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REVIEW

Treatment alternatives in massive hemorrhage☆

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Abstract Massive hemorrhage is the main cause of mortality and morbidity in trauma patients, and is one of the most important causes in any patient following major surgery. Conventional treatment consists of volume replacement, including the transfusion of blood products, so that tissue perfusion and oxygenation may be maintained. Associated hypothermia, acidosis and coagulopathy is a lethal triad.

This review focuses on the latest therapeutic management of massive hemorrhage. The authors advocate the use of crystalloids as per protocol (controlled volumes) in order to achieve a systolic blood pressure of 85 mmHg. The administration of the three blood products (red cells, plasma, and platelets) should be on a 1:1:1 basis. Where possible, this in turn should be guided by thromboelastography performed at *point of care* near the patient. Coagulopathy can occur early and late. With the exception of tranexamic acid, the cost-benefit relationships of the hemostatic agents, such as fibrinogen, prothrombin complex, and recombinant F VII, are subject to discussion.

PALABRAS CLAVE
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Pruebas a pié de cama

Alternativas terapéuticas de la hemorragia masiva

Resumen La hemorragia masiva es la principal causa de morbimortalidad en el paciente traumatizado, y una de las más importantes en el paciente sometido a cirugía mayor. El tratamiento convencional se basaba en la reposición inicial de la volemia con la infusión de grandes cantidades de fluidos y en la transfusión de hemoderivados, con objeto de asegurar la perfusión y oxigenación tisular. Hipotermia, acidosis y coagulopatía se considera triada letal.

En esta revisión los autores abordan un enfoque terapéutico actualizado del manejo de la hemorragia masiva. Se preconiza infundir cristaloides de forma pautada (no masiva) para lograr una presión arterial sistólica de 85 mmHg. La administración de hemoderivados debe ser precoz y con ratio 1:1:1 (cantidades equiparables de concentrados de hematíes, plasma y plaquetas), y si es posible, guiada por tromboelastograma a la cabecera del paciente. La coagulopatía puede ser precoz y tardía. Salvo el ácido tranexámico, se discute la relación coste-beneficio de fármacos prohemostáticos, como fibrinógeno, complejo protrombínico, y FVII recombinante.

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Introduction

Each year over 100 million people suffer traumatism of some kind, and over five million—particularly young individuals–die as a result of violence or accidents. Massive bleeding and brain damage due to traumatic brain injury (TBI) are the main causes of death in severe trauma. Massive bleeding is also an important cause of morbidity–mortality in major surgery, including oncological, cardiac and solid organ transplant surgery. The estimated mortality associated to such bleeding varies from 30 to 70%.[1]

Massive bleeding is defined as hemorrhage requiring the transfusion of 10 or more red cell concentrate units in 24 h. Other arbitrary definitions include 6 or more such units in 12 h or over 50 blood product units in 24 h–including red cells, platelet concentrates and fresh frozen plasma (FFP).

Classically, massive bleeding has been subjected to damage control surgery designed to arrest the source of bleeding, with fluid replacement therapy and the administration of blood products. Despite such measures, however, the morbidity–mortality associated to massive hemorrhage remains unacceptably high. As a result, new treatment strategies have been developed in the last decade with a view to improve patient survival. These measures include the early replacement of coagulation factors, platelets and red cells in equivalent proportions (i.e., so-called 1:1:1 ratio replacement), the use of prohemostatic drugs (prothrombin complex, activated factor VII and tranexamic acid), the introduction of tests at the patient bedside and the thromboelastogram for the individualized and effective management of massive bleeding.

Conventional management of massive hemorrhage

The three key elements in the treatment of massive bleeding are volume expansion or replacement with crystalloids and colloids, the optimization of tissue oxygenation with the transfusion of red cells, and the correction of coagulopathy. In general, the principles described below should be followed.

The main objective is to restore circulating volume and arrest the source of bleeding (damage control surgery). In this context, normovolemic anemia is better tolerated than hypovolemic anemia.[2]

The infusion of fluids should be guided by the blood losses, the rate of bleeding, and the hemodynamic condition of the patient. Hemoglobin initially may be normal, even in the presence of important hemorrhage.[3]

No ideal volume replacement fluid has been defined to date. In principle, crystalloids (Ringer lactate or saline solution) may be a good choice, and are recommended by the American College of Surgeons, depending on the magnitude of the losses (Table 1). However, the aggressive use of crystalloids dilutes the coagulation factors and platelets, favoring coagulopathy and multiorgan dysfunction.[4,5] As a result, earlier administration of colloids is advised, especially in hemorrhagic shock. Nevertheless, the infusion of colloids such as hydroxyethyl starch or dextrans has been associated with alterations in platelet function, inhibition of fibrin polymerization, and the stimulation of fibrinolysis.[6,7]

The objective or goal of resuscitation has not been clearly defined. Keeping normal blood pressure and hemoglobin values can lead to an increased use of fluids, favoring coagulopathy and exacerbating the bleeding. Possibly ''permissive hypotension'' (i.e., blood pressure values slightly below normal) may be a better objective,[8] except in TBI, where higher pressure values may be needed in order to maintain brain perfusion. In monitored patients, maintenance of the cardiac index and of oxygen transport and consumption may constitute an adequate objective of resuscitation. In order to assess the blood losses and the success of resuscitation with fluids, venous oxygen saturation and acidemia are more sensitive measures than the traditional hemodynamic measurements.[9]

Massive transfusion protocol (MTP). 1:1:1 ratio

Validated algorithms have been developed for predicting whether a patient is suffering from massive blood loss and requires inclusion in a massive transfusion protocol (MTP).[10] If transfusion is urgent, we request 0 negative red cell concentrate and AB plasma, until cross-testing is performed.

The concept of MTP is recent,[11] and such protocols are advised in patients with massive bleeding who present the lethal triad of acidosis, hypothermia and coagulopathy. The aim is to treat the patient early and aggressively with blood products, in order to avoid exsanguination and coagulopathy. MTP requires coordination with the blood bank, core laboratory and intensivist for requesting tests referred to coagulation, hemoglobin and platelets. In MTP, the patient is administered equivalent amounts of the three blood products (Table 2).

Conventional resuscitation with large volumes of fluids can lead to dilutional coagulopathy–the latter in turn being worsened by the hypothermia and acidosis that accompany trauma. In order to deal with this problem, the United States Army's Institute of Surgical Research conference[12] in 2005 proposed a transfusion strategy involving immediate administration of the three blood products in massive bleeding secondary to trauma (Table 3).

Since then, transfusion strategies have been introduced with higher plasma and platelet to red cell concentrate ratios, simulating whole blood. Although some non-randomized observational studies have found these ratios to improve survival among patients with massive bleeding,[13,14] other recent studies have been unable to confirm these findings.[15,16]

Despite the disparity of published data and the increase in resource consumption associated with the use of such high ratios, MTP has been accepted in many centers in North America and Europe. In this sense, the Canadian Blood Services reported a 50% increase in the demand for AB plasma between the years 2007 and 2009.[17]

While acknowledging these data, the European massive transfusion guideline of 2007 gave no specific recommendations referred to the mentioned ratio, in the same way as the more recent guides of the European task force[18] and the American Association of Blood Banks,[19] which recommend early intervention with FFP, though without establishing ratios.