Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

The effect of fluid resuscitation strategy on monocyte and T-cell surface markers

Alexander Bonde, BSc,[a] *Rasmus Kirial, BSc,*[a] *Peter Svenningsen, MD,*[a] *and Martin Sillesen, MD, PhD*[a,b,*]

[a] *Department of Surgical Gastroenterology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*

[b] *Institute for Inflammation Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*

ARTICLE INFO

Article history:
Received 28 November 2017
Received in revised form
26 February 2018
Accepted 13 April 2018
Available online xxx

Keywords:
Inflammation
Resuscitation
Transfusion

ABSTRACT

Background: Despite initial lifesaving benefits, posttraumatic resuscitation strategies have been associated with immunologic complications leading to systemic inflammatory response syndrome, sepsis, multiple organ failure, and late trauma death. Nevertheless, the direct effect on immunologic surface markers remains inadequately described. We hypothesized that changes in monocyte and T-cell surface markers were associated with initial posttraumatic fluid resuscitation.

Materials and methods: Data were extracted from the inflammation and host response to injury (Glue Grant) study. Blood samples were drawn from 492 patients on days 0, 1, 4, 7, 14, and 28 and analyzed for 31 monocyte and T-cell surface markers. Resuscitation strategies during the initial 48 h were quantified, including transfusion of packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, and crystalloids. Longitudinal surface marker concentration changes were quantified by the calculation of a within-patient signal intensity change and were associated with resuscitation strategy while controlling confounders. *P*-values were post hoc corrected using the false detection rate q-value.

Results: The monocyte surface marker (CD83) trajectory (as measured by a within-patient signal intensity change) was found to be positively associated with volume of PRBCs transfused ($q = 0.002$) and negatively associated with the transfused volume of FFP ($q = 0.004$). T-cell surface marker (CD3) was found to be negatively associated with volume of PRBCs transfused ($q = 854 \times 10^{-9}$) and positively associated with the transfused volume of FFP ($q = 0.022$). Platelets and crystalloid transfusion volumes were not associated with any surface marker trajectories.

Conclusions: PRBC and FFP transfusion was associated with opposing effects on CD3 and CD83 trajectories, which may in part explain some of the protective effects of a high FFP:PRBC ratio in trauma-related resuscitation.

* *Corresponding author*. Department of Surgical Gastroenterology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9 2100, Copenhagen Ø, Denmark. Tel.: +45 35452123; fax: +45 35452111
E-mail address: Martin.Sillesen@regionh.dk (M. Sillesen).

0022-4804/$ – see front matter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.jss.2018.04.029

Introduction

Massive injury remains the most common cause of death among individuals aged 1-44 y.[1] Traumatic hemorrhage accounts for more than 40% of deaths within the initial 24 h of injury. Immunologic complications are the leading cause of late trauma deaths.[2] Despite initial lifesaving benefits, replacement of circulating blood volume in exsanguinating patients has been suggested to confer additional morbidity, leading to systemic inflammatory response syndrome, sepsis, and multiple organ failure (MOF).[3] Packed red blood cell (PRBC) transfusion and aggressive crystalloid resuscitation have both been associated with detrimental proinflammatory effects,[3,4] whereas fresh frozen plasma (FFP) and platelet (PLT) transfusions appear to have protective antiinflammatory properties.[5,6] Recent literature from military and civilian sources have indicated hemostatic and potential survival benefits associated with an increased FFP:PRBC or PLT:PRBC ratio.[7,8] The exact immunologic mechanism of action, however, remains poorly understood.

We have previously demonstrated limited associations between posttraumatic fluid resuscitation strategy and longitudinal inflammation marker trajectories.[9] The focus of the present study is to assess whether the expression of monocyte and T-cell surface markers is associated with initial posttraumatic fluid resuscitation strategies.

Materials and methods

On evaluation, the Massachusetts General Hospital Institutional Review Board found the protocol to be exempt from approval requirements. Data were extracted from the inflammation and host response to injury (Glue Grant) study collaboration.[1] The protocol enrolled blunt trauma patients between the age of 16 and 90 y, with the following inclusion criteria: Abbreviated Injury Scale score of two or more in any body region excluding the brain, blood transfusion requirements within 12 h following admission and base deficit (BD) greater than 6 mEq/L, or a prehospital/emergency department systolic blood pressure less than 90 mmHg. Obvious brain injury, defined as a Glasgow Coma Scale <8, was regarded as an exclusion criterion.

Flow cytometry was used to analyze the expression of cell surface markers in a subset of 492 patients, with sampling on admission days 0, 1, 4, 7, 14, 21, and 28, where applicable. Before analyzing the surface markers, cell populations were sorted by flow cytometry into monocyte and T-cell populations as described by the Glue Grant protocols.

The association between resuscitation strategy and longitudinal surface marker concentration changes

Resuscitation strategy during the initial 48 h following admission was quantified by calculating the total volume of PRBCs, FFP, PLTs, and crystalloids infused/transfused.

Signal intensity of 31 monocyte and T-cell surface markers were extracted from the Glue Grant database. Table 1 provides a list of the surface markers and information on general biological function.

A within-patient signal intensity change (WPSIC), as defined per the Glue Grant protocols,[1] was calculated to quantify longitudinal cell surface marker signal intensity changes. This was calculated by regressing surface marker signal on time, and the regression coefficient was then used as a marker of the hourly log-fold signal intensity change (WPSIC).

Volumes of the given blood products (PRBC, FFP, or PLT) over the initial 48 h, and crystalloids were subsequently associated with the surface marker trajectories (as assessed by the WPSIC), utilizing multiple linear regression models while correcting for the volume of other blood products and crystalloids transfused/infused (i.e., FFP, PLTs, and crystalloids if PRBC was assessed). The model was also corrected for potential confounders, including age, sex, shock (BD on admission), injury severity (injury severity score [ISS]), and neurotrauma (Glasgow Coma Scale on admission).

To account for multiple comparisons, *P*-values obtained from the multiple regression model were post hoc corrected using the false detection rate q-value.[10] A q-value <0.05 was considered statistically significant.

Statistical considerations

Data are presented as medians with interquartile range. Regression results are presented as β-coefficients with standard errors. All statistical calculations were performed using the "r" software package (www.r-project.org).

Results

Patient demographics have previously been described in detail.[9] Briefly, the cohort consisted of 492 young (median age 38 y [25-51]) and predominantly male (67.5%) patients from the Glue Grant study collaboration. Median ISS was 34 y (22-41) with an initial BD of −7.7 (−10.4 to −5.1). A median of 2100 mL (1200-3500 mL) PRBCs, 0 mL (0-302 mL) PLTs, 800 mL (0-1885 mL) FFP, and 16,393 mL (12,225-21,870 mL) crystalloids were infused during the initial 48 h. Overall mortality was 5.7%, with a median hospital length of stay of 19 (12-30) d. Median APACHE II score was 28 (24-32). Median max Denver two-organ failure score was 2 (0-3), with 14% of the cohort exceeding a score 3, thus meeting criteria for MOF.

No association between mortality and volume of PRBCs ($P = 0.14$) or FFP ($P = 0.12$) transfused could be identified.

CD83 expressed on monocytes was positively associated with PRBC volume transfused ($q = 0.002$) (Table 2) and negatively associated with the transfused volume of FFP ($q = 0.004$) (Table 3). CD3 expressed on T-cells was negatively associated with PRBC volume transfused ($q = 8.54 \times 10^{-9}$) (Table 2) and positively associated with the transfused volume of FFP ($q = 0.022$) (Table 3).

Expression of monocyte and T-cell surface markers was not found to be associated with PLT- (Table 4) or crystalloid resuscitation (Table 5).