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MINIREVIEWS

Acute coagulopathy of trauma: Mechanism, monitoring, management

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Abstract

Coagulopathy is a well-known consequence of trauma and is the most common cause of mortality in the young. However, its cause and management is still controversial. A new concept in the understanding of coagulopathy in trauma is the occurrence of Acute coagulopathy of trauma (ACoT). ACoT is associated with hypo perfusion and tissue trauma as seen in massive injury. The incidence of coagulopathy increases with injury scores and is associated with higher number of ventilator days, higher morbidity and mortality. The process of coagulation is better described by the cell based model with a central role for platelets rather than the older plasma based model. This shift in our understanding supports the theory that ACoT results from the endothelial release of thrombomodulin and activated protein C in the presence of hypoperfusion. This in turn leads on to a hyperfibrinolytic and hypocoagulable state. Viscoelastic hemostatic assays are replacing the older tests like prothrombin time in the assessment of coagulopathy. These tests are accurate, determine the need for transfusion and can be performed at the point of care. Damage control resuscitation includes newer concepts like permissive hypotension, increased use of plasma as a part of massive transfusion protocols and damage control surgery.

Key words: Trauma; Coagulopathy; Massive transfusion; Bleeding; Thromboelastography

Core tip: Coagulopathy associated with trauma is a poorly understood and managed complication seen in severely injured patients. Acute coagulopathy of trauma, as it is currently described is attributed to trauma shock and associated tissue hypoperfusion. The traditionally attributed causes of acidosis and hypothermia contribute to a delayed form of coagulopathy, which is now considered different from early coagulopathy. Timely and appropriate use of blood and blood products along with the management of hypotension is termed damage control resuscitation. Early treatment to reverse and prevent acidosis, hypothermia and coagulopathy is the main focus.

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INTRODUCTION

World wide, injury due to trauma is the major cause of morbidity and mortality in young adults[1,2]. About half of all deaths during the initial hours following trauma are due to uncontrolled bleeding[3]. Localised anatomical bleeding from vessel or tissue injury is a potentially preventable cause of death and standard trauma protocols prioritise this appropriately[4]. Another cause for bleeding, which is not as well understood or managed, is due to coagulopathy[5]. Presence of coagulopathy in injured

patients results in a fourfold increase in overall mortality, higher intensive care unit (ICU) admission rate, longer hospital stay and a higher rate of organ failure[6,7].

Coagulopathy seen in injured patients was initially considered a response to massive bleeding, dilution associated with massive fluid resuscitation, hypothermia and acidosis. As a result, among the "lethal triad" of trauma, namely, hypothermia, acidosis and coagulopathy, most treatment protocols aim at correcting or preventing hypothermia and acidosis without directly addressing coagulopathy[8]. This view has undergone a sea change in the last ten years recognizing coagulopathy as an independent prognostic factor and current concepts in damage control resuscitation (DCR) emphasize addressing all three components of the lethal triad following trauma at admission[9]. Acute coagulopathy of trauma (ACoT), trauma induced coagulopathy or ACoT shock are all newer terms used to describe coagulopathy seen in injured patients[5].

ACoT has been the subject of intense research especially over the last five years resulting in a large volume of literature. There is however no consensus on its pathophysiology nor is there a recommended management strategy. This is in part because of the difficulty in formatting and testing new guidelines for a condition that is seen in only about 1%-2% of patient population[10]. There is also a general lack of awareness of the significance of ACoT. This review is an attempt to summarise the state of science in ACoT.

MECHANISM

The initiation of the coagulation pathway always results in the activation of the inflammatory system. When this activation is widespread, the inflammatory response initiates a downward spiral rapidly leading on to organ failure and death. Recent advances in trauma research have provided newer insights into this complex process. An important offshoot of this understanding is the incorporation of aggressive and targeted hemostatic control resuscitation or DCR in trauma protocols[8,11,12].

A landmark paper by Karim Brohi analyzing data from 1088 United Kingdom civilian trauma patients over 5 years reported that about one fourth of all trauma victims had a disturbed coagulation profile on admission[1]. This study defined a disturbed coagulation profile as a prothrombin time (PT) or an activated partial PT (aPPT) 1.5 times the normal. Significantly, coagulopathy was more likely in patients with higher injury severity scores and had no relation to the volume of intravenous fluids administered in the pre-hospital setting for resuscitation. This study also found coagulopathy to be an independent predictor of mortality. Karim Brohi's paper set the direction for research on coagulopathy in establishing coagulopathy as an event which set in early. Many other studies found similar results although the definitions for coagulopathy varied. A study by MacLeod *et al*[7] found the presence of coagulopathy in 28% of trauma patients on admission. Maegele *et al*[13] in a retrospective study found 34.2% patients coagulopathic on admission following blunt trauma. It can be reasonably concluded from these studies that about one third of patients admitted following trauma have early onset coagulopathy.

The last ten years have witnessed a shift in the understanding of the coagulation process from a plasma borne factor cascade with fibrin as a central player to a cell-based theory centred around platelets[14]. The haemostatic process is now described as occurring in three phases, initiation, amplification and propagation. Initiation occurs when tissue factor activates V, IX, X and produces a small amount of thrombin. The amplification phase involves platelet activation causing thrombin burst, which ultimately leads on to fibrin and clot formation in the propagation phase.

Shock and tissue hypo-perfusion are now considered central to the initiation of ACoT[15]. This is in contrast to the traditionally accepted causes of coagulopathy in trauma, namely, consumption, dilution, dysfunction, hypothermia and acidosis. According to current concepts, these factors come into play much later. It is therefore easy to understand the mechanism of ACoT by differentiating coagulopathy as early (primary, endogenous response) and late (acquired, systemic response)[5,8].

Tissue hypo-perfusion

A fine balance between procoagulant and anticoagulant pathways exists to prevent clot propagation beyond the site of injury. Plasmin, responsible for fibrinolysis, exists as plasminogen in its inactive form. Tissue plasminogen activator (tPA) is inhibited by plasminogen activator inhibitor (PAI). Thrombomodulin secreted by the endothelium complexes with thrombin and activates protein C which in turn inactivates factors V and VIII irreversibly thereby disrupting the procoagulant process[16]. It also inhibits PAI disinhibiting tPA which leads to the conversion of plasminogen to plasmin and results in fibrinolysis.

Tissue hypo-perfusion leads to excessive endothelial expression of thrombomodulin which binds to thrombin and this complex results in the activation of protein C pathway and hence the fibrinolytic cascade[15]. Brohi *et al*[15] in an important study involving 208 trauma patients found hypoperfusion (defined as base deficit > 6) to be associated with coagulopathy [defined as activated partial thrombin time (aPTT) or PT values > 1.5 times the normal]. These patients had elevated levels of thrombomodulin- thrombin complex and reduced protein C levels, indicating an increased activation of protein C. Platelet count and fibrinogen levels were found to be normal implying that thrombin was unavailable to cleave fibrinogen and to consume platelets. Thus, they concluded that it is the enhanced activity of activated protein C that is central to ACoT[17,18].

In a translational mouse model it was demonstrated that a combination of tissue trauma and hypo-perfusion is prerequisite for early coagulopathy to manifest[3,8] Hypocoagulability is often seen in the presence of acidosis due to decreased factor activity. However, early in trauma, there appears to be coagulopathy even with mild academia. This is due to the shock and state of hypo-perfusion which

results in anticoagulation and hyperfibrinolysis[5,19,20]. It is seen that platelet counts are generally normal[5,13,15].

Tissue injury

Endothelial damage secondary to injury exposes sub endothelial type Ⅲ collagen and tissue factor that trigger the initiation of clot formation and thrombin release. Endothelial injury also releases tPA in the presence of thrombin and in the presence of ischemia, results in excess fibrinolysis. Traumatic brain injury causes release of thromboplastins and phospholipids which also ultimately result in inflammation and fibrinolysis. Injury severity is closely associated with coagulopathy and therefore with mortality[5,13,15,21]. Hyperfibrinolysis is clearly a direct consequence of shock and tissue injury[8].

Hypothermia

Hypothermia, defined as core body temperature lower than 35 degrees C, has an incidence of 1.6% to 8.2% in trauma victims[9]. Hypothermia in trauma occurs either spontaneously as a result of radiation heat loss due to over exposure or secondary to aggressive fluid resuscitation. Impaired heat production due to reduced muscle perfusion also contributes to hypothermia. Hypothermia in trauma is found to be directly related to injury severity.

The activity of proteases decreases linearly and proportionally with temperature resulting primarily in platelet dysfunction[22-25]. There is a decrease in interaction between vWF and collagen glycoproteins 1b and X leading to decreased platelet activation. Clinically significant effects on coagulation and platelet function are seen below 34 ℃. However since most trauma patients present in mild to moderate hypothermia (33 ℃-36 ℃), it rarely has an effect, in isolation, on coagulation[5]. Coagulopathy is worsened by the resulting vasoconstriction due to sympathetic response to hypothermia. Hypothermia also leads to acidosis and therefore worsens coagulopathy. Mortality reaches 100% when temperature falls below 32 ℃.

Acidosis

Acidosis is common in trauma and is attributed either to hypo-perfusion or administration of chloride-based fluids or a combination of the two. It significantly alters platelet physiology as well as clotting factor activity to varying degrees. Affinity to calcium binding sites is reduced, as is thrombin clot propagation. In general, at a pH of 7.2, activity of factor Xa/Va reduces by 50%, platelet count reduces by 50% and fibrinogen reduces by 35%[23].

Hemodilution

Aggressive fluid resuscitation leads on to dilution of clotting factors. Transfusing whole blood devoid of clotting factors as well as inhibition of clotting mechanism by colloid infusions contribute to coagulopathy[26]. Fluid resuscitation can also lead on to a fibrinolytic state by diluting the antifibrinolytic proteins[27,28].

Inflammation

Trauma induces systemic inflammatory response syndrome due to both humoral and systemic activation of inflammatory mediators early in its course[28]. Inflammatory system is closely related to the coagulation and complement systems. Endothelial activation, by itself and by the activation of coagulation proteases and protein C through thrombomodulin results in a widespread inflammatory response. This response is effected by transmembrane protease receptors on cell surfaces and complement system through the alternate pathway[16].

To summarise, the pathophysiology of coagulopathy is a complex multifactorial process with several unexplained responses. Shock and tissue hypoperfusion are central to the initiation of early coagulopathy of trauma by the thrombomodulin-activated protein C (aPC) pathway. This is the primary or endogenous response and it occurs very early following injury. As resuscitation proceeds, hemodilution, hypothermia and acidosis further exacerbate coagulopathy either due to loss, by consumption or dilution, inhibition or dysfunction. This is known as the systemic acquired coagulopathy[17]. It is now generally accepted that primary and secondary coagulopathy are to be considered as separate entities. The role of inflammation and tissue injury in primary coagulopathy is not fully understood[3]. A late prothrombotic phase sets in after the depletion of aPC and there is a time lag before the liver synthesises protein C. Inflammatory process also shifts the hemostatic response in favour of thrombosis[12]. There is a real risk of thromboembolic complications during this phase. ACoT is associated with increased mortality, more days on ventilator, longer ICU and hospital stay and greater likelihood of receiving blood and products[1,7,13,15].

There is opposition to this theory, with one group reporting similarity between disseminated intravascular coagulation (DIC) and the early coagulopathy seen in trauma. This group describes early coagulopathy of trauma as DIC with a fibrinolytic phenotype manifesting as hyperfibrinolysis and consumption coagulopathy contributing to massive haemorrhage. This, at a later stage of trauma, establishes as DIC with a thrombotic phenotype resulting in fibrin clot deposition and subsequent organ dysfunction. It is argued that all the six factors discussed above lead on to similar nonspecific inflammatory and haemostatic responses[29].

ASSESSMENT AND MONITORING

The main challenges faced in monitoring injured patients are to rapidly diagnose patients who are hypocoagulopathic and in fibrinolysis, to assess adequacy of tissue perfusion and to accurately predict the need for massive transfusion.

All injured patients, especially those following high energy trauma, should be suspected of having ACoT. Massive bleeding, tachycardia, hypotension, weak pulses, altered mentation, oliguria are indicators of severe injury. Presence of hypoperfusion is suspected if there is an increase in base deficit or serum lactate levels. ACoT is defined as a functional reduction in clot strength with a smaller change in clotting time. There is however no clear

consensus on what lab values can determine the presence or absence of ACoT[30,31].

Routine coagulation tests (RCoT), namely, PT and PTT have been traditionally used to assess coagulation. A value of international normalized ratio > 1.2 is regarded as the clinically significant threshold for defining ACoT[3]. Plasma based assays, like PT and PTT, have many limitations as they have limited utility in monitoring coagulopathy or in guiding transfusion therapy in trauma[32]. RCoTs assess a small part of the plasma-based component of coagulopathy pertaining only to thrombin formation. As a generalization, these tests assess only the initial 20 s of the clotting mechanism[19]. Further, studies have shown no correlation between these assays and the presence of clinically significant bleeding or with clotting factor activity[33]. These assays were developed half a century ago to monitor haemophilia and anticoagulation therapy. With the shift in understanding of coagulation to a cell based theory and the more recent concepts of ACoT and DCR, there is an urgent need felt for reliable haemostatic assays to guide therapy.

Viscoelastic hemostatic assays (VHA) assess the whole blood components of coagulation including platelet function. The common VHAs in practice are thromboelastography, thromboelastometry and platelet function analysis[2,34]. These tests have several advantages. They assay the whole blood with all the components of coagulation, results are available in a short time, end points are clinically relevant and they have been shown to correlate well with patients who have clinically significant bleeding requiring transfusion. They also correlate well with the cell based model, hence referred to as cell based assays. Recent studies have shown a hypocoagulable picture in the early phase of trauma with the use of VHA while the results of RCoT in the same group of patients were normal. VHAs can identify patients with increased fibrinolysis[35] and can be used to predict patients requiring massive transfusion[31]. One study demonstrated a significantly lower mortality rate in bleeding patients when VHA was used to guide the administration of blood and blood products. There are two main lacunae identified with respect to the use of VHAs in clinical practice. Firstly, there is no universally accepted definition of clinical coagulopathy defined by thromboelastography or thromboelastometry (TEM) and there is a need to standardize the methods[20]. Secondly, their value in predicting coagulopathy in the patients who are on antiplatelet therapy is not known[19].

Presence of two or more abnormal values from clot initiation, amplification or clot strength and stability is regarded as clinical coagulopathy by most centers[36]. TEM has been shown to detect coagulopathy in ten minutes and this is available at the point of care. Rotational thromboelastometry can identify ACoT in 5 min when defined as a clot amplitude lesser than 35 mm[3]. Some smaller series have even suggested using VHAs for goal directed therapy[34,37,38]. TEM is also useful in differentiating the causes of coagulopathy thereby suggesting appropriate correction[31,39].

MANAGEMENT

Currently used guidelines for management of injured patients reflect the deeper understanding of the pathophysiology of trauma in general and coagulopathy in particular. The conventional approach where the primary goal for resuscitation in trauma shock was to maintain blood pressure, urine output and to reverse metabolic effects of tissue hypoperfusion failed to address coagulopathy[40,41]. In contrast, DCR is targeted at proactively managing the physiological consequences of injury by following a hemostatic resuscitation strategy that controls bleeding in order to avoid death[42]. Early treatment to reverse and prevent acidosis, hypothermia and coagulopathy is the main focus. Damage control surgery is an operative strategy wherein the focus is shifted from completion of surgical repair to a minimal approach to limit the physiological consequence of surgery superimposed on that caused by trauma. Administration of blood products and factors in order to minimise blood loss, maximise oxygen transport and tissue oxygenation is the main goal. This is done by utilising seven key steps.

It is important to recognize that this approach is reserved only for the most seriously injured patients in coagulopathy amounting to about 10% of trauma victims. Though the involved group is proportionally smaller, this is the group with maximum mortality[9]. DCR as a structured intervention begins immediately following rapid assessment, continues into the operation room and further in the ICU[9]. Resuscitation aiming at tissue oxygenation, interventions to prevent or ameliorate coagulopathy and surgical intervention aiming at rapid control of bleeding should take place simultaneously.

Permissive hypotension

Aggressive fluid resuscitation is indicated in injured patients to ensure tissue perfusion[40,41]. Recent studies focusing on adverse effects of large volume infusions found that patients receiving less than 1500 mL of fluids in the pre-hospital setting had a higher chance of survival than patients who received higher volumes. The incidence of coagulopathy was higher (> 40%) when volumes more than 2000 mL was given[7,43,44]. Incidence of secondary abdominal compartment syndrome also increased with increased fluid administration[43]. There is no consensus on the choice of fluid for resuscitation with studies comparing colloids and crystalloids being inconclusive[19]. Some studies have shown benefit with hypertonic crystalloids and found hypotonic crystalloid administration to be harmful.

Permissive hypotension is based on the concept that maintaining a low volume fluid resuscitation avoids adverse effects of large volume infusions[19,45]. Also, in order to support clot formation, a lower mean arterial pressure of 65 mmHg and a systolic blood pressure of 90 mmHg is preferable till bleeding is surgically arrested. This strategy is beneficial as long as the delay in achieving such control does not exceed 120 min[46].

Fluids are used sparingly while maintaining perfu-

sion[45]. In a recent prospective study involving trauma patients presenting with shock, patients who received hypotensive resuscitation with restricted fluid administration had lesser incidence of coagulopathy and better 24 h postoperative survival rate. Permissive hypotension is contraindicated in the presence of traumatic brain injuries, coronary artery disease or hypertension[47].

Blood products

Transfusion protocols administering red blood cells (RBCs), plasma and platelets in the ratio of 1:1:1 in patients requiring massive transfusion have been found to lower mortality rates as well as reducing the requirement for multiple transfusions[9,48,49]. Massive transfusion (MT) protocols are controversial and there are no guidelines or randomised control trials that have evaluated the correct ratio of blood and products to be administered.

There is evidence to suggest that an increased ratio of fresh frozen plasma (FFP) to packed RBC (pRBC) reduces mortality in injured patients receiving MT. Duchesne found a lower mortality rate in patients receiving MT with a FFP to pRBC ratio of 1:1 when compared to ratio of 1:4[50]. Magele also found a similar reduction in mortality when the ratio was close to 1:1[13]. Bhangu *et al*[51] in a meta analysis found a reduced mortality in patients receiving FFP to pRBC in a ratio of 1:2 and no further reduction in mortality was found when the ratio was increased to 1:1. Snyder, in a retrospective study on trauma patients requiring MT, reported a reduced 24 h mortality when FFP and pRBC were given in a ratio of greater than 1:2[52]. Holcomb *et al*[49] reported an association between higher ratio of plasma and platelet to blood pRBC with increased survival.

Currently, protocols have been developed to counter the dilutional effect of MT. Early recognition of patients requiring massive transfusion is key and is often very difficult to predict as the definitions require waiting for a period of 24 h. Hence, the trigger for initiating MT protocol is largely based on hemodynamic variables, laboratory tests and injury severity scores[53]. Selected patients receiving a high ratio of FFP to pRBC during surgery are found to have decreased intraoperative coagulopathic bleeding, and are warm, euvolemic and nonacidotic following surgery[9,12]. A high ratio of FFP to RBC has shown an improvement in mortality[54]. European guidelines recommend plasma transfusion at an early stage in patients with massive bleeding[19]. However, it is important to note that this proactive strategy should not be adopted in patients who have already been stabilised or in the presence of minor injuries to prevent unnecessary exposure to transfusion related complications and risks[2].

Rewarming

Attempts to prevent loss of body temperature should be initiated as early as possible. Only warmed fluid infusions (at a temperature of 40 ℃ to 42 ℃) should be administered[17]. Passive and active warming techniques should be adopted. The steps that are suggested to prevent and treat hypothermia include passive methods like covering the patient to avoid heat loss and active methods using fluid warmers, forced air warmers and in severe cases extracorporeal rewarming[19]. Operating room should be at a thermally neutral temperature of 28 ℃-29 ℃[54].

Correction of acidosis

The severity of shock and hypoperfusion can be assessed indirectly by measuring serum lactates and base deficit. Serial values of lactate are useful in predicting survival as well as in assessing response to therapy. Similarly, base deficit can independently predict mortality and is especially useful in inebriated patients likely to have falsely elevated lactate levels. Restoration of normal perfusion aimed at correcting base deficit and pH is the main stay of treating and preventing acidosis. MT of blood also exacerbates acidosis and requires scrupulous monitoring. It is aggressively managed by maintaining volume with blood and products and administering Tromethamine[9].

Calcium homeostasis

Calcium is necessary for fibrin clot stabilisation. Hypocalcemia (< 0.9 mmol/ L) should be treated[55]. Hypocalcemia is aggravated by rapid infusion of blood products and also due to chelation of calcium by the anticoagulant citrate. Low levels of ionised calcium are associated with higher mortality and increased need for blood transfusion.

Pharmacological methods of controlling bleeding

Local modalities: Application of fibrin glue, hemostatic bandages and argon lasers reduce blood loss even in the presence of coagulopathy[19,54].

Antifibrinolytics: Tranexamic acid (TxA) was studied in a double blinded, randomised, multi centric trial (clinical randomisation of an antifibrinolytic in significant hemorrhage) involving 10060 adult trauma patients, with 1 g of tranexamic acid administered over 10 min, 1 g over the next 8 h, irrespective of the risk of hemorrhage. Another 100067 patients received saline. TxA significantly reduced "all cause" mortality and mortality due to bleeding[56]. It should be administered within 3 h of trauma, in a dose of 1-2 g over 10min and repeat 1 g over 8 h[19,54].

Recombinant factor Ⅶ: Very high dose of recombinant factor Ⅶa (rFⅦa) are required for the formation of tissue factor complex to activate the clotting system. It bypasses several steps of coagulation and interacts directly with activated platelets to form thrombin. Early use of rFⅦa was associated with a decreased 24 h and 30 d mortality in severely injured combat patients[57]. Hospital length of stay, days on ventilator, blood and FFP requirements were shown to be reduced. rFⅦa may be used in blunt trauma where all the standard methods have failed to control bleeding. However, a large multicentric phase Ⅲ trial was terminated recently due to its futility as the planned reduction in mortality could not be achieved[54]. The administration of rFⅦa is associated with a higher incidence of thromboembolism. It is imperative that several concomitant factors be maintained at certain levels:

fibrinogen > 1 g/dL, Hb > 7 g/dL, platelets > 50000 cells/L, Ca^{2+} > 0.9 mmol/L, temperature > 34 degree C and pH > 7.2. The therapeutic dosage for this factor is still not known[58]. Off label, the drug is administered at a dose of 90 μg/kg of body weight. It's safety is not established as yet.

Combination of fibrinogen and prothrombin complex concentrates: Fibrinogen levels are the first to decline in case of haemorrhage[59]. Use of prothrombin complex concentrates (PCC) can reduce the risk of transfusion associated acute lung injury and other viral infections. In a study on combat related trauma requiring massive transfusion, high fibrinogen to RBC ratio (> 1 g/L to 5 units packed RBCs) was found to decrease death from haemorrhage. A fibrinogen level of > 1.5 g/L should be maintained following trauma[55] and transfusion of fibrinogen or cryoprecipitate may be considered if it is below this level. PCC or a complex of factors Ⅱ, Ⅶ, Ⅸ, Ⅹ is found to shorten the time to coagulation and reduce blood loss following trauma[54].

Rapid control of bleeding

Damage control surgery is employed for trauma patients who are in hemorrhagic shock, acidotic (pH < 7.2), hypothermic (temperature < 34 degrees C) and coagulopathic[19]. These patients are at the ends of their physiological reserves. Damage control surgery involves techniques of planned temporary sacrifice of normal anatomy to preserve physiology like abbreviated laparotomies, packing for uncontrolled bleeding, diversion of injured ureter and so on[12,20].

Thromboprophylaxis: Pharmacological techniques of thromboprophylaxis should be started 24 h after bleeding has been controlled.

CONCLUSION

The last five years have seen tremendous advances in our understanding of ACoT. Though we are far from having all the answers, it is understood that coagulopathy sets in much earlier than traditionally believed. Trauma shock and tissue hypo perfusion are central to the causation of early ACoT. Routine tests of coagulation are ineffective in diagnosing or monitoring coagulopathy and should be replaced by better tests. Presently viscoelastic hemostatic assays are the most reliable among existing tests in monitoring coagulopathy. Damage control resuscitation is the umbrella term to several measures, including but not limited to permissive hypotension, plasma transfusions, recombinant factors, that can counter worsening of coagulopathy and result in a reduction of morbidity and mortality.

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