

# Literature review for management of massive hemorrhage

## Abstract

**Introduction:** Management of massive hemorrhage has been advanced in the last decade and the survival rate of patients who suffered from massive hemorrhage had been improved. Evidence-based recommendations are required to guide the management of such situations, which when implemented may improve patient outcomes.

**Methods:** Data were collected by review for articles, clinical trials and guidelines. Searches were restricted to articles written in English that were published during the period January 1988 through August 2015. The key recommendations in this article were made based on The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

**Discussion:** Over the recent years, massive hemorrhage is been managed by blood components transfusion and surgical or radiological intervention as applicable. With the advanced laboratory assays and point of care tests, surgical and radiological intervention methods and the availability of factor concentrates preparations, the survival of patients with massive hemorrhage has been improved significantly.

**Conclusion:** This article discusses the available evidences and recommendations regarding management of patients with massive hemorrhage.

**Keywords:** massive transfusion, massive transfusion protocols, blood components therapy, prothrombin complex, acidosis, hypothermia, hypocalcaemia

Volume 2 Issue 3 - 2016

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**Received:** March 08, 2016 | **Published:** May 16, 2016

**Abbreviations:** MeSH, medical subject heading; GRADE, grading of recommendations assessment, development and evaluation; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; PFA, platelets function assay; TEG, thromboelastography; ROTEM, thromboelastometry; MTP, massive transfusion protocols; RFVIIa, recombinant FVIIa

## Introduction

Based on WHO mortality data and a systematic review of the literatures, about 400,000 in-hospital deaths from bleeding each year worldwide were estimated.<sup>1,2</sup> Uncontrolled bleeding is the leading cause of potentially preventable death among trauma patients. Coagulopathy is a common finding in patients with massive hemorrhage at the time of hospital arrival. Coagulopathy may increases the risk of multiple organ failure and death compared to patients with similar injury patterns in the absence of a coagulopathy.<sup>3,4</sup> The transfusion approach to massive hemorrhage has continually evolved since early 1900s. This evolution has changed from the use of fresh whole blood transfusion to the current practice of administration of intravenous fluids, blood component therapy, factor concentrates, and antifibrinolytics therapy. Whole blood transfusion is being reserved for uncommon indications.<sup>5</sup> Although still not optimized, introduction of massive transfusion protocols have improved the outcome and overall survival in such patients.

## Method

Preparation of this review article included comprehensive computer database literature searches including Cochrane Database and MEDLINE/PubMed and consultation with representatives of

relevant specialties. Recommendations are based on appraisal of the relevant literature and expert consensus. This search was supplemented by a web-based search through Google. Manual searches of relevant journals, reports, and books were also undertaken. The reference sections of the identified articles were reviewed to identify further relevant papers.

The terms; massive hemorrhage, massive transfusion, massive transfusion protocols, prothrombin complex concentrates, recombinant factor VIIa, fibrinogen concentrate, antifibrinolytics agents, blood components therapy, thromboelastography, acidosis, hypothermia, and coagulopathy were used in the search. Searches were restricted to articles written in English that were published during the period January 1988 through August 2015.

Inclusion criteria included randomized controlled trials, review articles, guidelines, case control or observational cohort studies that had assessed the transfusion practice in patients with massive hemorrhage. Boolean operators and Medical Subject Heading (MeSH) thesaurus keywords were applied as a standardized use of language to unify differences in terminology into single concepts. Also, other medical terms were used for web-based search when applicable. Original publications were evaluated for abstracts that were deemed relevant. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, table 1 and table 2, was used in the evaluation of the key recommendations in this article.<sup>6,7</sup>

## Discussion

Massive hemorrhage leads to severe tissue injury, release of inflammatory mediators and activation of anticoagulant and fibrinolytic

pathways. This may lead to further coagulopathy. Resuscitation with huge amount of crystalloid fluids and blood components can cause hemodilution, dilution coagulopathy, hyperfibrinolysis, decreased oxygen carrying capacity and delivery.<sup>8,9</sup> Hypothermia and metabolic acidosis may worsen the coagulopathy and lead to further hemorrhage, shock and may be death.<sup>10,11</sup>

In the past, loss of 50% of blood volume, that is equivalent to 7% of body weight for adult and 8-9% of body weight for pediatric, within 3 hours was used as definition for massive bleeding. Arbitrarily, it was defined as the loss of one blood volume within a 24hour period. Massive Blood loss with a rate equal or exceeding 150ml/min is considered the current standard as it allows early recognition and therefore early management.<sup>12,13</sup> The important key management for patients with massive hemorrhage includes early surgical or radiological intervention to stop or eliminate hemorrhage, treat or prevent hypovolaemia and hypotension, prevention and treatment of acidosis, hypothermia, and hypocarbia, avoidance of hemodilution, blood components therapy and the appropriate use of coagulation factors concentrates and antifibrinolytic agent as required. As much as possible, a patient with massive hemorrhage should have a patent airway and is adequate breathing with adequate oxygenation. If patient is not intubated and ventilated, high flow Oxygen is recommended. However, ventilation with low tidal volume is recommended in patients with acute lung injury (Grade 1C).<sup>14</sup>

Patients presenting with hemorrhagic shock and an identified source of bleeding should undergo an immediate interventional bleeding control procedure unless initial resuscitation measures are successful (Grade 1B).<sup>15</sup> The time elapsed between injury and operation should be minimized for patients in need of urgent surgical bleeding control (Grade 1A). Applying tourniquet represents a simple and efficient method to control bleeding (Grade 1C).<sup>16</sup> It is more useful in the pre hospital situations example trauma, combat or war related injuries. Tourniquets should be left in place until surgical control of bleeding is achieved yet it is important to keep this time period as short as possible. It worth mentioning that Improper or prolonged placement of a tourniquet can lead to complications such as nerve paralysis and limb ischemia.<sup>17</sup>

A large bore peripheral intravenous line cannula or central venous or arterial line access is recommended to allow the rapid administration of fast amount of intravenous fluids, blood components, electrolytes, factor concentrates and antifibrinolytic drugs as well as allows blood sampling as applicable(Grade 2C).<sup>18</sup> Early communication and consultation with expert surgical, anesthetic, radiology, intervention radiology and transfusion medicine consultants are crucial for proper management. An expertise trained team leader should be assigned to facilitate communications and documentation. An intensive care bed is more likely to be required and early warning is advisable.

Patients presenting with massive hemorrhagic and an unidentified source of bleeding should undergo immediate further investigations (Grade 1B) which may include further assessment of the chest, abdominal cavity and pelvis by radiological methods or surgical intervention.<sup>19,20</sup> The early introduction of imaging studies e.g. ultrasound or Computed tomography scan for the assessment of hemorrhage severity are very advisable (Grade 1B).<sup>21,22</sup> An early application of measures to reduce heat loss and warm the hypothermic patient is recommended in order to achieve and maintain normothermia (Grade 1C). Hypothermia, defined as a core body temperature below 35°C, is associated with acidosis, hypotension and coagulopathy, altered platelet function and fibrinolysis.<sup>23,24</sup> The

laboratory and transfusion service play an important role in the management of patients with massive hemorrhage. The results of laboratory are needed to be fast and accurate as possible it could be. Laboratory and transfusion service must be informed at the earliest possible opportunity as this will provide an opportunity to check stock, reschedule non-urgent work and call in additional staff if required out of hours. However, there are limitations to standard laboratory measures as the results are often not yet available when decisions are to be made. The use of point of care testing is strongly recommended in the situation of massive hemorrhage.

The current standard practice is Laboratory tests are to be done at initial management, and then every 15-30minutes or as clinically indicated (Grade 1C). Every institution should have a system for emergency investigation orders (stat order) and the immediate release of result to the assigned personnel(s).<sup>25,26</sup> Monitoring of coagulation profile should be initiated as early as possible (Grade 1C). the main aim is to keep PT and APTT below 1.5times mean of normal control, INR below 1.5 and Fibrinogen level above 1.5g/L and in obstetric cases, it is recommended to be above 2g/L. Fibrinolysis is more difficult to be assessed rapidly from laboratory prospective however use of point of care tests e.g. Thromboelastography is very useful in this regard.

Hypocalcaemia is a serious side effect and must be diagnosed and treat immediately. Therefore ionized calcium level should be monitored during massive transfusion (Grade 1C). Calcium chloride should be administered during massive transfusion if ionized calcium levels are below the normal ranges (Grade 2C).<sup>27,28</sup> Serum lactate and base deficit measurements are recommended to estimate and monitor the extent of acidosis which if not treated may lead to bleeding and shock (Grade 1B).<sup>29</sup> Volume replacement is a key part of massive hemorrhage therapy. This is essential for maintenance of tissue perfusion and oxygenation, which is critical in prevention of hypovolaemia shock and consequent high mortality from multi-organ failure. The use of intravenous colloids versus crystalloids fluids for volume replacement has been the subject of debate and institutions should develop appropriate practice guidelines in this regard (Grade 2A).<sup>30,31</sup>

The available data show that hypotensive resuscitation is considered a safe strategy and significantly decreases coagulopathy and lowers the risk of early death (Grade 1C). However, hypotensive resuscitation approach is contraindicated in patients suspected or diagnosed to have brain or spinal injury.<sup>32,33</sup> In common practice, resuscitation is usually started with crystalloid, such as normal saline or Hartmann's solution (Grade 1B). Hypertonic solutions can also be considered during initial treatment (Grade 2B). Resuscitation with crystalloids alone requires more fluid and results in more edema. Colloids are considered to have a greater intravascular persistence when compared to crystalloids and are recommended to be considered within prescribed limits in hemodynamically unstable patients (Grade 2C).<sup>34,35</sup> The addition of colloids should be considered in hemodynamically unstable patients.<sup>36,37</sup> patient with massive hemorrhage and receiving large amount of rapid fluid infusion may develop hypothermia. Hypothermia is found to increase the risk of end organ failure and coagulopathy. Hypothermia may be prevented by pre-warming of resuscitation fluids, patient warming devices such as warm air blankets and the use of temperature controlled blood warmers (Grade 4C).<sup>38</sup>

Along with other important measures, blood components transfusion saves the life of such patients. Blood components

therapy is not without a risk as it may cause serious side effects e.g. acute hemolytic transfusion reactions and acute lung injury. Also, blood components are of a limited availability and the special requirements of rare blood components phenotype or the need of special preparations e.g. irradiated blood components may complicate the situation. In all cases, it is advisable to use leukodepleted blood products as possible.<sup>39,40</sup> Hemoglobin and hematocrit levels should be measured frequently, but in the knowledge that the hemoglobin level is not an accurate indicator of blood loss in the acute situation. A single Hematocrit or hemoglobin measurement as an isolated laboratory marker for severity of hemorrhage is not recommended and repeated testing is advisable (Grade 1B).<sup>41,42</sup>

It is advisable that the clinician communicating with the transfusion service to indicate the timescale within which blood is needed at the bedside, in order that the laboratory staff knows how much time is available for ABO and Rh-D grouping and pre-transfusion testing. In an extreme situation where blood is required immediately and the patient's blood group is unknown, it may be necessary to issue Group O un-cross matched red cells. Females of reproductive age whose blood group is unknown must be given group O Rh-D negative PRBCs, according to availability, in order to avoid sensitization and the risk of hemolytic disease of the newborn in subsequent pregnancy. ABO group-specific red cells should be given at the earliest possible opportunity. It takes less than 10 minutes for laboratory to determinate the patient's ABO and Rh-D group. Pre-transfusion compatibility should be done as early as possible and fully compatible PRBCs will be given if time permits. Further serological cross-match is not usually required after replacement of 1 blood volume.<sup>43,44</sup>

In a patient with known significant allo-antibodies against red cell antigens, the risk of a hemolytic transfusion reaction will need to be assessed against the risk of withholding transfusion until compatible blood can be provided. It is advised to keep cross match compatible blood until bleeding is stopped or controlled.

Fresh Frozen Plasma (FFP) is used to control coagulopathy in patients with massive hemorrhage. If the patient's blood group is unknown, it is a practice to give AB group FFP. A time period of 30minutes are required to be allowed for thawing time. For patients on Warfarin, intravenous Vitamin K at dose of 5–10mg can be administered as applicable. In this situation, Prothrombin complex concentrate (PCC) is recommended instead of FFP transfusion. For patients who are not on anticoagulant or their medication status is not known, FFP transfusion is recommended over PCC and vitamin K therapy can be considered if there is an evidence of liver impairment or vitamin K deficiency or antagonism.

Cryoprecipitate can be used to treat or prevent hypofibrinogenemia that can be resulted from dilution coagulopathy. FFP transfusion may supply enough fibrinogen to correct any deficiency however large volume of FFP may be required. Again, a time period of 30minutes must be allowed for thawing time. Fibrinogen concentrate administration is preferred to cryoprecipitate, if available.<sup>45,46</sup> Thrombocytopenia less than  $50 \times 10^9/L$  can be anticipated after one blood volume replacements resulting from dilution and increase consumption. Platelets transfusion is recommended to keep Platelets count more than  $75 \times 10^9/L$ , and more than  $100 \times 10^9/L$  if brain or spinal hemorrhage is expected. Patient with known or suspected platelets dysfunction must be assessed clinically and laboratory wise for evidence of platelets dysfunction as time permits. It is recommended to transfuse adequate dose of platelets concentrates if platelets dysfunction is suspected regardless

of platelets count. The available methods to assess platelets functions include Platelets Function Assay (PFA) and Thromboelastography (TEG) or Thromboelastometry (ROTEM). If available, TEG/ROTEM is preferred over PFA as it is more accurate and results are easier and faster to be obtained in this regard considering that TEG is a near patient testing. Bleeding time is not recommended in this situation as its result is not accurate and needs specialized person to perform it in an appropriate way.<sup>47,48</sup>

The ideal ratio of FFP: PRBC for Massive Transfusion Protocols (MTP) has not been identified, but the best available evidence supports that a ratio closer to 1:1-2 is the best ratio to be utilized in massive transfusion protocols (Grade 1C).<sup>49,50</sup> An MTP incorporating FFP: RBC ratio of 1:1-2 is associated with decreased use of blood components and may obviate the need for RFVII. It may also reduce the risk of mortality and acute respiratory distress syndrome (grade C). There is association between optimum MTP transfusion and improvement of acidosis, hypothermia and hypocalcaemia.<sup>51,52</sup>

Some of MTP provide blood component therapy in two separate forms of packs as the initial pack that contains no Platelets or cryoprecipitate units in it unless there are clinical indications (grade C). The following packs will contain adequate doses of platelets and cryoprecipitate. In addition, it is advisable to consider administration of Fibrinogen concentrates instead of cryoprecipitate, if available. Some other packs of MTP involve platelets and cryoprecipitate transfusion upfront. More studies may compare the differences and effect of such MTP packs.<sup>53,54</sup> It is recommended that institutions develop an MTP that includes the dose, timing and ratio of blood component therapy for use in trauma patients with, or at risk of, critical bleeding requiring massive transfusion (Grade 1C).

The use of intra and or post operative cell salvage can be very effective at both reducing demand on allogeneic supplies and providing a readily available red cell supply in massive hemorrhage. It's of use where large blood loss is experienced. Cell salvage is not recommended when blood/area of collection is suspected to be infected or contaminated. Also it is not recommended if salvaged blood is suspected to be contaminated by malignancy cells (Grade 2C).<sup>55,56</sup> Infusion devices, gravity or electronic, may be used for the administration of blood and blood components in situation where rapid infusion seems necessarily (Grade 2C).<sup>57,58</sup> However, a close observation is needed to avoid risk of hemolysis that can be endured by rapid infusion or malfunction of such devices. Pressure devices are not recommended as a routine standard practice. If the use of pressure devices is deemed necessary, it should exert pressure evenly over the entire bag, have a gauge to measure the pressure and not exceed 300mmHg of pressure. These devices should be monitored at all times when in use (Grade 1C).<sup>59,60</sup>

Blood warmers are recommended for all patients undergoing massive and rapid infusion of intravenous fluid and blood components (Grade 1 C) as it is crucial to avoid and treat hypothermia in a timely manner in order to avoid fatal complications.<sup>61,62</sup> Thromboelastography® (TEG®) and Thromboelastometry (ROTEM®) are point-of-care testing methods that qualitatively measure the entire coagulation cascade, including fibrinolysis, in whole blood and provide fast results which will allow more rapid and accurate decision in regard to blood components or blood products therapy. TEG/ROTEM appear to be more efficient and faster than conventional laboratory tests at detecting multiple aspects of coagulopathy and possibly for predicting blood product requirements.

TEG / ROTEM may give better prediction of fibrinogen and platelet function compared to standard testing. TEG/ROTEM is that it may be used as a guide for appropriate use of RFVIIa and may provide more accurate measurements of RFVIIa efficacy than PT. It is important to put into consideration that TEG/ROTEM are an expensive point of care instruments that needs trained staff to operate and interpret the results.<sup>63,64</sup>

The routine use of Recombinant FVIIa (RFVIIa) in massive bleeding patients is not recommended due to its lack of supporting evidences (Grade 2C). Its use can be justified in life saving situation when used. Use of RFVIIa concentrate, as off-label last ditch therapy, may be considered for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy (Grade 2B).<sup>65</sup> The optimal condition for RFVIIa usage as off label is salvageable patients with uncontrolled hemorrhage and that surgical or radiological measures failed to control bleeding, adequate blood component replacement are ongoing,  $P^H$  is more than 7.2, and temperature of patient is more than 34°C. It is difficult to control such conditions at the time of massive hemorrhage.

When RFVIIa is decided to be given, an initial dose of 90 microgram/kg is considered reasonable.<sup>66,67</sup> Close evaluation of side effects e.g. thromboembolism and response to therapy is recommended. Hyperfibrinolysis in patients with massive hemorrhage is adversely correlated with mortality. Early administration of an anti-fibrinolytic agent tranexamic acid, advisably within 3 hours of onset of bleeding, may result in reduced mortality and morbidity (Grade 2C) and it is even more recommended to use of antifibrinolytic agents in patients with established hyperfibrinolysis (Grade 1B). The dose of tranexamic acid must be adjusted to creatinine level and should be avoided if haematuria is present or renal injury is suspected.<sup>68</sup>  $\epsilon$ -Aminocaproic acid 100 to 150mg/kg followed by 15mg/kg/hour infusion also been reported to be effective in some of similar situations.<sup>69</sup> The use of TEG/ROTEM, if available, is recommended to monitor the therapy with antifibrinolytic agents (Grade 2C).<sup>70</sup>

There are no strong recommendations to support the routine use of Prothrombin Complex Concentrates for patient with massive hemorrhage except when patient is known or suspected to have vitamin K deficiency or antagonism or when patient has deficiency of the corresponding coagulation factors (Grade 1B).<sup>71</sup> Optimal dosage for a given situation is unclear, many studies consider dose of 25-35units per kg.<sup>72</sup> Fibrinogen concentrate has several advantages over cryoprecipitate transfusion. Fibrinogen concentrate has better safety profile, more accurate and consistent dosing regimen and also

rapidly administered. In addition, although cryoprecipitate is cheaper than fibrinogen concentrate, yet the overall costs of cryoprecipitate and fibrinogen concentrate are quite similar.<sup>73</sup>

Substitution therapy with fibrinogen concentrate, as a supplementary intervention in bleeding patients with low plasma levels of fibrinogen, may contribute to reduce transfusion requirements, decrease blood loss, and lead to an overall improvement of laboratory coagulation tests. The recommended initial dose of fibrinogen concentrate is 3 to 4g. Repeat doses may be guided by laboratory monitoring of fibrinogen levels (Grade 2C).<sup>74</sup> Desmopressin (1-deamino-8-D-arginine) is not recommended to be used routinely in the bleeding trauma patient (Grade 2C). It can be considered in refractory microvascular bleeding if the patient has been treated with platelet-inhibiting drugs such as acetylsalicylsalicylic acid (Grade 2C). The use of antithrombin concentrates in the treatment of the bleeding trauma patient is not recommended (Grade 1C).<sup>75</sup>

The use of topical haemostatic agents in combination with other surgical measures or with packing for significant venous or arterial bleeding associated with parenchymal injuries are to be considered when applicable (Grade 1B).<sup>76</sup> Local haemostatic agents include collagen based products, gelatin or cellulose based products, fibrin and synthetic glues or adhesives that can be used for both external and internal bleeding while polysaccharide-based and inorganic hemostatics are still mainly used and approved for external bleeding.<sup>77,78</sup> Patients with trauma or massive hemorrhage may develop a prothrombotic state following massive hemorrhage. Therefore, unless contraindicated, standard thrombo prophylaxis should be considered as soon as patient is stabilized, hemorrhage is stopped and bleeding is not considered a risk any more (Grade 4C).<sup>79</sup>

Complications of massive blood transfusion include disseminated intravascular coagulation partly due to dilution coagulopathy and systemic hyperfibrinolysis. Also, adverse events associated with blood transfusion as hemolytic reaction, Transfusion-related acute lung injury, immunologically mediated reactions and Transfusion transmitted infections should not be overlooked. Hypocalcaemia, Hyperkalemia and renal impairment are also been a recognized side effects of massive blood transfusion. Acidosis has deleterious effects on the cardiovascular system include decreased cardiac contractility and cardiac output, vasodilation and hypotension, decreased hepatic and renal blood flow, bradycardia, and increased susceptibility to ventricular dysrhythmias. Acidosis should be treated promptly<sup>80,81</sup> (Table 1).

**Table 1** Grading of recommendations assessment, development and evaluation (GRADE)

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect: Several high-quality studies with consistent results, In special cases: one large, high-quality multi-centre trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, One high-quality study, Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain: Expert opinion, No direct research evidence, One or more studies with very severe limitations

**Source:** GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group 2007 (modified by the

EBM Guidelines Editorial Team). [http://www.essentialEvidenceplus.com/product/ebm\\_loe.cfm?show=grade](http://www.essentialEvidenceplus.com/product/ebm_loe.cfm?show=grade) [Table 2].

**Table 2** Quality and of evidence

Level	Description
IA	Evidence from meta-analysis of randomized controlled trials
IB	Evidence from at least one randomized controlled trial
IIA	Evidence from at least one controlled study without randomization
IIB	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

## Acknowledgements

None.

## Conflict of interest

The author declares no conflict of interest.

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