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Transfusion of Blood Products is not Associated with Intensive Care Unit-Acquired Weakness when Corrected for Illness Severity

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Abstract

Introduction

Intensive Care Unit-acquired weakness (ICU-AW) is a common and severe complication of intensive care admission. We studied the effect of blood product transfusion (possibly a modifiable risk factor) on ICU-AW.

Methods

Records of blood product transfusion (red blood cell, platelet and plasma) were analyzed in a database from a prospective observational cohort study where newly admitted ICU patients who were mechanically ventilated ≥2 days were included. Manual muscle strength was measured according to the Medical Research Council (MRC) scale, when patients were awake and attentive. ICU–AW was defined as an average MRC score <4.

Results

Of 196 patients, 98 patients (50%) were diagnosed with ICU-AW. A significantly higher odds ratio (OR) for ICU-AW was found in patients receiving red blood cells(OR 2.85, 95% CI 1.58-5.15), plasma (OR 2.38, 95% CI 1.30–4.35) or platelet transfusion (OR 2.09, 95% CI 1.16–3.75) compared to non-transfused patients. The number of red blood cell units (OR 1.07, 95% CI 1.02-1.13) and platelet units (OR 1.24, 95% CI 1.07-1.43) were also associated with ICU-AW. However, when corrected for illness severity, these associations were no longer significant.

Conclusion

The association between transfusion and ICU-AW is explained by illness severity. Risk reducing strategies to prevent development of ICU-AW should focus on other possible risk factors.

Keywords

Transfusion; Intensive care unit acquired weakness; Illness severity; Critical illness; Manual muscle strength

Introduction

Intensive Care Unit-acquired weakness (ICU-AW) is a common and severe complication of intensive care admission [1,2], associated with increased length of stay and mortality. Since no treatment currently exists, prevention by minimizing risk factors currently seems the only option of influencing ICU-AW [3-5]. Sepsis, illness severity and multiple organ dysfunction syndrome have been shown to be risk factors in developing ICU-AW [6]. Recently, a correlation between ICU-AW and transfusion of red blood cells (RBC) was described [7], although no underlying mechanism for this association is currently known. We investigated whether blood transfusion is an independent risk factor for the development of ICU-AW.

Methods and Materials

Design and Ethical Approval

We performed a secondary analysis on a prospective observational cohort study on ICU-AW recently performed in our center. Because no additional procedures were performed, the institutional review board of the Academic Medical Center, Amsterdam, The Netherlands, decided that the study did not fulfill the criteria for medical research stated in the Dutch 'Law on medical research' and data could be collected and analyzed without informed consent of the patient (W13_080#13.17.0100) [8].

Study Setting

The study was performed in a 30 beds tertiary mixed medical-surgical ICU of the Academic Medical Center in the Netherlands. In this ICU, several standards of care are applied including glucose control between 90 mg/dl and 144 mg/dl and short sedation times. Nor epinephrine is the first line vasopressor drug and corticosteroids are given in refractory septic shock. All patients receive early rehabilitation. RBCs are transfused at one unit a time to correct for anemia with hemoglobin of 7 g/dl as a general transfusion trigger. Platelets are transfused prophylactically at a platelet count of 10 x 10^9/L and during bleeding. Fresh frozen plasma (FFP) is given on suspicion of bleeding.

In–and Exclusion Criteria

Consecutive newly admitted ICU patients, mechanically ventilated for ≥2 days, were included. We excluded patients who had a neuromuscular disorder, stroke, out-of-hospital cardiac arrest or spinal injury as reason for ICU admission. In addition, we excluded patients with a poor pre-hospital functional status (modified Rankin scale ≥4 [9,10]) patients with pre-existing spinal injury and patients whose strength assessment was performed more than four days after ICU discharge.

Strength Assessment (Reference Standard)

Physical therapists, blinded for all other parameters, assessed muscle strength when patients were alert (Richmond Agitation and Sedation Scale between -1 and 1[9]) and attentive (able to follow verbal commands using arms or eye-lids). MRC scores were assessed bilaterally in 6 pre-specified muscle groups. MRC scores of muscle groups were summated and divided by the number of muscle groups tested to obtain an average MRC score. ICU–AW was diagnosed when the average MRC score was <4 [2].

Blood Transfusion

Transfusion rates of RBC, FFP and platelets were obtained from the electronic patient file. Transfusions were included from 24 hours before ICU admission until moment of first MRC measurement.

Additional Data Collected

The following additional clinical characteristics were collected: the Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score and the maximal Sequential Organ Failure Assessment (SOFA) score during the first two days after ICU admission. Also, data on the number of days with mechanical ventilation, length of stay in the ICU and ICU mortality were collected.

Statistical Analysis

Mean values are presented with standard deviation (±SD), median values with interquartile range (IQR) and proportions with percentages and total numbers. Differences between groups with and without ICU-AW were described using the Welch's *t*-test for normally distributed variables. Differences between non-normally distributed continuous variables were assessed using Wilcoxon rank-sum test. Differences between proportions were assessed using chi-square test.

Univariate logistic regression was used to calculate odds ratios and 95% confidence intervals (95% CI) between the different transfusion products received before muscle strength assessment and ICU-AW. Transfusion products were analyzed dichotomously (received yes/no) and as a continuous variable (number of products transfused). In multivariable logistic regression the associations between the different transfusion products and ICU-AW were corrected for illness severity using the maximal SOFA score before muscle strength assessment. Analyses were done using R (version: 2.15.2).

Results

Patients were screened from January 2011 until December 2012. Muscle strength could be assessed in 196 patients.Of these, 98 patients (50%) were diagnosed with ICU-AW. Patients diagnosed with ICU-AW had higher APACHE IV scores, longer duration of mechanical ventilation, longer length of stay, higher ICU mortality and higher SOFA scores (Table 1).

A higher proportion of patients with ICU-AW received RBC, FFP and platelets compared to controls. Also, patients with ICU-AW received more RBC units, compared to transfused controls (Table 2).

On univariate regression analyses, both transfusion as well as the amount of RBC or platelets was associated with ICU-AW (Table 3). The amount of FFP products transfused was not significantly associated. When corrected for illness severity with maximal SOFA score before strength assessment, these associations were no longer significant.

Table 1: Patient and admission characteristics

	ICU-AW (N:98)	no ICU-AW (N:100)	p-value
age	62 ± 15	59 ± 16	0.13
females, n (%)	49 (50)	38 (38)	0.12
unplanned admission, n (%)	81 (83)	78 (78)	0.52
APACHE IV score, mean ±SD (3 missing)	89 ± 26	76 ± 28	<0.01
days with mechanical ventilation, median days (IQR)	14 (6 to 22)	6 (4 to 8)	<0.01
length ofICU stay, median days (IQR)	17 (9 to 28)	8 (6 to 11)	<0.01
medianMRC score, (IQR)	2.5 (1.3 to 3.2)	4.7 (4 to 5)	n.a.
days to MRC assessment, median (IQR)	9 (6 to 14)	7 (5 to 9)	<0.01
maximal SOFA score before MRC, mean ±SD	13 ± 4	10 ± 4	<0.01
ICU mortality, n (%)	33 (34)	10 (10)	<0.01

Table 2: distribution of transfusion products received before muscle strength assessment between patients with and without ICU-AW

	ICU-AW (N:98)	no ICU-AW (N:100)	p-value
patients receiving RBC's, n (%)	71 (72)	48 (48)	<0.01
number of RBC units transfused before MRC, median (IQR)	3 (0-10)	0 (0-5)	<0.01
patients receiving FFP, n (%)	44 (45)	25 (25)	<0.01
number of FFPproducts before MRC, median (IQR)	0 (0-4)	0 (0-1)	0.01
patients receiving platelets, n (%)	47 (48)	30 (30)	0.01
number of platelet products before MRC, median (IQR)	0 (0-3)	0 (0-1)	<0.01

Table 3: associations between transfusion products received before muscle strength assessment and ICU-AW

	univariate association (OR 95% CI)	corrected for maximal SOFA score before strength assessment (OR 95% CI)
RBC	2.85 (1.58-5.15)	1.38 (0.69-2.75)
number of RBC's	1.07 (1.02-1.13)	1.02 (0.97-1.07)
plasma	2.38 (1.30-4.35)	1.17 (0.58-2.36)
Number of plasma's	1.05 (0.98-1.12)	0.97 (0.90-1.04)
platelets	2.09 (1.16-3.75)	0.83 (0.40-1.71)
Number of platelet products	1.24 (1.07-1.43)	1.05 (0.91-1.21)

Discussion

In this study we demonstrated an association between transfusion of different types of blood products and ICU-AW. An earlier study has shown a relation between transfusion of RBC and ICU-AW [7], suggesting RBC to be a modifiable risk factor in the development of ICU-AW. However, in our study, when corrected for illness severity this association was no longer significant. This lack of association may be explained by a different definition of ICU-AW (hand grip strength vs MRC measurement) or a larger cohort. Alternatively, use of a maximal SOFA score as we did may more accurately represent true illness severity compared to using a SOFA score on a fixed day. To our knowledge no plausible theory explaining a causal relationship between transfusion of blood products and ICU-AW has been described. This study demonstrates the relevance of correcting for illness severity to identify independent risk factors for ICU-AW. Either there is no direct relationship between the two, or illness severity is too strong a determinant for development of ICU-AW to detect a subtle association between transfusion and ICU-AW.

Conclusion

Transfusion of blood products in the critically ill is associated with ICU-AW. However, in our study this association is not apparent when corrected for illness severity. Strategies to prevent ICU-AW may be more efficient if focused on other possible risk factors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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