

# Massive hemorrhage management – a best evidence topic report

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**Introduction:** Massive hemorrhage remains a major cause of potentially preventable deaths. Better control of bleeding could improve survival rates by 10%–20%. Transfusion intervention concepts have been formulated in order to minimize acute traumatic coagulopathy. These interventions still have not been standardized and vary among medical centers.

**Materials and Methods:** Based on a literature search using free term keywords and Medical Subject Heading (MeSH) index, we analyzed published articles addressing massive hemorrhage, component therapy, fresh whole blood, and fibrinogen from the year 2000 onward, in journals with impact factor >1.000, in Medline, PubMed, and Google Scholar. The evidence was grouped into topics including laboratory testing and transfusion interventions/viscoelastic assays vs standard laboratory tests, the effect of component therapy on patient outcome, the effect of warm fresh whole blood on patient outcome, and the effects of fibrinogen in severe bleeding. The obtained information was compared, evaluated, confronted, and was focused on to present an adequate and individual-based massive hemorrhage management approach.

**Results:** Viscoelastic whole-blood assays are superior to standard coagulation blood tests for the identification of coagulopathy and for guiding decisions on appropriate therapy in patients with severe bleeding. Replacement of plasma, red blood cells, platelets, and fibrinogen in a ratio of 1:1:1:1 has appeared to be the best substitution for lost whole blood. There is no evidence that cryoprecipitate improves the outcome of patients with severe hemorrhage. Current literature promotes the transfusion of warm fresh whole blood, which seems to be superior to the component therapy in certain clinical situations. Some authors recommend that fibrinogen and other coagulation factors be administered according to the viscoelastic attributes of the blood clot.

**Conclusion:** This best-evidence topic report brings comprehensive information about massive hemorrhage management.

**Keywords:** coagulopathy, fibrinogen, transfusion, viscoelastic assay

## Introduction

Massive hemorrhage remains a major cause of potentially preventable deaths. All over the world, more than 5 million people die every year from massive hemorrhaging, and it is estimated that 10%–20% would have survived with better control of bleeding.<sup>1</sup> Trauma, perioperative period, and massive transfusions are associated with coagulopathy secondary to tissue injury, hypoperfusion, and consumption of clotting factors (especially fibrinogen) and platelets, together with hypothermia, hemodilution and hypothermia (due to crystalloid overload), and acidosis (as a result of administering NaCl 0.9 % solution).<sup>2–5</sup> Bleeding is the primary cause of death, and coagulopathy contributes significantly to hemorrhage and subsequent poor outcomes.<sup>4–6</sup> The current view emphasizes an endogenous origin of severe coagulopathy. The key role play the massive release of tissue factor, activation of protein C pathways, disturbances in tPA-1 and PAI-1 plasmatic levels and depletion of factors II, V, VII, VIII, IX and X.<sup>3,7,8</sup>

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In past decades, transfusion interventions have been changing to reflect the accessibility of blood products, the development of new hemostatic drugs, and better training at medical centers.

## Point of care tests

Since 1956, the PubMed database has featured more than 4,000 full-text articles on thromboelastography (TEG) and 170 articles about rotational thromboelastometry (ROTEM) as diagnostic and therapeutic methods in cases of coagulopathy. ROTEM broadens diagnostic alternatives and consequently helps physicians to create goal-targeted, individually tailored treatment of coagulopathy. ROTEM enables the investigation of both intrinsic (INTEM test) and extrinsic (EXTEM test) hemocoagulation pathways, including investigation of the participation of fibrinogen (FIBTEM test) and thrombolysis (APTEM test) and how they play a role in the final quality of the blood clot. Standard plasma coagulation tests take up to 45 minutes to produce results, and the samples must be transported to a hematology laboratory, while TEG and ROTEM can be done as bedside monitoring techniques. Furthermore, both of these viscoelastic assays are unique because they investigate whole fresh blood and thus respect physiological conditions and circumstances, such as blood temperature, pH, hemoglobin and platelet concentrations, and the plasma levels of coagulating factors. Both ROTEM and TEG seem to be superior to standard coagulation blood tests, such as partial thromboplastin time (PTT) and international normalized ratio (INR), for identifying coagulopathy, and for setting appropriate therapy and predicting massive transfusion.<sup>9-14</sup>

## A short history of transfusion interventions

Over the last century, there have been major changes in blood transfusion practices, which largely occurred due to the experience of military physicians during major war conflicts. At the end of the World War I, whole blood in combination with saline and colloids was, remarkably, successfully used.<sup>15</sup> During World War II, albumin and freeze-dried (lyophilized) plasma with whole blood were used to achieve balanced volume resuscitation.<sup>16</sup> During the Vietnam war in the 1970s, transfusion practice dramatically changed for the worse due to a lack of blood derivatives on the battlefield and a high risk of infectious disease transmission. Consequently, inadvertent hemodilution became routine and resulted in failure to control bleeding, massive blood loss, and the progress of coagulopathy, hypothermia, and

acidosis. Furthermore, the significant volume of crystalloids created abdominal compartment syndrome, acute respiratory distress syndrome, and multiple organ failure.<sup>17</sup> In the late 1990s, it was proved that the excessive volume of crystalloids are harmful,<sup>18,19</sup> and transfusion techniques returned to those that were in practice during World War II. Throughout the following decades, the concept of damage control resuscitation was proposed and began to be used routinely, not only in US combat hospitals.

## Component therapy

Damage control resuscitation and massive transfusion techniques involve the rapid control of trauma- and surgery-related bleeding; early and increased use of red blood cells, plasma, and platelets in a 1:1:1 ratio; limitation of excessive crystalloid use; prevention and treatment of hypothermia, hypocalcemia, and acidosis; and permissive hypotension.<sup>2,8,17,20</sup> The same results have been described in civilian patients receiving massive transfusions. Thirty-day survival has been reported to be significantly increased in patients with high plasma to red blood cell ratios (>1:2) compared with those with low ratios (<1:2). It was also shown that a combination of high plasma to platelet ratios (>1:2) increased 1-day and 30-day survival.<sup>21-24</sup> Higher platelet to red blood cell ratios (>1:2) have also been shown to improve 1-day and 30-day survival after massive transfusion secondary to civilian trauma.<sup>4,21,25,26</sup> Thus the current resuscitation approach is to use the 1:1:1 ratio for all casualties expected to receive a massive component transfusion.<sup>18</sup> Component transfusion therapy in similarly economically and socially developed countries is highly variable and is independently associated with adverse events.<sup>27,28</sup> The possible harm from stored red blood cells and platelets has focused attention on the detailed analysis of transfusion practices. It has been found that 8 days is the threshold after which stored red cells begin to have harmful effects on patients.<sup>28,29</sup> This period was consistently found in the most recent reviews of studies investigating the effects of stored red blood cells on critically ill patients.<sup>28,30,31</sup> Similarly, when comparing the in vivo properties of platelets that are stored for 7 versus 5 days, platelets that were stored for a longer period were found to have significantly deteriorated in function;<sup>32</sup> the clinical implications of platelet storage-related defects have been repeatedly reported.<sup>33,34</sup> One last finding of interest is the strong association of reduced plasma fibrinogen level and activated coagulation time (ACT).<sup>3,5,35-38</sup> When taking this into account, the ratio 1:1:1:1, which includes fibrinogen, seems to be very smart and advantageous.<sup>3,5,14,21,25,36-38</sup>

## Warm fresh whole-blood (WFWB) transfusion

The primary blood product that is currently the safest and has the least side effects is WFWB.<sup>28,39–41</sup> If complete component therapy is not available or does not adequately correct coagulopathy in patients with life-threatening hemorrhage at risk for massive transfusion, the risk–benefit ratio favors the use of WFWB transfusion. In addition, recent evidence suggests that WFWB is potentially more efficacious than stored component therapy. Efforts must continue to improve the safety of WFWB transfusion for patients when it is required in emergency situations.<sup>22,26,41</sup> The risk of infectious disease transmission with WFWB transfusion can be minimized by rapid screening tests before transfusion. Even the best clinical practice component therapy using the 1:1:1:1 formula is not as effective as WFWB transfusion.<sup>4,28,41</sup> The use of WFWB in cases of massive hemorrhage is associated with improved survival and reduced recipient exposure to the harmful effects of stored blood cells and platelets. However, there can be major logistical difficulties in supplying WFWB.<sup>17,42</sup>

## Fibrinogen

There is a strong correlation between massive hemorrhage and low fibrinogen level.<sup>5,3,35–38</sup> Therefore a single injection of fibrinogen concentrate at a dose of 2–4 g intravenously seems to be a smart and useful intervention.<sup>3,5,14,21,25,36–38</sup> There is no evidence that cryoprecipitate would improve the outcome of patients with low fibrinogen levels caused by massive bleeding.<sup>43</sup> Hypothermic coagulopathy is very challenging to treat in bleeding patients, but it was shown that coagulopathy caused by hypothermia can be reversed and successfully corrected by fibrinogen concentrate.<sup>44</sup> However, the prothrombin complex is not able to correct hypothermic coagulopathy.<sup>44</sup>

## Topical use of thrombin

Massive hemorrhage during trauma and surgical procedures is common and is potentially life-threatening for patients.<sup>45</sup> In the case of cardiac surgery, eg, bleeding may result from several aspects inherent to cardiac procedures, including the placement of cardiac suture lines in great vessels or chambers of the heart, as well as the creation of high-pressure anastomoses. Therefore, effective and rapid hemostasis is critical to optimize surgical outcomes.<sup>46</sup> For this reason, various topical hemostatic agents, such as thrombin, porcine gelatin, bovine gelatin, bovine collagen, regenerated oxidized cellulose, and their combination products, have been frequently used when hemorrhage cannot be controlled by conventional hemostatic

methods. Among them, thrombin is of increasing interest and can be applied to the bleeding site in dry form or after reconstitution with sterile isotonic saline.<sup>47–49</sup>

## Conclusion

Viscoelastic assays are superior to standard coagulation tests in the diagnosis of coagulopathy and support of individualized, goal-directed therapy. In general, the most common transfusion intervention is to use fresh frozen plasma, red blood cells, platelets, and fibrinogen concentrate in a ratio of 1:1:1:1 for all patients expected to receive a massive component transfusion. The limitation is the storage duration of the single products, which should not exceed 8 days in red blood cells and 5 days in blood platelets. Even the best-practice component therapy using the 1:1:1:1 formula is not as effective and safe as WFWB transfusion. A limitation of this method is the possible transfer of infectious diseases, and there also can be major logistical difficulties in supplying WFWB. WFWB is not routinely available in most medical centers. There is strong evidence supporting a single-dose injection of fibrinogen to all patients with severe bleeding immediately after admission to the hospital. Following this, individual goal-directed treatment of coagulopathy, based on administration of coagulation factors and fibrinogen, is guided by viscoelastic assay results. This massive hemorrhage management approach appears to be superior to and safer than both component transfusion therapy and WFWB administration, at present. In massive surgical bleeding, various topical hemostatic agents, such as thrombin, are also recommended to minimize bleeding.

## Disclosure

The author reports no conflicts of interest in this work.

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