors such as clopidogrel within less than 5 days of surgery.[15]

The average tranexamic acid use was comparable in both groups and therefore showed no clinically significant difference in dosing. However, in the 2020 TEG® group, the average tranexamic acid use was statistically significantly lower ($p=0.0001$). The correlation of these findings may potentially be as a result of the significantly lower 2020 sample size. No need nor use of bioplasma was documented in both study groups.

The limitations to this study include small population size, underpowered, single centre and partly retrospective. The strength is the prospective clinical part.

Conclusions

Cell saved blood and FFP transfusion were statistically and clinically significantly reduced in the **TEG® protocol group**. While platelet, cryoprecipitate and total blood product transfusion had reduced trends in the **TEG® protocol group** though not of statistical significance.

We suggest that this preliminary report be considered for future MMed or PhD research because it was a first in our institution and there is great potential to improve patient outcomes and contribute to best practice regarding patient blood management in the perioperative period.

Acknowledgement

The authors would like to thank the theatre staff of the cardiothoracic theatre at Universitas Academic Hospital for their enthusiasm with the data collection especially the perfusionists who diligently collected the blood samples timeously. A special mention to Mrs Marlee Janssen Van Vuuren, head of clinical perfusion department.

We thank the registrars and consultants of the Anaesthesia and Cardiothoracic departments for their roles in communicating theatre lists, help identifying patients, recording of the findings, and liaising between all role players during data collection. Dr C.A. Barrett was instrumental in help setting up the RedCap® data collection form as well as her critical analysis of the clinical relevance of the study, and for this we are grateful.

Thank you to Prof. G. Joubert from Biostatistics at the University of the Free State for her invaluable input from the inception of the study design right through the final analysis of the results.

We recognise the NHLS, pathology and haematology department together with the registrars and clinical technicians for physically running the tests, countless telephone calls to report the test findings and give input regarding further patient management.

Conflict of interest

The authors declare no conflict of interest.

Funding source

This study was funded by the University of the Free State Postgraduate Research Fund.

Ethical approval

Ethics was obtained from the University of the Free State Research Ethics Committee UFS-HSD2019/0184/2807 on 25 June 2020

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APPENDIX A

HSREC LETTER OF RESEARCH APPROVAL

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES

Health Sciences Research Ethics Committee

25-Jun-2020

Dear **Mr Jerome Magorani**

Ethics Clearance: **The use of a Thromboelastogram (TEG) protocol to decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa.**

Principal Investigator: **Mr Jerome Magorani**

Department: **Anaesthesiology Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/0184/2807**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7703/7794 | E: ethicsfhs@ufs.ac.za
IRB 0001 1992; REC 230408-011; IORG 0010096; FWA 00027947
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40)| Bloemfontein 9300 | South Africa

APPENDIX B

PARTICIPANT INFORMATION FORM AND CONSENT FORM

Information document

Study title: Will a TEG® protocol decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa?

Good day

We, Drs JB Mogorosi and EW Turton, are doing research on the blood product usage during cardiac surgery. Research is the process to learn the answer to a question. In this study we want to learn if there is any change in the amount of blood product usage when a Thromboelastography protocol is applied to cardiac surgery. A thromboelastography is a machine that evaluates the blood clotting process and gives accurate guide as to which blood components are lacking and need to be given to a patient.

We are asking you to participate in this research study.

For your scheduled cardiac surgery, we will take blood samples soon after the arterial drip line has been inserted and again towards the end of the procedure. This is to evaluate for blood clotting function to provide for the necessary replacement of these products. How we have been doing blood transfusions thus far is to evaluate the operation site as well as limited laboratory tests. With this study we will continue to do this in addition to making use of a special machine that tests blood clotting (Thromboelastogram). Participation is voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are entitled to. There will be no costs payable by you as participant neither will you be remunerated for participating in the study.

There will be no risk of harm to you.

You may discontinue participation at any time without loss of benefits. Efforts will be made to keep personal information confidential however absolute confidentiality cannot be guaranteed and personal information may be disclosed if required by law.
Organisations that may inspect your research record for quality assurance and data analysis include the Ethics Committee for Medical Research. If results are published it may lead to cohort identification. Should you require the results of the study after completion, it will be available to you. Contact details of researchers for further information or reporting of study-related adverse events:

Name: Dr JB Mogorosi Dr EW Turton
Phone: (051) 405 3307 (051) 405 3307

Contact details of Secretariat and Chair: Ethics Committee of the Faculty of Health Sciences, University of Free State - for reporting of complaints:
Phone (051) 405 2812.

INFORMED CONSENT

Consent to participate in research

Study title: Will a TEG® protocol decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa?

You have been asked to participate in a research study.

You have been informed about the study by Dr JB Mogorosi or Dr EW Turton.

You may contact Dr J.B. Mogorosi or Dr E.W. Turton at (051) 405 3307 anytime if you have questions about the research or if you are injured as a result of the research.

You may contact Secretariat of the Health Science Ethics Committee of the Faculty of Health Sciences, University of the Free State at telephone number (051) 405 2812 if you have any questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

Signature of Participant ……
Date……...

Signature of Witness……
Date……...

Signature of Translator…….
Date……..

APPENDIX C

FSDOH LETTER OF APPROVAL

health
Department of Health
FREE STATE PROVINCE

22 April 2020

Mr J Mogorosi
Dept. Of Anaesthesiology
UFS

Dear Mr. J Mogorosi

Subject: The use of a Thromboelastrogram (TEG) protocol to decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** [redacted] **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: _____

Head : Health
PO Box 227 Bloemfontein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and Harvey Road, Bloemfontein
Tel: (051) 405 1045 Fax: (051) 405 1558 e-mail: [redacted]
www.fs.gov.za

APPENDIX D

BIOSTATISTICS LETTER OF APPROVAL

05 March 2019

For attention: Health Sciences Research Ethics Committee
Faculty of Health Sciences

Title of project:

The use of a Thromboelastogram (TEG®) protocol to decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa.

Researchers:

JB. Mogorosi

I have given input regarding the above mentioned project's protocol on the following aspects of the protocol, namely the study design, sample, measurement, measuring instrument and statistical analysis.

Yours faithfully

Mpendulo Mamba

APPENDIX E

PERMISSION LETTERS TO HOD'S

Letter to Clinical Head, Universitas Academic Hospital

Dr Nathan
Clinical Head
Universitas Academic Hospital
Bloemfontein
9301

Dear Dr Nathan

Re: REQUEST FOR PERMISSION TO CONDUCT A STUDY

I hereby apply for permission to conduct a study for the purposes of the MMed degree in Anaesthesiology. My study title is: "Will a Thromboelastogram (TEG®) protocol decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa?" Dr Edwin Turton, the Head of Department of Anaesthesiology, is my study leader.

Cardiac surgery is associated with the use of a significant amount of blood and blood products. Transfusion related complications like increased length of hospital stay and transfusion reactions constantly require attention to improve patient outcomes. This study aims to research whether a TEG®-based protocol can reduce the rate of blood transfusions in adult patients undergoing cardiac surgery compared (post-intervention group) to cardiac surgery without TEG® (retrospective pre-intervention group). The study will take place over a three-month period at Universitas Hospital.
An informed consent document will be handed to every participant. Details of the study will be explained in the language best understood by the participant, making use of translators if necessary. This should not take longer than fifteen minutes of the participants' time. The results of the study might be published and presented at a meeting or congress.

Yours sincerely

Dr J.B. Mogorosi
Phone 0826460180
katlego4jerome@gmail.com
Registrar: Department of Anaesthesiology, Universitas Hospital.

Letter to HOD, Cardiothoracic surgery

Prof. F.E. Smit
Head: Cardiothoracic Surgery Department
Universitas Hospital
Bloemfontein
9301

Dear Prof Smit

Re: REQUEST FOR PERMISSION TO CONDUCT A STUDY

I hereby apply for permission to conduct a study for the purposes of the MMed degree in Anaesthesiology. My study title is: "Will a Thromboelastogram (TEG®) protocol decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa?" Dr Edwin Turton, the Head of Department of Anaesthesiology, is my study leader.

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Yours sincerely

Dr J.B. Mogorosi
Phone 0826460180
katlego4jerome@gmail.com
Registrar: Department of Anaesthesiology, Universitas Hospital.

Letter to Head of the School of Pathology, NHLS

Dr J Naicker
Head of School of Pathology
Faculty of Health Sciences
University of the Free State
Bloemfontein
9301

Dear Dr Naicker

Re: REQUEST FOR PERMISSION TO CONDUCT A STUDY

I hereby apply for permission to conduct a study for the purposes of the MMed degree in Anaesthesiology. My study title is: "Will a Thromboelastogram (TEG®) protocol decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa?" Dr Edwin Turton, the Head of Department of Anaesthesiology, is my study leader.

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Yours sincerely

Dr J.B. Mogorosi
Phone 0826460180
katlego4jerome@gmail.com
Registrar: Department of Anaesthesiology, Universitas Hospital.

Letter to HOD, Haematology

Prof M Coetzee
Head: Department of Haematology
National Health Laboratory Service (NHLS)
Bloemfontein
9301

Dear Prof Coetzee

Re: REQUEST FOR PERMISSION TO CONDUCT A STUDY

I hereby apply for permission to conduct a study for the purposes of the MMed degree in Anaesthesiology. My study title is: "Will a Thromboelastogram (TEG®) protocol decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa?" Dr Edwin Turton, the Head of Department of Anaesthesiology, is my study leader.

Cardiac surgery is associated with the use of a significant amount of blood and blood products. Transfusion related complications like increased length of hospital stay and transfusion reactions constantly require attention in order to improve patient outcomes. This study aims to research whether a TEG®-based protocol can reduce the rate of blood transfusions in adult patients undergoing cardiac surgery compared (post-intervention group) to cardiac surgery without TEG® (retrospective pre-intervention group). The study will take place over a three-month period at Universitas Hospital.

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Yours sincerely

Dr J.B. Mogorosi
Phone 0826460180
katlego4jerome@gmail.com
Registrar: Department of Anaesthesiology, Universitas Hospital.

APPENDIX F

COPY OF RESEARCH PROTOCOL APPROVED BY HSREC

Researcher:
J.B Mogorosi
Department of Anaesthesiology
Universitas Academic Hospital
01 Logeman Street
Bloemfontein
P.O. Box X20660
Phone: (051) 405 3307
06 January 2020

The Chair: Health Sciences Research Ethics Committee
Dr SM le Grange
For Attention: Mrs M Marais
Block D, Room 104,
Francois Retief Building

PO Box 339 (G40)
Nelson Mandela Drive
Faculty of Health Sciences
University of Free State
Bloemfontein
9300

Dear Dr SM, le Grange,

PROJECT TITLE: **The use of a Thromboelastogram (TEG®) protocol to decrease the usage of blood products in adult patients undergoing cardiac surgery at Universitas Academic Hospital, Bloemfontein, Free State, South Africa.**

Enclosed please find the above research protocol for your evaluation and approval.

Yours faithfully,
……
Jerome Bobby Mogorosi
katlego4jerome@gmail.com
0826460180

DECLARATION BY INVESTIGATORS

1. I hereby agree to conduct the clinical research trial as indicated in the protocol and obtain in writing the necessary authorization from the relevant ethics or clinical bodies.
2. I agree to obtain informed consent from patients who are legally competent.
3. I agree to obtain permission from the Ethics Committee in writing if I make any changes to the protocol.
4. I agree to provide a full report of my findings at the conclusion of this trial and a progress report periodically as instructed.

Signature: _____

Date:	06 January 2020	
Names:	J B Mogorosi	E W Turton
Designation:	Researcher	Supervisor
Qualification(s):	MBChB, DA (SA)	MBChB, DA (SA), M. Med, FCA

ABSTRACT

Blood transfusion during cardiac surgery is known to carry a whole range of potential complications like transfusion reactions, increased length of hospital stays and increased financial costs (1-4). More and more efforts are made worldwide through research to reduce the rate of transfusions. Examples of this work is the use of Point of Care (POC) strategies TEG® that provide health care practitioners with rapid, predictive and outcome based POC coagulation testing algorithms (5, 6) to guide perioperative blood transfusions. There is currently no clear POC protocol in place to guide blood product use at Universitas Hospital for patients undergoing cardiac surgery and the decision regarding transfusion is currently based on physician discernment of the operative field, experience and limited Standard Laboratory Tests (SLT) available (2, 4, 5). The aim of the study is to establish whether the use of a TEG® protocol versus physician decision will reduce blood product usage in adult patients undergoing open heart surgery at Universitas Academic Hospital in Bloemfontein, Free State.

SUMMARY

Blood transfusion during cardiac surgery is known to carry a whole range of potential complications like transfusion reactions, increased length of hospital stays and increased financial costs (1-4). More and more efforts are made worldwide through research to reduce the rate of transfusions. Examples of this work is the use of Point of Care (POC) strategies TEG® that provide health care practitioners with rapid, predictive and outcome based POC coagulation testing algorithms (5, 6) to guide perioperative blood transfusions.

1.1 INTRODUCTION

Cardiac surgery uses a significant portion of an institutions financial budget in the form of replacement devices, complexity of the surgical techniques and the use of blood and blood products.

Universitas Academic Hospital (UAH) is the only public hospital in the Free State that provides cardiac surgery. Patients from the Northern Cape and Lesotho are operated in the facility.

Usual practice:

The participant enters theatre for his/her cardiac surgery. Monitors such as blood pressure, pulse oximetry and electrocardiogram are attached by the anaesthesiologist with the assistance of the nursing staff. Peripheral venous lines are inserted. The patient is induced with general anaesthesia (GA). Intubated and ventilated with volatile anaesthetic gasses. An arterial line and central venous line are then inserted using ultrasound guidance.

The first blood samples for an arterial blood gas (ABG) and activated clotting time (ACT) are drawn from the arterial line by one of the perfusionists for testing. It is at this point that a sample for a baseline thromboelastogram (TEG) will also be drawn.

The rest of the monitors are applied, Bispectral Index monitoring (BIS), urinary catheter. The participant is then positioned for cleaning and draping of the operative field by the scrub nurse. The surgeon and his/her assistant scrub and proceed to do the set operation.

During the operation arterial blood gasses are frequently drawn by either anaesthesiologist or a perfusionist to monitor the participant's physiological status. For this reason, a second sample for TEG will be drawn at ninety minutes.

Once the surgery has been concluded before the closure of the sternum and wound a third TEG sample will be drawn for analysis. These results will be used to direct the decision to order blood and blood products in conjunction with the surgeon.

Regarding the ordering of blood products:

The usual practice regarding the ordering of blood and blood products happens during the pre-operative period the day before the scheduled surgery. A blood sample is sent to the South African National Blood Services (SANBS) with a form stating the possible need for blood and blood products on the day of the surgery. A request is made to have the patient's sample crossmatched and products kept on standby for ease of access once needed.

The decision to transfuse is currently based on physician discernment of the operative field, experience, and limited Standard Laboratory Tests (SLT) available (2, 4, 5). There is currently no clear point of care (POC) protocol in place to guide blood product use in cardiac surgery at Universitas hospital. There is thus a lack of accurate scientific evidence of coagulopathy patterns during cardiac surgery at our institution.

TEG® (thromboelastogram) is a POC device that evaluates various aspects of the coagulation cascade like clot formation, clot strength and fibrinolysis (1, 3, 6-8). Adding a TEG® guided algorithm to current clinical practice provides an additional focussed assessment, which may possibly reduce blood product use and potentially contribute to good patient outcome and financially to this institution and the Free State at large.

Literature done in Europe and America has shown superiority of POC haemostasis practice over standard laboratory testing (9-12). This applies to viscoelastic testing such at Thromboelastography.

This encouraged the question: Will a point of care visco-elastic protocol reduce intra- and early post-operative blood and blood product usage in patients undergoing cardiac surgery at UAH?

1.2 AIM

The aim of the study is to establish whether the use of a TEG® protocol versus physician decision will reduce blood product usage in adult patients undergoing open heart surgery at Universitas Academic Hospital in Bloemfontein, Free State.

1.3 METHODS

1.3.1 Study design

A comparative study will be performed.

C. The **physician decision group** will consist of a retrospective file review of the usual clinical practice.
D. The **TEG® protocol group** will consist of a prospective cohort of patients using the usual clinical practice with the addition of TEG®-based protocol.

1.3.2 SETTING

The study will be conducted at Universitas Academic Hospital, Bloemfontein. This is a tertiary training public hospital in the Free State, South Africa. Approximately 16 patients undergo cardiac surgery per month. We estimate that approximately 8-12 eligible cardiac cases may be done in a month. Physician decision group may accumulate these many cases per month. For the three-month period = 24-36 eligible cases.

TEG® protocol group may also include approximately 8-12 eligible cases, meaning 24-36 over the three months. An estimated total of 50 for the two groups combined would be acceptable. The two groups will be selected during identical time periods in two different years, June to September 2019 and June to September 2020.

Our focus however is on the duration of data collection and not so much the number of patients, meaning three months for each group (TEG® protocol group in 2020, and Physician decision group same period in 2019).

1.4 PARTICIPANT SELECTION

The study consists of two groups of participants:

E. For the **physician group**:
    - Patients operated between 24 June to 24 September 2019
    - Cases will be identified from the theatre register
    - Files will be retrieved from records.
F. For the **TEG® group**:
    - Patients operated between 24 June to 24 September 2020
    - Cases will be identified during the pre-operative assessment

1.5 LIGIBILITY

Applies to Physician and TEG® groups

1.5.1 Inclusion criteria

- Operated at Universitas Academic Hospital
- Age greater than 18 years
- First cardiac surgery
- No known bleeding tendency
- Elective cases
- Signed informed consent (for the post-intervention group)

1.5.2 Exclusion criteria

- Emergency cases
- Paediatric cardiac surgery
- Redo surgery

1.6 SAMPLING

G. For the **physician group:** All files which meet the inclusion and exclusion criteria as described will be included in the study.
H. For the **TEG® group**: All patients who meet the inclusion and exclusion criteria who are planned for cardiac surgery in the study period will be approached for inclusion in the study.

1.7 MEASUREMENT

The following data points will be collected:

- Sex
- Date of birth
- Pre-operative weight (kg)
- Pre-operative height (cm)
- Body Mass Index (will be calculated)
- Comorbidities (multiple answers)
  - Diabetes mellitus
  - Hypertension
  - Hypercholesterolaemia
  - Asthma
  - Thyroid disease
  - Other (specified)
- Indication for surgery (multiple answers):
  - Mitral valve repair
  - Tricuspid valve repair
  - Aortic valve repair
  - Pulmonary valve repair
  - Coronary artery bypass graft
  - Other (specified)
- Most recent pre-operative laboratory investigations:
  - Haemoglobin (g/dL), haematocrit (%), platelet count ($x10^9$/L), PT (sec), aPTT (sec), INR
- Blood products used intra-operatively and for the first 6 hours post-operatively (number of units)
  - Red cell concentrate (number of units)
  - Fresh frozen plasma (number of units)
  - Cryoprecipitate
  - Platelets (number of units includes pooled and single donor)
  - Cell salvage (ml)
- Haemostatic drugs used intra-operative
  - Tranexamic acid (intra-operative dose, mg)
  - Protamine (intra-operative dose, mg)
  - Bioplasma (intra-operative dose, ml)
  - Other haemostatic drugs administered intra-operatively (Generic name, dose, route)
- **For the TEG group: A two-point TEG® to be done**
  - Post-induction, pre-surgery TEG® (Baseline)
    - R time
    - K time
    - Alpha angle
    - Maximum amplitude
    - LY30
    - Action taken

- Post-operative TEG®, at 35 degrees Celsius rewarming
  - R time
  - K time
  - Alpha angle
  - Maximum amplitude
  - LY30
  - Action taken
- Together with the post-operative TEG® a PFA 100 (Platelet Function Assay) and Fibrinogen level will be drawn for each patient for complete assessment of coagulation profile.

1.8 DATA COLLECTION

Physician group:

After participants have been identified and selected for eligibility based on inclusion criteria, files will be retrieved from UAH records by the researcher, Dr JB Mogorosi. Data will be collected by the researcher from these patient files onto the electronic data form using the Research Electronic Data Capture (REDCap®) software (Section A of Appendix H). This will be done at Universitas Academic Hospital's filing department. Upon completion these data forms will be taken by the researcher to the office of the study supervisor Dr EW Turton, at the faculty of health sciences department of anaesthesiology for safe keeping until the time for analysis when the Biostatistics department will get involved.

The data form consists of two sections, section A and section B. Section A (A1-A4) will collect data for both Physician and TEG groups. Section B will collect data from TEG® group only.

TEG® group:

The researcher will request fellow anaesthesiology registrars who are assigned to the cardiothoracic theatre during data collection period to assist with data collection as per the data sheet. (Section B Appendix H). After eligibility has been confirmed through inclusion criteria the researcher and his fellow anaesthesiology registrars will draw the blood specimens for the baseline and post-operative TEG® evaluation from the participant. These will be handed over to the allocated perfusionist of the day who is also in theatre to take the specimen to the TEG® bench at the National Health Laboratory Services for testing within three minutes.

Other role-players are:

- *Medical technologist:* situated at the TEG® bench, will perform the TEG® according to standard operating procedure of the NHLS and communicate the results with the surgical team in theatre as soon as is available.
- *Cardiothoracic surgeon:* performs the cardiac surgery and gives input regarding the surgical procedure and its influence on coagulation.

1.9 LABORATORY METHODS

TEG® machine in use at NHLS haematology is the TEG® Thromboelastograph Haemostasis Analyzer system, 400 Wood Rd, Braintree, MA

1.10 PILOT STUDY

- Will be done by the researcher
- **Physician group**: Five (5) files will be selected, and data will be captured.

- **TEG® group**: A pilot of two (2) patients will be performed

If no changes are made to the data sheet, the data from the pilot will be included in the main study data.

1.11 STUDY PROCEDURE FOR TEG® GROUP

In addition to standard of care, a TEG® will be performed at two intervals: post induction, pre-surgery (baseline) and post operatively during rewarming of at least 35 degrees Celsius including a PFA 100 and Fibrinogen for each patient.

TEG ® report will be communicated to the cardiothoracic surgeon and anaesthetist as soon as the result is available.

1.12 MEASUREMENT AND METHODOLOGICAL ERRORS

- Missing data from physician group: The researcher will use the available data for analysis
- Missing data from TEG group: The researcher will use the available data for analysis

1.13 STATISTICAL ANALYSIS

Data will be summarised by frequencies and percentages (categorical variables), means and standard deviations or medians and percentiles (numerical variables). Subgroups will be compared using 95% confidence intervals for differences for differences in means or medians. Appropriate statistical testing (t-test, Mann-Whitney, or Chi-squared test) will be performed at 5% significance level.

The Department of Biostatistics from the Faculty of Health Sciences, University of Free State will perform the statistical analysis.

1.14 TIME SCHEDULE

The study will be conducted over a period of four to six months as soon as the necessary approval has been obtained after which the data forms will be submitted for analysis.

i. Protocol submission to Free State Department of Health (FSDOH) and Health Sciences Research Ethics Committee of Free State University (HSREC) (06 January 2020-31 March 2020)
ii. Pilot study (24-25 June 2020, 2 days)
iii. Data collection (29 June-30 September 2020, 3 months)
iv. Data analysis (25 September-25 October 2020, 4 weeks)
v. Writing (26 October-23 November 2020, 4 weeks)
vi. Submission (30 November 2020)

1.15 BUDGET

Item	**Cost**
Stationery	R400.00
TEG® (R244*2*25)	R12200.00
PFA 100 (R200*25)	R5000.00
Fibrinogen (R36*25)	R900.00
Total cost	**R18500.00**

Funding will be applied for from the research committee for the project. If no funding is obtained from the committee, the anaesthetic department will provide funding.

1.16 ETHICS ASPECTS

This study is subject to approval by the Free State Department of Health and the Health Sciences Research Ethics Committee of the University of the Free State.

Permission will be obtained to perform the study from the Heads of Department the following departments:

- Cardiothoracic surgery
- Haematology
- Head of the School of Clinical Medicine
- Head of the School of Pathology

Informed consent for participation in the study will be obtained, and available in English, Afrikaans, and Sesotho.

All data will be managed confidentially.

1.17 CONFLICT OF INTEREST

None to declare.

APPENDIX G

DATA COLLECTION FORM

SECTION A1: Baseline clinical data

Record ID	_____
Procedure date	_____
Sex	○ Female ○ Male ○ Unknown
Participant date of birth	_____
Pre-op weight (kg)	_____
Pre-op height (m correct to 2 decimal places)	_____
Body mass index	_____
Comorbidities (more than one option may be selected)	☐ Diabetes mellitus ☐ Hypertension ☐ Hypercholesterolaemia ☐ Asthma ☐ Thyroid disease ☐ Other ☐ None
If other, please specify	_____
Indication for surgery (more than one answer is allowed)	☐ Mitral valve repair ☐ Tricuspid valve repair ☐ Aortic valve repair ☐ Pulmonary valve repair ☐ Coronary artery bypass graft ☐ Other
If indication was "other", please specify	_____

This section pertains to pre-operative medication that may affect haemostasis.

Were any of the following drugs prescribed and used in the 30 days preceding surgery.
More than one may be selected if appropriate

- ☐ Aspirin
- ☐ Clopidogrel
- ☐ Warfarin
- ☐ Enoxaparin
- ☐ Heparin (UF)
- ☐ Dabigatran
- ☐ Rivaroxaban
- ☐ Other
- ☐ None

Please note the last date that asprin was used preceding surgery. _____

Please note the last date that clopidogrel was used preceding surgery. _____

Please note the last date that warfarin was used preceding surgery. _____

Please note the last date that enoxaparin was used preceding surgery. _____

Please note the last date that UF heparin was used preceding surgery. _____

Please note the last date that dabigatran was used preceding surgery. _____

Please note the last date that rivaroxaban was used preceding surgery. _____

Please list other drugs used in the 30 days preceding surgery that may affect haemostasis.

Please report as follows: drug name, dose, frequency, route. _____

Did the patient take any of the following drugs/pharmaceuticals that may affect coagulation in the WEEK preceding surgery?

- ☐ Garlic as a supplement/pharmaceutical
- ☐ Ginger as a supplement/pharmaceutical
- ☐ Tumeric as a supplement/pharmaceutical
- ☐ Vitamin E as a supplement/pharmaceutical
- ☐ Cayenne peppers as a supplement/pharmaceutical
- ☐ Other drugs/pharmaceuticals that may affect coagulation
- ☐ None

Please note other supplements that may have affected coagulation in the week preceding surgery _____

SECTION A2: Baseline laboratory data

Pre-op Hb (g/dL)	_____
Pre-op haematocrit (%)	_____
Pre-op platelet count (x10^9/L)	_____
Pre-op PT (sec)	_____
Pre-op aPTT (sec)	_____
Pre-op INR	_____
Activated clotting time (ACT) prior to heparin (sec)	_____
Activated clotting time (ACT) after protamine (sec)	_____

SECTION A3: Blood product use

In this section, only mention blood products that were used in the intra-operative period and for the first 6-hours post-op	
Cell salvage volume transfused (ml)	_____
Number of units of red cell concentrate (RCC)	_____
Number of units of fresh frozen plasma (FFP)	_____
Number of units of cryoprecipitate (Cryo)	_____
Number of units of platelets (includes pooled and single donor platelets)	_____

SECTION A4: Haemostatic drugs

Total intra-operative dose of tranexamic acid (cyklokapron) (mg)	_____
Total intraoperative heparin dose (IU)	_____
Total intra-operative dose of protamine sulphate (mg)	_____
Total intra-operative volume of bioplasma (freeze dried plasma) (ml)	_____
Mention other haemostatic drugs administered intra-operatively. Generic name - dose - route	_____

SECTION B: TEG intervention

Was a TEG performed on this patient
○ Yes
○ No

Post-induction, pre-surgery TEG

R-time (minutes)
_____
(Reaction time)

K-time (minuters)
_____

Alpha angle (degrees)
_____

Maximum amplitude (mm)
_____

Clot stability (LY30) (%)
_____

Laboratory TEG comment
_____

Action taken in response to TEG
_____

Post-operative TEG, with rewarming to 35 degrees celsius

R-time (minutes)
_____
(Reaction time)

K-time (minuters)
_____

Alpha angle (degrees)
_____

Maximum amplitude (mm)
_____

Clot stability (LY30) (%)
_____

Laboratory TEG comment
_____

Action taken in response to TEG
_____

PFA and Fibrinogen

PFA: Col/Epi

_____

PFA: Col/ ADP

_____

Fibrinogen

_____

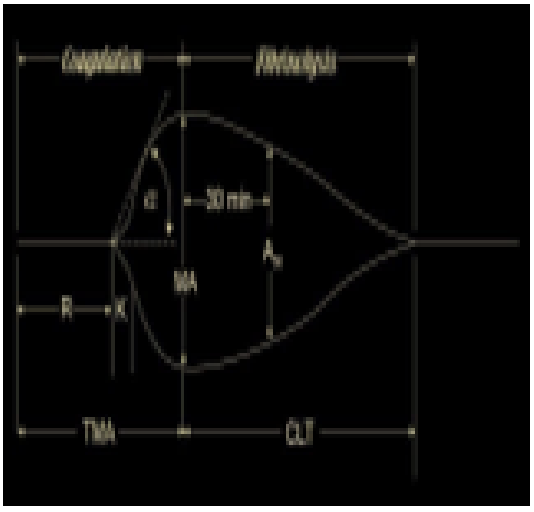
APPENDIX H

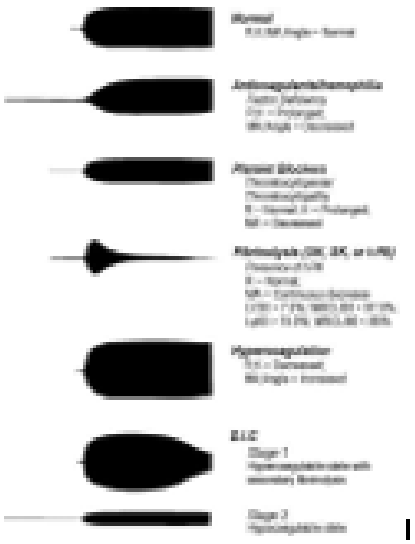
TEG PROTOCOL

Clinical Interpretation of TEG Results as Recommended by Manufacturer

1. TEG (Baseline and Post Protamine): May need additional TEGs if patient continues to bleed.

TEG Result	Haemostasis State	Recommended Treatment
Reaction time (R value) <4 minutes	Enzymatic hypercoagulability	Anticoagulant
11–14 minutes	Low clotting factors	2-4 U of FFP
>14 minutes	Very low clotting factors	4-6 U of FFP
K time 1-4 minutes	Fibrin cross link reach 20mm	If increased- 0.05 U/kg cryoprecipitate
Angle <45degrees	Low fibrinogen level	0.05 U/kg cryoprecipitate
Maximal amplitude 46–54 mm	Low platelet function	0.3 mg/kg DDAVP
41–45 mm	Very low platelet function	1 U of platelet pheresis
<40 mm	Extremely low platelet function	2 U of platelet pheresis
>73 mm	Platelet hypercoagulability	Antiplatelet therapy
LY30 0-8%	Fibrinolysis at 30minutes	If increased- Antifibrinolytic





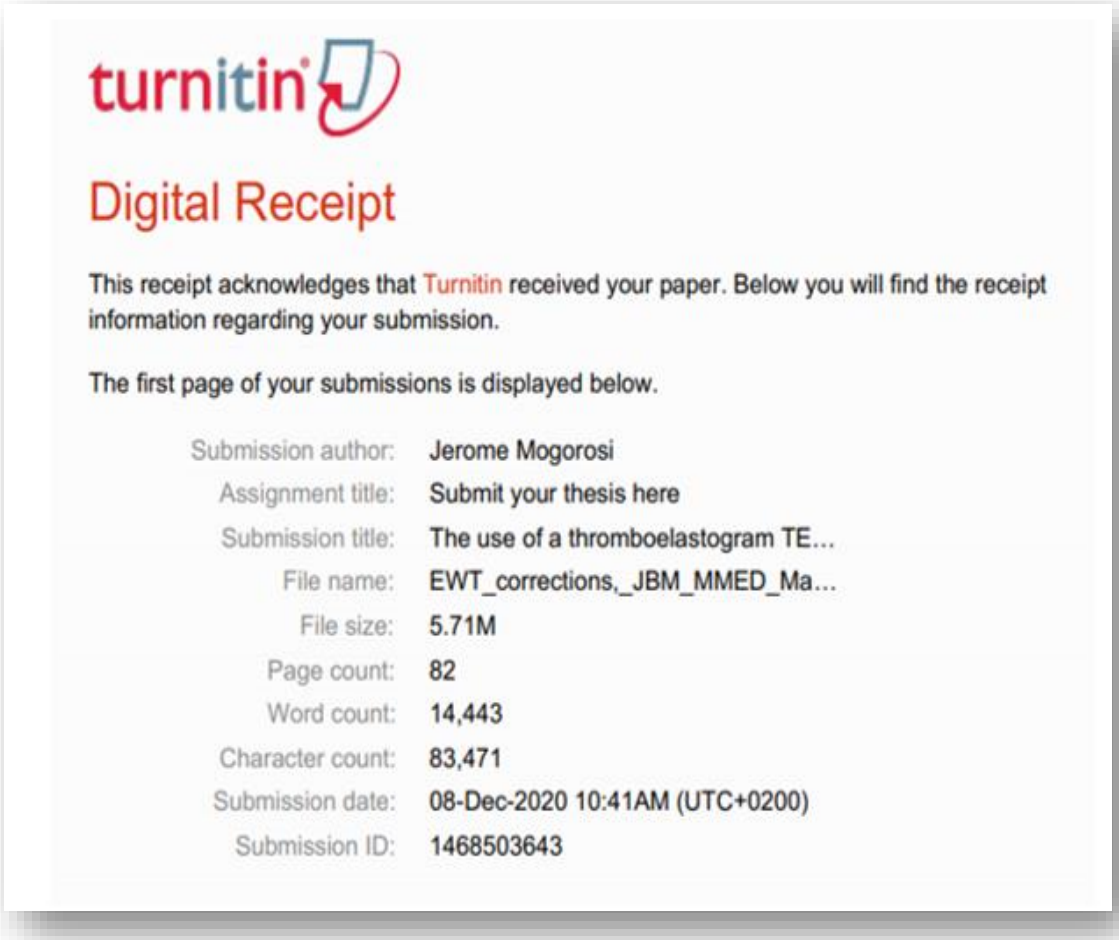
2. PFA 100 (with Post Protamine TEG)

3. Fibrinogen level (with post Protamine TEG)

JB Mogensi, EW Tarton

APPENDIX I

TURNITIN PLAGIARISM REPORT



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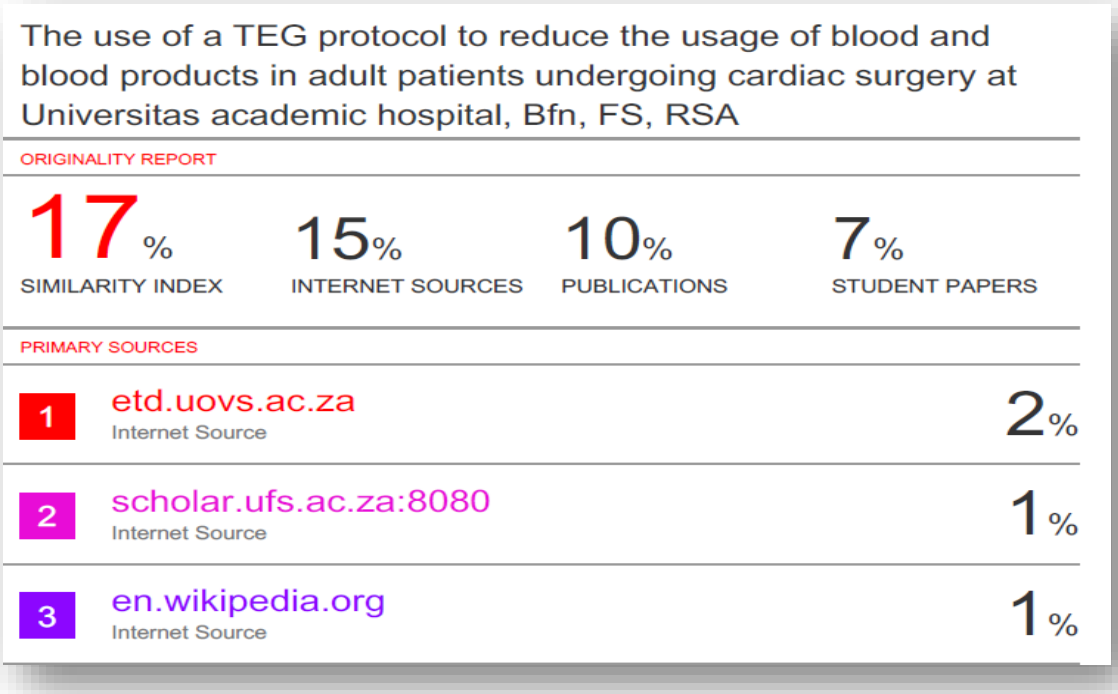

The use of a TEG protocol to reduce the usage of blood and blood products in adult patients undergoing cardiac surgery at Universitas academic hospital, Bfn, FS, RSA

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APPENDIX J: INSTRUCTIONS TO AUTHORS OF THE SAJAA

Author Guidelines

Submitted manuscripts that are not in the correct format and without the required supporting documentation specified in these guidelines will be returned to the author(s) for correction and will delay publication.

AUTHORSHIP

Named authors must consent to publication **by signing a covering letter** which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;
(ii) drafting or critical revision for important intellectual content; and
(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**); and
(iv) exact contribution of each author must be stated.

DECLARATION OF CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute a conflict of interest. If there is no conflict of interest to declare please include the following statement: The authors declare no conflict of interest.

FUNDING SOURCE

All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated as follows: No funding source to be declared.

RESEARCH ETHICS COMMITTEE APPROVAL

The submitting author must provide written confirmation of Research Ethics Committee approval for all studies including case reports. The ethics committee as well as the approval number should be included.

STATISTICAL ANALYSIS

Authors are advised to involve medical statisticians at the protocol stage of their research project: to plan sample size, and the selection of appropriate statistical tests for analysis and presentation.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

CATEGORIES OF SUBMISSIONS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles

Original articles on research relevant to anaesthesia and analgesia should not exceed 3 200 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 300 words.

Clinical Review articles

Review articles relevant to anaesthesia and analgesia should not exceed 2 400 words, with a maximum of 20 references and no more than 6 tables or figures. A summary of 300 words or less is required.

Case reports
Case reports should not exceed 1 800 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version.

Scientific Letters
Scientific Letters should not exceed 2 400 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings, Background, Methods, Results, and Conclusions, is a requirement and should not exceed 250 words.

Letters to the editor
Letters to the editor should be 800 words or less with only one image or table.

MANUSCRIPT PREPARATION
Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details
This information must be provided for ALL authors and must be submitted as a supplementary file.
Email addresses of all author must be provided.
ORCID number of **ALL** authors must be provided – if authors do not have ORCID, please register at https://orcid.org/

Abbreviations
All abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements
Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age) should also be preceded by a space e.g. > 20 years. No spaces should precede ± and °, i.e. '35±6' and '19°C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting
The manuscript must be in Microsoft Word or RTF document format. Text must be 1,5-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, except for Tables). *The manuscript must be free of track changes.*

Disclaimers should follow the Conclusion and it should be in the following order: Acknowledgements, Declaration conflict of interest, Funding source, Ethics declaration and ORCID.

ILLUSTRATIONS AND TABLES
If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file **and** provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes, tabs or enters) and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Figure 1)'. Figure legends: Figure 1: 'Title...'. All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is

preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft PowerPoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists may be generated with the use of reference manager software, but the final document must be delinked from the reference database or otherwise generated manually. Citations should be inserted in the text as superscript, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] The superscript reference number should come after the punctuation mark and should not be in brackets.

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first four names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by **CrossRef**. Crossref DOIs should always be displayed as a full URL link in the form https://doi.org/10.xxxx/xxxxx

Journal references:

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