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Original article

Age of blood and survival after massive transfusion

Importance de l'âge dans une transfusion massive

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Abstract

Background. – Massive transfusion is the clinical scenario where the presumed adverse effects of stored blood are expected to be more evident because the whole patient's blood volume is replaced by stored blood.
Objective. – To analyse the association between age of transfused red blood cells (RBC) and survival in massively transfused patients.
Methods. – In this retrospective study, clinical and transfusion data of all consecutive patients massively transfused between 2008 and 2014 in a large, tertiary-care hospital were electronically extracted from the Transfusion Service database and the patients' electronic medical records. Prognostic factors for in-hospital mortality were investigated by multivariate logistic regression.
Results. – A total of 689 consecutive patients were analysed (median age: 61 years; 65% males) and 272 died in-hospital. Projected mortality at 2, 30, and 90 days was 21%, 35% and 45%, respectively. The odds ratio (OR) for in-hospital mortality among patients who survived after the 2nd day increased with patient age (OR: 1.037, 95% CI: 1.021–1.054; per year $P < 0.001$), with the number of RBC unit transfused in the first 48 hours (OR: 1.060; 95% CI: 1.038–1.020 per unit; $P < 0.001$), and the percentage of such RBC stored for more than 28 days (1.010, 95% CI: 1.005–1.018 per percent point; $P = 0.01$).
Conclusion. – Mortality after massive transfusion was associated with a higher proportion of old RBCs transfused in the first 48 hours. Other factors associated with poor prognosis were older patient's age and larger volumes of transfused RBCs.

Keywords: Blood transfusion; Red blood cells; Survival

Résumé

Contexte. – La transfusion massive est le scénario clinique où les effets néfastes présumés du sang stocké devraient être plus évidents car l'ensemble du volume sanguin du patient est remplacé par du sang stocké.
Objectif. – Analyser l'association entre l'âge des globules rouges transfusés (RBC) et la survie chez des patients massivement transfusés.
Méthodes. – Dans cette étude rétrospective, les données cliniques et transfusionnelles de tous les patients consécutifs massivement transfusés entre 2008 et 2014 dans un grand hôpital de soins tertiaires étaient extraites électroniquement de la base de données du service Transfusion et des dossiers médicaux électroniques des patients. Les facteurs pronostiques pour la mortalité hospitalière ont été étudiés par une régression logistique multiple.
Résultats. – Au total, 689 patients ont été analysés (âge médian : 61 ans, 65 % d'hommes) et 272 sont morts à l'hôpital. La mortalité prévue à 2, 30 et 90 jours était respectivement de 21 %, 35 % et 45 %. Le rapport de cote (OR) pour la mortalité hospitalière chez les patients qui ont survécu après le 2e jour augmenta avec l'âge du patient (OR : 1.037, IC 95 % : 1.021–1.054, par an $p < 0{,}001$), avec le nombre d'unités RBC transfusées dans les premières 48 heures (OR : 1,060 ; IC 95 % : 1,038–1,020 par unité ; $p < 0{,}001$) et le pourcentage de ces RBC stockés pendant plus de 28 jours (1,010, IC 95 % : 1,005–1,018 par point de pourcentage, $p = 0{,}01$).
Conclusion. – La mortalité après une transfusion massive a été associée à une proportion plus élevée de vieux globules rouges transfusés au cours des premières 48 heures. D'autres facteurs associés à un mauvais pronostic ont été l'âge des patients et de plus grands volumes de globules rouges transfusés.

Mots clés : Transfusion sanguine ; Globules rouges ; Survie

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1. Introduction

Critical haemorrhage requiring massive transfusion is a leading cause of death in trauma patients and a relevant contributor to surgery-related mortality [1]. In addition, massive transfusion accounts for a large share of all the blood components used in many trauma centres and tertiary-care hospitals [2,3]. Clinical research on the haemotherapy of critical haemorrhage has traditionally been focused on the prevention and treatment of the coagulopathy associated with trauma and massive transfusion. As a result, long established paradigms have changed in recent years, with emphasis now being placed on controlled hypotensive resuscitation and early, proactive transfusion of plasma and platelets [4]. In contrast, little attention has been paid to the attributes of transfused RBCs.

Preclinical studies have shown that transfusion of stored RBCs impairs the microcirculation dynamics and the delivery of oxygen to tissues [5]. However, the clinical relevance of such pathophysiologic features remains a matter of discussion because retrospective and prospective observational studies have yielded conflicting results [5–8], and the few available clinical trials may have been unable to detect infrequent but clinically relevant effects [9–11].

Massive transfusion is a unique scenario where the presumed adverse clinical effects of stored blood are expected to be more evident. First, patients usually present in a critical condition in which any disequilibrium of the already precarious homeostasis can be life threatening. Second, the whole patient's blood volume may end up replaced by stored blood. Nevertheless, clinical guidelines on the management of critical haemorrhage and massive transfusion do not make any recommendation about the age of RBCs [12–16].

The present study was aimed at investigating the association between age of transfused RBCs and in-hospital, all-cause mortality in a large series of massively transfused patients. Additionally, we provide a clinical description of an unselected population of massive transfusion recipients as it was seen in a large, tertiary-care hospital.

2. Material and methods

For the purpose of this retrospective study, massive transfusion was defined as the infusion of 8 or more RBC units in less than 24 hours. The Transfusion Service database was queried for all consecutive adult patients (> 16 years) who met the above criterion from January 2008 to December 2014. We also retrieved the date of delivery of every unit of RBC, plasma, platelets, and cryoprecipitate received by the patients within the first 15 days after the massive transfusion as well as the storage time of transfused RBCs. In patients who had more than one episode of massive transfusion, only the first one was taken into account. Surviving patients were followed up until hospital discharge or the study closing date on July 1st, 2015.

Information on the medical condition triggering the massive transfusion, the patient's sex and age, clinical course until death or hospital discharge, and use of manufactured coagulation products was obtained from the patients' electronic medical records. We also recorded whether the haemorrhage triggering the massive transfusion begun out-of-hospital or while the patient was already admitted in the hospital. In order to avoid selection and recall biases, all the variables were selected automatically from the electronic databases and only the cause of haemorrhage was assigned subjectively from a pre-established list after reviewing the medical records.

Over the period under study, all the RBC units were stored in SAG-M and leukoreduced before storage. Platelet units consisted in a 5-donor pooled concentrate or an equivalent aphaeresis unit. All the plasma was from male donors and most of the units were photo-inactivated with methylene blood.

2.1. Statistics

The study's main outcome was in-hospital mortality (up to the 90th admission day) in patients surviving more than 48 hours after starting the massive transfusion. Patients whose length of stay was longer than 90 days were censored at that follow-up time point (see Fig. S1). Continuous variables were summarized as median and interquartile range (IQR). Statistical comparisons of variables were done by the Mann-Whitney *U*-test for continuous or ordered data and the Chi-square test for categorical variables. The overall survival curve was drawn by the method of Kaplan and Meier. Patient- and transfusion-related factors associated with in-hospital mortality were investigated by multivariate binary logistic regression. Factors analysed for a possible prognostic significance included sex, age, ABO/Rh blood group, whether the haemorrhage begun in-hospital or out-of-hospital, number of RBC units transfused within the first 48 hours, proportion of RBCs transfused within the first 48 hours that had been stored for more than 28 days, plasma- and platelet-to-RBC ratios, and calendar year (from 2008 to 2014). For the purpose of prognostic analysis only RBC units transfused within the first 48 hours were taken into account. All the statistical analyses were performed by using Stata, version 11 (www.satata.com). The study was approved by the Hospital Clinic's Committee for Ethics in Research (reference: HCB/2016/0533).

3. Results

A total of 689 patients met the inclusion criteria and constituted the subject of this study (four patients were excluded because RBCs were actually used in exchange transfusion for haemoglobinopathy or paludism). Median age was 61 (IQR: 45–71) years and 65% patients were males. The main patient characteristics at the time of the massive transfusion are shown in Table 1. As can be seen, 56% of patients were already admitted in the hospital at the time of massive bleeding and the most frequent underlying conditions were cardiac surgery (36% of cases), abdominal surgery (17%), and liver transplant (16%). In patient in whom the haemorrhage started out-of-hospital, blunt or penetrating trauma (33% of cases), gastrointestinal bleeding (21%), and ruptured aneurisms of large vessels (16%) were the most frequent conditions. Patients already in-hospital at the start of massive haemorrhage were older than those in whom the

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