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A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIAROLLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.SC., ELIZABETH YETISIR, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

ABSTRACT

Background To determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients, we compared the rates of death from all causes at 30 days and the severity of organ dysfunction.

Methods We enrolled 838 critically ill patients with euvolemia after initial treatment who had hemoglobin concentrations of less than 9.0 g per deciliter within 72 hours after admission to the intensive care unit and randomly assigned 418 patients to a restrictive strategy of transfusion, in which red cells were transfused if the hemoglobin concentration dropped below 7.0 g per deciliter and hemoglobin concentrations were maintained at 7.0 to 9.0 g per deciliter, and 420 patients to a liberal strategy, in which transfusions were given when the hemoglobin concentration fell below 10.0 g per deciliter and hemoglobin concentrations were maintained at 10.0 to 12.0 g per deciliter.

Results Overall, 30-day mortality was similar in the two groups (18.7 percent vs. 23.3 percent, P=0.11). However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill — those with an Acute Physiology and Chronic Health Evaluation II score of ≤20 (8.7 percent in the restrictive-strategy group and 16.1 percent in the liberal-strategy group, P=0.03) — and among patients who were less than 55 years of age (5.7 percent and 13.0 percent, respectively; P=0.02), but not among patients with clinically significant cardiac disease (20.5 percent and 22.9 percent, respectively; P=0.69). The mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.2 percent vs. 28.1 percent, P=0.05).

Conclusions A restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina. (N Engl J Med 1999;340:409-17.)

RED-cell transfusions are a cornerstone of critical care practice,[1] but there are divergent views on the risks of anemia and the benefits of transfusion in this setting. One important concern is that anemia may not be well tolerated by critically ill patients.[2,3] Indeed, two recent studies suggested that anemia increases the risk of death after surgery in patients with cardiac disease[2] and in critically ill patients.[3] Red-cell transfusions are used to augment the delivery of oxygen in the hope of avoiding the deleterious effects of oxygen debt.[4] This view prompted the routine use of transfusion in patients with hemoglobin concentrations that were often more than 10.0 g per deciliter in studies evaluating resuscitation protocols.[5,6]

Critically ill patients may, however, be at increased risk for the immunosuppressive[7,8] and microcirculatory[8,10] complications of red-cell transfusions. In addition, concern about the supply and safety of blood has also encouraged a conservative approach to transfusions. For these reasons, the optimal transfusion practice for various types of critically ill patients with anemia has not been established.

To elucidate the potential risks of anemia and possible benefits of transfusions in critically ill patients, we conducted a randomized, controlled, clinical trial to determine whether a restrictive approach to red-cell transfusion that maintains hemoglobin concentrations between 7.0 and 9.0 g per deciliter is equivalent to a more liberal strategy of maintaining hemoglobin concentrations between 10.0 and 12.0 g per deciliter in critically ill patients with euvolemia after initial treatment.

From the Critical Care Program (P.C.H., G.P.) and the Clinical Epidemiology Unit (P.C.H., G.W., I.S., E.Y.), University of Ottawa, Ottawa; the Department of Pathology, McMaster University, Hamilton, Ont. (M.A.B.); the Critical Care Program, University of Toronto, Toronto (J.M.); the Critical Care Program, University of Western Ontario, London (C.M.); and the Critical Care Program, University of British Columbia, Vancouver (M.T.) — all in Canada. Address reprint requests to Dr. Hébert at the Department of Medicine, Ottawa General Hospital, 501 Smyth Rd., Box 205, Ottawa, ON K1H 8L6, Canada.

*Study investigators are listed in the Appendix.

METHODS

Study Population

We enrolled patients who were admitted to 1 of 22 tertiary-level and 3 community intensive care units in Canada (see the Appendix) between November 1994 and November 1997. We included patients who were expected to stay in the intensive care unit more than 24 hours, had a hemoglobin concentration of 9.0 g per deciliter or less within 72 hours after admission to the intensive care unit, and were considered to have euvolemia after initial treatment by attending physicians. Patients were excluded for any of the following reasons: an age of less than 16 years; inability to receive blood products; active blood loss at the time of enrollment, defined as evidence of ongoing blood loss accompanied by a decrease in the hemoglobin concentration of 3.0 g per deciliter in the preceding 12 hours or a requirement for at least 3 units of packed red cells during the same period; chronic anemia, defined as a hemoglobin concentration of less than 9.0 g per deciliter on at least one occasion more than one month before admission to the hospital; pregnancy; brain death or imminent death (within 24 hours); a question on the part of attending physicians whether to withhold or withdraw ongoing treatment; and admission after a routine cardiac surgical procedure. The study protocol was approved by the institutional review board of each participating institution, and informed consent was obtained from either the patient or the closest family member before enrollment in the study.

Study Design and Treatment Protocols

Consecutive critically ill patients with normovolemia were assigned to one of two treatment groups, stratified according to center and disease severity (an Acute Physiology and Chronic Health Evaluation [APACHE II] score of 15 or less or a score of more than 15, with higher scores indicating more severe disease),[11] and balanced with the use of permuted blocks of four or six.[12] Sealed, opaque envelopes arranged in a computer-generated random order were prepared by the data-coordinating center and distributed to each participating institution, where they were opened sequentially to determine the patients' treatment assignments. The envelopes were returned periodically to the coordinating center for auditing.

Transfusion guidelines for both study groups were developed from information obtained in a national survey of critical care practitioners in Canada[13] and a pilot study.[14] The hemoglobin concentrations of patients assigned to the restrictive strategy of transfusion were maintained in the range of 7.0 to 9.0 g per deciliter, with a transfusion given when the hemoglobin concentration fell below 7.0 g per deciliter. Among patients assigned to the liberal strategy of transfusion, the hemoglobin concentrations were maintained in the range of 10.0 to 12.0 g per deciliter, with a threshold for transfusion of 10.0 g per deciliter. It was not feasible to mask the assigned transfusion strategy from health care providers.

In Canada, red cells are separated from whole blood and stored in citrate–phosphate–dextrose–adenine anticoagulant solution without leukodepletion. The volume of a unit of red cells ranges from 240 to 340 ml, with a hematocrit of approximately 80 percent.[15]

The physicians caring for the patients were instructed to administer transfusions, one unit at a time, and to measure a patient's hemoglobin concentration after each unit was transfused. Although specific goals for oxygen delivery were not part of the protocol, we provided suggestions for the use of fluids and vasoactive drugs, when necessary, and advice when a transfusion was not indicated by the study protocol. All other management decisions were left to the discretion of the patients' physicians. Adherence to the transfusion protocols was required only during the patient's stay in the intensive care unit. When a patient was discharged from the intensive care unit, a copy of the American College of Physicians guidelines for transfusion[16] was placed in his or her medical record.

Compliance with the two transfusion protocols was monitored by daily measurements of hemoglobin concentrations in each patient. In addition, transfusion records were sent regularly to the study coordinating center, which monitored the ability of individual centers to maintain hemoglobin concentrations in the target range.

Base-Line Assessment and Data Collection

At the time of randomization, demographic, diagnostic, and therapeutic information as well as information necessary to determine the severity of illness — including APACHE II scores,[11] calculated from data gathered within 24 hours after admission to the intensive care unit, and the multiple-organ-dysfunction score[17] — was obtained for each patient. The worst laboratory values recorded during each patient's stay in the intensive care unit were noted for use in assessing organ dysfunction with use of the multiple-organ-dysfunction score[17] and the multiple-system organ-failure score.[18] Hemoglobin concentrations; the use of red-cell transfusions; medications given, including vasoactive drugs; and the need for mechanical ventilation, dialysis, and surgical intervention were recorded on a daily basis.

The principal reason for admission to the intensive care unit was recorded. We included as many as three secondary diagnoses and eight coexisting conditions. In postoperative patients, the underlying diagnosis and the surgical procedure were recorded. All data were abstracted from clinical records by trained study personnel and coded according to the *International Classification of Diseases, 9th Revision, Clinical Modification*. All diagnoses were reviewed by two of the four critical care physicians, and disagreements were resolved by consensus.

Outcome Measures

The primary outcome measure was death from all causes in the 30 days after randomization. Secondary outcomes included 60-day rates of death from all causes, mortality rates during the stay in the intensive care unit and during hospitalization, and survival times in the first 30 days. Measures of organ failure and dysfunction, including the number and rates of organ failure as defined previously[18] and the multiple-organ-dysfunction score,[17] were also assessed. To improve our ability to detect meaningful differences between groups, we used some composite outcomes that included death and organ dysfunction or failure as indicators of morbidity. Patients who died were assigned a multiple-system organ-failure score of 7 and a multiple-organ-dysfunction score of 24, the worst possible values for each scale, as a means of adjusting measures of organ dysfunction and failure for deaths. Lengths of stays in the intensive care unit and the hospital were also recorded.

Statistical Analysis

Since this was an equivalency trial, we used 95 percent confidence intervals to estimate the number of patients necessary for the study to have the power to rule out clinically meaningful differences in outcomes. We estimated that 2300 patients would be needed to rule out an absolute difference of 4 percent in 30-day mortality between the two groups, assuming a combined mortality rate of 18 percent (the rate for a group receiving standard care was estimated to be 20 percent[3]). An interim analysis conducted in a blinded fashion by the data-monitoring committee after 404 patients had been enrolled revealed that the combined 30-day mortality rate was actually 23 percent. This change increased the detectable difference to 4.5 percent for a sample of 2300 patients. Because of this increase in observed mortality, we decided to decrease the target sample to 1620 patients (primarily on the basis of the hypothesis-testing method, in which the mortality rate for the standard-care group was 26.6 percent, the type 1 and type 2 error rates were 5 percent, and there was no change in the relative