# A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture

*J.L. Carson, M.L. Terrin, F.B. Barton, R. Aaron, A.G. Greenburg, D.A. Heck, J. Magaziner, F.E. Merlino, G. Bunce, B. McClelland, A. Duff, and H. Noveck*

**BACKGROUND:** The indications for transfusion have never been evaluated in an adequately sized clinical trial. A pilot study was conducted to plan larger clinical trials.

**STUDY DESIGN AND METHODS:** Hip fracture patients undergoing surgical repair who had postoperative hemoglobin levels less than 10 g per dL were randomly assigned to receive 1) symptomatic transfusion: that is, transfusion for symptoms of anemia or for a hemoglobin level that dropped below 8 g per dL or 2) threshold transfusion: that is, patients receive 1 unit of packed RBCs at the time of random assignment and as much blood as necessary to keep the hemoglobin level above 10 g per dL. Outcomes were 60-day mortality, morbidity, functional status, and place of residence.

**RESULTS:** Among 84 eligible patients enrolled, mean (±SD) prerandomization hemoglobin was 9.1 (± 0.6) g/dL. The median number of units transfused in the threshold transfusion group was 2 (interquartile range, = 1-2), and that in the symptomatic transfusion group was 0 (6; interquartile range, = 0-2) ($p<0.001$). Mean hemoglobin levels were approximately 1 g per dL higher in the threshold group than in the symptomatic group: for example, on Day 2, 10.3 (± 0.9) g per dL versus 9.3 (± 1.2) g per dL, respectively ($p<0.001$). At 60 days, death or inability to walk across the room without assistance occurred in 16 (39.0%) of the symptomatic transfusion group and 19 (45.2%) of the threshold transfusion group. Death occurred by 60 days in 5 (11.9%) of the symptomatic transfusion group and 2 (4.8%) in the threshold transfusion group (relative risk = 2.5; 95% CI, 0.5-12.2). Other outcomes were similar for the two groups.

**CONCLUSIONS:** Symptomatic transfusion may be an effective blood-sparing protocol associated with the transfusion of appreciably fewer units of RBCs and lower mean hemoglobin levels than are associated with the threshold transfusion policy. However, it is unknown whether these two clinical strategies have comparable mortality, morbidity, or functional status. A definitive trial is needed.

In 1992, over 11 million units of red cells (RBCs) were transfused in the United States.[1] Each unit of RBCs is estimated to cost about $150 to $200, for a total annual expenditure of approximately $2 billion.[2-4] Most RBC transfusions are given to surgical patients. While there is extensive literature documenting the risks associated with transfusion,[5,6] much less is known about the indications for transfusion and the benefits of transfusion in the perioperative setting.

In five small randomized clinical trials that contrasted transfusion thresholds, no differences were observed between transfusion groups,[7-11] except for the finding in one study of delayed myocardial recovery in patients with lower hemoglobin (Hb) levels.[9] However, the largest of these trials included only 69 patients. An observational cohort study of 1957 surgical patients who refused blood transfusion for religious reasons suggests that mortality in surgical patients starts to increase at Hb levels below 10 g per dL; patients with cardiovascular disease had higher mortality with anemia than those without cardiovascular disease. A retrospective cohort study of 8787 hip fracture patients found no association between postoperative transfusion and 30- or 90-day mortality.[13]

**ABBREVIATIONS:** ASA = American Society of Anesthesiologists; CDC = Centers for Disease Control and Prevention; Hb = hemoglobin; MI = myocardial infarction; RBC(s) = red cell(s).

From the Division of General Internal Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey; the Maryland Medical Research Institute, and the Department of Epidemiology and Preventive Medicine, University of Maryland, Baltimore, Maryland; the Department of Surgery, Miriam Hospital, Providence, Rhode Island; the Department of Orthopaedic Surgery, Indiana University, Indianapolis, Indiana; and the Department of Transfusion Medicine, University of Edinburgh, The Royal Infirmary of Edinburgh, Edinburgh, Scotland.

Received for publication September 26, 1997; revision received December 8, 1997, and accepted December 22, 1997.

**TRANSFUSION** 1998;38:522-529.

As a preliminary step in evaluating the clinical benefit of transfusion, we conducted a pilot study for a randomized clinical trial comparing two transfusion strategies. The goals of this pilot study were to demonstrate 1) that recruitment of an elderly population of patients with hip fracture was feasible, 2) that the study protocol could be implemented and would result in different mean Hb levels and numbers of units transfused in the groups, and 3) that follow-up for mortality, place of residence, and functional status could be completed.

## METHODS AND MATERIALS

### Study design and study population

We performed a randomized clinical trial in hip fracture patients who underwent surgical repair from March 1996 to March 1997. All patients presenting for hip fracture repair were assessed for eligibility for the study. Patients were eligible for the trial if their Hb levels were less than 10 g per dL in the immediate postoperative period, defined as the time from the end of anesthesia in the operating room to 11:59 PM 3 days after surgery (counted from 12:00 midnight on the first day after surgery). Hb levels were measured on each of the first three postoperative days to identify eligible subjects. Patients who refused transfusion because of religious beliefs, suffered multiple trauma (defined as any injury that required surgical repair in addition to the hip fracture), or had symptoms of anemia were excluded from the trial.

The study was performed at Robert Wood Johnson University Hospital, a 491-bed university hospital located in New Brunswick, NJ; St. Peters Medical Center, a 450-bed university-affiliated hospital also located in New Brunswick; Miriam Hospital, a 247-bed university-affiliated hospital located in Providence, RI; and The Royal Infirmary of Edinburgh (for only 1 month), an 828-bed university hospital located in Edinburgh, Scotland. The Edinburgh site was added at the end of recruitment and was included in the evaluation of treatment outcome but not in the evaluation of recruitment experience. In accordance with the principle of intention to treat, all randomly assigned patients are counted in treatment comparisons. Random treatment allocation and ongoing monitoring of enrollment were managed on an automated telephone-response system at the Maryland Medical Research Institute (Baltimore, MD). Institutional review board or an ethics committee approved the study at each institution.

### Transfusion strategies

Eligible patients who gave informed consent (or, for those not mentally competent, whose relatives gave informed consent) were randomly assigned to one of two transfusion strategy groups. The threshold transfusion strategy required patients to receive 1 unit of packed RBCs at the time of randomization and as much additional blood as needed to keep the Hb level above 10 g per dL during the hospital admission. The symptomatic transfusion strategy required that transfusion be delayed until the patient developed symptoms or experienced consequences of anemia, but transfusion was permitted in the absence of symptoms if the Hb level fell below 8 g per dL. If transfusion was given for symptoms of anemia, enough blood was given to relieve the symptoms; if transfusion was given because the Hb level fell below 8 g per dL, enough blood was given to increase the Hb level above 8 g per dL. Postrandomization Hb level evaluations were performed at least twice in all patients and as clinically indicated.

Symptoms and consequences of anemia were defined as chest pain thought to be cardiac in origin; myocardial infarction (MI); congestive heart failure; unexplained tachycardia, hypotension, or decreased urine output that was unresponsive to fluid replacement; and poor rehabilitation, defined as inability to get out of bed for rehabilitation by the third postoperative day.

### Outcomes

**Primary outcome.** The outcome of most interest was death within 60 days of the operative procedure or the inability to walk 10 feet or across a room without human assistance 60 days after surgery. These possible outcomes were chosen because the main objective after hip fracture surgery is to restore function, and Hb levels may be important to patient recovery. Information about walking ability was ascertained by telephone interviews. If the patient could not be interviewed directly, information was obtained from either a family member or health care provider.

**Secondary outcomes.** Secondary outcomes were 30- and 60-day mortality, place of residence at 60 days, functional status at 60 days, in-hospital myocardial infarction, thromboembolism, stroke, and pneumonia. Residence status for the patients were classified as follows: community dwelling (home alone, home with others), retirement home (e.g., sheltered housing, congregate housing, halfway house, or board and care facility), nursing home (e.g., skilled-nursing facility, intermediate-care facility, extended-care facility), or other.

We assessed functional status with questions designed to evaluate lower extremity function after hip fracture.[14,15] The activities queried were 1) getting in and out of bed, 2) walking 10 feet or across the room, 3) walking one block on level sidewalk, 4) climbing five stairs, 5) getting into and out of a car, 6) rising from an armless chair, 7) putting on pants, 8) putting socks and shoes on both feet, 9) getting in and out of bath or shower, and 10) taking a shower, bath, or sponge bath. For each task, patients were classified as requiring no help, requiring the use of equipment only, requiring human assistance (with or without equipment), or being unable to perform the task for health reasons. Any

patient who died within the first 60 days was classified as being unable to perform the task for health reasons. If the patient did not perform the task for reasons other than health or was unable to accurately define the level of assistance needed, the score for that specific task was treated as missing.

Postoperative MI was defined as definite if the patient had positive CK-MB enzymes, if an electrocardiogram was interpreted locally as consistent with a MI, or if there was postmortem evidence of an acute MI. MI was defined as possible if the patient had chest pain and an electrocardiogram interpreted as consistent with possible new MI.

Thromboembolism was defined as deep venous thrombosis confirmed by duplex ultrasound, impedance plethysmography, venogram, or postmortem examination or as pulmonary embolism confirmed by a high-probability ventilation-perfusion scan, or pulmonary angiogram, or postmortem examination.[16-21]

Stroke was defined as definite if there was evidence of a new hemorrhage or infarction on a magnetic resonance image study, CT scan of the head, or autopsy. Stroke was defined as possible if there was an unsupported physician diagnosis of neurologic deficit.

We used a modified Centers for Disease Control and Prevention (CDC) case definition of pneumonia[22]: chest radiograph with new or progressive infiltrate, consolidation, or cavitation and any of the following: new onset of purulent sputum or change in character of sputum, or the isolation of the organism from blood culture, transtracheal aspirate, bronchial brushings, or biopsy. We did not consider a patient with rales and purulent sputum to have pneumonia, nor did we use pleural effusion in our chest radiograph definition.

### Randomization

Study personnel at the clinical sites randomly assigned patients by contacting the data coordinating center's 24-hour automated telephone service. Randomization schedules were stratified by clinical site and cardiovascular disease status; the randomization was designed in blocks of two to eight patients to avoid imbalance within a site. Balanced randomization of patients with cardiovascular disease was deemed important because prior data suggested that patients with cardiovascular disease may not tolerate anemia as well as patients without cardiovascular disease.[12]

Cardiovascular disease was defined by a history of ischemic heart disease (MI, angina pectoris, or evidence of coronary artery disease) or by an electrocardiogram with evidence for previous MI, history or presence of congestive heart failure, chest radiograph consistent with congestive heart failure, history or presence of peripheral vascular disease, or history of stroke or transient ischemic attack.

### Data collection

Study nurses abstracted data primarily from the patients' medical records and the administered study questionnaires. Additional information was obtained from the patients' physician(s) as needed. Chronic lung disease was defined by a history, chest radiograph interpretation, or pulmonary function test consistent with chronic obstructive pulmonary, chronic bronchitis, emphysema, or restrictive lung disease. Diabetes mellitus was defined by a history of diabetes mellitus treated with oral medication or insulin. Dementia or confusion was defined by a prefracture history of confusion, disorientation, global intellectual impairment, or memory loss.

The type of hip fracture was classified as femoral neck (subcapital, cervical, midcervical, transcervical, intracapsular), intertrochanteric (basilar, basicervical, pertrochanteric, or extracapsular), or subtrochanteric (proximal femur). The American Society of Anesthesiologists (ASA) physical status assessment was recorded.[23,24] Thromboem-bolism prophylaxis was classified as warfarin, low-molecular-weight heparin, intravenous heparin, or subcutaneous heparin (10,000-30,000 units/day), pneumatic compression stockings, or aspirin. The type of thromboembolism prophylaxis was chosen by the attending physician. We recorded the number of blood transfusions during the preoperative, intraoperative, and postoperative periods; the last preoperative Hb level; and the postoperative Hb levels.

Data collection was completed with a telephone interview 60 days after. Study nurses, blind to the transfusion status of the patient, obtained information from patients or proxies on survival, place of residence, and functional status.

### Statistical analysis

We performed all the analyses using the intention-to-treat principle. Patient characteristics were compared by using tests for homogeneity of proportions for categorical variables and the *t* test to test for differences in mean (± SD) or Wilcoxon's rank sum test for distributions represented by median and interquartile ranges. Relative risk and 95% CI were calculated by standard methods.

## RESULTS

There were 192 eligible hip fracture patients admitted to the three US study hospitals. We obtained consent from 143 (74%) of these patients. Ninety-six (67%) of these 143 patients had a Hb level less than 10 g per dL in the immediate postoperative period. We randomly assigned 80 (83%) of the 96 patients—40 in each of the two treatment groups. The reasons for not enrolling the remaining 16 patients were that the attending physician declined to permit random assignment of 14 patients, one patient had been randomly

assigned within the previous month, and one patient was withdrawn by the spouse. We recruited 42 percent of eligible hip fracture patients at the US study sites (Fig. 1). In addition, 4 (9.8%) of 41 patients were enrolled in Edinburgh; 2 patients were randomly assigned to each of the two treatment groups.

Of the 84 enrolled patients, 3 refused to comply with the study protocol after randomization, although follow-up was completed at 60 days. The assigned transfusion strategy was successfully implemented in 93.8 percent (76/81) of the remaining patients. One patient in the threshold transfusion group did not receive a transfusion, and four patients in the symptomatic transfusion group received a transfusion in violation of the protocol (i.e., they did not have symptoms of anemia or a Hb of <8 g/dL). Sixty-day follow-up was obtained in all patients. The overall study population had a mean age of 82.3 (±9.5) years and was predominately white and female (Table 1). Cardiovascular disease was present in 45.2 percent and a history of dementia or confusion in 35.7 percent. Most patients had intertrochanteric fractures (65.5%) and underwent general anesthesia (60.7%). The mean prerandomization Hb level was 9.1 g per dL (± 0.6). The two groups were similar in these baseline characteristics.

The median number of units transfused differed in the two transfusion groups: in the threshold transfusion group, it was 2 (maximum of 4, interquartile range = 1-2), and in the symptomatic transfusion group, it was 0, (maximum of 6, interquartile range = 0-2), $p<0.001$ (Table 2). Nineteen patients (45.2%) in the symptomatic transfusion group received transfusion(s).

The lowest mean Hb level after randomization in the symptomatic transfusion group was 8.75 g per dL (SD ± 1.2; range, 5.6-11.4 g/dL). The highest mean Hb level in the threshold transfusion group was 11.1 g per dL (SD ± 0.9; range, 8.6-14.0 g/dL). Mean daily Hb levels in the transfusion groups differed by approximately 1 g per dL from the time of randomization until discharge from the hospital (Fig. 2).

Sixty days after randomization, 16 (39.0%) patients in the symptomatic transfusion group and 19 (45.2%) in the threshold transfusion group were dead or could not walk across the room or 10 feet without human assistance (relative risk = 0.9, 95% CI 0.5-1.4, p = 0.57) (Table 3). Five (11.9%) patients in the symptomatic transfusion group and two (4.8%) in the threshold transfusion group were dead at 60 days (relative risk = 2.5; 95% CI, 0.5-12.2; p=0.43). Residence in a nursing home and length of hospital stay were similar in the groups. Morbid events were uncommon (Table 3). There were no appreciable differences in outcomes in patients with and without cardiovascular disease.

Many patients had important limitations in function at 60 days (Table 4). Only 57.8 percent of patients could walk across the room or 10 feet, and 51.8 percent could get in and out of bed without the assistance of another person.

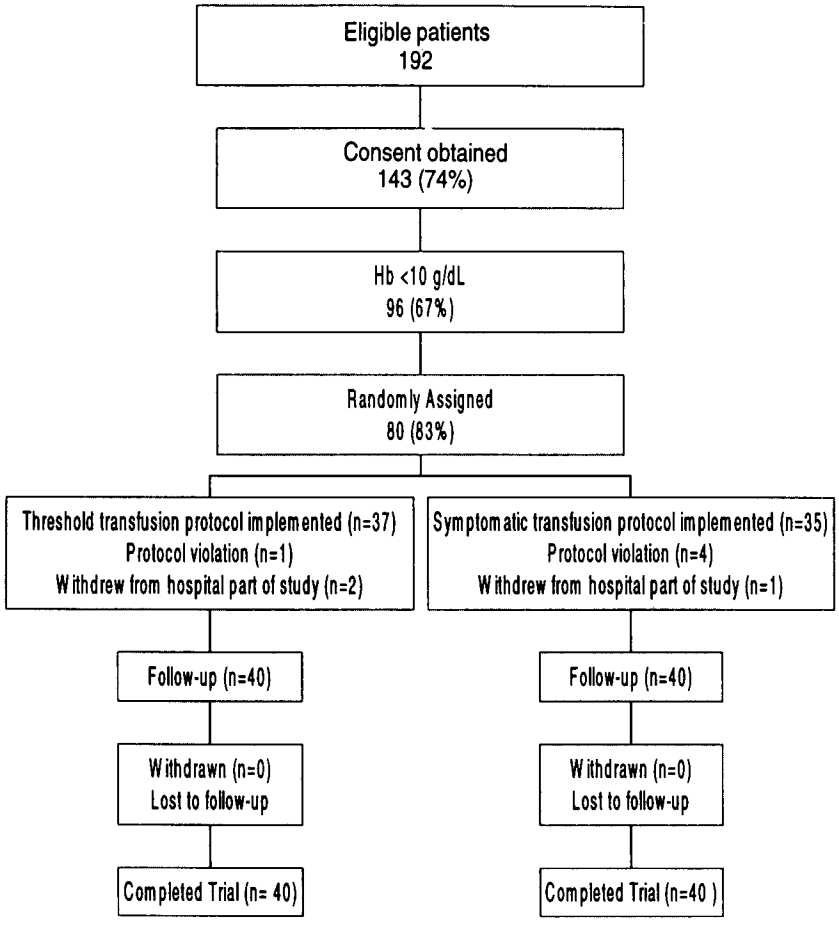


**Fig. 1. Trial profile for US portion of the study. Overall, 42 percent of eligible patients were randomly assigned. The three patients who withdrew from the hospital part of the study permitted telephone follow-up at 60 days. Four additional patients from Edinburgh, two in each group, were randomly assigned and followed up without protocol violations.**

**TABLE 1. Patient characteristics***

| | Threshold group n = 42 | Symptomatic group n = 42 | Total n = 84 |
|---|---|---|---|
| Hospital | | | |
| Robert Wood Johnson University | 7 (16.7%) | 8 (19.1%) | 15 (17.9%) |
| St. Peters Medical Center | 23 (54.8%) | 22 (52.4%) | 45 (53.6%) |
| Miriam Hospital | 10 (23.8%) | 10 (23.8%) | 20 (23.8%) |
| Royal Infirmary of Edinburgh | 2 (4.8%) | 2 (4.8%) | 4 (4.8%) |
| Age (mean ±standard deviation) | 81.3 ± 8.1 | 83.3±10.8 | 82.3 ± 9.5 |
| (range) | (50-94) | (32-95) | (32-95) |
| Gender (percentage female) | 33 (78.6%) | 31 (73.8%) | 64 (76.2%) |
| Race (percentage white) | 40 (95.2%) | 41 (97.6%) | 81 (96.4%) |
| Cardiovascular disease | 19 (45.2%) | 19 (45.2%) | 38 (45.2%) |
| Coronary artery disease | 12 (28.6%) | 12 (28.6%) | 24 (28.6%) |
| Congestive heart failure | 6 (14.3%) | 6 (14.3%) | 12 (14.1%) |
| Peripheral vascular disease | 3 (7.1%) | 1 (2.4%) | 4 (4.8%) |
| Cerebral vascular disease | 6 (14.3%) | 10 (23.8%) | 16 (19.0%) |
| Chronic lung disease | 10 (23.8%) | 6 (14.3%) | 16 (19.1%) |
| Diabetes treated | | | |
| (percentage receiving tablets or insulin) | 4 (9.5%) | 5 (11.9%) | 9 (10.7%) |
| History of dementia or confusion | 13 (31.0%) | 17 (40.5%) | 30 (35.7%) |
| Malnourished or cachectic | 3 (7.1%) | 3 (7.1%) | 6 (7.1%) |
| Preadmission residence† | | | |
| Community dwelling | 33 (78.6%) | 31 (73.8%) | 64 (76.2%) |
| Nursing home | 8 (19.1%) | 11 (26.2%) | 19 (22.6%) |
| Rehabilitation hospital | 1 (2.4%) | 0 | 1 (1.2%) |
| Type of hip fracture‡ | | | |
| Femoral neck | 13 (31.0%) | 17 (40.5%) | 30 (35.7%) |
| Intertrochanteric | 29 (69.0%) | 26 (61.9%) | 55 (65.5%) |
| Subtrochanteric | 5 (11.9%) | 1 (2.4%) | 6 (7.2%) |
| ASA score§ | | | |
| Mean | 2.8 (±0.6) | 2.9 (±0.5) | 2.9 (±0.5) |
| 1 | 0 | 0 | 0 |
| 2 | 11 (26.2%) | 8 (19.1%) | 19 (22.6%) |
| 3 | 28 (66.7%) | 31 (73.8%) | 59 (70.2%) |
| 4 | 3 (7.1%) | 3 (7.1%) | 6 (7.1%) |
| 5 | 0 | 0 | 0 |
| Anesthesia¶ | | | |
| General | 25 (59.5%) | 26 (61.9%) | 51 (60.7%) |
| Regional | 17 (40.5%) | 16 (38.1%) | 33 (39.3%) |
| Local | 1 (2.4%) | 0 | 1 (1.2%) |
| Surgical procedure | | | |
| Multiple screws/plate | 33 (78.6%) | 26 (61.9%) | 59 (70.2%) |
| Hemiarthroplasty | 2 (4.8%) | 10 (23.8%) | 12 (14.3%) |
| Bipolar hemiarthroplasty | 7 (16.7%) | 6 (14.3%) | 13 (15.5%) |
| Total hip replacement | 0 | 0 | 0 |
| Thromboembolism prophylaxis | | | |
| Warfarin, low-molecular-weight | | | |
| heparin, or intravenous heparin | 15 (35.7%) | 14 (33.3%) | 29 (34.5%) |
| Pneumatic compression stockings | 22 (52.4%) | 27 (64.3%) | 49 (58.3%) |
| Low -dose heparin | 13 (31.0%) | 18 (42.9%) | 31 (36.9%) |
| Aspirin | 15 (35.7%) | 12 (28.6%) | 27 (32.1%) |
| Prerandomization transfusion | 0.5 ±1.0 | 0.3 ± 0.6 | 0.4 ± 0.8 |
| (mean ±SD) | 0 (median) | 0 (median) | 0 (median) |
| | (0,1)‖ | (0,0)¶ | (0,0.5)¶ |
| Last preoperative Hb (mean ± SD) | 11.7 ± 1.6 | 11.6 ± 1.0 | 11.7 ± 1.3 |
| Randomization Hb (mean ± SD) | 9.1 ± 0.6 | 9.1 ± 0.6 | 9.1 ± 0.6 |

* All values represent the number and percentage of that group, unless noted otherwise.
† Community dwelling (home alone, home with others, retirement home [e.g., sheltered housing, congregate housing, halfway house, or board and care facility]), nursing home (e.g., skilled nursing facility, intermediate care facility, extended care facility, nursing home), or other.
‡ Five and two patients had more than one type of hip fracture in the threshold transfusion group and symptomatic transfusion group, respectively.
§ ASA Score: physical status 1 defined as normal, healthy patient; physical status 2 as patient with mild systemic disease; physical status 3 as patient with severe systemic disease that limits activity but is not incapacitating; physical status 4 as patient with an incapacitating systemic disease that is a threat to life; and physical status 5 as moribund patient not expected to survive 24 hours, even with operation.
‖ One patient had both regional and local anesthesia.
¶ Interquartile range.

## DISCUSSION

RBC transfusion is a commonly used treatment that is expensive and involves important risks. In this pilot study, we successfully enrolled elderly patients with hip fracture, and in most patients the assigned transfusion protocol was appropriately followed. The two transfusion strategy groups had clinically important and significant differences in the number of RBC units transfused and in the mean Hb levels during the hospitalization for hip fracture repair.

Before the National Institutes of Health 1988 consensus conference report on red cell transfusions,[29] patients often received transfusion(s) when the Hb level fell below 10 g per dL. However, the conference report concluded that patients should be given transfusion(s) on the basis of an overall assessment of clinical status and symptoms rather than a threshold Hb level, although there are few data to support this or any other transfusion strategy. Our trial was designed to document the feasibility of testing the clinical strategy suggested in the consensus statement and evaluate if patients would benefit from higher Hb levels.

The two transfusion strategies tested in this trial have an empirical and theoretical basis. The rationale for the threshold transfusion strategy (keeping the postoperative Hb level >10 g/dL) include the following. 1) A recent study of 1958 Jehovah's Witness patients undergoing surgery suggests that the risk of mortality and morbidity begins to increase when the postoperative Hb falls below 10 g per dL, especially in patients with concomitant cardiovascular disease.[12] 2) Transfused patients may have more "energy" and be better able to get out of bed (which reduces the risk of pneumonia and thromboembolism) and may be able to work harder at rehabilitation, which results in better functional status, reduced use of nursing home, and shorter length of hospital stay. 3) Greater oxygen-carry-

**TABLE 2. Mean Hb levels and units of blood transfused**

| After-enrollment values | Threshold group (n = 42) | | Symptomatic group (n = 42) | | p value |
|---|---|---|---|---|---|
| | Mean (±SD) | Range | Mean (±SD) | Range | |
| Hb | | | | | |
| Lowest | 9.4 (± 1.0) | 7.3 -11.6 | 8.8 (±1.2) | 5.6 -11.4 | 0.004* |
| Highest | 11.1 (± 0.9) | 8.6 -14.0 | 10.0 (±1.1) | 7.9 -12.5 | 0.001* |
| Last | 10.7 (± 0.9) | 8.0 -12.4 | 9.7 (±0.9) | 7.9 -11.4 | 0.001* |
| Units transfused | 2 (median) (1,2)† | 0 -4 | 0 (Median)(0,2) | 0 -6 | 0.001‡ |

* *t* test.
† Interquartile range
‡ Wilcoxon's rank sum test.

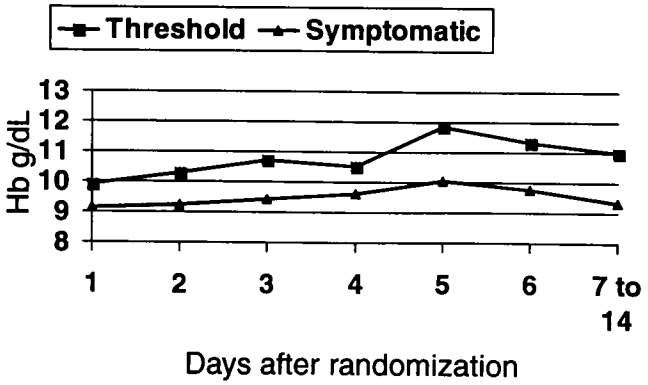


**Fig. 2. Mean Hb levels each day after randomization, stratified by assignment.**

ing capacity might result in fewer MIs and fewer episodes of congestive heart failure. The rationales for the symptomatic transfusion strategy are: 1) a cohort study of 8787 hip fracture patients found no apparent effect of transfusion on mortality in patients with Hb levels as low as 8 g per dL, even those with cardiovascular disease[13]; 2) a lower Hb level would reduce blood viscosity, which might lower the risk of fatal and nonfatal thrombosis resulting in MI, stroke, and thromboembolism; 3) less blood use would result in lower risk of transfusion-related complications, such as the immunomodulating effect of allogeneic blood, and of rare viral infections; and 4) less blood use might reduce the risk of transfusion complications resulting from human errors, such as the use of mismatched blood.

The options for blood management are rapidly expanding and include the use of autologous blood donation, erythropoietin, intraoperative hemodilution, and blood substitutes. The rationale for the use of each of these new treatments is to reduce allogeneic blood transfusion. When we have a clearer understanding of how to treat patients with allogeneic blood transfusions, we will be better able to determine the appropriate indications for these new blood-management strategies and drugs.

The results from a definitive trial are likely to change RBC transfusion practice. If the study shows that blood can be safely withheld until the patient is symptomatic, that should lead to more widespread acceptance and use of lower transfusion thresholds. Alternatively, if a definitive trial demonstrates that higher Hb levels are needed to maintain function or reduce mortality (as the trend in this analysis showed), then current transfusion guidelines would have to be updated. Large, simple, randomized clinical trials are feasible and are needed to provide a scientific basis for transfusion decisions.

**TABLE 3. Clinical outcomes**

| Outcome | Threshold group (n = 42) | | Symptomatic group (n = 42) | | Total (n = 84) | |
|---|---|---|---|---|---|---|
| Death or inability to walk across room or 10 feet without human assistance* | 19 | (45.2%) | 16 | (39.0%) | 35 | (42.2%) |
| Mortality | | | | | | |
| in-hospital | 0 | | 0 | | 0 | |
| 30-day† | 1 | (2.4%) | 1 | (2.4%) | 2 | (2.4%) |
| 60-day‡ | 2 | (4.8%) | 5 | (11.9%) | 7 | (8.3%) |
| MI | | | | | | |
| Definite | 0 | | 0 | | 0 | |
| Possible | 0 | | 1 | (2.4%) | 1 | (1.2%) |
| Stroke | | | | | | |
| Definite | 1 | (2.4%) | 0 | | 1 | (1.2%) |
| Possible | 0 | | 0 | | 0 | |
| Pneumonia | 2 | (4.8%) | 0 | | 2 | (2.4%) |
| Thromboembolism | 0 | | 1 | (2.4%) | 1 | (1.2%) |
| Discharge destination§ | | | | | | |
| Community dwelling | 2 | (4.8%) | 5 | (11.9%) | 7 | (8.3%) |
| Nursing home | 26 | (61.9%) | 19 | (45.2%) | 45 | (53.6%) |
| Rehabilitation hospital | 14 | (33.3%) | 18 | (42.9%) | 32 | (38.1%) |
| Residence at 60 days‖ | | | | | | |
| Nursing home | 15 | (35.7%) | 14 | (33.3%) | 29 | (34.5%) |
| Community dwelling | 25 | (59.5%) | 22 | (52.4%) | 47 | (59.5%) |
| Rehabilitation hospital | 0 | | 1 | (2.4%) | 1 | (1.2%) |
| Death | 2 | (4.8%) | 5 | (11.9%) | 7 | (8.3%) |
| Length of stay | 6.4 | (±3.4) | 6.3 | (±3.4) | 6.3 | (±3.4) |

* Or inability or choice not to perform the task because of health problems, p = 0.57; symptomatic n = 41; total n = 83
† p = 1.0 (Fisher's exact).
‡ p = 0.43 (Fisher's exact); relative risk = 2.5; 95% CI, 0.5-12.2.
§ p = 0.24 (chi-square).
‖ p = 0.36 (chi-square).

**TABLE 4. Tasks that were performed without human assistance***

| Task | Threshold group (n = 42) (%) | | Symptomatic group (n = 42) (%) | | Total | |
|---|---|---|---|---|---|---|
| Walk across room or 10 feet | 23 | (54.8%) | 25 | (61.0%)† | 48 | (57.8%) |
| Get into and out of bed | 22 | (52.4%) | 21 | (51.2%)† | 43 | (51.8%) |
| Walk one block on a level surface | 7 | (17.5%)‡ | 10 | (27.0%)§ | 17 | (22.1%) |
| Climb 5 stairs | 12 | (31.6%)‖ | 12 | (31.6%)‖ | 24 | (31.6%) |
| Get in to and out of car | 13 | (31.7%)† | 17 | (41.5%)† | 30 | (36.6%) |
| Rise from armless chair | 20 | (47.6%) | 15 | (39.5%)‖ | 35 | (43.8%) |
| Put on pants | 21 | (50.0%) | 14 | (34.1%)† | 35 | (42.2%)¶ |
| Put on shoes and socks on both feet | 18 | (42.9%) | 12 | (30.0%)‡ | 30 | (36.6%) |
| Get in and out of bath or shower | 10 | (24.4%)† | 8 | (20.0%)‡ | 18 | (22.2%) |
| Take a shower or bath or sponge bath | 20 | (47.6%) | 20 | (48.8%)† | 40 | (48.2%) |

* Patients who refused to answer question, responded don't know, or did not perform the activity for other reasons were considered missing for question. Number of subjects included in analysis for each question are †n = 41; ‡n = 40; §n = 37; ‖ n = 38.
¶ p=0.14, all other p >0.2.

**ACKNOWLEDGMENTS**

The authors are extremely grateful to the orthopedic surgery residents and attending physicians, the blood transfusion services, and the nursing staffs at our participating hospitals.

## REFERENCES

1. Wallace EL, Churchill WH, Surgenor DM, et al. Collection and transfusion of blood and blood components in the United States, 1992. Transfusion 1995;35:802-12.
2. Forbes JM, Anderson MD, Anderson GF, et al. Blood transfusion costs: a multicenter study. Transfusion 1991; 31:318-23.
3. Lubarsky DA, Han C, Bennett DH, et al. The hospital cost (fiscal year 1991/1992) of a simple perioperative allogeneic red blood cell transfusions during elective surgery at Duke University. Anesth Analg 1994;790:629-37.
4. Etchason J, Petz L, Keeler E, et al. The cost effectiveness of preoperative autologous blood donations. N Engl J Med 1995;332:719-24.
5. Dodd RY. The risk of transfusion-transmitted infection. N Engl J Med 1992;327:419-21.
6. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ, The risk of transfusion-transmitted viral infections. Retrovirus Epidemiology Donor Study. N Engl J Med 1996;334:1685-90.
7. Topley E, Fisher MR. The illness of trauma. Br J Clin Pract 1956;1:770-6.
8. Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal haemorrhage. Br J Surg 1986;73:783-5.
9. Weisel RD, Charlesworth DC, Micklebourough LL, et al. Limitations of blood conservation. J Thorac Cardiovasc Surg 1984;88:26-38.
10. Johnson RG, Thurer RL, Kruskall MS, et al. Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovas Surg 1992;104:307-14.
11. Herbert PC, Wells G, Marshall J, et al. Transfusion requirements in critical care. JAMA 1995;273:1439-44.
12. Carson JL, Duff A, Berlin JA, et al. Effect of anemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348:1055-60.
13. Carson JL, Duff A, Berlin JA, et al. Influence of perioperative blood transfusion on postoperative mortality. JAMA 1998;279:199-205.
14. Magaziner J, Zimmerman SI, Gruber-Baldini AL, et al. Proxy reporting in five areas of functional status: comparison with self-reports and observations of performance. Am J Epidemiol 1997;146:418-28.
15. Kenzora JE, Magaziner J, Hudson J, et al. Outcomes of treatment of intracapsular fractures by hemiarthroplasty in patient over the age of 65. Clin Ortho 1998;348:51-8.
16. White RH, McGahan JP, Daschbach, Hartling RP. Diagnosis of deep-vein thrombosis using duplex ultrasound. Ann Intern Med. 1989;111:297-304.
17. Huisman MV, Buller HR, ten Cate JW, Vreeken J. Serial impedance plethysmography for suspected deep venous thrombosis in outpatients: the Amsterdam General Practitioner Study. N Engl J Med 1986;314:823-7.
18. Kelley MA, Carson JL, Palevsky HI, Schwartz JS. Diagnosing pulmonary embolism: new facts and strategies. Ann Intern Med 1991;114:300-6.
19. Value of the ventilation/perfusion scan in acute pulmonary embolism: Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. JAMA 1990;263:2753-9.

20. Hull RD, Hirsh J, Carter CJ, et al. Diagnostic value of ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. Chest 1985;88:819-28.
21. Hull RD, Raskob GE, Coates G, et al. A new noninvasive strategy for patients with suspected pulmonary embolism. Arch Intern Med 1989;149:2549-55.
22. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128-40.
23. Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. JAMA 1961;178:261-6.
24. New classification of physical status. Anesthesiology 1963;24:111.
25. Feinberg SE. The analysis of cross classified data. Cambridge, MA: The MIT Press, 1977:9.
26. Hays WL. Statistics for the social sciences. 2nd ed. New York: Holt, Rinehardt, and Winston, 1973:404-10.
27. Conover WJ. Practical non-parametric statistics. 2nd ed. New York:John Wiley and Sons, 1980.
28. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiological Research: principles and quantitative methods. Belmont, CA: Wadsworth, 1982:299.
29. Perioperative red blood cell transfusion. Consensus conference. JAMA 1988;260:2700-3.

## AUTHORS

Jeffrey L. Carson, MD, Richard C. Reynolds Professor of Medicine and Chief, the Division of General Internal Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, 125 Patterson Street, New Brunswick, NJ 08903. [Reprint requests]

Michael L. Terrin, MPH, Vice President, Maryland Medical Research Institute, Baltimore, MD.

Franca B. Barton, MS, Statiistician, Maryland Medical Research Institute.

Roy Aaron, MD, Clinical Associate Professor of Orthopedics, Brown University School of Medicine, Miriam Hospital, Providence, RI.

A. Gerson Greenburg, MD, Professor of Surgery, Brown University School of Medicine, and Surgeon-in-Chief, Miriam Hospital.

David A. Heck, MD, Professor, Department of Orthopaedic Surgery, Indiana University, Indianapolis, IN.

Jay Magaziner, PhD, Associate Professor, Department of Epidemiology and Preventive Medicine, University of Maryland, Baltimore, MD.

Frances E. Merlino, RN, Research Nurse, Division of General Internal Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey.

Gail Bunce, RN, CNP Staff Nurse, Department of Surgery, Miriam Hospital.

Brian McClelland, MD, Director, Department of Transfusion Medicine, University of Edinburgh, The Royal Infirmary of Edinburgh, Edinburgh, Scotland.

Amy Duff, MHS, Teaching and Research Specialist, Division of General Internal Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey.

Helaine Noveck, MPH, Teaching and Research Specialist, Division of General Internal Medicine, Department of Medicine, University of Medicine and Dentistry of New Jersey.