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Review

Transfusion in trauma☆

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ABSTRACT

Massive transfusion is considered a key component in the acute management of massive hemorrhage. While the existing protocols do not standardize its use, they do recommend its timely administration and a dose adjusted to the type of blood product, a proportionate ratio between hemocomponents and appropriate adjuvant drug support, in addition to techniques that promote bleeding control and prevent syndromes that could trigger a fatal outcome. This non-systematic review is intended to summarize the current concepts on the acute management of massive bleeding in trauma, from a non-surgical perspective.

The search was limited to the articles of the last 10 years and included primary and secondary data basis, leading to a snowball technique.

Transfusión en trauma

Palabras clave:
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Factor VIIa Recombinante activado
Ácido tranexámico
Coagulopatía

RESUMEN

La transfusión masiva es considerada como pieza fundamental en el manejo agudo de la hemorragia masiva. Si bien los protocolos existentes no estandarizan su uso, sí recomiendan su aplicación oportuna y una dosificación ajustada al tipo de hemoderivado, una relación proporcionada entre hemocomponentes y coadyuvancia justa de medicamentos, así como técnicas que promuevan el control de la hemorragia y prevengan síndromes desencadenantes de muerte. Esta revisión no sistemática tiene como objetivo resumir los conceptos actuales sobre el manejo agudo de la hemorragia masiva relacionada con trauma desde una perspectiva no quirúrgica.

La búsqueda de artículos se limitó a los últimos 10 años, y se realizó en bases de datos primarias y secundarias; todo ello terminó en una técnica de bola de nieve.

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Introduction

The evolutionary plan of the species has enabled the development of multiple organ systems to prolong life. In this regard, cell perfusion presents coagulation as the cornerstone for microvascular hemostatic control.

In the light of modern knowledge, the coagulation system presents serious weaknesses, including those relating to its effectiveness in major trauma. Severe trauma bleeding is strongly linked to mortality; in fact, it is the second cause of early hospital death[1–5] and is more frequent in 1–46-year-old men in the United States.[1,6]

The emergence of up-to-date trauma care guidelines, international protocols, international resuscitation protocols, the requirement of certification in advanced vital support, transfusion or trauma management of physicians in different countries, the structuring of developed care systems for trauma patients and more effective pre-hospitalization networks have all contributed to the improvement in morbimortality rates.[1,2,5,7,8]

It is surprising that over 12 million units of hemoderivatives are being used in the United States on an annual basis, of which around 40% are used in resuscitation and 10% in trauma patients[9]; this encourages researchers to constantly update their knowledge about transfusion therapies, which provide mortality-modifying scenarios as a frequent and extensively used practice.

This non-systematic review is intended to summarize the current concepts on acute management of trauma-related massive hemorrhage from a medical perspective. The article search was limited to the last 10 years and used primary and secondary data basis, which concluded in a snowball technique.

Myth or reality

The main goal in trauma patient care is to be able to lower mortality rates, in addition to providing timely care; in fact, the ATLS course (*advanced trauma life support*) focuses on identifying surgical causes of bleeding and its timely control, while improving the cell perfusion indexes based on target guided therapies.[3] It is important to note that not all hemorrhages are controlled surgically, and not all bleedings are similar in nature.[10]

The classical intervention has suggested the use of crystalloids as a liberal strategy to maintain mean perfusion pressures of key organs for vital support, neglecting consideration of the histotoxic impact and harmful influence on hemostasis; in fact, the emergence of recurrent hypotension and coagulopathy has been observed as outcomes of hemodilution with such strategy.

Pre-hospital care of critical patients in conflict zones is studied for the relevancy of resuscitation techniques with hypotension and restrictive crystalloid therapies while the source of bleeding is controlled. This approach has improved the survival rates. Bickell[11] studied 598 patients with stab wounds to the chest and observed that the survival was better in those individuals managed with a slow rehydration technique *versus* liberal crystalloid use.

Trauma-related coagulopathy

Trauma-related coagulopathy is quite common. Tieu's study[12] refers an incidence between 24% and 28% during critical care. The Houston group[13] found a prevalence of prolonged international normalized ratio (INR), with a mean of 1.8 in 97 trauma patients during their first ER admission.

The diagnostic values of this syndrome have usually been based on the measurement of clotting times, the number of platelets and the circulating fibrinogen; the problem is that such tests do not value the quality of platelet activity or the fibrinolytic systems; in other words, the tests lack the expected precision and do not provide for a comprehensive evaluation of coagulation in the current model.

The treatment of coagulopathy apparently compromises not just the management of coagulation factors and platelets, but also temperature compensation, calcium plasma levels, acidosis and multiple organ function. In this regard, Boffard's study[14] is striking, because while transfusion is the gold standard, it lacks effectiveness due to the absence of an environment conducive to coagulation and cell perfusion; it is interesting that the adequate control of systolic blood pressure (SPB) (TAS) >90, platelets >100,000 and arterial pH > 7.2 resulted in improved overall survival, as referenced by Jiménez et al. in 2010,[15] with a much more specific analysis for each entity.

Stratification

While the decision to transfuse is obvious in some cases, in most scenarios it requires clinical measurement of relevant variables. Considering arterial hypotension, hemoglobin values, pallor or tachycardia to diagnose the anemic syndrome in trauma is usually misleading for making sound transfusion decisions.

In the Bruns et al.[16] trial, a hemoglobin of <10 mg/dL during the first 30 min of hospital care was strongly correlated to severe, uncontrolled bleeding and was indicative for massive transfusion and urgent intervention, as opposed to what is usually done in other medical surgical environments.

In order to determine which variables are directly related to the need for an early massive transfusion and lower global overall mortality, Reiner et al.[17] conducted a retrospective study in 4336 transfusions, from which he chose 92 massive transfusions. The following variables were analyzed: TAS, Glasgow, heart rate, pelvic fracture, abdominal ultrasound (eco fast), base excess arterial blood gasses and hemoglobin as the most concordant and with the best predictive capacity. The model revealed that scores >6 were associated with massive transfusion (sensitivity: 96.6%; specificity: 99.7%; positive predictive value: 82.9%) and a subsequent lower mortality in individuals with a score >6 and early transfused (7.9% *vs.* 54.3%).

Hemoderivatives and massive transfusion

Massive transfusion has been defined as the use of >10 units in the course of the first 24 h,[2,4,18–20] over 4 units in 1 h or replacement of >50% of the blood volume in 3 h.[21] According to Scully et al.,[22] this intervention consumes about 71% of the deposits of hemoconcentrates in the US blood banks and exhibits a high correlation to mortality.[23] So much so, that in Como's study in 5645 patients, a 59% mortality was established for those who used >40 PRC units and hence the author was unable to conclude that the outcome could improve with an adequate use of the *damage control* strategy, early transfusion and intraoperative blood saving techniques.[2,24,25]

In the last few years, the early administration of hemocomponents (even without crossing) and O negative type has been described in the literature, but paradoxically enough, has not given rise to controversy, contrary to the interest in reducing the ratio of the hemoderivatives administered (ratio at the time of administration of PRC, FFP and PLA).[8,24,26]

Initial changes in the proportion of components were established in field hospitals, favoring stabilization and subsequent early diagnosis, and then transfusion: packed red cells (PRC), fresh frozen plasma A or B (FFP) and platelet apheresis (PLA); plus, if needed, cryoprecipitates, whole blood or rFVIIa (activated recombinant factor VII).[27]

Both in Iraq and in Afghanistan, evidence showed that the use of the aforementioned hemocomponents in a 1:1:1 ratio (dose of PRC:FFP:PLA) improved the survival; in fact, the restriction of crystalloids was combined with an average of 10 to 40 units of hemoderivatives per day.

Borgman et al.[27] published that in the treatment of soldiers in combat, the most balanced ratio (1:1:1) was associated with 19% mortality (*vs.* 65% and 34% of those with ratios of 1:8 and 1:2.5, respectively). Similarly, González et al.[13] showed that in severe hemorrhage patients at the time of admission to hospital, a diagnosis of coagulopathy was very frequent and only the use of early massive transfusion decreased its severity and reversed prolonged prothrombin times in most cases; furthermore, an association was established between mortality and a persistently prolonged INR (mortality >50%).

Several studies have shown equivalent results with the use of hemoderivatives and whole blood in terms of mortality; according to Repine et al.,[18] the only statistical difference – not clinical – was the number of units used (29 *vs.* 5.3 $p < 0.001$). Consequently, the author suggests its use as an alternative in combat zones but not as the treatment of choice for civilians.[18,28]

Holcomb and Spinella,[29] as well as other authors,[19,30–35] claims that the effect of whole blood is superior to the effect of fractionated components, due to similar effectiveness but with less volumes infused and a short time elapsed from the moment the request is placed to the effective administration. In contrast, it has been shown that outside combat areas, massive transfusion does not exhibit improved mortality rates, despite the suggestion by some of restricting the quantity; In fact, Scully et al.[22] in the U.K. showed a similar mortality in both transfused groups (massive *vs.* non-massive transfusion); the same author showed a similar rate in both cases (33% *vs.* 25%, $p = 0.575$).

A different situation is described by Fries and Snyder[36,37]; they have concluded from an unsupported hypothesis, based on evidence and with a very erratic and poor deconstructionist model, the uselessness of early transfusion of FFP or PLA.

Therefore, at what level should it be started? Is there a need to be restrictive (Hb < 7), or rather be liberal (Hb < 10)? These questions are crucial for the management of trauma with hemorrhage in the first few hours. According to The Canadian Transfusion Trial, the liberal use of these units showed similar safety outcomes,[13,38] but exhibited a proven lower mortality at 30 days.

The administration of PLA with ratios close to 1:1:1 in trauma has shown lower mortality. Inaba et al.[39] showed that early PLA administration should be considered as a protective factor against death (OR 0.96; CI 95% 0.95–0.97), with a mortality of 14.5% and 16.9% at 12 and 24 h, respectively.

Sinha and Roxby,[40] on the other hand, evaluated the relationship between hemocomponents, blood byproducts usage and mortality at two different points in time; in his article the author published different mortality rates and a lower number of blood components used in 2008 *vs.* 1998 (number of units ratio: 1:10.5 in 1998 and 1:6 in 2008; $p = 0.02$); similarly, a significant reduction in mortality was recorded (52% *vs.* 34.8%, $p = 0.05$). Such results were similar to Johansson et al.'s,[41] who using a thromboelastography (TEG) guided massive transfusion protocol found an inverse relationship between PLA-FFP and mortality. Kashuk et al.'s[42] findings were similar using a target-based protocol according to rotational TEG.

The use of TEG regardless of the context is the test that most closely resembles hemostasis evaluation in trauma and has been shown to decrease the amount of bleeding and the transfusion of hemoderivatives. It must be kept in mind however, as Gempeler et al.[43] claim, that "laboratory tests alone are not absolute, but only complementary, in the clinical management of patients." This is also true for TEG, despite its advantages.

Alternatives

Two drugs stand out in the management of severe hemorrhage in trauma: activated recombinant factor VII (rFVIIa) and tranexamic acid (AC); both intended to interfere with coagulation, but on different theoretical grounds.

Different doses have been tried for rFVIIa, ranging from 60 μg/kg to 200 μg/kg; however, the optimal universal doses with the best cost-effectiveness ratio and the minimum adverse events is yet to be determined.[4,5,12,44]

Boffard et al.'s[14] trial used 200 μg/kg to 100 μg/kg to 100 μg/kg doses *vs.* placebo, following the use of more than one dose of PRC during the first 4 h and statistically significant differences were found in the number of patients with massive transfusion in the group of blunt trauma patients. In contrast, these results could not be validated in penetrating trauma patients with equal frequency of thrombotic and embolic complications between interventions. Mortality was similar in both groups (penetrating and blunt trauma).

In a second study, Knudson in a retrospective and prospective review between 2003 and 2008 evaluated two groups based

on the timing of rFVIIa usage (before and after the administration of 4 units of PRC). The former group was recorded as early usage and the latter as late usage. From a total of 716 patients, 326 were included in the analysis. The result was that in most patients, rFVIIa was used prior to completing the transfusion of 18 units; such an approach (referred to as late usage) was associated to 54.5% mortality and was also linked to coagulopathy, acidosis, old age and chest trauma. In contrast, early administration did not generate any impact on mortality (OR 1,04, CI 95% 0.4; 2.7 $p = 0.94$),[45] which suggests the need for early intervention studies that directly evaluate mortality.

The decision to use rFVIIa is usually based on economic considerations; while rFVIIa is administered for improving the patient's health, there is some debate about its level of effectiveness to warrant its use in every patient who fails to respond to initial medical and surgical management. Using a cost-effectiveness design Patel et al.[46] showed an improvement in quality of life of 26.54 QALY (*quality adjusted life years*) with a dose of 90 μg/kg of rFVIIa and a 25% reduction in the adult respiratory distress syndrome (ARDS).

In a US Navy study[47] the early use of rFVIIa showed a significant reduction in the number of hemocomponent units used (20.6 *vs.* 25.7; $p = 0.048$). Spinella[48] found lower hemorrhage-associated mortality in patients undergoing massive transfusion and early rFVIIa, 57% *vs.* 78%, $p = 0.12$ (*we suggest a careful evaluation of these data*). Doses of 40 μg/kg according to Harrison et al.,[49] and 100–120 μg/kg according to the Israeli Task Force[50] and the European Consensus,[51] were reported as effective for controlling trauma-associated coagulopathy, decreasing the number of units required and reducing mortality.

The CRASH-2[52] trial was conducted using TA, due to its potential beneficial effects in massive hemorrhage trauma patients. 20,211 patients were evaluated (10,096 patients in the TA group and 10,067 patients in the placebo group). The results published in 2010 reported that the use of TA according to the protocol resulted in a decline in overall mortality and in the hemorrhage-associated mortality, with values of 14.5 % *vs.* 16 %, $p = 0.0035$ and OR = 0.91 (CI 95% 0.85; 0.97), and 4.9% *vs.* 5.7%, $p = 0.077$ with a RR = 0.85 (CI 95%; 0.76; 0.96), respectively, with no statistically significant differences reported in terms of adverse events when administered during the first 8 h of the injury.

Other hemostatic options include the use of fibrin sealants, modified hemoglobin and perfluorocarbons; however, these are all beyond the scope of this review.[2,4,7,38,44]

Conclusions

At the end of this review, what remains to be done is to assess the decision to design a practical clinical guide for transfusion in trauma, on the basis of the large number of articles published in the last decade. According to Nicolas Curry,[53] such decision should be postponed; based on the systematic analysis of 37 reviews (14,377 *abstracts*), he was able to conclude that despite the evidence, it is still risky to make recommendations.

While some authors suggest the use of early transfusion of hemocomponents or whole blood, the evidence must be more specific and unwavering to make any recommendations; in the end, protecting the patient if the primary goal of the specialist's intervention and should never be intended to harm the patient. The literature shows positive and critical effects in a large number of patients in terms of outcomes with considerable epidemiologic strength; such outcomes should in themselves lead to better treatment that could well be summarized in optimal clinical practice guidelines.

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Conflicts of Interest

None declared.

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