



University of Cape Town

Department of Surgery

**THE IMPACT OF THROMBOELASTOGRAPHY ON PATIENTS WITH
PENETRATING ABDOMINAL TRAUMA REQUIRING INTENSIVE CARE**

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DECLARATION

I, Matthew Ross Hannington, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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ABBREVIATIONS

ATLS	Advanced Trauma Life Support
CCA	Conventional coagulation assay
CD	Clavien-Dindo
Cryo	Cryoprecipitate
DCL	Damage control laparotomy
FFP	Fresh frozen plasma
GCS	Glasgow Coma Scale
GSH	Groote Schuur Hospital
GSW	Gunshot wounds
HG	High grade
ICU	Intensive care unit
ISS	Injury Severity Score
LOS	Length of stay
PATI	Penetrating Abdominal Trauma Index
RCC	Red cell concentrate
TEG	Thromboelastography
TIC	Trauma induced coagulopathy
TRISS	Trauma Injury Severity Score
VEA	Viscoelastic Assay
VTE	Venous thromboembolism

ABSTRACT

Background

Trauma induced coagulopathy is a complex multifaceted process which contributes to higher mortality rates in severely injured trauma patients. Thromboelastography (TEG) is an effective test to detect TIC which assists in instituting goal directed therapy as part of damage control resuscitation.

Methods

This retrospective study included all adult patients over a 36-month period with penetrating abdominal trauma who required a laparotomy, blood product transfusion and admission for critical care. Analysis included: demographics, admission data, 24-hour interventions, TEG parameters and 30-day outcomes.

Results

Eighty-four patients with a median age of 28 years were included. The majority (93%) suffered from a gunshot injury with 75% receiving a damage control laparotomy. Forty-eight patients (57%) had a TEG. Injury Severity Score and total fluid & blood product administered in the first 24 hours were all significantly higher in patients that had a TEG ($p < 0.05$). TEG profiles were: 42% normal, 42% hypocoagulable, 12% hypercoagulable and 4% mixed parameters. Fibrinolysis profiles were: 48% normal, 44% fibrinolysis shutdown and 8% hyperfibrinolysis. Mortality rate was 5% at 24 hours and 26% at 30 days, with no difference between the two groups. High grade complication rates, days on a ventilator and intensive care unit length of stay were all significantly higher in patients who did not have a TEG.

Conclusion

Trauma induced coagulopathy is common in severely injured penetrating trauma patients. The usage of a thromboelastogram did not impact on 24-hour or 30-day mortality but did result in a decreased intensive care stay and a decreased high grade complication rate.

LITERATURE REVIEW

1. INTRODUCTION

Trauma is a leading cause of death worldwide accounting for 8% of all deaths, with an estimated 4.4 million deaths annually. Ninety percent of these deaths are said to be in low and middle-income countries, such as South Africa. [1] Groote Schuur Hospital (GSH) is the academic hospital of the University of Cape Town and serves as a tertiary referral centre in the Western Cape Province of South Africa. The Trauma Unit manages approximately 10 000 patients per year and is amongst the busiest Trauma Units world over. [2] A disproportionate number of trauma cases presenting to this Unit are due to penetrating trauma.

Uncontrolled exsanguinating haemorrhage is the leading cause of potentially preventable mortality in trauma patients, with rates of up to 40% of trauma related deaths due to haemorrhage. [3–5] Globally approximately 1.5 million deaths are attributable to uncontrolled haemorrhage with 75 million years of life lost. [6] The modern trauma literature has shown that the majority of early haemorrhage-related deaths in trauma occur in the first 2-3 hours. [5, 7] Despite a better understanding of trauma induced coagulopathy (TIC), as well as more tailored treatment, the high rate of haemorrhage related mortality remain. [8, 9]

The presentation and diagnosis of trauma induced coagulopathy varies widely. It can be challenging to assess clinically and address appropriately. One of the tools utilised to assist to evaluate TIC is viscoelastic assays (VEA) such as thromboelastography (TEG). Studies have shown that TEG may more accurately diagnose TIC than other conventional measures which assist in guiding appropriate management. [10–12] As evolving evidence is demonstrating that

the use of viscoelastic assays (VEA) may improve outcome, it is essential that their use is adopted and optimized for management of severely injured trauma patients. [9, 13]

2. HISTORICAL PERSPECTIVE

Despite the advances in modern medicine there is still a significant proportion of trauma patients that succumb to their injuries. A recent report of a large population-based study found that most trauma related deaths still occur in the first 24 hours. This is likely as a result of either injuries that are not survivable or access to prompt appropriate medical attention not being immediately available. [14]

The understanding of the fundamental factors that contribute to coagulopathy in trauma have been known for decades. [8, 15] However, a more intricate understanding of the clotting process has led to more directed tests and therapies being utilized. [16] These ultimately act to avoid the consequences of the lethal triad of coagulopathy, hypothermia and acidosis. [8, 15] Trauma management was revolutionized decades ago by the Advanced Trauma Life Support[®] system. This together with the advent of damage control surgery and damage control resuscitation aimed to arrest the vicious cycle of the lethal triad. [8] Traditionally this encouraged infusion of clear resuscitative fluids immediately to restore intravascular volume. This technique has been criticized recently as it was noted that this empirical technique to fluid management may worsen hypothermia, coagulopathy and acidosis. [8, 13]

As the understanding of the clotting process has improved, a search for optimal coagulation assays was needed in order to convert this theoretical knowledge into clinical practice. [16] The cell-based understanding of haemostasis, which emphasizes the importance of platelets

and tissue factor, challenges the fundamentals that the conventional coagulation tests is based on and has led to more interest for the use of VEA. [8, 16] This model describes initiation, amplification and propagation of clotting that are overlapping events regulated by cell surfaces. [8] VEA has historically been used successfully in liver transplant and cardiac surgery, with their use in trauma only more recently being adopted. The benefits notably being: assisting in diagnosing TIC and guiding resuscitation especially during massive transfusions. [17]

3. TRAUMA INDUCED COAGULOPATHY

3.1. ALTERED COAGULATION

Trauma induced haemorrhage often produces a triad of acidosis, hypothermia, and coagulopathy. This complicates further resuscitation and control of ongoing haemorrhage. [3, 8, 10] The combination of shock and tissue injury result in failure of the normal haemostatic mechanisms.[8] Trauma induced coagulopathy, also known as Acute Coagulopathy of Trauma or Coagulopathy of Trauma, is a complex multifaceted process. It is defined by reduced clot strength with altered fibrinolysis in response to a traumatic insult. [11, 13, 18] It is a multifaceted physiological and molecular aberration which may have distinct clinical implications. [8] It is important to understand that a variety of different coagulopathies fall under the broad term of TIC. [8, 13]

Following severe trauma about 25-35% of patients present to the hospital with TIC. [4, 8, 11, 18] This has been shown to be associated with increased blood product transfusions, multi-organ failure, and death. [3, 8] Hypocoagulability which can more simply be described as inadequate formation of a stable clot or accelerated breakdown of clots that have formed or are

forming. This is the most common form of TIC and is associated with four fold higher mortality than a normal profile. [13] As the injury severity score (ISS) increases the incidence of hypocoagulability increases significantly. With this there is an associated increased risk of a massive blood transfusion as well as an increased risk of death. [12]

A state of hypercoagulability appears to be a normal response to injury due to the platelet and cellular response to damaged tissue. This is largely mediated by exposure to tissue factor which can lead to vasoconstriction and release of: epinephrine, thromboxane, serotonin and other local mediators. [12] Pathological hypercoagulability, is the result of uncontrolled clot formation or dampened fibrinolysis, also known as “fibrinolysis shutdown”. [13] VEA’s have been able to detect this phenomenon which was largely unrecognized with use of conventional coagulation assays (CCA). [13] This has assisted in understanding hypercoagulable states which may be advantageous as well as deleterious in the setting of haemorrhage. This appears to be a very common finding with as much as 50% of trauma patients presenting with this finding. [13] A study evaluating the TEG’s of 2540 severely injured patients found that hypercoagulability is the most common phenotype of coagulopathy, being found in 38% of patients. It was associated with a higher mortality when compared to patients with normal TEG parameters. A higher proportion of deaths in this group were attributed to: traumatic brain injury, septic complications, thrombotic complications and organ failure. [19] A prospective study by Branco et al. assessing serial TEGs on high level trauma activations found that 26% were hypercoagulable on admission. These patients required less crystalloid and blood products and had an improved 24 hour and 7-day mortality compared to patients with normal or hypocoagulable TEG parameters. This study however showed no difference in need for surgical intervention or ICU & hospital length of stay. [12]

3.2. DYSREGULATED FIBRINOLYSIS

Regulated fibrinolysis is a vital component of the coagulation process following injury. The local effects of hypercoagulability at the site of injury are thought to activate the fibrinolytic system to function systemically to prevent uncontrolled thrombosis distant from the site of injury. Both hyperfibrinolysis as well as fibrinolysis shutdown have been implicated in higher mortality rates in the trauma population. [8] Although fibrinolysis shutdown may be advantageous in some patients its effects have been associated with an increase in mortality rates in severely injured trauma patients. [18, 20, 21]

The abnormalities at a cellular level can be very subtle and difficult to assess clinically. In addition to this the treatment for these specific abnormalities may be vastly different with potentially dramatic clinical consequences. For example, antifibrinolytics such as tranexamic acid (TXA) is beneficial for hyperfibrinolysis. Anticoagulants such as low molecular weight or unfractionated heparin may be necessary in a state of fibrinolysis shutdown.[13] Incorrect use of these drugs in a trauma patient could lead to potentially fatal consequences. In a trauma patient balancing the risk of further bleeding against the consequences of uncontrolled harmful clotting may be a very difficult decision. One which may be impossible to make without the information of a VEA. [13, 20]

The ideal response following trauma is to establish a balance of arresting ongoing haemorrhage without causing detrimental thrombosis. [19] This, however, is not always the case and may result in a mix of hypercoagulability and hypocoagulability being present in a patient presenting following trauma. This is a result of a combination of tissue injury and a state of shock working in contradictory mechanisms. [8, 19] This initial mixed state often transitions

to a hypercoagulable state in the next 48 hours following trauma. This has shown to worsen outcomes and may not be possible to be completely pharmacologically corrected with heparin. [19]

4. CONVENTIONAL COAGULATION ASSAYS

Prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen and platelet count, are the traditional routine plasma-based coagulation tests used to monitor coagulation. These conventional tests only indicate the initiation of the clotting process. [3, 17, 22] Clot formation composes of primary and secondary haemostasis. Primary haemostasis involves platelet aggregation and secondary haemostasis involves clotting factor functioning to form fibrin. Traditionally measures of platelet aggregation and fibrinogen were used as surrogates of primary haemostasis with PT and aPTT used to demonstrate secondary haemostasis. [13]

There are several practical and theoretical shortcomings of CCA's. These include: (1) Plasma based tests are not conducted on whole blood and thus don't take into account cellular components of coagulation which is now known to be at the core of the process of coagulation. [13, 16]; (2) long turnaround time, which is approximately 45 to 60 minutes, this is in contrast to TEG's which have certain values available within minutes and provides an ongoing real time monitoring as the process of clot development progresses [13, 17]; (3) CCA's provide a value in the form of time, but do not supply any information about which specific deficiency in clotting the patient has; (4) the process of fibrinolysis is not assessed which is vital in understanding the full clotting status of a patient. [13] As a result these tests have a limited ability to diagnose early coagulopathy and thus guide treatment. [16]

A randomised control trial (RCT) comparing massive transfusions guided by TEG vs CCA's in severely injured trauma patients revealed that there was a significant survival benefit to utilizing the former. [4] This RCT is supported by many observational studies that show either no difference or poorer predictive value of CCA's in predicting mortality or transfusion requirements. [23, 24]

The ability of TEGs to assess hypercoagulability appears to be vastly superior to CCA with one study demonstrating that 26% of patients presenting with a hypercoagulable TEG demonstrated completely normal CCA. In addition to the 12% of patients who developed hypocoagulability, none demonstrated abnormal CCA which highlighted the inability of CCA to assess a subtly changing coagulation profile. [12]

5. VISCOELASTIC ASSAYS

Thromboelastography (TEG) and thromboelastometry (ROTEM) are viscoelastic assays. They are performed on whole blood and reflect the status of the complete haemostatic process. [3, 13, 16] The TEG was established in 1948. [17] It provides a graphic representation of the clotting process. This graphic shows the entire process from initiation of the clotting cascade through to fibrinolysis.[10, 13, 16, 23]

It comprises a number of measurements including: reaction time (R-time) from the start until thrombus formation begins; α -angle representing the increase in clot strength; the maximum amplitude (MA) is the highest point of the curve and indicates maximal clot strength; Ly-30 displays fibrinolysis in the first 30minutes after MA. [3, 4, 13, 17] These values together with knowledge of the cell-based theory of haemostasis assist in identifying which blood

constituents are best represented for each value. The R-time reflects coagulation factor activity, the α -angle represents fibrin polymerization and propagation of the clot. K-time is another less utilized parameter in the literature, which also indicates propagation of the clot and may be interpreted with the α -angle. [23] The clot strength as measured by the MA is due to fibrin crosslinking and Ly-30 representative of the process of fibrinolysis. [13, 17]

There are several different TEG systems available depending on the manufacturer. An example of a traditional TEG system, is the TEG 5000. A cup containing 360 μ L of whole blood is in contact with a suspended pin on a torsion wire. The cup then oscillates at 0.1Hz around the pin. Clot formation causes resistance to movement which produces torque. This is recognised by an electromagnetic transducer and gives a graphic tracing. [13, 17] Activators including kaolin, tissue factor and phospholipids can be added to speed up results. This is the “kaolin TEG”, “Rapid-TEG” or “R-TEG”. [13] The reference ranges for bleeding trauma patients may be significantly different from treatment thresholds suggested by manufacturers of TEG machines with suggestion that development of local reference ranges being most prudent. [17, 19] Rotational thromboelastometry functions in a similar manner to TEG but in an inverse manner. A static pin is suspended into a cup which then rotates around the pin. The tracing achieved is similar to a TEG with variation in the names of the parameters. [13] The full details of this are beyond the scope of this paper as TEG was used.

Barriers to the widespread usage of TEG is the initial cost of the equipment. Once this is acquired the cost to conduct a TEG is equivalent to CCA and with new evidence suggesting the decreased usage of blood products and better outcomes associated with its use, there may be an argument that it is more cost effective in the long-run. [17]

5.1. CLINICAL APPLICATION OF VEA

The trauma literature has shown TEGs to provide a quick and accurate diagnosis of trauma-induced coagulopathy. [8, 13] It helps predict the need for blood product transfusion and assists as a major component in guiding goal directed resuscitation. [10, 25] TEGs can also provide the clinician with rapid real time information, often in a more comprehensive manner than CCAs. [10] A systematic review of fifty-five studies concluded that the use of TEG/ROTEM tests assist to diagnose early TIC and may predict transfusion requirements and death. The review however failed to show clearly that their use had a positive benefit on mortality or blood product usage. [16]

TEG based resuscitation in a RCT by Gonzalez et al. demonstrated a significant 50% decrease in mortality compared to CCA guided resuscitation (28-day mortality). This study showed that TEG guided resuscitation utilised less plasma and platelet transfusions in the first several hours (six hours) and less cryoprecipitate overall. This notion supports the judicious use of blood products, which is specifically directed to certain deficiencies, while maintaining the benefits. The mortality benefit was specifically shown to hold true in haemorrhage-related and early deaths (less than six hours). The study also demonstrated that the amount of blood products at 24 hours did not differ and therefore mortality benefit may not be in the amount of blood product given but rather administering the appropriate product at the appropriate time. [4]

i) Emergency Department/Pre-Operative

Ideal timing of conducting a TEG is not well established with different literature advocating on admission, during resuscitation or after a certain number of blood products. In addition the

specific patient population and frequency of testing is unclear. [13] A favourable approach may be to acquire a baseline admission TEG and then a repeat following initial resuscitation or if signs of coagulopathy is detected clinically. [17] As VEAs have a rapid turn around time and can impact in almost real time the management of bleeding trauma patients, it is important to recognise on initial assessment which patients may benefit from a VEA. [13]

Mechanism of injury that are associated with a significant risk of severe injury or objective signs of ongoing haemorrhage are broadly speaking the indications to get an early VEA. This depends on resource availability and may differ within each trauma unit. [13] Tachycardia and hypotension can be used as screening tools, because when present in trauma patients suggest high risk of haemorrhage. Specific triggers for heart rate (HR) and systolic blood pressure (SBP) have been suggested to predict ongoing bleeding. However, the shock index (SI), calculated as HR divided by SBP may be utilised to foresee the need for a massive transfusion (MT). A value ≥ 1 being the value used. [13] Other parameters available in the initial stages which could guide who gets a VEA are: Hb ≤ 11 g/dL, pH < 7.25 , base deficit > 5 and temperature < 35.5 C. [13, 26] Mechanism of injury and suspected or known injuries can also trigger the acquisition of a VEA. These may include but are not limited to: head trauma, solid organ injury such as liver injury or pelvic fracture for example. [13] Penetrating mechanism of injury in a combat setting was also shown to be a predictor for need of massive transfusion. [26] This has not however been shown in civilian trauma, and whether penetrating mechanism should trigger the use of a VEA, is debatable.

ii) Operating Theatre

The use of VEA intra-operatively has mainly been used in the arena of cardiac and liver surgery. Their use has been associated with: lower blood product use, reduced massive transfusion rates and a reduction in complications including mortality. [13] Until the results of a TEG are available standard management of haemorrhage with transfusion of products in a 1:1:1 ratio or whole blood during a trauma procedure is appropriate. [13]

The process of control of haemorrhage, resuscitation and re-evaluation is dynamic in a severely injured trauma patient. This is arguably most dynamic in a theatre setting and thus the use of TEG and the serial re-evaluation should be done in an individualised manner. There has been no literature describing a specific protocol for timing of repeating TEG's during a trauma operation. However, control of surgical bleeding and adequate resuscitation to specific goals may obviate the need for ongoing TEGs. [13]

iii) Post-Operative And ICU

The post-operative phase of care shifts from a purely haemostasis focus to balancing haemostasis and pathological thrombosis in the form of venous thromboembolism (VTE). This is of concern in a severely injured trauma patient who is at considerable risk due to several factors which contribute to a high rate of venous thromboembolism. A hypercoagulable state in response to injury as well as fibrinolysis shutdown can contribute to microvascular thrombosis. This has been implicated as a contributor to organ failure and delayed mortality associated with major trauma. [13, 20, 21] VEA have been shown to be able to detect hypercoagulable states more reliably than CCA.[13] This would then assist in supporting the

use of prophylactic and sometimes even therapeutic anticoagulation for patients at high risk of venous thromboembolism (VTE).

6. DAMAGE CONTROL RESUSCITATION

The core fundamentals of management of haemorrhage are: mechanical control of bleeding, resuscitation and focused management of TIC. [13] There are several methods for mechanical control of haemorrhage in a trauma setting. These may include but are not limited to: direct pressure, tourniquet use, surgical control and newer methods including resuscitative balloon occlusion of the aorta. [13]

The concept of damage control resuscitation was established to target restoring homeostasis by amongst others: restoring intravascular volume deficits; addressing trauma-induced coagulopathy, avoidance of dilutional coagulopathy; encouraging endothelial repair; and maintaining the body's oxygen carrying capacity. [5] This practice is well established and centres on early transfusion of red blood cells, plasma, and platelets. It is combined with early surgical control of bleeding. [10, 13] The definition may be broadened to include: minimizing administration of crystalloid fluids, preventing and rapidly correcting coagulopathy and early use of blood products in a balanced proportion.[5, 17] Traditional measures to counter hypothermia and acidosis while allowing permissive hypotension until definitive control of haemorrhage is attained is also fundamental to damage control resuscitation. [13]

The decision to transfuse blood products is often made clinically or empirically in the emergency unit or theatre because of the absence of a fast, reliable measure of a patient's

coagulation status. [23] The TEG is arguably the most reliable, complete, and fastest way to assess this in the trauma setting.

Damage control surgery is part of damage control resuscitation and involves an abbreviated surgical technique in patients whose physiological state is threatening their survival. [27, 28] The high mortality rates of 50% associated with damage control surgery as reported at the turn of the century have improved. [28] A more recent local study reported a mortality of 27% associated with damage control surgery. [27] These rates are likely to improve with the adoption of VEA guided damage control resuscitation principles.

6.1. MASSIVE BLOOD TRANSFUSION

The most severely injured trauma patients may require a massive transfusion, traditionally defined as ten or more units of red cell concentrate in a 24-hour period [10, 12], although there is no unanimous decision for the definition of a massive blood transfusion. [22] Recommended ratios of blood products for massive transfusions have been established in large trials and have generally been accepted as a 1:1:1 or 1:1:2 ratio of plasma, platelets, red blood cells. [5, 7]. Although this ratio appears desirable it is rarely achieved in developing countries due to limited supply of these blood products. [22] A massive transfusion protocol (MTP) has been shown in the literature to improve mortality as a result of a more balanced administration of blood products, administered in a more timely fashion. [10] This is usually an institutionally based protocol that attempts to prioritize coagulopathy correction by systematically providing blood products timeously to a patient's bedside. MTPs have now become standard of care in major trauma centres. [4] There has been a significant decrease in mortality rates associated with massive transfusions over the past 40-50 years. This can largely be attributed to the plasma

utilisation, which has proven to improve mortality due to haemorrhage in trauma patients. [10] Traditionally CCA's were used to help guide massive transfusion protocols. These have more recently been substituted for an alternate approach with viscoelastic tests guiding a goal-directed transfusion administration approach. [4] In massively bleeding patients the use of TEG to guide transfusion has been shown to decrease peri-operative haemorrhage, transfusion requirements and mortality. [3, 4]

Although the generally accepted ratio of blood products for massive transfusion is 1:1:1 there has been some reports that a reduced ratio of 1:2 (RBC:Plasma) and 1:3 had a better prediction value for mortality. [10, 29] A large, randomized trial comparing the ratios of 1:1:1 (platelets:plasma:RBC's) vs 1:1:2 showed an improvement in early death and haemorrhage-related death. It however, showed no superiority in improving 30day mortality. [5] In addition, a study from Davenport et al. indicated that the benefit of an increased ratio closer to 1:1 is likely only beneficial in patients who are actually coagulopathic. [10, 30] It remains uncertain at what exact time or point in resuscitation that the high ratios of RBC:plasma loses its benefit. [4] Consideration that these unguided ratios don't consider a patient's distinctive coagulation profile could lead to unnecessary use of blood products with its associated negative cost and adverse effects. [17] This highlights that a TEG guided transfusion practice, in addition to being more beneficial, is also more likely to prevent potential waste of precious blood products. [10] As TEGs have a rapid turnaround time this may assist in decreasing the administration of FFP with its associated expense and adverse effects. [16]

The management of severely injured trauma patients has evolved substantially over the last few decades. Damage control resuscitation including damage control surgery and massive transfusion protocols have given patients with previously dismal prognoses an improved

chance of survival. Together with this, the vastly improved understanding of the coagulation process and advent of viscoelastic assays now mean that detection of trauma induced coagulopathy can be more reliably detected with more goal directed therapy instituted. However, the literature, particularly with regards to penetrating trauma is still in its infancy with more high-level evidence needed to answer some of the unanswered questions in this ever-evolving field.

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PUBLICATION READY MANUSCRIPT

THE IMPACT OF THROMBOELASTOGRAPHY ON PATIENTS WITH PENETRATING ABDOMINAL TRAUMA REQUIRING INTENSIVE CARE

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ABSTRACT

Background

Trauma induced coagulopathy (TIC) is a complex multifaceted process which contributes to higher mortality rates in severely injured trauma patients. Thromboelastography (TEG) is an effective test to detect TIC which assists in instituting goal directed therapy as part of damage control resuscitation.

Methods

This retrospective study included all adult patients over a 36-month period with penetrating abdominal trauma who required a laparotomy, blood product transfusion and admission for critical care. Analysis included: demographics, admission data, 24-hour interventions, TEG parameters and 30-day outcomes.

Results

Eighty-four patients with a median age of 28 years were included. The majority (93%) suffered from a gunshot injury with 75% receiving a damage control laparotomy. Forty-eight patients (57%) had a TEG. Injury Severity Score and total fluid & blood product administered in the first 24 hours were all significantly higher in patients that had a TEG ($p < 0.05$). TEG profiles were: 42% normal, 42% hypocoagulable, 12% hypercoagulable and 4% mixed parameters. Fibrinolysis profiles were: 48% normal, 44% fibrinolysis shutdown and 8% hyperfibrinolysis. Mortality rate was 5% at 24 hours and 26% at 30 days, with no difference between the two groups. High grade complication rates, days on a ventilator and intensive care unit length of stay were all significantly higher in patients who did not have a TEG.

Conclusion

Trauma induced coagulopathy is common in severely injured penetrating trauma patients. The usage of a thromboelastogram did not impact on 24-hour or 30-day mortality but did result in a decreased intensive care stay and a decreased high grade complication rate.

INTRODUCTION

Uncontrolled haemorrhage with exsanguination is the leading cause of potentially preventable mortality in trauma patients, with rates of up to 40% of deaths due to haemorrhage. [1–3] Despite a better understanding of trauma-induced coagulopathy (TIC), as well as a more adjusted and tailored approach to TIC, the high rate of haemorrhage related mortality remains. [4]

The understanding of the fundamental factors that contribute to coagulopathy in trauma have been known for decades. [4, 5] However, a more intricate understanding of the clotting process has led to more directed tests and therapies being utilized. [6] These ultimately act to avoid the consequences of the lethal triad of coagulopathy, hypothermia and acidosis. [4, 5] The cell-based understanding of haemostasis, which emphasizes the importance of platelets and tissue factor, challenges the fundamentals that the conventional coagulation tests are based on and has led to more interest for the use of viscoelastic assays (VEA). [4, 6] One of the major advantages of VEA are detection of an altered fibrinolysis. This allows for assessing the balance of the risk of further bleeding against the consequences of uncontrolled harmful clotting. The assessment of which may be impossible to make without the information of a VEA. [7] The aim of this study is to assess whether the use of TEG in a group of severely injured patients with penetrating abdominal trauma improves outcomes.

METHODS

All patients with penetrating abdominal trauma (PAT) from 1 January 2016 to 31 December 2018 (36 months), requiring a laparotomy and post-operative intensive care were included in the study. Patients over the age of 18 years, requiring a laparotomy for PAT and transfusion of any blood products during the first 24 hours of injury were included. Patients with severe traumatic brain injury were excluded. Files of all eligible patients were retrospectively reviewed, and relevant data extracted. Two groups were analysed based on whether a TEG was done. Only the results of the first TEG were examined.

Reviewed data included: basic demographics, mechanism of injury, admission vital signs and blood gas analysis. Injury severity was categorised by the Penetrating Abdominal Trauma Index (PATI), Injury Severity Score (ISS) and the Trauma and Injury Severity Score (TRISS). Interventions in the first 24-hours including details of fluid and blood product usage and details of laparotomy were recorded. First recorded TEG parameters were analysed. Coagulation was assessed as normal, hypocoagulable, hypercoagulable or mixed based on reference range values suggested by the manufacturer. Fibrinolysis was assessed as a percentage of clot breakdown on Ly-30 and described as: normal (0.9-2.9%), hyperfibrinolysis ($\geq 3\%$) and fibrinolysis shutdown ($\leq 0.8\%$). [8, 9] Outcomes at 30-days included: length of stay (LOS) in ICU, ventilation days, complications as per Clavien-Dindo (CD) categorisation. CD grading greater than two was considered high grade (HG) complications. Mortality was determined at 24 hours and 30 days.

Analysis was performed using the R language for statistical computing (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria). Parametric numerical comparisons were done after interrogating the data for normality. Non-parametric methods were used when these assumptions failed. Data expressed as median or mean based on this. Where central tendency for more than 2 continuous variables was compared, the ANOVA and Kruskal-Wallis tests were used as appropriate. Categorical data were analyzed using the Fisher's exact and Chi-squared test of independence. An alpha-value of 0.05 was used as discriminant for significance. This study was approved by the University of Cape Town Human Research Ethics Committee HREC Reference number: 545/2019.

RESULTS

Description of patients

Eighty-four patients with PAT were included in the study. Seventy-eight (93%) patients sustained gunshot wounds, and the rest stab injuries. The median age was 28 (IQR 25-34) years. Forty-eight (57.1%) patients had at least one TEG performed within the first 24 hours and 36 (42.9%) patients did not have a TEG done. Admission parameters showed no difference between these two cohorts (Table 1). Patients with a TEG had significantly higher ISS ($p < 0.01$) and TRISS ($p = 0.02$) scores. The PATI showed a median score of 28 (IQR 22-40) with no difference between the groups.

Interventions within 24 hours

All patients underwent a laparotomy. Overall, 63 (75%) patients had a damage control laparotomy (DCL). At 24 hours the median number of blood products in the patients who had a TEG was: red cell concentrate (RCC) [7 (IQR 4-11) units], fresh frozen plasma (FFP) [3 (IQR

2-6] units, platelets [1 (IQR 0 – 2) megaunit] and one standard issue of cryoprecipitate (Cryo) [1 (IQR 0– 2)]. Patients who did not have a TEG done had statistically significant less blood products ($p < 0.01$) administered with a median of four RCC (IQR 3-5) units with no other blood products given. The overall 24-hour total fluid administered (clear fluid and blood products) was significantly different between the two groups with a median 10150 (IQR 8375-12000) millilitres (ml) being administered to the TEG group and 8320ml (IQR 6850-10025) to the no-TEG group ($p < 0.01$). See table 2.

Coagulation & fibrinolysis profiles

Normal coagulation parameters were found in 20 (42%) patients. This was equaled by 20 (42%) patients that had hypocoagulable TEG parameters. The remaining patients had hypercoagulable (12%), or mixed TEG parameters (4%), demonstrating both elements of hyper and hypocoagulability. No significant differences were found between the four different coagulation phenotypes with regards to patient characteristics, admission parameters and injury severity scores. Only patients with hypocoagulable TEG parameters received FFP. See table 4. Majority of patients had normal fibrinolysis (48%) or fibrinolysis shutdown (44%). The remaining 8% of patients manifested hyperfibrinolysis. Patients with hyperfibrinolysis had significantly lower: lactate [2.7 (IQR 1.9-3.3)], 24-hour total fluid [7300ml (IQR 6525-7900)] and 24-hour blood products (p -value < 0.05). All other parameters when compared across the three groups did not demonstrate statistical significance as depicted in Table 5.

Outcomes

The overall mortality rate was 5% ($n=4$) at 24 hours and 26% ($n=22$) at 30 days. All four mortalities occurring in the first 24 hours demonstrated a hypocoagulable TEG. Two of these patients had a normal fibrinolysis profile and the other two had fibrinolysis shutdown. No

mortalities occurred within 24 hours in the patients that did not have a TEG done. Thirty-day mortality was 31% in patients who had a TEG done and 19% in patients with no TEG (p=0.33). No differences in mortality at 24 hours or 30 days was demonstrated in patients with different coagulation and fibrinolysis profiles. See tables 4 and 5. High grade (HG) complication rate, days on a ventilator and ICU LOS were all significantly higher in patients who did not have a TEG done (p-value <0.01). No statistically different rates of HG complications were noted in the different coagulation and fibrinolysis groups. (Table 4 and 5). Table 6 lists the complications as per CD classification in the two groups.

DISCUSSION

Thromboelastography has evolved as the gold standard test to recognise TIC. A better understanding of the complexities of coagulation has led to an increased utilization of viscoelastic assays. It is also reliable and effective in guiding damage control resuscitation. [4, 7, 10]

This retrospective study analysed the TEGs of severely injured patients with penetrating abdominal trauma. The two cohorts, those who had a TEG and those who did not, were comparable except for a higher ISS and TRISS in the patients that had a TEG. The premise that more severely injured patients had TEGs done in this study was supported by a significantly higher 24-hour total fluid requirement and blood product usage seen in this group. Despite this the 24-hour and 30-day mortality rates were not significantly different. Three quarters of patients underwent damage control surgery (DCS) with an overall mortality of 5% and 26% at 24 hours and 30 days, respectively. The high mortality rate of 50% associated with DCS as reported at the turn of the century have improved. [11] Local studies have reported mortality

rates of 29-60% associated with DCS in trauma patients. [12–15] There was a higher rate of high-grade complications (Clavien-Dindo ≥ 3) and intensive care length of stay in patients that did not have a thromboelastogram. This is in keeping with the current trauma literature that demonstrates lower complication rates and decreased ICU stay in patients receiving a VEA to guide resuscitation. [2, 10, 16]

Hypocoagulability was the most frequent (42%) abnormal finding followed by hypercoagulability (12%) and mixed parameters (4%). A large study by Moore et al. evaluating the coagulation status of 2540 severely injured trauma patients (median ISS 25) demonstrated: 15% hypocoagulable, 38% hypercoagulable and 11% mixed parameters on initial TEG. [17] In contrast to our study, the majority of patients (83%) sustained blunt trauma and all TEGs were conducted within an hour of injury, which may explain the difference in coagulation phenotypes. Plotkin et al. retrospectively reviewed 44 patients with penetrating trauma and showed that 52% of patients manifested a hypocoagulable state within the first 24 hours of injury. Similar median ISS and 24-hour blood product usage may make this study of exclusively penetrating trauma patients a more contextually relevant comparator to our study. However, Plotkin et al. study did not elaborate on the anatomic details of injury or surgical intervention required.[18]

Hypercoagulability may vary considerably within the first 24 hours following injury. This may be affected by injury mechanism and severity, clear fluid and blood products or tranexamic acid administration. [18] A mix of hypercoagulability and hypocoagulability may also be present in the same patient following trauma. This is a result of a combination of tissue injury and a state of shock working in opposing mechanisms. [4, 17] This initial mixed state often transitions to a hypercoagulable state in the 48 hours following trauma. A large prospective

study of 948 trauma patients found that 10% of patients were hypercoagulable at some point in the first 24 hours following injury. [19] This is in keeping with our findings of a hypercoagulable state in 12% of patients. None of these patients died within the first 24 hours. However, a 30-day mortality rate of 50% was found in this group. This is consistent with other reports that show an increase in delayed mortality in patients with hypercoagulable TEGs. This is likely a result of sepsis, thrombotic complications or organ failure in severely injured patients. [17]

There was a trend toward higher 24-hour total fluid and blood product administration in hypocoagulable patients, although this did not reach statistical difference. Despite this, 30-day mortality and high-grade complication rate was lowest in hypocoagulable patients when compared to the other groups with abnormal TEG parameters. Again, this did not reach statistical significance likely owing to the small sample size. This is in contrast to a study by Johansson et al. who demonstrated a higher rate of ventilator days, renal replacement therapy and mortality in patients with a hypocoagulable state on admission to ICU. [20] In their cohort of all comers to ICU, 42% of patients were hypocoagulable with a 30-day mortality of 42%. This compares to our study of 42% of patients being hypocoagulable with a 30-day mortality of 40%. Only four (5%) mortalities occurred in the first 24 hours and all four of these patients were hypocoagulable. This is in keeping with a study by Branco et al. who reported the 24 hour mortality rates in patients with the following coagulation profiles as: hypercoagulable (0%), normal (6%) and hypocoagulable (28%). [21]

The ideal response following trauma is to establish a balance of arresting ongoing haemorrhage without causing harmful thrombosis. [17] Both hyperfibrinolysis as well as fibrinolysis shutdown have been implicated in higher mortality rates in the trauma population. [4, 8, 9, 22]

Three distinct phenotypes, namely: normal or physiological fibrinolysis, hyperfibrinolysis and fibrinolysis shutdown have been used to evaluate fibrinolysis in previous studies. [8, 9] In this study, the two dominant phenotypes were normal (48%) and fibrinolysis shutdown (44%), with hyperfibrinolysis only present in 4 (8%) patients. This is a similar distribution to a large study of 2540 patients by Moore et al. which described fibrinolysis shutdown as the most predominant phenotype at 46% and hyperfibrinolysis the least at 18%. [9] In contrast to that study, which reported the highest mortality with hyperfibrinolysis (34%), no deaths or high-grade complications were seen in the four patients with hyperfibrinolysis in this study.[9] The small study sample may have contributed to this difference. The patients in our study with hyperfibrinolysis had a significantly lower lactate and 24-hour clear fluid and blood product administration than the other two groups with a trend to lower ISS and TRISS, which did not reach statistical difference. Independent effects of hypothermia and acidosis on fibrinolysis have been evaluated on in vitro [23] and in vivo (porcine) models. [24] Both of these studies demonstrated no significant effect of induced hypothermia or acidosis on the fibrinolytic system as measured by thromboelastometry. [23, 24] These are in keeping with our results that also showed no difference in pH or temperature across the fibrinolysis phenotypes. All patients with confirmed hyperfibrinolysis received tranexamic acid.

The retrospective observational nature of this study and small sample size are the major limiting factors when considering whether these results are generalizable to a local population. In addition, although the local policy adopts a 1:1:1 ratio of blood products, the execution is dependent on the surgical and anaesthetic team involved. The timing of the TEG was also at the discretion of the treating physicians and as such no standard timing of the acquisition of a TEG was undertaken. The response to the TEG results with fluid or blood products was not protocolized and was as per the clinician's preference. As repeat TEGs were not protocolized

and not done in all patients, these were not included in the analysis. All the TEGs that were included were attained within the first 24 hours of injury.

CONCLUSION

Trauma induced coagulopathy is commonly found in severely injured penetrating trauma patients. Forty-two percent of patients with penetrating abdominal trauma requiring a laparotomy and post-operative critical care admission are hypocoagulable. This group showed a high mortality of 40%. While only 12% of our patients portrayed a hypercoagulable profile, fibrinolysis shutdown was seen in 44% of patients. This latter group showed a high mortality rate of 38%. The overall use of thromboelastography did not impact on 24-hour or 30-day mortality but did result in a decreased intensive care stay and a lower high grade complication rate.

Table 1: Patient characteristics, admission vital signs, trauma severity scores

	Total	TEG	No TEG	p-value
Study Sample	84 (100%)	48 (57%)	36 (43%)	
Age	28 (25-34)	28 (23-33)	28 (26-34)	0.44
Mechanism-GSW	78 (93%)	45 (94%)	33 (92%)	1
SBP	110 (94-127)	104 (86-120)	117 (94-127)	0.02
Pulse	107 (93-122)	107 (89-124)	108 (95-119)	0.66
Temperature	35.5 (34.0-36.0)	35.0 (33.8-36.1)	35.9 (35.0-36.0)	0.08
GCS	15 (14-15)	15 (14-15)	15 (15-15)	0.40
pH	7.3 (7.2-7.3)	7.2 (7.2-7.3)	7.3 (7.2-7.3)	0.11
Lactate	4.3 (2.8-6.0)	4.8 (2.9-7.2)	4.0 (2.6-5.2)	0.08
Trauma Severity Scores				
ISS	24 (20-29)	25 (20-29)	20 (17-25)	<0.01
TRISS	96.7 (92.9-98.1)	96.6 (92.1-97.2)	97.6 (95.8-98.2)	0.02
PATI	28 (22-40)	30 (22-44)	25 (22-35)	0.18

Values displayed as median with interquartile range.

GSW=gunshot wound, SBP=systolic blood pressure, GCS=Glasgow coma scale, ISS=injury severity score, TRISS=trauma injury severity score, PATI=penetrating abdominal trauma index.

Table 2: Interventions in the first 24hours

	Total	TEG	No-TEG	p-value
Total Fluid (ml)	9450 (7600-10925)	10150 (8375-12000)	8320 (6850-10025)	<0.01
RCC (units)	5 (3-8)	7 (4-11)	4 (3-5)	<0.01
FFP (units)	2 (0-4)	3 (2-6)	0 (0-2)	<0.01
Platelets (MU)	1 (0-1)	1 (0-2)	0 (0-1)	<0.01
Cryoprecipitate	0 (0-1)	1 (0-2)	0 (0-0)	<0.01

Values displayed as median with interquartile range.

ml=millilitres, RCC=Red cell concentrate, FFP=fresh frozen plasma, MU=Megaunits

Table 3: Outcomes

	Total	TEG	No-TEG	p-value
24h Mortality	4 (5%)	4 (8%)	0 (0%)	0.13
30d Mortality	22 (26%)	15 (31%)	7 (19%)	0.33
HG Complication	48 (57%)	21 (43%)	27 (75%)	<0.01
ICU LOS	4 (3-8)	4 (3-5)	5 (4-16)	<0.01
Hospital LOS	16 (7-35)	13 (6-25)	21 (10-49)	0.20
Ventilation Days	3 (2-5)	2 (1-4)	4 (3-9)	<0.01
PF Ratio 24h	353 (269-440)	358 (296-441)	348 (254-432)	0.68

Values displayed as median with interquartile range.

HG =high grade, ICU=intensive care unit, LOS=length of stay, PF=PaO2/FiO2 ratio.

Table 4: TEG Analysis- Coagulation Profile

	Normal	Hypocoagulable	Hypercoagulable	Mixed	p-value
Study Sample	20 (42%)	20 (42%)	6 (12%)	2 (4%)	
24h Mortality	0 (0%)	4 (20%)	0 (0%)	0 (0%)	0.17
30d Mortality	3 (15%)	8 (40%)	3 (50%)	1 (50%)	0.17
HG Complication	7 (35%)	9 (45%)	4 (67%)	1 (50%)	0.64
Age	30 (22-33)	28 (23-34)	29 (24-31)	26 (25-26)	0.94
SBP	102 (89-113)	103 (80-126)	116 (92-130)	104 (103-105)	0.73
Pulse	105 (91-119)	108 (98-127)	103 (81-122)	86 (75-96)	0.61
Temp	34.8(34.0-36.0)	35.2(33.9-36.2)	34.8(33.2-36.3)	33.5(32.9-34.2)	0.56
GCS	15 (14-15)	15 (14-15)	14 (10-15)	15 (15-15)	0.27
ISS	23 (20-29)	26 (20-30)	25 (25-30)	30 (27-32)	0.30
TRISS	96.7(96.2-96.7)	97.4(93.1-98.0)	88.8(79.0-91.5)	96.0(96.0-96.0)	0.12
PATI	31 (26-46)	34 (20-39)	23 (12-24)	62 (58-67)	0.07
pH	7.2 (7.2-7.3)	7.2 (7.1-7.3)	7.3 (7.2-7.3)	7.3 (7.3-7.3)	0.47
Lactate	5.1 (3.8-5.6)	4.5 (3.0-9.1)	2.5 (2.2-4.2)	6.0 (4.9-7.0)	0.38
24h Fluid	9600 (7750-11200)	11250 (9050-17225)	9950 (8275-11100)	10400 (10250-10550)	0.41
24h RCC	6 (4-9)	8 (5-15)	8 (6-11)	7 (5-8)	0.38
Post-TEG RCC	0 (0-0)	1 (0-4)	0 (0-1)	0 (0-1)	0.09
24h FFP	4 (2-4)	2 (1-6)	5 (3-7)	3 (2-3)	0.81
Post-TEG FFP	0 (0-0)	2 (0-2)	0 (0-0)	0 (0-0)	<0.01
24h Platelets	1 (0-1)	1 (1-2)	1 (0-2)	1 (0-2)	0.55
Post-TEG Platelets	0 (0-0)	1 (0-1)	0 (0-0)	1 (0-1)	<0.01
24h Cryo	1 (0-1)	1 (0-2)	1 (0-2)	1 (1-2)	0.95
Post-TEG Cryo	0 (0-0)	0 (0-1)	1 (0-1)	0 (0-0)	0.08
Blood Loss	2650 (2225-4000)	3700(2175-5125)	2400(1650-2700)	4900(3600-4200)	0.39
Procedure Length	175 (143-188)	130 (116-180)	143 (120-266)	135 (123-148)	0.57

Values displayed as median with interquartile range.

HG =high grade, SBP=systolic blood pressure, GCS=Glasgow coma scale, ISS=injury severity score, TRISS=trauma injury severity score, PATI=penetrating abdominal trauma index, RCC=red cell concentrate, FFP=fresh frozen plasma, Cryo=cryoprecipitate

Table 5: TEG Analysis- Fibrinolysis Profile

	Normal (0.9-2.9%)	Hyperfibrinolysis (≥3%)	Shutdown (≤0.8%)	p-Value
Study Sample	23 (48%)	4 (8%)	21 (44%)	
24h Mortality	2 (9%)	0 (0%)	2 (10%)	1
30d Mortality	7 (30%)	0 (0%)	8 (38%)	0.42
HG Complication	13 (57%)	0 (0%)	8 (38%)	0.10
Age	30 (26-33)	32 (24-41)	26 (22-32)	0.71
SBP	111 (89-130)	94 (85-102)	100 (76-112)	0.27
Pulse	108 (89-125)	107 (97-110)	105 (91-125)	0.78
Temperature	35.0 (34.0-36.0)	35.1 (34.1-36.3)	34.9 (33.3-35.5)	0.56
GCS	15 (14-15)	15 (13-15)	15 (14-15)	1
ISS	25 (20-29)	20 (20-22)	25 (20-29)	0.50
TRISS	95.9 (91.6-97.1)	96.6 (95.8-96.7)	97.0 (91.0-97.7)	0.76
PATI	26 (22-41)	28 (22-35)	38 (26-53)	0.37
pH	7.3 (7.2-7.3)	7.3 (7.2-7.4)	7.2 (7.1-7.3)	0.09
Lactate	4.5 (2.5-5.4)	2.7 (1.9-3.3)	6.4 (4.0-9.1)	<0.01
24h fluid	9700 (7900-11400)	7300 (6525-7900)	11400 (10000-16300)	<0.01
24h RCC	6 (4-9)	3 (3-4)	9 (7-15)	0.01
24h FFP	3 (2-4)	1 (0-1)	4 (2-6)	0.04
24h Platelets	1 (0-1)	0 (0-0)	1 (1-2)	0.02
24h Cryo	1 (0-1)	0 (0-0)	1 (0-2)	0.20
Blood Loss	2550 (2000-4000)	1750 (1250-2400)	3500 (2400-5400)	0.06
Procedure Length	163 (120-235)	180 (150-195)	150 (110-180)	0.65

Values displayed as median with interquartile range.

HG =high grade, SBP=systolic blood pressure, GCS=Glasgow coma scale, ISS=injury severity score, TRISS=trauma injury severity score, PATI=penetrating abdominal trauma index, RCC=red cell concentrate, FFP=fresh frozen plasma, Cryo=cryoprecipitate

Table 6: Clavien-Dindo Complications

Clavien-Dindo	TEG	No-TEG
1	5 (16%)	2 (7%)
2	5 (16%)	1 (3%)
3a	3 (10%)	6 (20%)
3b	6 (19%)	12 (40%)
4a	1 (3%)	2 (7%)
4b	4 (13%)	0 (0%)
5	7 (23%)	7 (23%)

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APPENDICES

APPENDIX 1: ETHICS APPROVAL – UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E53-46 Old Main Building
Grote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 August 2019

HREC REF NO: 545/2019

Prof Pradeep Navsaria
Trauma
Surgery

Dear Prof Navsaria

PROJECT TITLE: THE IMPACT OF THROMBELASTOGRAPHY USE ON PATIENTS WITH PENETRATING ABDOMINAL TRAUMA REQUIRING INTENSIVE CARE (MASTERS - DR MATTHEW HANNINGTON)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)


Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledges that the student, Dr Matthew Hannington will also be involved in this study.

Yours sincerely


PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

APPENDIX 2: INTENDED JOURNAL FOR PUBLICATION - WORLD

JOURNAL OF SURGERY: SUBMISSION INSTRUCTIONS TO

AUTHORS.

WORLD JOURNAL OF SURGERY INSTRUCTIONS FOR AUTHORS

GENERAL

World Journal of Surgery (WJS) publishes original articles that offer significant contributions to knowledge in the broad fields of clinical surgery, innovative developments in surgery, global surgical practice and economics, surgical education, rural surgery and surgical history. WJS welcomes predominantly human research, including clinical research, outcomes, and health service research. Laboratory research will be published only if it is highly significant and with clear and immediate translational potential to surgical care. WJS has an international circulation and is designed to serve as a medium for rapid dissemination of new and important information about the science and art of surgery throughout the world. In the interests of a wide international readership, use of the English language is required. Articles that are accepted for publication are done so with the understanding that they, or their substantive contents, have not been and will not be submitted to any other publication.

TYPES OF MANUSCRIPTS

PLEASE NOTE: *World Journal of Surgery* does not accept Case Reports and Book Reviews for review or publication.

Word Limit Table

Word Limits do not include abstract and reference list.

	Article Type	Word Limit	Other Notes
	Original Reports	2,500	
	Original Reports with Video	2,500	
	Scientific Review	3,000	Limit of 75 references
	Innovative Techniques in Surgery Around the World	1,000	Limit of 5 references and 3 authors, limit of 8 figures/video
	Surgery in Low and Middle Income Countries	2,500	
	Letter to the Editor	500	Limit of 5 references
	Surgical History	2,000	Limit of 5 references and 3 authors, limit of 8 figures / tables
	Surgical Symposia Contribution	3,000	Limit of 75 references and 3 authors, limit of 10 figures/tables
By Invite Only	<i>Editorial Perspective</i>	1,000	Limit of 5 references and 2 authors
By Invite Only	<i>Invited Commentary</i>	1,000	Limit of 5 references and 2 authors
By Invite Only	<i>We Asked the Experts</i>	1,000; 750 with table/figure	Limit of 5 references and 3 authors, no abstract

Original Reports (Including Papers Presented at Surgical Conferences):

Original Scientific Reports are full-length reports of original basic or clinical investigations. All clinical trials must be registered through a public trials registry that is acceptable to the International Committee of Medical Journals Editors (ICMJE). For information on ICMJE's statement to register clinical trials, please go to <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>. The trial registration number and agency should be listed on the title page and at the end of the abstract.

Randomized clinical trials should be reported following the CONSORT criteria and provide a completed checklist and flow diagram upon manuscript submission. For information on CONSORT and to download the CONSORT checklist and flow diagram, please go to <http://www.consortstatement.org/>.

→ Original Scientific Reports must adhere to a 2,500 word limit (not including the title page, abstract, references, tables, and figures). The final word count should be included in the title page of the manuscript.

Surgery in Low and Middle Income Countries

WJS seeks high quality manuscripts describing the unique problems and unique solutions facing surgeons in rural and impoverished settings, globally. WJS requires that manuscripts that use primary data from a low- or middle-income country should include one or more local co-authors. A local co-author is defined as a national of that country who is living and working in their home country. All other author requirements need to be met for the author(s) from the low and middle income country. The editors understand that there may be extenuating circumstances in which this requirement cannot be met. In such cases, a cover letter should explain why a local co-author is not included. Further details on this editorial policy can be found at: [Editorial Policy on Co-authorship of Articles from Low- and Middle-income Countries](#); DOI: 10.1007/s00268-011-1255-8

Cost-effectiveness research is especially valuable for the field of global surgery. However, unless the methods are sound, findings can sometimes be erroneous. WJS calls upon authors who undertake cost-effectiveness research in global surgery to review the methodologic points brought out by the following article when they develop, conduct, and write up their studies: World J Surg. 2017 Jan 19. DOI: [10.1007/s00268-017-3875-0](#) PMID: 28105528.

WJS also requires completion of the checklist contained in the above article at the time of submission of cost effectiveness studies. The checklist is available at: <https://scholar.harvard.edu/shrime/cost-effectiveness-analysischecklist>

If the authors feel another checklist is more suitable for their particular study, they may use that checklist. In all cases of cost effectiveness studies, the checklist used should be stated in the cover letter and the completed checklist attached to the cover letter.

→ Surgery in Low and Middle Income Countries articles must adhere to a 2,500 word limit (not including the title page, abstract, references, tables, and figures). The final word count should be included in the title page of the manuscript.

MANUSCRIPT PREPARATION AND ORGANIZATION

General instructions:

- Use a normal, plain font (e.g., 10-12 point Times Roman or Arial) for text
- Double-space the text
- Use italics for emphasis
- Include page numbers
- Do not use field functions
- Use tab stops or other commands for indents, not the space bar
- Use the table function, not spreadsheets, to make tables

Manuscript style and text formatting:

Styling and text formatting refers to the use of special effects to enhance the appearance of the published article. Please make note of the following "Dos and Don'ts" regarding styling:

- DO enter all lists as single column lists.
- DO use your word processing features to indicate bold, italic, superscript, and subscript text within a paragraph or heading.
- DO NOT center text for headings. All text should be justified left, with ragged (unjustified) right margins.
- DO NOT use italic, underline, or other type effects for the entire text of a heading.
- DO NOT use all capital letters for a heading; use initial caps instead.
- DO NOT use multiple spaces to set up columns or tables; use tabs instead.
- DO NOT use carriage returns at the end of each line of text (use the word wrap feature).

REFERENCES:

Reference citations in the text should be identified by numbers in brackets (e.g. [4]). Number the references in order of their first appearance in the text (not alphabetically). Once a reference is cited, all subsequent citations should be to the original number. References may not appear in your Reference List unless they have been cited in the text or tables. Manuscripts that have been accepted for publication or are in press may be listed as references, but the Journal does not reference unpublished data and personal communications. Use the form for references adopted by the U.S. National Library of Medicine, as in Index Medicus. For each reference, show inclusive page ranges (e.g., 7-19).

In references to journal articles, please include:

1. surname and initials (without periods) of the first three authors and 'et al' for all others,
2. the year in parentheses
3. title of article
4. abbreviated Journal name
5. volume number
6. inclusive page numbers, in that order.

An example follows:

1. Honda T, Nozaki M, Isono N, et al (2001) Endoscope-assisted facial fracture repair. *World J Surg* 25:1075-1083

In references to books, please include :

1. surname and initials (without periods) of the first three authors and et al. for all others
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3. chapter title, if any
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