ejpmr, 2016,3(3), 171-176

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

TRAUMA AND COAGULOPATHY: FINDINGS OF THE LAST DECADE

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Article Received on 01/01/2016 **Article Revised on 21/01/2016** **Article Accepted on 11/02/2016**

ABSTRACT

Acute traumatic Coagulopathy (ATC) is a factor of concern that must be addressed in the care of severely injured patients. In this review article, we discuss the pathophysiology of ATC, the diagnosis and recommendations for its treatment. In the last decade, lots of studies have been reported regarding management of trauma cases with guidelines advocated by each and every researcher .Concept of damage controlled resuscitation has come up in the back ground of Gulf war and intensive research work by British and US Military setup. Apart from ATC, there is Coagulopathy which is secondary to overt volume therapy, leading to other conditions like acidosis, hypothermia, and dilution. This Coagulopathy may, then, be an integral component of the so- called ‘‘vicious cycle’’ when combined with acidosis and hypothermia, also termed as lethal triad. The awareness of the specific pathophysiology and management of a case of Coagulopathy with a specific guideline is of paramount importance. The guidelines and protocol stand firm till date with some minor changes in priorities in conditions where patients are already a known case of Coagulation disorder. In this article we have tried to correlate the recent outcomes of ATC and practical problems encountered in routine practice.

KEYWORDS: Acute Traumatic Coagulopathy Damage Control Resuscitation Pathophysiology of Coagulopathy.

INTRODUCTION

Trauma is considered a health problem very serious in nature which accounts for nearly 50% of injury-related mortality is in young people between the ages of 15 and 44 yr.[1] The burden to society due to loss of productivity is enormous, amounting to a total of 182 million disability adjusted life years lost annually.[2] Homeostasis can be achieved by surgically repairing vascular injury but bleeding due to Coagulopathy following trauma is often more difficult to manage. Uncontrolled bleeding remains a major challenge, accounting for around 40% of trauma-related deaths.[3] Bleeding in trauma patients is usually caused by a combination of Coagulopathy and vascular injury. Coagulopathy along with hypothermia and acidosis is often termed as the ‘lethal triad’ because of the high mortality and poor outcome.[4]

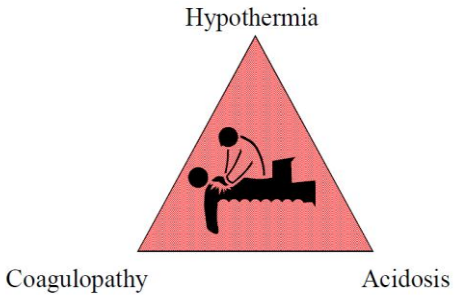

Fig 1: Lethal Triad.

Normal Homeostasis

Before going into the discussion of ATC, let us discuss about the basic mechanism of homeostasis which is body protective mechanism to prevent blood loss. It is a combination of cellular and biochemical process which helps in

1. Limiting blood loss.
2. Maintaining intravascular blood fluidity.
3. Promoting revascularization of thrombosed vessels after injury.

It is a balance between procoagulant pathway (responsible for generation of a stable localized haemostatic plug) and counter regulatory pathway i.e. prevention of thrombus formation beyond the injury site. The process of homeostasis can be broadly classified into two steps—Primary homeostasis and Secondary homeostasis. Primary homeostasis is mainly the process of platelet deposition at the injury site and it helps in prevention of bleeding in minor injury. Secondary homeostasis is a complex phenomenon and it is more in a situation to control significant bleeding. Vascular endothelium has major role in homeostasis. Healthy endothelial cells possess antiplatelet, anticoagulant, and profibrinolytic effects to inhibit clot formation. Negatively charged vascular endothelium produces prostacyclin (PGI_2) and nitric oxide (NO), which are potent platelet inhibitors. Adenosine diphosphatase

(ADPase) synthesized by vascular endothelial cells degrades adenosine diphosphate (ADP), another potent platelet activator. Given these endogenous antiplatelet effects, non activated platelets are no table to remain adhered to the healthy vascular endothelial cells. Vascular endothelium further expresses several inhibitors of plasma-mediated homeostasis which includes.

1. Thrombomodulin (an indirect thrombin inhibitor)
2. Heparin-like glycosaminoglycans.
3. Tissue factor pathway inhibitor (TFPI)
4. Tissue plasminogen activator (t-PA), which is responsible for activating fibrinolysis—a primary counter regulatory mechanism limiting clots propagation.[5]

Now, what happens when there is an Injury?

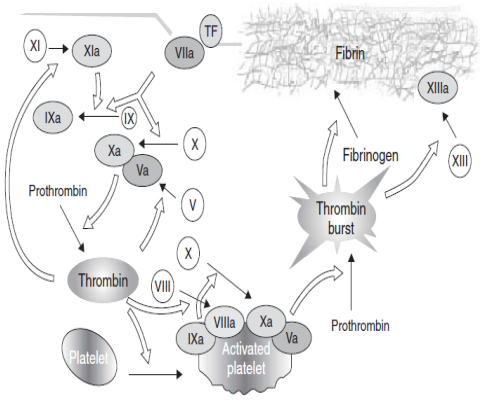

Fig 1: Coagulation cascade following a Injury.

Damage to vascular endothelial cells exposes the underlying extracellular matrix (ECM) including collagen, von Willebrand factor (vWF) and other platelet-adhesive glycoproteins. Platelets bind to and are activated by exposure to ECM components. Exposure of tissue factor, constitutively expressed by fibroblasts in the ECM, activates plasma-mediated coagulation pathways to generate thrombin and ultimately, fibrin clot. Certain cytokines (i.e., interleukin-1, tumor necrosis factor and γ-interferon) and hormones (i.e., desmopressin acetate or endotoxin) induce prothrombotic changes in vascular endothelial cells, including synthesis and expression of vWF, tissue factor, plasminogen activator inhibitor (PAI-1, an inhibitor of fibrinolysis), as well as down regulate normal antithrombotic cellular and biochemical pathways.[6,7] Plasma-mediated homeostasis, the coagulation cascade, might best be summarized as an amplification system to accelerate thrombin generation from an inactive precursor (i.e., prothrombin). Trace plasma proteins, activated by exposure to tissue factor or exposure to foreign surfaces; initiate a cascading series of reactions culminating in conversion of soluble fibrinogen to insoluble fibrin clot.[8]

PATHOPHYSIOLOGY OF ACUTE TRAUMATIC COAGULOPATHY

It is a complex pathophysiology of coagulation disorder which includes

1. Activation or dysfunction of fibrin generation or both.
2. Dysfunction of Platelet and endothelium.
3. Stable clot formation is disturbed by ineffective anticoagulant and fibrinolytic pathways.
4. Consumption or inhibition of coagulation proteases.

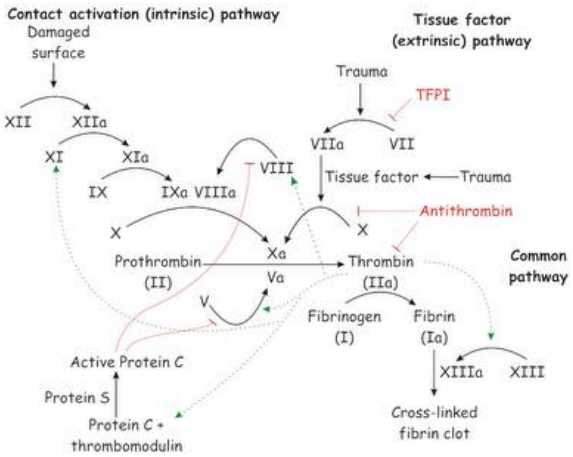

Fig 3: Intrinsic and Extrinsic Pathway of Coagulation cascade.

Correction of fluid deficit with an intention to restore the intravascular volume in cases of trauma has been a common response. In the last decade studies have shown that in trauma cases transfusion of packed red blood cells (PRBC's) and crystalloid infusion contributes to dilutional Coagulopathy. Hypothermia and acidosis also contributes to Coagulopathy and add to continuous blood loss. Shock following acute blood loss or RBC's appears to be the most important factor in the development of Coagulopathy. The initiating factors for Coagulopathy are tissue trauma, shock, hemodilution, hypothermia, acidemia and inflammation.[9]

Conditions leading to Coagulation changes

1. Pregnancy

While handling a case of trauma in a pregnant lady one should bear in mind the physiological changes in pregnant state. The changes are increased heart and the increased cardiac output 30% to 50% before it slows down at the end of the second trimester. There is significant decrease in the total peripheral resistance due to progesterone-related smooth muscle relaxation and thus the central venous pressure slowly drops by third trimester. Blood pressure gradually decreases in the first trimester while during the third trimester, the blood pressure gradually climbs, returning to nearly pre pregnancy readings at term. During pregnancy, blood volume increases by 50%, while red blood cell volume increases only about 30%. This dilution results in the so-called ''physiologic anemia'' of pregnancy. These changes help the pregnant patient to tolerate the increase

in the metabolic demands of the fetus and the expected hemorrhage of childbirth. Around 500-1000 ml of blood loss (which is normal at the time of delivery) typically causes no change in hemodynamic parameters. With significant blood loss, the maternal systemic blood pressure is preserved at the expense of the uteroplacental and splanchnic circulation. Thus, the pregnant trauma patient's vital signs may lead to a false sense of security, because changes in pulse and blood pressure may not occur until hemorrhage of 1500 to 2000 mL.[10] Pregnancy is a state of both increased platelet turnover and clotting. Platelet count can be decreased, but bleeding time remains normal. Clotting factors increase in pregnancy resulting in shortened prothrombin time (PT) and partial thromboplastin time (PTT). The changes observed in the thromboelastogram combined with the above are all suggestive of hypercoagulable state.[11] So the major changes are-

i) Factors VII, VIII, X, XII, vWF and plasma fibrinogen (I) are increased after the 3rd Month.
ii) Factors II, V and IX are unchanged or slightly increased.
iii) Factors XI and XIII are decreased.
iv) 20% decrease in platelet count doesn't increase bleeding time.
v) PT and PTT decreased 20%.
vi) AT3 decreased.

Also there are other coagulation disorders associated with pregnancy like.

a) Gestational Thrombocytopenia: It typically occurs in the 3rd trimester, affects almost 5% pregnancies. It has been observed that in a patient of Gestational thrombocytopenia, Platelet counts are typically > 70,000/μL with 70% of cases platelets are > 130,000/μL.

b) Immune Thrombocytopenia (ITP): ITP occurs 1 to 2 in every 1000 pregnancies which is difficult to distinguish from benign gestational thrombocytopenia. It is mainly due to insufficient production & increased destruction .It may be idiopathic or secondary to medicines, viral, or autoimmune. Severe neonatal thrombocytopenia has been observed in 9% - 15% with reported cases of neonatal intracranial hemorrhage in 1% to 2%.[12]

2. Hemophilias. - It is the best-known coagulation factor disorder. Different types are hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency or "Christmas disease") and hemophilia C (factor XI deficiency, mild bleeding tendency).
3. Von Willebrand disease- It is the most common hereditary bleeding disorder. In this disease, there is a defect in von Willebrand factor (vWF), leading to impairment of the binding of glycoprotein Ib (GPIb) to collagen and ultimately deactivation of platelets.
4. Bernard-Soulier syndrome-It is a defect or deficiency in GPIb. GPIb, the receptor for vWF, can be defective and lead to lack of primary clot formation (primary homeostasis) and increased bleeding tendency.
5. Liver Failure - There is insufficient production of coagulation factors by the liver; this may increase bleeding risk. Vitamin K deficiency may also contribute to bleeding disorders.
6. Thromboembolic disorders- a) venous thrombosis are due to acquired states (older age, surgery, cancer, immobility) or b) inherited thrombophilias - antiphospholipid syndrome, factor V Leiden etc.
7. Hereditary angioedema (type III) essentialism.

Tests for coagulation

While testing for the Coagulation changes, one should keep in mind the other physiological and pathological conditions. In this regard one can quickly go through the common coagulation disorders if possible. Various parameters like INR (International Normalized Ratio), APTT (Activated Partial Thromboplastin Time), platelet counts and fibrinogen levels are considered as indicator of coagulation. Deranged APTT and INR screen the status of coagulation; however, these tests may remain normal in a patient of Coagulopathy. Moreover these tests are time consuming. For a real time picture and as a bed side procedure thromboelastography is now widely used as a point of care tool to detect acute Coagulopathy of trauma. It gives a rapid overview of the factors in the coagulation system like initiation factors, fibrinogen, platelet function and fibrinolytic components.[13] The pregnant patient may warrant more laboratory testing than other trauma patients. These laboratory tests should include hemoglobin, hematocrit, typing and cross matching, and a gross inspection of the urine. A serum bicarbonate level, blood gas analysis, or lactate level may be considered because there is some evidence that maternal acidosis may be linked to fetal outcome.[14,15,16] Prenatal laboratory tests may be helpful for comparison. Placental abruption may be added to the list of possible causes of disseminated intravascular coagulation (DIC) in trauma. A fibrinogen level that is normal in a non pregnant patient may be an early indicator of DIC and placental abruption in a pregnant trauma patient. A Kleihauer-Betke (KB) test may be considered in an Rh-negative patient with significant trauma.[17]

MANAGEMENT

Most of the recommendations are based on the updated European Guideline by Spahn et al. in 2013. This is a consolidated guideline with details of rationale and it helps to set an Institutional protocol. Here we have emphasized on the salient features of this guideline. It depends on the Institution to standardize the protocol depending on the level of care provided and availability of well equipped emergency department(ED) and blood bank. But every physician should know the concept specially working in the ED to provide a better care and to minimize the incidences of iatrogenic Coagulopathy by overt fluid resuscitation.[18]

I. Initial resuscitation and prevention of further bleeding- Minimal elapsed time

Trauma patients in need of emergency surgery for ongoing hemorrhage have increased survival if the elapsed time between the traumatic injury and admission to the operating theatre is minimized. More than 50% of all trauma patients with a fatal outcome die within 24 h of injury.[19]

II. Tourniquet use

Tourniquet application has become standard of care for the control of severe hemorrhage following military combat injuries and several publications report the effectiveness of tourniquets in this specific. A study of volunteers showed that any tourniquet device presently on the market works efficiently. The study also showed that 'pressure point control' was ineffective because collateral circulation was observed within seconds. Tourniquet-induced pain was not an important consideration. Tourniquets should be left in place until surgical control of bleeding is achieved. Reports from military settings report cases in which tourniquets have remained in place for up to six hours with survival of the extremity.[20]

III. Ventilation

avoid hyperventilation.

IV. Diagnosis and monitoring of bleeding – investigation

early imaging-FAST to CT/multi-slice CT (MSCT), do not recommend the use of single haematocrit measurements , recommend both serum lactate and base deficit, Coagulation monitoring (INR and APTT), Thrombo elastometry-for more accurate targeting of therapy.

V. Damage control surgery

Immediate intervention and rapid control of bleeding. Also recommendation is that early bleeding control of the abdomen be achieved using packing, direct surgical bleeding control and the use of local haemostatic procedures. Aortic cross-clamping may be employed as an adjunct in an exsanguinating patient. Damage control surgery is employed in the severely injured patient presenting with deep hemorrhagic shock, signs of ongoing bleeding and Coagulopathy. Other factors to be considered for damage control approach are severe Coagulopathy, hypothermia, acidosis, an inaccessible major anatomic injury, a need for time-consuming procedures or concomitant major injury outside the abdomen.[18]

I. Volume replacement

target SBP of 80 to 100 mmHg until major bleeding has been stopped - concept of low-volume fluid resuscitation, so-called 'permissive hypotension. Crystalloid should be applied initially for bleeding trauma patients. Hypertonic saline to be considered for hemodynamic ally unstable patients. Addition of colloid to be considered within the prescribed limits for each solution in hemodynamic ally unstable patients.

a) Fluid therapy

addition of colloids is considered. Recent study showed that overly aggressive fluid treatment accelerated hepatocellular injury while another suggested that slower rates of fluid resuscitation led to improvements in cell mediated immunity.[21] Numerous studies have shown that immediate fluid resuscitation caused increases in the rate, volume and duration of hemorrhage. Before discussing human data on restrictive resuscitation strategies, it must be noted that all strategies that permit hypotension are absolutely contraindicated in patients with traumatic brain injury (TBI). It has been shown that even a single episode of hypotension causes a doubling of mortality in this patient population. In the presence of uncontrolled hemorrhage in patients with concurrent TBI, prevention of secondary brain injury from hypotension is crucial as a SBP <90 mmHg is associated with poor outcomes. Infuse of small aliquots of fluid (100-200 ml) to maintain SBP above 90 mmHg is the present concept.[22] Concept of permissive hypotension should be carefully considered in the elderly patients and are relatively contraindicated in patients with chronic arterial hypertension, carotid stenosis, angina pectoris and compromised renal function. If we look at the concept of Damage control resuscitation (DCR), three limbs of the approach are.

i) Early delivery of blood component therapy (PRBC, plasma, platelets)
ii) Permissive hypotension and
iii) Minimal crystalloid based resuscitation

X. Normothermi

achieve and maintain normothermia. Hypothermia is associated with an increased risk of severe bleeding, and hypothermia in trauma patients represents an independent risk factor for bleeding and death. The effects of hypothermia include altered platelet function, impaired coagulation factor. 1ºC drop in temperature is associated with a 10% drop in function), enzyme inhibition and fibrinolysis.[18]

XI. Management of bleeding and coagulation

1. Erythrocytes- target Hb of 7 to 9 g/dl.

2. Coagulation support: Research work done during Gulf-war documented improved survival using protocol of PRBC: FFP: Platelet in 1:1:1 fashion**.** Early FFP in patients with massive bleeding is to be considered. Platelet transfusion is mainly to maintain the platelet count above 50 × 109/L in a patient of trauma who are severely bleeding or have TBI. Tranexamic acid 10-15 mg/kg followed by infusion of 1-5 mg/kg/h is recommended in some cases.

3. Calcium-calcium chloride be administered during massive transfusion if findings are s/o hypocalcaemia

4. Fresh frozen plasma-thawed FFP in patients with massive bleeding is recommended. The initial dose is 10 to 15 ml/kg.
5. Platelets- Maintenance of a platelet count above 100 × 10^9/l in patients with multiple traumas who are severely bleeding or have TBI is desirable.
6. Fibrinogen and cryoprecipitate- If significant bleeding is accompanied by thromboelastometric signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5 to 2.0 g/l .Recommendation is an initial fibrinogen concentrate dose of 3 to 4 g or 50 mg/kg of cryoprecipitate, which is approximately equivalent to 15 to 20 units in a 70 kg adult.
7. **Antifibrinolytic agents-**Tranexamic acid 10 to 15 mg/kg followed by an infusion of 1 to 5 mg/kg per hour or ε-aminocaproic acid 100 to 150 mg/kg followed by 15 mg/kg/h.
8. Activated recombinant coagulation factor VII - consider if major bleeding in blunt trauma persists despite standard attempts to control bleeding and best-practice use of blood components.
9. Prothrombin complex concentrate-for the emergency reversal of vitamin K-dependent oral anticoagulants.
10. Desmopressin-not routinely recommended - considered in cases of refractory micro vascular bleeding.

Trauma Exsanguinations Protocol (TEP)
Recent studies have noted a dramatic reduction in mortality amongst severely injured patients when trauma exsanguinations protocols (TEP) are employed. Exsanguinating hemorrhage has been addressed by the development of transfusion protocols in a number of trauma centers' specifically designed by multidisciplinary committees, consisting of surgeons, anesthesiologists, hematologists and blood bank personnel, to restore blood loss after a severe injury, these trauma exsanguinations protocols (TEP) aim for the appropriate replacement of blood product ratios and minimization of crystalloid-based resuscitation. Recent studies have demonstrated substantial improvement in survival of critically injured trauma patients managed with TEP.[23] It creates a framework for the Operating Room (OR) to access large quantities of blood products for patients with injuries likely to result in rapid and massive blood loss. Main concept is based on the goal to restore blood volume, tissue perfusion and oxygenation, achieve homeostasis via surgical control and Coagulopathy and ensure prompt action and communication between the OR, Lab and blood bank. Action is started by the attending trauma surgeon based on physiology/injury complex. Initial Blood Bank Response: 10 RBC's (O positive for males and females with expected age>50 and O negative for females with expected age <50), 6 AB FFP, 2 platelet aphaeresis units. Products are sent to the OR in a blood cooler (platelets in external mesh bag). If FFP is not thawed at the time the PRBCs and platelets are ready, PRBC and platelets are sent with follow up of the as soon as it is ready. Additional coolers are prepared immediately and supplied to the OR on demand. The 2nd and subsequent rounds consist of: 6 RBC's (type specific if typing complete), 4 FFP (type compatible if typing complete), 1 platelet dose (RDPs if type complete). Anesthesiology team administers all products sent in cooler (as volume management requires). Continue with this process until additional products are no longer needed. All TEP activations reviewed as part of the Trauma Performance Improvement Program.

CONCLUSION

To conclude, this is a vast topic which should be viewed from multiple angles in terms of physiological changes. In the last decade, lots of scope for studying the physiology and outcome were there which enriched us with the findings. Discussing over and again the concept and management of Coagulopathy give us the stimulus for research work. The most important aspect is control of bleeding, early damage control surgery with maintaining a lower mean arterial pressure till control of bleeding. Transfusion of blood and blood products at an early stage should be encouraged. Volume expanders should be used carefully. Also consideration should be there for other conditions leading to Coagulopathy. Not only the trauma management centers' but also the emergency department of all the hospitals should come up with a guideline of their own depending on the availability of Blood Bank and investigation facility. One should be cautious about the transfusion protocol and likely complications associated with blood and blood products, more so when there is a massive transfusion.

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