

## Physiopathology and Clinical Management of Massive Transfusion and Hemostatic Dysfunction

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Although the need for massive transfusions occurs relatively frequently in clinical practice, optimal management of hemorrhagic complications remains problematic. Therefore, a group of experts reviewed the literature to provide an update on this topic. The review deals with the physiopathology of hemostatic deficits associated with massive transfusions in adults during the course of planned or emergency surgery, and makes practical recommendations for optimizing the transfusion strategy.

Numerous factors are responsible for the hemostatic dysfunction associated with massive transfusions, including hemodilution, hypothermia, the use of fractionated blood products, and disseminated intravascular coagulation. The clinical importance of the effects of hydroxyethyl starches on hemostasis remains uncertain.

The earliest complication in the course of planned surgery is a drop in fibrinogen concentration, whereas thrombocytopenia is a late event. In the polytrauma victim, the trauma and tissue hypoxia, shock, and hypothermia, contribute to disseminated intravascular coagulation and microvascular bleeding.

The maintenance of normothermia is recommended and is effective for improving hemostasis during massive transfusions. Red cells also play an important role and a hematocrit > 30% may be necessary to ensure normal hemostasis. The administration of platelets and/or fresh frozen plasma should be guided by clinical judgment and coagulation test results, and hemostatic blood products should be used primarily to treat clinical hemostatic dysfunction.

The hemostatic dysfunction associated with massive transfusions is a complex, multifactorial, multicellular phenomenon. Therapeutic strategies are based on maintaining tissue perfusion, correcting hypothermia and anemia, and using transfusions of hemostatic products to control microvascular bleeding. A more detailed version of this review on massive transfusions will be published in the April 2004 issue of the *Canadian Journal of Anesthesia*.

Uncontrolled bleeding and, consequently, massive transfusions (MT) are frequent complications in major surgery and trauma. MT is usually defined as the replacement of one total blood volume within 24 hours. On the other hand, more dynamic definitions, such as the transfusion of  $\geq 4$  units of packed red cells in 1 hour while bleeding is still active or the replacement of 50% of whole blood volume within 3 hours, are often more clinically pertinent.

Most studies of MT have been conducted on polytrauma victims and, for obvious reasons, are retrospective or observational as well as uncontrolled. Given the variable and complex clinical context, these studies have rarely been conclusive. One can readily imagine that the physiopathological mechanisms are different (at least initially) in the case of hemorrhage during controlled surgery compared to a trauma case complicated by cerebral lesions, hypothermia, disseminated intravascular coagulation (DIC), etc. In addition, the available blood products have changed over time, such that practices useful in the days when whole blood was still available are no longer so today in this era of packed blood cells.

This issue of *Anesthesiology Rounds* on management of MT and hemostatic complications is prepared in collaboration with the GIHP (Groupe d'Intérêt en Hémostase Périopératoire) and examines two issues:

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- The pathophysiology of hemostatic complications in adults receiving MT during major surgery or polytrauma;
- The management of blood products in these contexts.

The review will not deal with obstetric or pediatric patients or hemostatic complications specific to extracorporeal circulation, liver transplants, or congenital hemostatic deficits.

## PHYSIOPATHOLOGY OF HEMOSTATIC COMPLICATIONS OBSERVED DURING MT

During resuscitation following a hemorrhage, the initial concern is volemic replacement by crystalloids/colloids and the maintenance of normothermia. Subsequently, the patient will receive erythrocytes, plasma, and platelets. A DIC might further complicate the situation.

### Hemodilution

**Crystalloids:** In controlled surgery, rapid hemodilution by crystalloids causes hypercoagulability detectable by a thromboelastograph. The clinical importance of this observation, in particular with polytrauma patients, remains uncertain.<sup>1</sup>

**Colloids:** Fluid gelatins are believed to affect hemostasis solely through their dilutional effect, even though some studies have found greater clot friability in the presence of gelatins compared to normal saline. On the other hand, blood losses in hip surgery are less with a volemic gelatin-based replacement compared to a hydroxyethyl starch (HES).<sup>2</sup> The clinical importance of the hemostatic effects of fluid gelatins therefore remains uncertain.

HES is routinely used in Europe and North America. They result in effective volemic expansion, but interfere with hemostasis. High molecular weight solutions with a high degree of substitution accumulate in tissues and produce pronounced hemostatic effects.<sup>3</sup> Conversely, solutions with a low molecular weight and a lesser degree of substitution are eliminated more rapidly and have less effect on hemostasis. The complications of HES remain limited if there is adherence to the maximum daily dosages.<sup>4</sup> As in the case of gelatins, the clinical importance of the hemostatic effects of HES remains uncertain, particularly in polytrauma victims where numerous factors are involved and it is often difficult to pinpoint the exact nature of the hemostatic complications. Nonetheless, it is interesting to note that colloids are never mentioned in the American College of Surgeons recommendations for volume resuscitation.<sup>5</sup>

### Hypothermia

Maintaining a normal temperature makes it possible to preserve hemostasis and reduce blood loss during the perioperative period. In animals, it has been clearly demonstrated that hypothermia slows down the enzymatic activity of the coagulation cascade, reduces the synthesis of coagulation factors, increases fibrinolysis, and diminishes platelet count and function.

These anomalies are clinically significant, for example, moderate hypothermia ( $35 \pm 0.5^\circ\text{C}$ ) increases bleeding and the need for transfusions in hip surgery.<sup>6</sup> Hypothermia is a major contributor to hemostatic dysfunction in the polytrauma patient. In a study by Ferrara et al, bleeding and mortality were more frequent in hypothermic ( $< 34^\circ\text{C}$ ) and acidotic polytrauma victims, despite appropriate replacement therapy.<sup>7</sup> The clinician should remember that it is easy to underestimate the contribution of hypothermia to hemorrhagic diathesis, since coagulation tests are normally conducted at  $37^\circ\text{C}$ .<sup>8</sup>

### Transfusion of blood products and hemostatic complications

**Erythrocytes:** An often-ignored effect of erythrocytes is their contribution to hemostasis. The red blood cells contain adenosine diphosphate (ADP) that can activate platelets. Moreover, erythrocytes activate platelet cyclooxygenase, increase the production of thromboxane  $A_2$  and, by exposing procoagulant phospholipids, boost thrombin production. Thus, the red cells modulate platelet reactivity and can contribute to hemostasis and thrombosis, which supports the notion that thrombus formation is a multicellular event.

Another mechanism by which erythrocytes contribute to hemostasis is based on rheology. With a normal hematocrit, erythrocytes circulate at the center of the vascular lumen, pushing platelets to the periphery to maximize their interaction with the damaged endothelium. In experiments, the platelet concentration was found to be 7 times higher near the vascular wall.

In rabbits, with a reduction in the hematocrit ( $< 35\%$ ), bleeding time increases<sup>9,10</sup> and cyclical arterial thromboses diminish.<sup>10</sup> In humans, numerous studies indicate that bleeding time varies inversely with the hematocrit value. However, the clinical importance of these observations remains uncertain, since bleeding time is a poor predictor of hemorrhagic risk.

The hemostatic effects of normovolemic hemodilution have been studied in 8 children operated on for scoliosis.<sup>11</sup> A hemostatic deficit occurred before oxygen consumption was compromised. Unfortunately, the authors do not specify if the microvascular bleeding (MVB) was corrected by the transfusion of erythrocytes and the increase in hematocrit. Hemofiltration in pediatric heart surgery increases the hematocrit and reduces the need for transfusions.

While it seems clear that erythrocytes contribute to hemostasis, the minimal hematocrit required to prevent or treat hemostatic dysfunction in a bleeding patient receiving MT remains unknown. Based on experiments, a 35% hematocrit appears necessary to ensure optimal hemostasis.

### Coagulation factors

It remains difficult to precisely define the role of coagulation factors in the pathophysiology of hemostatic deficits associated with MT. In fact, these deficits are multiple and involve not only a reduction

in coagulation factors, but also anemia and thrombocytopenia.

It is important to realize that in the days when clinicians had access to fresh whole blood or modified whole blood (blood with the platelets and/or cryoprecipitates removed), a reduction in coagulation factors was rarely responsible for a hemostatic deficit.<sup>12-15</sup> Towards the end of the 1980s, with the use of packed red cells, the dilution or the consumption of coagulation factors became a real problem requiring replacement treatment, usually with fresh frozen plasma (FFP).<sup>16-19</sup> In major surgery, the fibrinogen concentration reaches a threshold of 1.0 g/L when a proportion of 1.42 blood volume has been lost. Blood losses in excess of 2 volumes produce, in sequence, a prothrombin, Factor V, platelet, and Factor VII deficit.<sup>19</sup> It is not known whether these observations made during controlled surgery apply to emergency surgery or poly-trauma patients.

Even today, clinicians do not use pure products for transfusions; packed red cell units and platelet concentrates (PC) contain respectively, 30 to 60 mL and 80 mL of plasma. This occasionally makes it difficult to distinguish the therapeutic effects of the various blood products transfused.

### Platelets

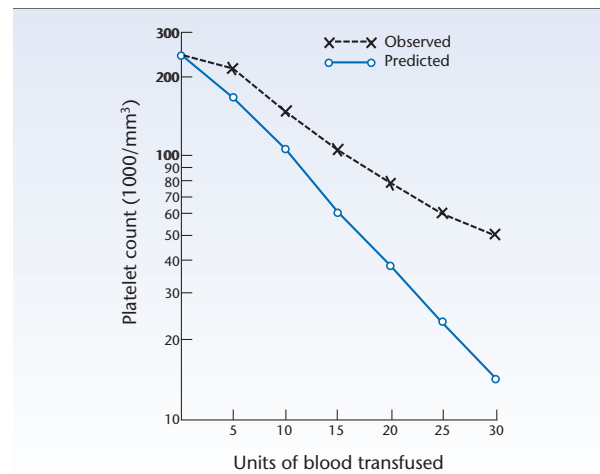
Primary hemostasis is characterized by the formation of a plug. The mechanism is complex; it requires the presence of fibrinogen (and von Willebrand factor) and results from the activation of numerous platelet receptors.

Since the study by Miller et al of the hemostatic deficits associated with MT,<sup>14</sup> dilutional thrombocytopenia is often wrongly considered the most significant anomaly in this context. The rationale is simple and attractive; the replacement of lost blood with solutions containing no platelets (or coagulation factors) causes dilutional coagulopathy. The reality is more complex.

In wounded soldiers, Simmons et al observed that platelet counts dropped and stabilized at 100 G/L with a transfusion of  $\geq 6$  L of whole blood.<sup>13</sup> Prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen concentrations were less affected. These anomalies do not accompany excessive perioperative bleeding. Counts et al estimated that only 43% of the variability in the platelet count could be attributed to the transfused volume.<sup>12</sup> Reed and colleagues showed that platelet counts were similar in surgery patients receiving a prophylactic transfusion with or without platelets.<sup>20</sup> Moreover, the two groups had a platelet count higher than the one predicted by simple hemodilution, as in the study by Miller et al (Figure 1). The release of immature platelets or platelets sequestered in the spleen or lungs could explain these observations.

In elective surgery, tissue trauma is better controlled, normovolemia is maintained, and losses are replaced in real time. In this context, a coagulation factor deficit is the first complication to arise and the role of fibrinogen is predominant.<sup>16,19</sup> A thrombo-

**FIGURE 1:** Measured vs predicted platelet count based on quantity of blood received<sup>14</sup>



Measured platelet counts are higher than those predicted by simple hemodilution; after administering 25 units, we see a platelet count of 60 G/L, although hemodilution predicts a count of 20 G/L.

cytopenia ( $\leq 83$  G/L) was found in 4 patients with MVB in the study by Murray et al, but PC transfusion remained ineffective in the presence of reduced fibrinogen.<sup>21</sup> A FFP transfusion, however, corrected the hemostatic deficit.

A hemostatic deficit is therefore multifactorial and involves both the platelets and coagulation factors, especially fibrinogen. A therapeutic approach should endeavour to characterize and treat each anomaly involved.

### Disseminated intravascular coagulation

**Definition:** According to the SRLF (Société de Réanimation de Langue Française), DIC "...is an acquired syndrome secondary to systematic and excessive activation of the coagulation encountered in many clinical resuscitation situations. This syndrome is defined by the association of biological anomalies, with or without clinical signs indicative of excess thrombin and fibrin production, and excess platelet and coagulation factor consumption."

The criteria developed by the SRLF for the diagnosis of DIC take into account the symptomology (biological, clinical, or complicated DIC), the D-dimer, and platelets and coagulation factors consumption. These criteria can be viewed at the SRLF Web site ([www.srlf.org/conferences/XXII-conf-Lille.html](http://www.srlf.org/conferences/XXII-conf-Lille.html)).

**DIC and the polytrauma victim:** The latest studies show that there is no correlation between the number of transfused units and the occurrence of a hemostatic deficit, which suggests that coagulation factors and platelets consumption are more important than hemodilution.<sup>22-25</sup> In the polytrauma patient, 2 key mechanisms are responsible for the occurrence of DIC: the nature and severity of the trauma, and the extent of shock and tissue anoxia. Thus, cranial trauma is accompanied by a particularly high incidence of hemostatic dysfunction, secondary to tissue factors

extravasation.<sup>26,27</sup> In the study by Cosgriff et al, a hemostatic deficit threatening the vital prognosis was associated with a pH < 7.10, hypothermia < 34°C, an Injury Severity Score > 25 and systolic blood pressure < 70 mm Hg.<sup>22</sup>

**DIC and controlled surgery:** DIC remains unusual even in the case of MT.<sup>16</sup> In a controlled surgery setting, this could be explained by the maintenance of tissue oxygenation, the prevention of hypothermia, and the control of surgical trauma.

## MANAGEMENT OF HEMOSTATIC DYSFUNCTION ASSOCIATED WITH MT

### Diagnosis

At present, there is no simple, reliable, and rapid hemostasis monitor for use at the bedside of a multitransfused patient during the perioperative period. The platelet count is the only variable that can be obtained quickly with automated analyzers. Conventional coagulation tests require centrifugation and take at least 30 minutes.

The platelet count must not be interpreted in isolation. Clinicians must take into account not only the number, but also the function of the platelets, the fibrinogen and hemoglobin concentration, and the risk of consumption coagulopathy, to arrive at the most accurate diagnosis possible.

Bleeding time has been studied on a few occasions. Bleeding time lengthens early during surgery and transfusions, and remains high for a few days thereafter. However, it is not a reliable predictor of the risk of bleeding, therefore, bleeding time is not useful in this situation.

Prolongation of PT and aPTT is common during MT. Slight prolongations do not predict the risk of bleeding. On the other hand, when the PT or aPTT ratio exceeded 1.8, the factors V and VIII concentration were < 30% and the risk of MVB approached 80%-85% in the study by Ciavarella et al.<sup>15</sup> In the presence of reduced fibrinogen, a PT or aPTT ratio of 1.5 is associated with factors V and VIII concentration < 20%.<sup>21</sup> In brief, only substantial prolongations of PT or aPTT (of the order of 1.5 if fibrinogen is reduced and 1.8 if normal) are significant in clinical practice.

Finally, the diagnostic value of the thromboelastograph or PFA-100® has not been proven for managing the hemostatic dysfunction associated with MT.

### Treatment of hemostatic dysfunction

This is no simple matter. Two complementary approaches are described in Table 1 and Figure 2. **Treatment objectives:** The precise etiological diagnosis of MVB remains difficult, but the clinician must nonetheless respond swiftly. Moreover, a transfusion is not without its own risks. Although today, the incidence of infectious complications (HIV or hepatitis C) is minimal, the risk of serious

**TABLE 1:** Proposals formulated by the French Health Products Safety Agency to help guide therapeutic transfusion decisions.

		Presence of Clinical Bleeding	
		Yes	No
Presence of biological anomalies*	Yes	PC or FFP transfusion depending on the biological test results (first favouring PC)**	Transfusion based on the risks inherent in the intervention (eg, neurosurgery and platelet count < 100 G/L)
	No	Look for a cause other than a hemostatic anomaly. Assess the importance of transfusions and eventually, use PC and FFP if over a blood mass (first favouring PC)**. Check the biological tests.	No indication for a transfusion
	Unknown	Transfusion depending on the probability of the type of hemostatic dysfunction.	No indication for a transfusion. Redo the biological tests.

\* Platelets < 50 G/L, fibrinogen < 0.5 to 0.8 g/L, PT and/or aPTT > 1.5 to 1.8 times the control.

\*\* The PC transfusion *could* precede the plasma one, even though this recommendation is the result of consensus from several professional groups; it is not based on any randomized study.

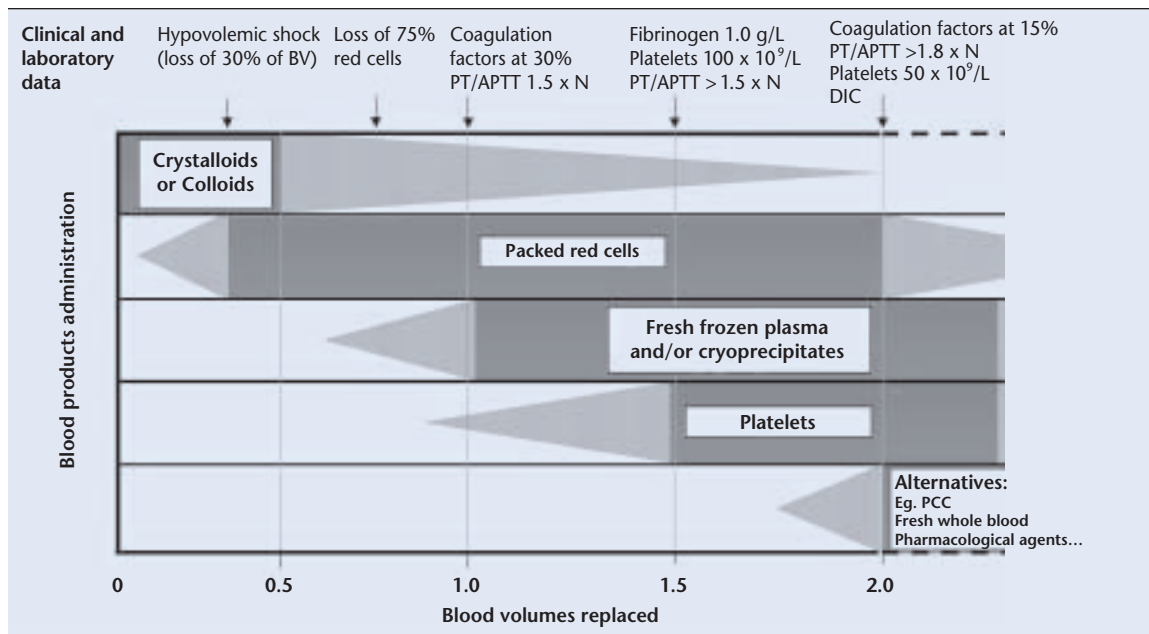
complications remains high. In Canada, the risk is estimated at 43.2 per 100,000 units of transfused red cells (primarily hemolytic reactions and volume overload) and 125.7 per 100,000 5-unit platelet pools (mainly allergic reactions and bacterial contamination).<sup>28</sup> Therefore, transfusions must be used advisedly, essentially to treat “clinical” bleeding (Table 1).

It has yet to be proven that a *prophylactic* PC or FFP transfusion is effective in a multitransfused patient. Nevertheless, depending on the context and given the time required to obtain blood products, it might be useful to order PC or FFP for transfusion in the event of MVB. The use of plasma or platelets from a single donor is recommended.

**Managing treatment:** Figure 2 provides a good synopsis of MT management principles in controlled surgery.<sup>29</sup> Crystalloids/colloids are used initially to maintain normovolemia then, based on laboratory data and in the following sequence, packed cells, FFP, and PC are transfused to replace losses. Pharmacological agents (protamine if applicable, desmopressin, aprotinin, activated Factor VII) are used if necessary. Although the diagram is useful for controlled surgery, the situation is frequently very difficult in emergencies where blood losses are difficult to quantify, the extent of shock, tissular anoxia, and hypothermia vary, and lab results are not immediately available.

Initially, normothermia must be maintained and anemia corrected. Warming the patient normalizes the hemostatic anomalies caused by hypothermia. As mentioned above, the hematocrit required for optimal hemostasis is unknown. Based on available data, we consider 30% the

**FIGURE 2:** Massive transfusion management in elective surgery<sup>29</sup>



minimum to maintain in the case of clinical bleeding.

PC and FFP transfusions depend on the results of coagulation tests and clinical judgment. Prolonged PT and aPTT suggests a coagulation factor deficit and requires FFP transfusions. A decline in fibrinogen also requires FFP transfusions. Doses of 800 to 1,000 mL are recommended for the average adult. It is important to administer the plasma in bolus form to keep the coagulation factors at an adequate level.<sup>17</sup> If the fibrinogen concentration remains < 1.0 g/L despite the FFP, cryoprecipitates (in North America) or fibrinogen concentrates (in Europe) must be administered.

PC are transfused to correct a thrombocytopenia accompanying clinical bleeding. It should be remembered that the platelet count drops in all MT patients, but thrombocytopenia does not cause clinical bleeding in all of them. Ever since packed cell units have replaced whole blood, a number of studies have suggested that FFP transfusions could precede the PC transfusions.<sup>16-18,21</sup> However, two studies suggest that the chances of survival are improved by an increased transfusion of PC in MT polytrauma patients.<sup>22,30</sup> Unfortunately, there is actually no reliable diagnostic test to serve as a guide for administering hemostatic products.

The use of recombinant activated factor VII to control clinical bleeding in MT patients looks promising.<sup>31</sup> The studies underway will make it possible to ascertain the value, dosage and optimal method of administration of this very expensive compound.

## CONCLUSIONS

The pathophysiology of hemostatic dysfunction accompanying MT is complex and calls for a multidisciplinary approach involving anesthesiologists, biologists, and surgeons. In the polytrauma victim, DIC often complicates the picture. Moreover, the “traditional” view that thrombocytopenia is responsible for most of the clinical bleeding associated with MT should be abandoned, since hemostatic dysfunction is a pluricellular, multifactorial phenomenon. The interaction among platelets, fibrinogen, and erythrocytes is particularly important, but the contribution of fluid replacement, hypothermia, and the drop in coagulation factors concentration should not be ignored.

In the absence of complete hemostasis monitors that can be used at the patient’s bedside, the management of blood products during MT remains difficult. Treatment must take into consideration *all* the factors affecting hemostasis. Hemostatic products transfusions should not follow predetermined schemes (eg, the administration of FFP after a set number of packed cell units), but should be based on appropriate lab tests and clinical indications. This being said, one must admit that the urgency of the situation does not always allow for methodical management of MT.

Hemorrhage and MT management is, with good reason, a priority for the anesthesiologist, intensivist, biologist, and surgeon. Yet, once the acute episode has been controlled, one must not

forget that these patients are at risk of postoperative thrombotic complications. Moreover, screening for an underlying hemostatic dysfunction that might manifest during major surgery or trauma may be indicated; only then will MT management be complete.

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