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REVIEW

# The coagulopathy of massive transfusion

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Recently, the Groupe d'Intérêt en Hémostase Périopératoire reviewed the pathophysiology of coagulopathy in massively transfused, adult and previously haemostatically competent patients in both elective surgical and trauma settings. In this article, we focus on our main observations.

First, in most cases, the onset and severity of coagulopathy associated with massive transfusion differs depending on whether haemorrhage occurs as a result of trauma or elective surgery. In trauma patients, tissue trauma is uncontrolled, the interval between haemorrhage and treatment can vary widely, hypovolemia, shock and hypothermia are frequent, and coagulopathy is often related to the development of disseminated intravascular coagulation. Monitoring of haemostasis occurs late, when coagulopathy is installed, and treatment can be very difficult. In elective surgery patients, the situation remains controlled and, in most cases, a decrease in fibrinogen concentration is observed initially while thrombocytopenia is a late occurrence. Monitoring of haemostasis is ongoing and treatment is usually much simpler.

Second, blood products have changed over time and this has affected the management of the bleeding patient. Contrary to the recommendations of studies published at a time when whole blood was readily available, the first line of treatment (at least in elective surgery patients) ought to be with fresh-frozen plasma to correct decreased levels of coagulation factors. The role of recombinant activated factor VII to treat bleeding that cannot be controlled by conventional measures remains to be clarified.

Coagulopathy associated with massive transfusion remains an important clinical problem. Treatment strategies must be adapted to the context and to the blood products available. Nevertheless, the level of evidence supporting specific treatment options is low and more studies are required to guide our management of massively transfused patients.

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Uncontrolled haemorrhage and, by way of consequence, massive transfusion, are frequent complications of trauma and surgery. Massive transfusion is defined commonly as the replacement of one blood volume in a period of 24 h, but a dynamic definition of massive transfusion, such as the transfusion of four or more red cell concentrates within 1 h when ongoing need is foreseeable [1], or the replacement of 50% of the total blood volume within 3 h, is more relevant in the acute clinical setting. Massively transfused patients will show evidence of coagulopathy in a high percentage of cases. The treatment of these patients is extremely difficult and the optimal management of coagulopathy remains unclear [2].

In 2004, in an attempt to clarify the situation, the Groupe d'Intérêt en Hémostase Périopératoire (GIHP; Perioperative Haemostasis Interest Group) reviewed the pathophysiology and implications for clinical management of massive

In this article, the term 'coagulopathy' is used interchangeably with the more general term 'defective haemostasis' and encompasses defects of both primary haemostasis (related to platelet count and function, and to von Willebrand factor) and coagulopathy (related to alterations of the plasma phase of coagulation).

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transfusion and coagulopathy. Details of this work have been published previously [3]. A narrative format was adopted because the heterogeneity of published studies is considerable and was not conducive to a more formal review. Obviously, the GIHP did not generate new knowledge. Nevertheless, the GIHP was able to highlight important points that should be helpful to those involved in the care of these patients. This review focuses on our main observations. First, in most cases, the onset and severity of coagulopathy associated with massive transfusion differs depending on whether haemorrhage occurs as a result of trauma or elective surgery. Second, blood products have changed over time and this has affected the management of the bleeding patient. We revisit these points briefly.

## Haemorrhage as a result of trauma or elective surgery

Coagulopathy is secondary to a number of factors. Some will be common to both situations, but others will be more prevalent and/or difficult to control in the context of trauma. The main differences between trauma and elective surgery are presented in Table 1. Volume replacement with crystalloids and colloids will result in the haemodilution of red cells and platelets, compromising primary haemostasis. In addition, colloids may interfere *per se* with coagulation, but the clinical significance of the phenomenon remains unclear.

Hypothermia (temperatures below 35 °C) is an important contributor to coagulopathy. It causes a reversible platelet dysfunction, alters coagulation and enhances fibrinolysis. Unfortunately, the contribution of hypothermia to the haemorrhagic diathesis may be overlooked because coagulation testing is usually performed at 37 °C [4].

The contribution of red blood cells (RBC) to haemostatic function is frequently underestimated. RBC contribute to the margination of platelets against the vessel wall and their availability to act at the site of a vascular lesion. They have also been shown to enhance thrombin generation and to modulate the biochemical and functional responsiveness of activated platelets. However, the optimal haematocrit or haemoglobin concentration to prevent or to initiate the treatment of coagulopathy in massively transfused patients remains unknown. Experimental evidence suggests that haematocrits as high as 35% may be required to sustain haemostasis in this context [5].

Since the publication of Miller's classic study on coagulation defects associated with massive blood transfusions [6], thrombocytopenia resulting from haemodilution has often been thought to be the most important haemostatic abnormality associated with massive transfusion. Yet, simple haemodilution has failed to explain several clinical observations. In wounded young, previously healthy, soldiers, platelet levels were observed to fall rapidly to $\approx 100 \times 10^9$/l during rapid transfusion and to remain at that level after transfusion of the first 6 l of stored whole blood [7]. On average, the platelet count was found to fall below $100 \times 10^9$/l after the transfusion of 18 units of blood in the study by Counts *et al.* [8]. Reed *et al.* observed that platelet counts were not different between massively transfused patients who received prophylactic platelet transfusions and those who did not, and that both

**Table 1** Massive transfusion: the main differences between elective surgery and trauma

| | **Elective surgery** | **Trauma** |
|---|---|---|
| Tissue trauma | Controlled | Massive and uncontrolled |
| Initiation of massive transfusion | No delay between haemorrhage and initiation of treatment | The interval between haemorrhage and treatment can vary widely |
| Volume status/shock | Normovolemia is maintained and shock is avoided | Hypovolemia and shock are frequent |
| Temperature | Normothermia is maintained | Hypothermia is frequent |
| Monitoring of haemostasis | Ongoing. Anticipation of haemostatic defects is possible | Late. Laboratory tests are obtained when coagulopathy is installed |
| Coagulopathy | More often related to decreased coagulation factors | Often related to disseminated intravascular coagulation |
| Treatment of coagulopathy | Correction of anaemia FFP and platelets as determined by laboratory tests (FFP should probably be administered first) | Correction of tissue hypoperfusion<br>Correction of hypothermia<br>Correction of anaemia<br>Platelets and FFP as determined by laboratory tests (platelets first?) |

FFP, fresh-frozen plasma.

groups had higher platelet counts than predicted by a standard washout equation [9]. This implies that platelets are being released into the circulation and counteract the effects of dilution. Sequestered platelets can be released from the spleen and the lung, in addition to the premature release of platelets from the bone marrow.

While resuscitation with crystalloids and colloids, hypothermia, anaemia and thrombocytopenia will be common to all massively transfused patients, the sequence of events may be noticeably different depending on whether haemorrhage occurs as the result of trauma or elective surgery. In the trauma patient, the extent of tissue injury may be considerable and is, by definition, uncontrolled. The initiation of fluid resuscitation and subsequent transfusion will be delayed until assistance becomes available and the patient can be transported to the hospital. Shock, tissue hypoxia and acidosis will ensue. Hypothermia is common and can be profound. Patients who are hypothermic and acidotic develop clinically significant bleeding, despite adequate blood, plasma and platelet replacement, and are more likely to die [10,11].

Disseminated intravascular coagulation (DIC) is an acquired clinico-pathological state secondary to the chaotic activation of the coagulation system. The International Society on Thrombosis and Haemostasis (ISTH) has defined DIC as 'an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction'.

The syndrome can be seen in numerous clinical situations and often complicates the management of massive transfusion. In trauma patients, two major mechanisms are responsible for the occurrence of DIC [12]. The first relates to the nature and to the importance of tissue trauma. The second relates to shock and tissue hypoxia. Brain injury is associated with a particularly high incidence of coagulopathy [13]. After blunt brain injury, extravasation of tissue factor can rapidly (within 1–4 h after injury) lead to DIC and is associated with a high frequency of death [14]. Regarding the importance of tissue trauma, in the absence of massive head injury and pre-existing disease, life-threatening coagulopathy was associated with a pH of < 7·10, a temperature of < 34 °C, an injury severity score of > 25, and a systolic blood pressure of < 70 mmHg. When all risk factors were present, the incidence of coagulopathy was 98% [15].

Conversely, in the context of elective surgery, tissue injury is controlled by the surgeon and remains limited. Patients at risk of haemorrhage are monitored extensively, peripheral and central venous accesses are secured, and resuscitation with crystalloids and colloids is prompt. Blood is available rapidly, if not immediately, and red cells can be replaced, as needed, in a timely manner. Except in the most extreme cases, shock and acidosis can be avoided. With the use of modern

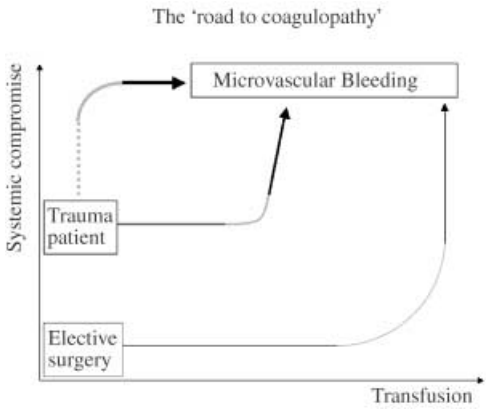


**Fig. 1** Massive Transfusion and the 'Road to Coagulopathy'. In elective surgical patients, tissue trauma is controlled, temperature is maintained, tissue hypoxia and acidosis are avoided, and haemostatic abnormalities are treated in a timely manner. In such patients, microvascular bleeding is unlikely to occur or will occur as a late event, usually when the situation becomes uncontrolled. In trauma patients, depending on the nature of the trauma and the appropriateness of intervention, systemic compromise will be moderate to severe. The more severely patients are compromised, the more likely microvascular bleeding is to occur.

body and intravenous (i.v.) fluid warmers, hypothermia can also be avoided. In the majority of elective surgical cases, coagulopathy will, essentially, be secondary to the dilution of coagulation factors [16]. Another important difference with the trauma setting is that coagulation can (and should) be monitored regularly and blood products ordered in anticipation of an unfavourably evolving situation [17].

Thus, in the purely elective setting, DIC complicating massive transfusion appears to be infrequent. No patient was found to suffer from DIC amongst the 32 young healthy patients undergoing posterior spinal stabilization and massive transfusion [18]. Clinically, increased surgical bleeding improved after the administration of fresh-frozen plasma (FFP) (≈ 10 ml/kg). Again, these results suggest that when tissue hypoxia is avoided and surgical trauma is controlled, the occurrence of DIC remains low, despite massive transfusion. Our concept of differing 'roads to coagulopathy' is illustrated in Fig. 1.

## Blood products have changed over time

The blood products administered to the massively bleeding patient [fresh whole blood, stored whole blood, modified whole blood (MWB, i.e. whole blood from which platelets and/or cryoprecipitate are separated before storage)] [8,9], packed red blood cells (PRBC), concentrated red cells, etc., have changed over the years [19]. Conventional teaching has sometimes failed to appreciate the evolution of transfusion practices and the context in which these were developed. As a result, clinicians have been led to apply transfusion strategies (e.g. those developed for trauma patients at a time

when MWB was available [6,8]) inappropriately to patients receiving red cell concentrates for massive bleeding during elective surgery [20]. In young and previously healthy soldiers who received large volumes of stored whole blood (prior to the era of blood components preparation), the prothrombin time (PT), the activated partial thromboplastin time (APTT) and fibrinogen levels were affected only minimally [7]. In this context, thrombocytopenia appeared to be the main factor responsible for coagulopathy [6].

In patients receiving more than 10 red cell concentrates or cell-saver units (i.e. poor in plasma), abnormalities of the PT and of the APTT were found to occur after the transfusion of 12 units of PRBC, and thrombocytopenia developed later, after the transfusion of 20 units [21]. In 1995, using plasma-poor red cell concentrates, Hiippala *et al.* showed, in patients undergoing elective major urological or abdominal surgery, that a concentration of 1·0 g/l fibrinogen was reached when the blood loss was 1·42 times the calculated blood volume, and that blood losses in excess of two blood volumes caused the deficiency of prothrombin, factor V, platelets and factor VII, in that order [16].

This leads us to conclude that, at least in elective surgical patients undergoing massive transfusion, the first line of treatment (with regard to haemostatic blood products) ought to be with FFP to correct the levels of coagulation factors [19]. However, despite the evidence that FFP may be required prior to platelet concentrates to treat a coagulopathy, two studies have shown that survival in massively transfused trauma patients is associated with the increased transfusion of platelet concentrates [15,22].

Several animal experiments, case reports and case series have reported the successful use of recombinant activated factor VII (rFVIIa) to treat bleeding that could not be controlled by the administration of haemostatic blood components [23,24]. Since then, randomized controlled studies have attempted to define the role of rFVIIa in the management of excessive perioperative bleeding. One published study presented positive, but controversial, results [25], while two did not demonstrate a beneficial effect of rFVIIa in the context of major, elective surgery [26,27].

Recently, Novo Nordisk, the manufacturer of rFVIIa, conducted a trial on the efficacy and safety of rFVIIa in the treatment of bleeding in severely injured trauma subjects. The objective of this prospective, multicentre, randomized, double-blind, placebo-controlled study was to evaluate the efficacy and safety of rFVIIa given in conjunction with standard therapy in the treatment of massively bleeding trauma patients. The study enrolled 283 subjects from 32 centres in eight countries. Patients received either rFVIIa (three doses for a total of 400 μg/kg) or an equal volume of placebo and were stratified to blunt or penetrating injury. At present, only incomplete results are available in abstract form [28]. The benefits of rFVIIa were apparent in patients who survived for 48 h, more so in the blunt trauma group (estimated reduction of 2·6 RBC units; $P = 0·02$) compared to penetrating injury (estimated reduction of 1·0 RBC unit; $P = 0·10$). The incidence of death was similar in all patient groups. rFVIIa did not increase the incidence of multiorgan failure (MOF) and acute respiratory distress syndrome (ARDS) and showed a potential to reduce these adverse events. Ongoing/upcoming studies will define more precisely the benefits, optimal dosage and safety of rFVIIa for the management of haemorrhage in trauma and surgery.

## Conclusions

Active and significant bleeding, leading to massive transfusion, is always dramatic and mobilizes all the resources surrounding the patient. The attending physicians, whether in the emergency room or in the operating theatre, attempt to control the source of haemorrhage while resuscitating the patient. Adhering to a research protocol under such extraordinary circumstances is difficult at best, if not altogether impossible. Thus, data, other than observational, have been difficult to gather and analyse. The available data are sparse and sometimes contradictory, but trends seem to emerge.

Coagulopathy associated with massive transfusion and surgery is an intricate, multicellular and multifactorial event. The interactions amongst red cells, fibrinogen and platelets are particularly important, but the contribution of fluid-replacement therapy, hypothermia and coagulation-factor deficiency must not be overlooked. Massively transfused trauma patients differ from their elective surgical counterparts, particularly with regard to DIC. The 'classic' view, that thrombocytopenia is responsible for the majority of bleeding complications in massively transfused patients, should be abandoned [29], especially with the use of blood component therapy.

Coagulation is a complex process that is difficult to monitor at the bedside. During massive transfusion, haemostatic defects can evolve extremely rapidly. In spite of our best efforts to monitor haemostasis in a timely manner, conventional coagulation tests take time to obtain and provide a limited evaluation of the situation. Unfortunately, the evidence supporting the use of real-time monitors of haemostasis is scant [30]. Improved monitors are required to optimize the care of these patients.

Finally, more research on transfusions and their alternatives is required. Huge sums of money are being spent on reducing the infectious risks of transfusions, but little on understanding when or how transfusions are truly effective [31]. Transfusion guidelines are, for the most part, based on expert consensus [32], and well-designed clinical trials have disproved commonly accepted dogma [33]. No adequately designed and powered trial has studied the effectiveness of FFP or platelet concentrates in trauma patients. The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage study (CRASH 2), a randomized, placebo-controlled

trial among 20 000 trauma patients with, or at risk of, significant haemorrhage, of the effects of tranexamic acid on death and transfusion requirement, has begun recently [34]. Obviously, more studies such as this are needed to guide our management of massively transfused patients.

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