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Red blood cell transfusion is associated with decreased in-hospital muscle strength among critically ill patients requiring mechanical ventilation☆,☆☆,★

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ABSTRACT

Purpose: Red blood cell (RBC) transfusion is linked to poor functional recovery after surgery and trauma. To investigate one potential mechanism, we examined the association between RBC transfusion and muscle strength in a cohort of critically ill patients.

Methods: We performed a secondary analysis of 124 critically ill, mechanically ventilated patients enrolled in 2 prospective cohort studies where muscle strength testing was performed at a median of 12 days after mechanical ventilation onset. We examined the association between RBC transfusion and dynamometry handgrip strength using multivariable linear regression, adjusting for study site, age, sex, Acute Physiology and Chronic Health Evaluation, Sequential Organ Failure Assessment score, days from hospital admission to examination, and steroid use. Secondary outcomes included systematic manual muscle strength and intensive care unit–acquired paresis.

Results: Among 124 subjects, 73 (59%) received RBC transfusion in the 30 days before examination. In adjusted analyses, RBC transfusion was significantly associated with weaker handgrip (adjusted mean difference, −9.9 kg; 95% confidence interval, −16.6 to −3.2; $P < .01$) and proximal manual muscle strength (adjusted mean difference in Medical Research Council score, −0.5; 95% confidence interval, −0.7 to −0.2; $P < .01$) but not intensive care unit–acquired paresis.

Conclusions: Red blood cell transfusion was associated with decreased muscle strength in this cohort of critically ill patients after adjusting for illness severity and organ dysfunction. Further studies are needed to validate these results and probe mechanisms.

1. Introduction

Neuromuscular impairment is common in the intensive care unit (ICU) [1]. Severe weakness, termed ICU-acquired paresis (ICU-AP), is associated with prolonged hospitalization and delayed liberation from mechanical ventilation [1]. Intensive care unit–acquired paresis may also play a role in long-term physical recovery [2]. There is limited evidence that intensive insulin therapy may be protective [3] and corticosteroids harmful in the development of ICU-AP [1,4], but little is known about whether these or other modifiable ICU practices may

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affect the risk of neuromuscular complications. Identifying modifiable ICU risk factors for neuromuscular impairment may help to guide clinical practice and improve outcomes.

Red blood cell (RBC) transfusion is a modifiable ICU practice that is increasingly implicated in adverse hospital events, although it has not been specifically examined in relation to neuromuscular outcomes. Red blood cell transfusion remains one of the most common therapies provided to ICU patients [5], despite a lack of strong evidence for improved outcomes outside specific clinical scenarios such as major bleeding [6] or, more controversially, as part of a goal-directed strategy in severe sepsis [7-9]. Red blood cell transfusion is an independent risk factor for acute respiratory distress syndrome and multiple organ dysfunction [10,11]. Studies in survivors of cardiac surgery [12] and traumatic brain injury [13] suggest that RBC transfusion is also associated with worse long-term functional outcomes. Although multiple mechanisms may be at play to explain the associations between RBC transfusion and long-term functional outcomes, it is possible that muscle dysfunction is yet another manifestation of transfusion-related multiple organ injury with implications for long-term recovery. Stored RBCs contain cytokines, bioactive lipids, and microparticles that, upon transfusion, may potentiate production of proinflammatory cytokines, including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) [14]. Circulating plasma levels of both TNF-α and IL-6 are associated with reduced muscle mass and grip strength in older adults [15]. This body of work suggests that inflammatory mediators produced as part of the RBC storage lesion have the potential to adversely impact muscle. Although ICU-acquired neuromuscular dysfunction remains a heterogeneous disease with unclear pathophysiologic mechanisms, animal models suggest that inflammatory mediators including TNF-α may have a modulatory role in its development [16]. No studies have specifically examined whether RBC transfusion may be related to the neuromuscular dysfunction commonly seen in critical illness.

In this study, we examined the hypothesis that RBC transfusion during critical illness is an independent risk factor for neuromuscular weakness. We analyzed data from a cohort of critically ill, mechanically ventilated patients who received in-hospital muscle strength testing by handgrip dynamometry (primary outcome) and systematic manual muscle strength testing (secondary outcome) [1].

2. Methods

2.1. Study population

We performed a secondary analysis of 124 critically ill, mechanically ventilated patients with muscle strength testing from 2 prospective cohorts at Harborview Medical Center (HMC) and The Ohio State University Medical Center (OSU). Eligible subjects were at least 18 years of age requiring mechanical ventilation in the intensive care unit. Exclusion criteria included preexisting neuromuscular disease and inability to obtain patient/surrogate consent. Study approval was obtained from local institutional review boards at the University of Washington and The Ohio State University.

Harborview Medical Center enrolled 61 subjects between November 2006 and November 2008 [17], with goals of defining the incidence of ICU-AP, its clinical risk factors, and associated long-term health-related quality of life in patients with acute lung injury. Subjects were critically ill medical and trauma patients who required at least 3 days of mechanical ventilation and met American-European Consensus Conference consensus criteria [18] for acute lung injury (ALI), enrolled within 7 to 10 days after ALI onset.

The Ohio State University Medical Center enrolled 111 subjects on day 5 of continuous mechanical ventilation as part of the multicenter Weakness and ICU Readmission Evaluation study performed by the Midwest Critical Care Consortium [19] between May 2005 and April 2007. The goal of this study was to examine associations between muscle weakness and hospital outcomes [19]. In addition to the aforementioned exclusion criteria, OSU excluded subjects for inability to communicate with the examiner or inability to assess muscle strength in at least 2 limbs [19].

2.2. Data collection

Demographic and transfusion data were obtained via systematic chart abstraction during the primary studies, including chronic comorbidities, ALI risk factors (eg, transfusion, trauma, medical illness), body mass index, use of paralytic or sedative medications, severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] III and Sequential Organ Failure Assessment [SOFA] score), and oxygenation (ratio of Pao_2 to fraction of inspired oxygen [P/F]). Acute Physiology and Chronic Health Evaluation III score was measured on ventilator day 5 (OSU) or ICU admission (HMC, median ventilator day 1.5).

2.3. Exposure classification

Our analysis included all 124 HMC and OSU subjects who underwent muscle strength testing. We examined our primary exposure of RBC transfusion as both a categorical exposure (receipt of $\geq$1 RBC transfusions within 30 days before muscle strength testing) and as a continuous exposure (no. of units transfused within 30 days before muscle strength testing). We examined transfusion of high plasma volume units, defined as the receipt of one or more fresh frozen plasma (FFP) or platelet transfusion in the 30 days before examination, as an adjustment variable.

2.4. Screening procedures for awakening

Subjects received daily systematic screening for awakening after enrollment, coordinated with daily sedation interruption by institution-specific protocols. In both studies, subjects underwent systematic muscle strength testing after demonstrating appropriate alertness and attention to be able to follow tasks, using the protocol described by De Jonghe et al (HMC) [1], the Richmond Agitation and Sedation Scale, and Attention Screening Exam (OSU) [19].

2.5. Procedures for systematic muscle strength testing

Systematic muscle strength testing was performed on the first day that patients achieved a consistent level of consciousness to comply with voluntary testing, at a median of 12 days after the onset of mechanical ventilation in the combined cohort. Each subject's handgrip strength was measured using a calibrated dynamometer [20] according to a systematic protocol. A single examiner performed handgrip testing using the dominant hand when possible, on a single day (HMC) or over 2 successive days (OSU). At each assessment, 3 separate maneuvers were performed after placing the arm in 90° of flexion. Manual muscle strength testing (graded on the Medical Research Council [MRC] scale) was performed according to study-specific protocols on the same day as handgrip testing. Manual muscle strength testing involves testing of multiple muscle groups in all 4 extremities and is commonly summarized as an average across all muscle groups or separately by muscle group (upper vs lower extremity, distal vs proximal). A single examiner performed manual muscle strength testing on 1 (HMC) or 2 successive days (OSU), according to previously described protocols [19,21]. For all analyses, each subject's strength was defined by the maximum handgrip or manual muscle strength achieved.