



EFFECTIVENESS OF GOAL-DIRECTED THERAPY VS MASSIVE TRANSFUSION PROTOCOL IN A TERTIARY CARE CENTER IN SOUTH INDIA

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Abstract

A comparative study was done, wherein the retrospective data were collected from the institutional MTP registry and compared with prospective data of patients managed by Goal-Directed Therapy using ROTEM.

Data about patient demographics, mode of admission, indication for massive transfusion, blood component usage, Morbidity, and mortality of 122 patients were collected and analyzed.

MTP was activated for PPH, Trauma & surgery at a rate of 45%, 36.1% & 11.5%. Goal-directed Therapy was initiated mainly for Trauma, surgery, PPH & snake bite at a rate of 42.6%, 23%, 19.7%, and 4.9% respectively. There was a significant reduction in blood component utilization for PRBC, FFP & platelet ($p < 0.05$) in GDT, but cryoprecipitate utilization remained the same.

There was a significant reduction in morbidity measured as the length of hospital stay (Sig=0.038) for patients managed by GDT (9.39 days) in comparison to those managed by MTP (17.05 days). There was no statistical difference in mortality among the comparison groups.

From the data, we were able to conclude that Goal-directed therapy shows a significant reduction in blood component utilization & morbidity without a significant change in mortality among patients in this study.

Keywords: ROTEM, CCT, Coagulation, Rotational thromboelastometry

Introduction

Massive hemorrhage is a common complication in a large number of clinical settings and management of such patients is challenging⁽¹⁾. Massive blood transfusion refers to the replacement

of a large volume of blood with blood products over a short period in a patient with uncontrolled hemorrhage. The present study defines Massive Transfusion as the transfusion of more than 4 Packed Red Blood Cell (PRBC) units within 1 hour with anticipation of the continued need for blood products.

Patients undergoing massive hemorrhage experience dynamic changes in hemostasis due to many factors like crystalloid use, transfusion of blood components, and certain etiology-specific causes⁽²⁾. Early recognition and rapid treatment of initial coagulation disturbances improve survival in massively bleeding patients. Damage control resuscitation through Massive Transfusion Protocols (MTP) with predetermined and standardized ratios of blood components is the current thought to actively address the issues of rapid blood loss and thus improve the clinical outcome of such patients^(3,4,5). The blood components widely used in the management of coagulopathy include PRBC, FFP(Fresh Frozen Plasma), PC(Platelet concentrate)/RDP(Random donor platelet), or cryoprecipitate.⁽⁶⁾

Rotational Thromboelastometry (ROTEM) is a whole blood viscoelastic hemostasis analyzer that has evolved from the TEG (Thromboelastography) system. TEG and ROTEM (combined called viscoelastic hemostatic assays) are being increasingly used in the diagnosis of coagulopathy as goal-directed therapy and aids in hemostatic resuscitation. Various ROTEM parameters could identify acute traumatic coagulopathy, Post-partum hemorrhage and predict the need for massive transfusion faster and more accurately. They also can provide rapid and accurate detection of hyperfibrinolysis.⁽⁶⁾

Viscoelastic assays like ROTEM provides a graphical representation of patients' coagulation demographics within 5 to 10 minutes using a minimal sample of whole blood. Henceforth, they have played an increasingly important role in the early identification of coagulopathy. Targeted blood component therapy can be started early and this will be beneficial to the patient as well as the treating physicians. A goal-directed therapy helps avoid unnecessary transfusion and thereby leads to better inventory management.

Materials and methods

The aim was to assess blood component utilization in goal-directed therapy versus protocol-based massive transfusion. It was an observational study.

Null hypothesis

Goal-directed transfusion with ROTEM has no role in improving transfusion services in massive transfusions.

Alternate hypothesis

Goal-directed transfusion with ROTEM has an important role in transfusion services in massive transfusions.

The study was conducted in a tertiary care hospital in South India.

Inclusion criteria

- Age >18 years
- Uncontrolled bleeding due to various causes

Exclusion criteria

- Patients who had received a blood transfusion from outside the hospital
- Patients who died within 30 minutes of arrival
- Patients not willing to participate in the study
- Samples not fulfilling sample acceptance criteria

Ethical Clearance: The study approval was taken from the Institutional Ethics Committee, JMMC&RI on 18.12.2020 with IEC Study Ref. No: 42/20/IEC/JMMC&RI **Date: 22.12.2020**

Consecutive requisitions were sent from any department in the hospital for ROTEM analysis which satisfy inclusion and exclusion criteria after obtaining ethical committee clearance was taken. Massive transfusion was defined as receiving more than 4 Packed Red Blood Cell (PRBC) units within 1 hour with the anticipation of the continued need for blood products or replacement of approximate total blood volume, or replacement of >50% of the total blood volume. Using this definition, all the massively transfused patients above 18 years of age regardless of the cause of bleed were included in this study.

A sample for ROTEM was collected in a sodium citrate tube (blue tube). A5 algorithm was used for goal-directed transfusion (Figure 1, Figure 2).

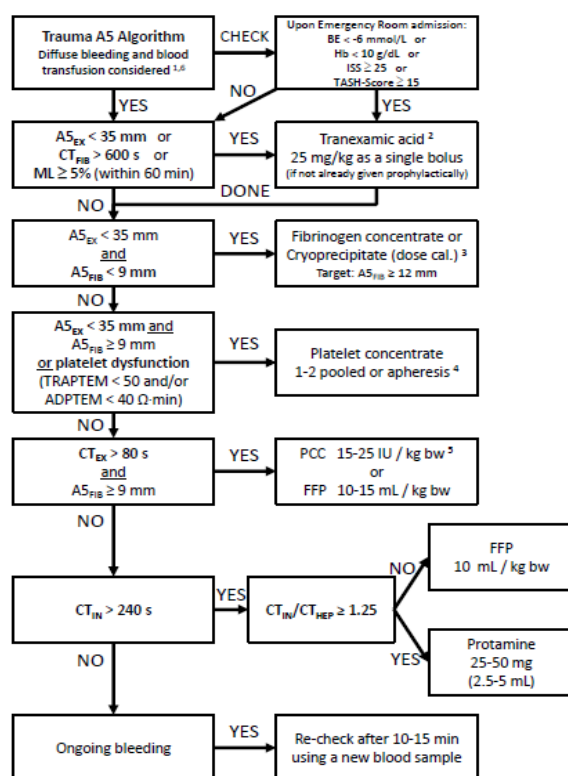


Figure 1 – A5 algorithm for trauma

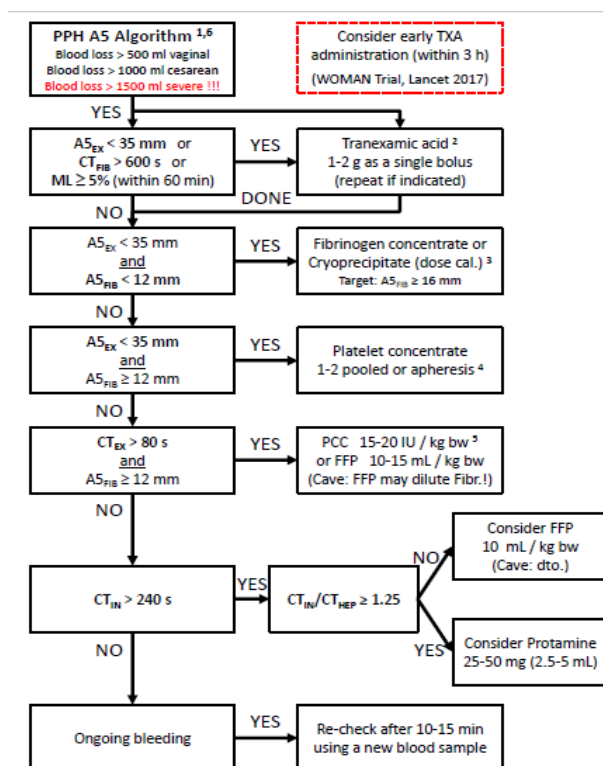


Figure 2 – A5 algorithm for PPH

Before the implementation of the goal-directed ROTEM transfusion protocol, an institutional protocol for massive transfusion was as follows(Figure 3):

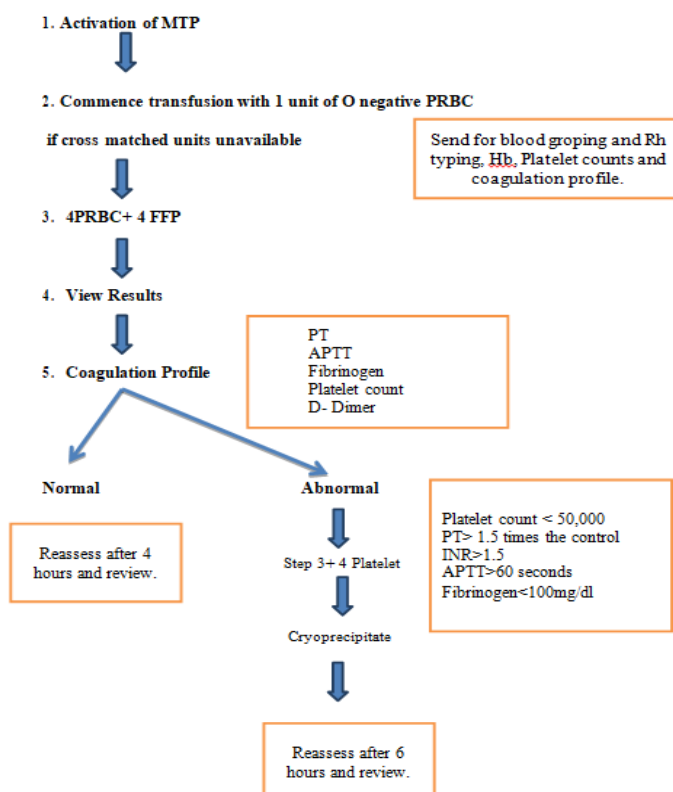


Figure 3 – Institutional massive transfusion protocol

Sub-group categorization of the study population was done followed by blood components issued were recorded for each patient within 24 hours of initiation of massive transfusion. Patient

populations matching the current samples are taken from the massive transfusion registry of the hospital. Each population was separated and Packed Red Blood Cell, Fresh Frozen Plasma, Platelet Concentrate, and Cryoprecipitate utilization was recorded.

Results

Total sample size was 122 which included 61 from MTP and GDT groups each. There was no statistical difference in gender, criteria of admission among the comparison groups (Figure 4, Figure 5).

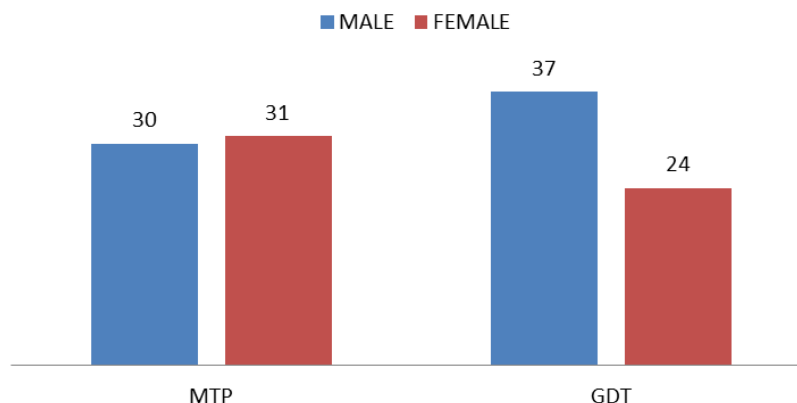


Figure 4 – Gender distribution in study population

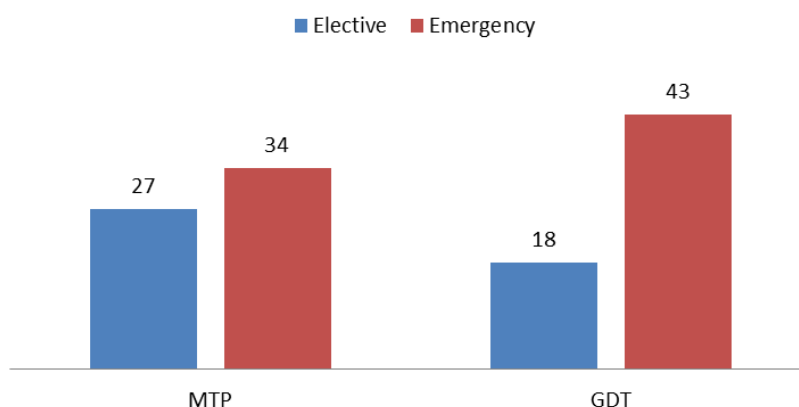


Figure 5 – Comparison of criteria of admission

Comparison of indications for which massive transfusion was initiated

When comparing the indications for which massive transfusion was initiated in both the groups, there was a statistical difference with a $P < .01$. MTP was activated for PPH, Trauma & surgery at a rate of 45%, 36.1% & 11.5%. Goal-directed Therapy was initiated mainly for Trauma, surgery, PPH & snake bite at a rate of 42.6%, 23%, 19.7%, 4.9% respectively (Figure 6).

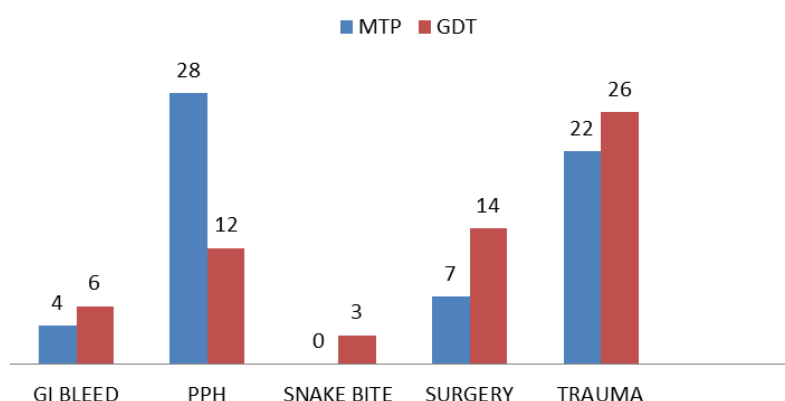


Figure 6 – Comparison of indications for which massive transfusion was initiated

Comparison of blood component utilization

When comparing the blood component utilization of PRBC, FFP, Platelet concentrate, and Cryoprecipitate, there was a significant difference with a reduction in blood component utilization for PRBC, FFP & platelet($p<0.05$) in GDT, but cryoprecipitate utilization remained the same(Figure 7).

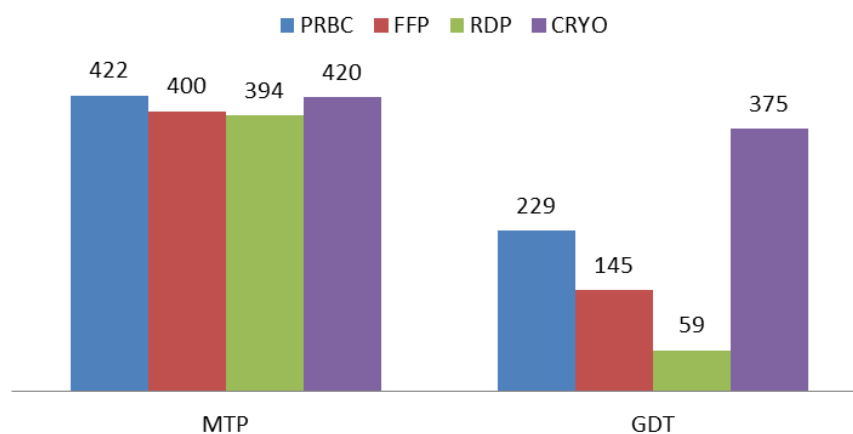


Figure 7 – Comparison of blood component utilization

Comparison of PRBC in MTP vs GDT

There was a significant reduction in PRBC utilization in the Goal-directed therapy group with ROTEM with a $P<0.01$. The median PRBC utilization was 6 and 4 respectively for MTP and GDT groups (Figure 8).

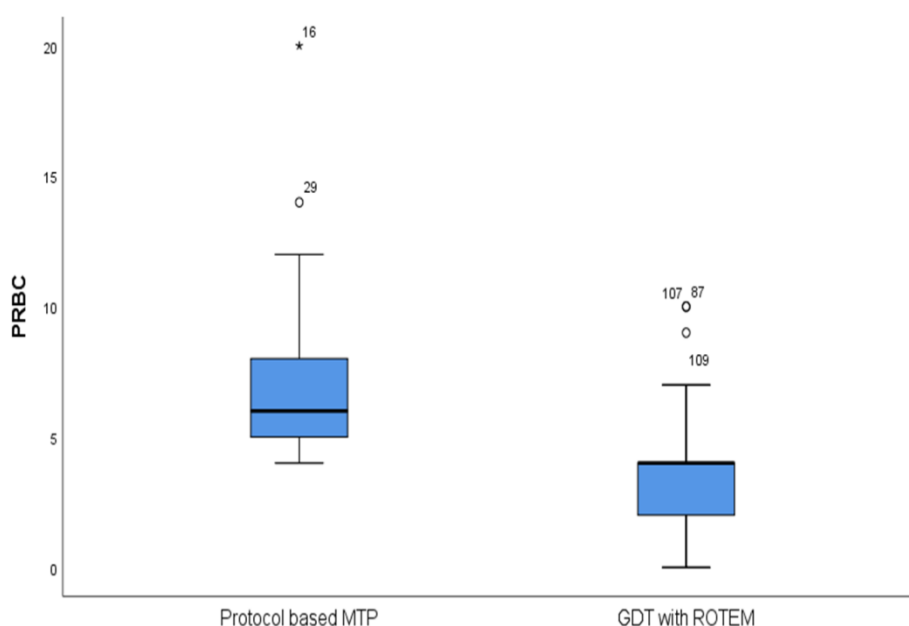


Figure 8 – Comparison of PRBC in MTP vs GDT

Comparison of FFP in MTP vs GDT

The GDT group with ROTEM had a significant reduction in FFP utilization than the MTP group with a P value <0.01 . The median FFP utilization was 6 for MTP and 2 for the GDT group(Figure 9).

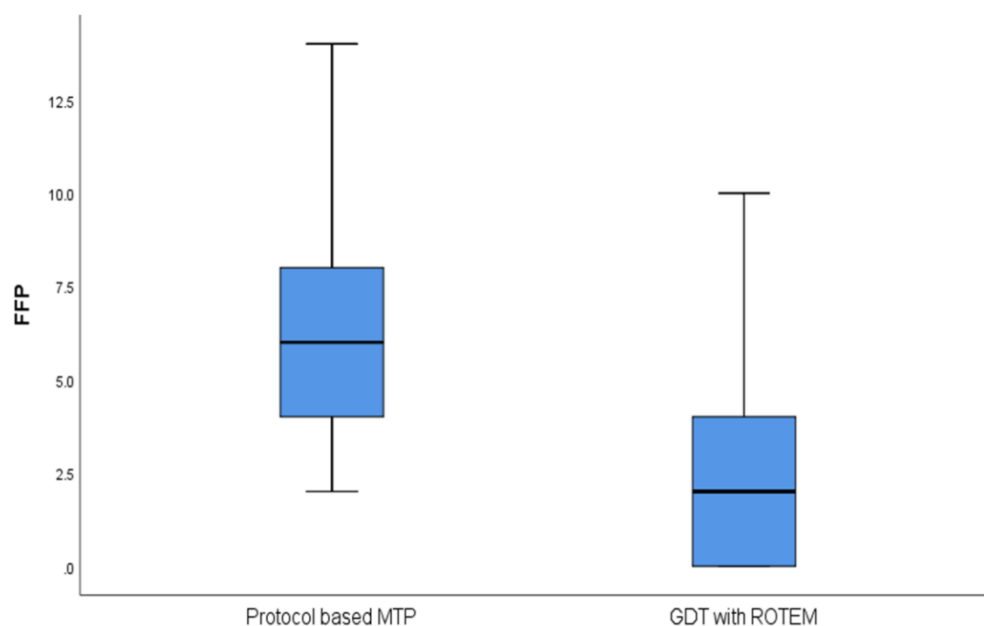


Figure 9 – Comparison of FFP in MTP vs GDT

Component utilization of Random donor platelet

Random donor platelet utilization had the most significant difference with reduced utilization in the GDT group with $P < 0.01$. Median utilization was 6 in the MTP group and 0 for GDT (Figure 10).

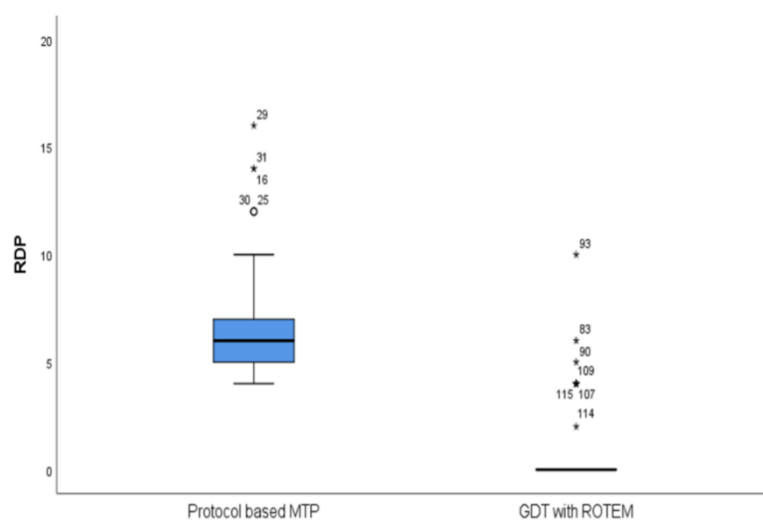


Figure 10 – Comparison of RDP in MTP vs GDT

Comparison of cryoprecipitate utilization

There was no significant difference in cryoprecipitate in both arms. $P = 0.38$ (Figure 11).

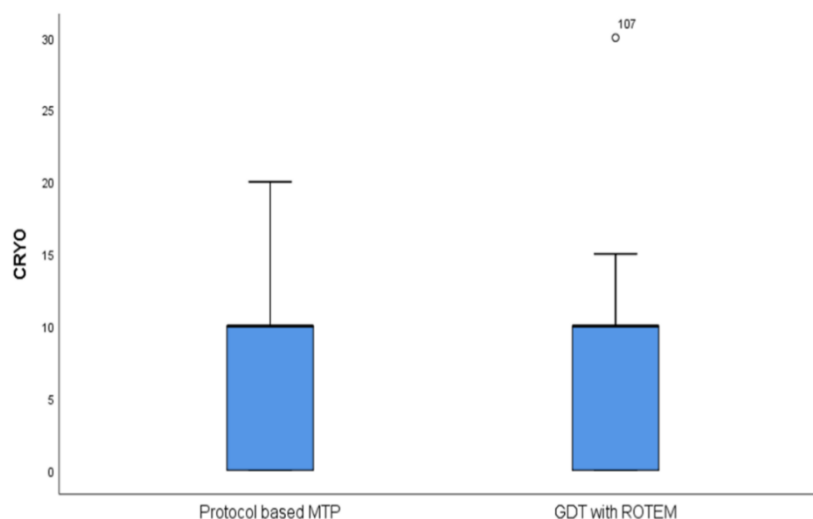


Figure 11 – Comparison of cryoprecipitate in MTP vs GDT

Comparison of total component utilization

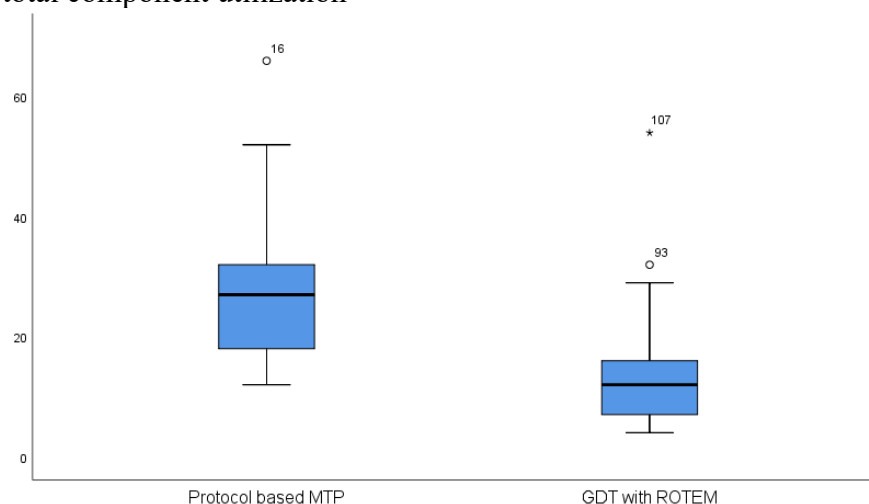


Figure 12 – Comparison of total component utilization in MTP vs GDT

When comparing the combined utilization of all components (PRBC, FFP, platelet concentrate & Cryoprecipitate) there is a significant reduction of utilization in the GDT arm ($P < 0.1$) with a median of 27 for MTP and 12 for GDT (Figure 12).

Table 1 – Table of comparison of MTP vs GDT

	MTP	GDT
Age	33.36±8.26	46.52±17.83
PRBC	6.92±2.95	3.75±2.23*
FFP	6.56±2.75	2.38±2.36*
RDP	6.46±2.71	0.97±2.05*
Cryoprecipitate	6.89±5.34	6.15±5.94
Total	26.82±11.33	13.25±8.62*
LOS	17.05±9.40	9.39±8.76 [#]

* $p < 0.01$, [#] $p = 0.03$

Comparison of morbidity

Morbidity was measured as the length of stay in the hospital. There was a significant reduction in the GDT arm of patients with $P = 0.03$. The average stay in the hospital was 17.05 days in MTP whereas it was only 9.39 days in GDT (Figure 13).

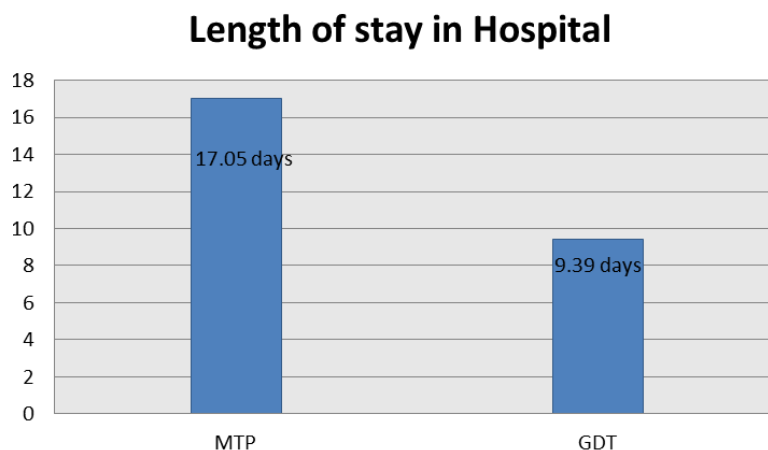


Figure 13 – Comparison of length of stay in the hospital

Comparison of mortality

When comparing the survivor status or mortality there were no significant changes in both the group ($P>0.05$) Figure 14.

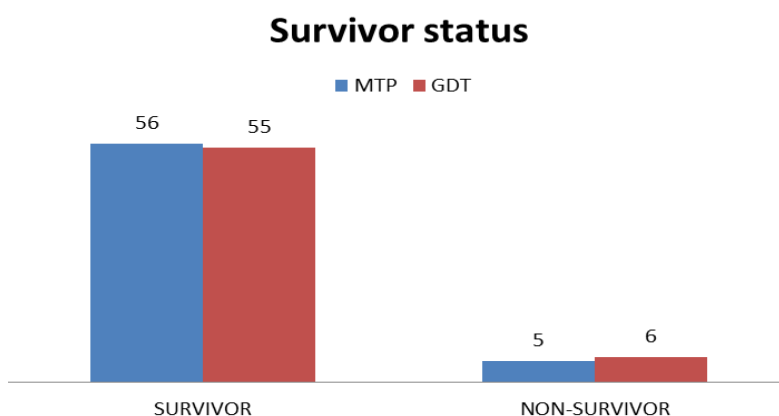


Figure 14 –Comparison of mortality

Discussion

Hemostasis is an intricate process that stops and prevents bleeding and comprises four phases namely vascular including endothelium, platelet, coagulation factors, and fibrinolytic process^{7,8}. It is classified as primary hemostasis, secondary hemostasis, and fibrinolysis⁹. Primary hemostasis is an early action at the site of damaged endothelium and involves vasoconstriction and platelet plug formation whereas secondary hemostasis includes a cascade of the longer intrinsic pathway, shorter extrinsic pathway, and common pathways through clotting factors leading to fibrin formation. The fibrinolytic pathway is a negative feedback mechanism to prevent over-coagulation¹. Defects in any of these areas lead to problems in blood clotting mechanisms called coagulopathy or blood hemostasis disorder. Coagulopathy is a major public health disorder affecting all age groups throughout the world. It is classified as primary hemostasis disorder and secondary hemostasis disorder¹. Primary hemostasis disorders are caused by either vascular anomalies, von Willebrand disease, and platelet formation whereas secondary hemostasis disorders are caused by either congenital disorders involving coagulation and fibrinolytic cascades like Haemophilia or acquired disorders like Vitamin K deficiency, liver diseases, malabsorption diseases like Coeliac diseases, Disseminated intravascular coagulation (DIC) including the current pandemic of covid-19^{10,11,12}. These diseases/disorders can hence occur in any age group with varying degrees of mortality and morbidity and early diagnosis helps in better management and outcome of these cases.

During world war II, Hartert was working on a technique to detect the coagulation process and introduced thromboelastography (TEG) to the world in 1948. It was a viscoelastic test where

viscosity was formed by turning a rotating cup around a pin and hence the measurement of the in-vivo global coagulation process (the method is explained in history). ROTEM was developed in 1995-1997 in Munich, Germany; using a similar process where TEM stands for thromboelastometry which is analogous to the term thromboelastography. The major difference between the two was that the cuvette was rotated in TEG and the pin is rotated in ROTEM.

In ROTEM, first, the sample of blood is placed in a cuvette and the cylindrical pin is immersed into the cuvette with a gap of 1mm between the pin and the cuvette where a sample of blood or in a later stage, a clot will bridge this gap. A spring oscillates the pin to right and left sides. This happens freely at the initial stage but as clot initiation and clot formation occur, there will be restriction of movement of the pin. Hence, the rotation of the pin is increased related to the firmness of the clot. These changes are detected optically and a computer integrated into the ROTEM calculates the ROTEM curve and its numerical parameters.

Since the study population in both the groups was similar with respect to gender and mode of admission (emergency or elective), analysis of the component utilization was standard.

In this study, we evaluated the blood component utilization on massive transfusion based on institutional protocol and goal-directed therapy with ROTEM. Goal-directed therapy shows a significant reduction in blood component utilization & morbidity without a significant change in mortality among patients in this study. The finding was in concordance with another study in South Wales where they found that the ROTEM analyzer was effective in managing Major Obstetric Hemorrhage at point-of-care and led to a reduction in the transfusion of CRC, FFP, and platelets.⁽¹³⁾ The significant reduction in PRBC utilization can lead to reduced allosensitization, better inventory management, and saving precious resources.

The current study found an overall reduction in blood component utilization except for cryoprecipitate which didn't reduce. A similar result was obtained in another study where ROTEM was utilized to control bleeding in orthotopic liver transplants. They noted that blood component utilization in orthotopic liver transplants showed significantly less intraoperative blood loss in ROTEM-guided therapy, along with overall blood component utilization. But they noted that the cryoprecipitate used increased in goal-directed therapy, but without increasing the cost of tests and blood^(14,15) Cryoprecipitate component was reserved in the last stage of institutional protocol-based massive transfusion. As our hospital is a tertiary care hospital that caters as a referral center for a lot of smaller hospitals, the majority of the patients were referred from other centers. Many of the massive bleeding patients were referred when management at the local centers was unable to restore coagulation.

A similar reduction in blood component utilization was obtained in a study in 2017 where Viscoelastic testing was used for surgery of thoracolumbar deformity. We were able to find that total blood component transfusion was reduced by 12 units.⁽¹⁵⁾ Majority of the patients that were referred or presented to our center had a history of trauma or major obstetric hemorrhage.

The morbidity was assessed as the length of stay in the hospital, which was significantly reduced for the GDT group with ROTEM, which most probably is due to the faster turnaround time and targeted component therapy. Unnecessary blood component therapy could be avoided and the coagulopathy was corrected as soon as possible. This led to faster control of bleeding. A faster recovery led to early discharge from the hospital.

Even though there was no significant difference in mortality, the morbidity in terms of length of stay was reduced and the number of blood component utilization has reduced. This, in turn, will lead to a reduction in overall expenses in the hospital.

Transfusion services must shift from the traditional approach to evidence-based guidelines as it can reduce transfusion-related adverse events and transfusion-related immunomodulation

GDT has the potential to impact the care of critically ill patients in Emergency through Patient blood management, but current evidence for their use is limited. Further high-quality research, including randomized controlled trials, is needed to elucidate the role of GDT.

Acknowledgement

Dr. Arun V J has performed the research and wrote the paper. Dr. Arun V J, Dr. Ramesh Bhaskaran, Dr. Aboobacker Mohamed Rafi and Dr. Susheela Jacob Innah designed the research study, contributed essential reagents or tools, analysed the data.

Authorship statement

All authors declare that they have no conflict of interest.

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