The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery

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BACKGROUND: Perioperative anemia leads to increased morbidity and mortality and potentially inhibits rehabilitation after hip fracture surgery. As such, the optimum transfusion threshold after hip fracture surgery is unknown.

PATIENTS AND METHODS: A total of 120 elderly, cognitively intact hip fracture patients admitted from their own home were randomly assigned to receive transfusion at a hemoglobin threshold of 10.0 g per dL (liberal) versus 8.0 g per dL (restrictive) in the entire perioperative period. Patients were treated according to a well-defined multimodal rehabilitation program. Primary outcome was postoperative functional mobility measured with the cumulated ambulation score (CAS).

RESULTS: Patients in the liberal group received transfusions more frequently than those in the restrictive group (44 patients vs. 22 patients; $p < 0.01$) and received more transfusions during hospitalization (median, 2 units [interquartile range, 1-2] vs. 1 [1-2]; $p < 0.0001$). There were no significant differences in postoperative rehabilitation scores (CAS: median, 9 [9-15] vs. 9 [9-13.5]; $p = 0.46$) or in length of stay (median, 18 days vs. 16 days, respectively; $p = 0.46$). There were fewer patients in the liberal transfusion group with cardiovascular complications (2% vs. 10%; $p = 0.05$) and a lower mortality (0% vs. 8%; $p = 0.02$).

CONCLUSION: Although a liberal transfusion trigger did not result in increased ambulation scores, restrictive transfusion thresholds should be treated with caution in elderly high-risk hip fracture patients, until their safety has been proved in larger randomized studies.

Hip fracture surgery is associated with perioperative blood loss leading to anemia, which in the elderly patient is associated with increased postoperative morbidity and mortality.[1-4] In addition, postoperative anemia leads to increased cardiac demand and tissue hypoxia,[5] and hemoglobin (Hb) levels below 8.0 g per dL have been associated with increased postoperative mortality.[6] However, moderate anemia in hip fracture patients with Hb levels between 8.0 and 10.0 g per L has not been demonstrated to increase mortality in hip fracture patients, but has been associated with decreased postoperative ambulation.[7-10]

Anemia has been shown to decrease functional outcome and increase morbidity and mortality, but the correction of moderate anemia with red blood cell (RBC) transfusions has not been shown to improve either rehabilitation or morbidity outcomes.[11] As such, the optimal transfusion threshold in elderly hip fracture patients is controversial.

ABBREVIATIONS: ASA = American Society of Anesthesiologists; CAS(s) = cumulated ambulation score(s); IMHS = intermedullary hip screw; PACU = postanesthesia care unit; SHS = sliding hip screw.

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We therefore conducted a randomized study of elderly cognitively intact hip fracture patients admitted from their own home and treated with a well-defined multimodal rehabilitation program to either a liberal or a restrictive transfusion threshold to assess the impact on postoperative ambulation, morbidity, and mortality.

PATIENTS AND METHODS

Inclusion

Hip fracture patients admitted to the hip fracture unit at the department of orthopedics at Hvidovre University Hospital were screened for inclusion between February 2004 and July 2006. Inclusion criteria were primary hip fracture occurring in the community in patients older than 65 years of age with an independent prefracture walking function, community dwelling, and intact cognitive status. Patients with multiple fractures, prefracture terminal condition, alcoholism, chronic transfusion needs, acute cardiac or other acute severe medical conditions, or contraindication to epidural analgesia were excluded. Furthermore, patients were excluded from the per-protocol analysis of rehabilitation if they were not able to participate in the physical therapy program due to mobilization restriction by the operating surgeon, transfer to another ward for medical complications, or reoperation within the first 4 days.

The study is part of Hvidovre University Hospitals Hip Fracture Project. The study protocol was approved by the local ethics committee and by the Danish data protection agency and was registered with ClinicalTrials.gov with the identifier NCT00162617. The study was conducted according to the CONSORT guidelines and the Helsinki declaration was adhered to.

Preliminary data indicated that 41 patients were needed in each group to demonstrate a 25 percent absolute reduction in the cumulated ambulation score (CAS) with a level of significance of 0.05 and a power of 0.80.[12] Since the preliminary data showed that only 69 percent of patients required transfusion with a liberal transfusion regimen, it was decided to include 60 patients in each group.

A total of 120 included patients were randomly assigned into two groups of 60. In the liberal transfusion threshold group the patients received transfusion when their Hb level decreased to below 10.0 g per dL, whereas patients in the restrictive threshold group received transfusion when their Hb level decreased to below 8.0 g per dL. The randomization was done via a computer-generated list by a person not affiliated with the project. Upon inclusion the sealed envelope, containing the transfusion threshold and with the patient's study number on it, was placed in the patient charts next to the transfusion papers concealing the allocation to both the patient and the physiotherapists conducting the ambulation assessments, making the study double-blind.

Perioperative procedures

The department's standardized multimodal rehabilitation program was instituted in all patients. The rehabilitation program included surgery within 24 hours, epidural anesthesia, and epidural analgesia initiated immediately after admittance and continued for 96 hours postoperatively.[13] All patients received oxygen therapy 2 L per minute whenever supine until the fourth postoperative day and were given antibiotics as 1.5 g of cefuroxim preoperatively and antithrombotic prophylaxis with low-molecular-weight heparin (40 mg enoxaparin subcutaneously once daily) from the time of admission. Patients were on a regular diet supplemented by three daily protein drinks. Patients' regular medications were continued throughout the entire stay except for warfarin, which was discontinued in the immediate perioperative period.

Preoperative fluid therapy consisted of 20 mL per kg intravenous (IV) rehydration fluid (40 mmol/L Na, 20 mmol/L K, 250 mmol/L glucose) immediately upon admission but after blood sampling; an intraoperative infusion of 5 mL per kg per hour isotonic saline was provided, supplemented by 6 percent hydroxyethyl starch (HES) 130/0.4 (Voluven, Fresenius KABI, Albertslund, Denmark) on signs of hypovolemia. Intraoperative blood loss was replaced by 6 percent HES 130/0.4, at a rate of 1:1. In the postanesthesia care unit all patients received 500 mL IV glucose (278 mmol/L). Postoperative fluid therapy was standardized and IV fluids were only administered if daily oral intake was less than 1500 mL or in the case of hypovolemia when 500 mL of 6 percent HES 130/0.4 was given.

Transfusion therapy

Hb was as a standard measured immediately upon admission via venous sampling and analyzed with cyanomethemoglobin method (Advia, Bayer, Lyngby, Denmark), again in the postanesthesia care unit (PACU) and every morning until the fifth postoperative day via venous sampling with an Hb analyzer (Hemocue, Hemocue Corp., Vedbæk, Denmark).

An intraoperative Hb was only measured and transfusions given when excessive blood loss was observed. In the PACU, any transfusions ordered as a consequence of anemia were initiated before the patients left the PACU. In the ward, the Hb values were measured in the morning and any indication for transfusion was to be acted upon immediately.

If a Hb level less than 10.0 g per dL was measured in a patient, the attending physician opened the sealed envelope to reveal the transfusion group to which the patient

Liberal transfusion threshold	
8.8 g/dl < Hb < 10 g/dl:	1 unit of RBC
7.2 g/dl < Hb ≤ 8.8 g/dl:	2 units of RBC
Hb < 7.2 g/dl:	3 units of RBC
All transfusions followed by control of Hb.	

Restrictive transfusion threshold	
7.2 g/dl < Hb < 8 g/dl:	1 unit of RBC
5.6 g/dl < Hb ≤ 7.2 g/dl:	2 units of RBC
Hb < 5.6 g/dl:	3 units of RBC
All transfusions followed by control of Hb.	

Fig. 1. Transfusion standards according to randomization.

belonged. The transfusion group was not disclosed to either the patient or the attending physiotherapists, and as such the study was double-blind.

Guidelines for transfusions were set according to randomization as outlined in Fig. 1. If a patient developed an acute cardiac condition he or she was transfused as in the liberal group regardless of randomization; if patients were transferred to other wards due to medical or surgical complications, they were here transfused at the discretion of the attending physicians. Leukoreduced RBC transfusions were not given. Transfusion indications were handled by the dedicated trauma surgeons attending the wards and supervised by MK.

Rehabilitation

If possible the patients were mobilized on the day of surgery. A physiotherapy program comprising two daily 30-minute sessions was initiated on the first postoperative day. Discharge criteria from the hip fracture unit were standardized: the ability to independently get in and out of bed and to and from a place of eating, the ability to independently perform bathroom visits, and the ability to walk with the walking aid to be used in the home. Patients were primarily rehabilitated in the orthopedic ward. Patients, who after initial rehabilitation in the hip fracture unit, still required an excessive length of intensive rehabilitation, were only then transferred to a secondary rehabilitation facility.

Study variables

Medical conditions, American Society of Anesthesiologists (ASA) classification, type of surgery, and residential status were recorded. Mental status was assessed by a validated 9-point Danish version of the abbreviated mental status test taken upon admission.[14] Functional level prefracture were assessed with the new mobility score.[15]

During the physiotherapy session the patients were evaluated on their ambulatory capacity via the CAS,[15] which allows day to day measurements of functional mobility in hip fracture patients in the early postoperative phase. The CAS describes the patients' independence in ambulation in transfer from supine-to-sitting-to-supine and sitting-to-standing-to-sitting and the patient's walking ability with an appropriate aid. Each function is assessed on a 3-point scale; 2 = independent of human assistance; 1 = patient requiring human assistance to perform function; and 0 = patient unable to perform function despite human assistance. The scores of each function are cumulated to provide a daily score between 0 and 6, with 6 indicating independent ambulation on that particular day. When cumulating the scores from the first 3 postoperative days, they combine to give a value (CAS) from 0 to 18, which has been validated and found to be predictive of postoperative rehabilitation outcome.[16]

During physiotherapy the patients were also evaluated for symptoms of anemia by the physiotherapists. The symptoms were evaluated by 5-point verbal rating scores for both dizziness on standing and feeling of general fatigue separately: 0 = none; 1 = slight; 2 = moderate; 3 = severe; and 4 = very severe, prohibiting patient from rising from bed.

Complication was registered in all patients by intention to treat. Length of stay and 30-day mortality were registered, the latter established via the Danish civil registry.

Primary outcome was the CAS as registered on the first 3 postoperative days. Secondary outcomes were length of stay, cardiac complications (defined as acute myocardial infarction, pulmonary edema/acute congestion, or new onset arrhythmia), infectious complications (pneumonia, sepsis, or wound infections), and mortality.

Statistical analysis

The CASs were analyzed per-protocol since these data were not obtainable in excluded patients, length of stay was analyzed both per-protocol and by intention-to-treat, and all other data were analyzed by intention-to-treat.

Tests for significant differences between groups were done with the chi-square test for categorical data, t tests were used for parametric data, and the U test was used for nonparametric numeric data. For the analysis of differences between types of surgery one-way analysis of variance and Kruskall-Wallis test were used. The level of significance was set at 0.05 or less. All data analysis was conducted with computer software (SPSS for Windows Version 10.1, SPSS, Inc., Chicago, IL).

RESULTS

Inclusion of patients is shown in Fig. 2. A total of 120 patients were available for intention-to-treat analysis and 107 patients for the per-protocol analysis. Demographic data are shown in Table 1. The randomization did not succeed in making two completely comparable groups;

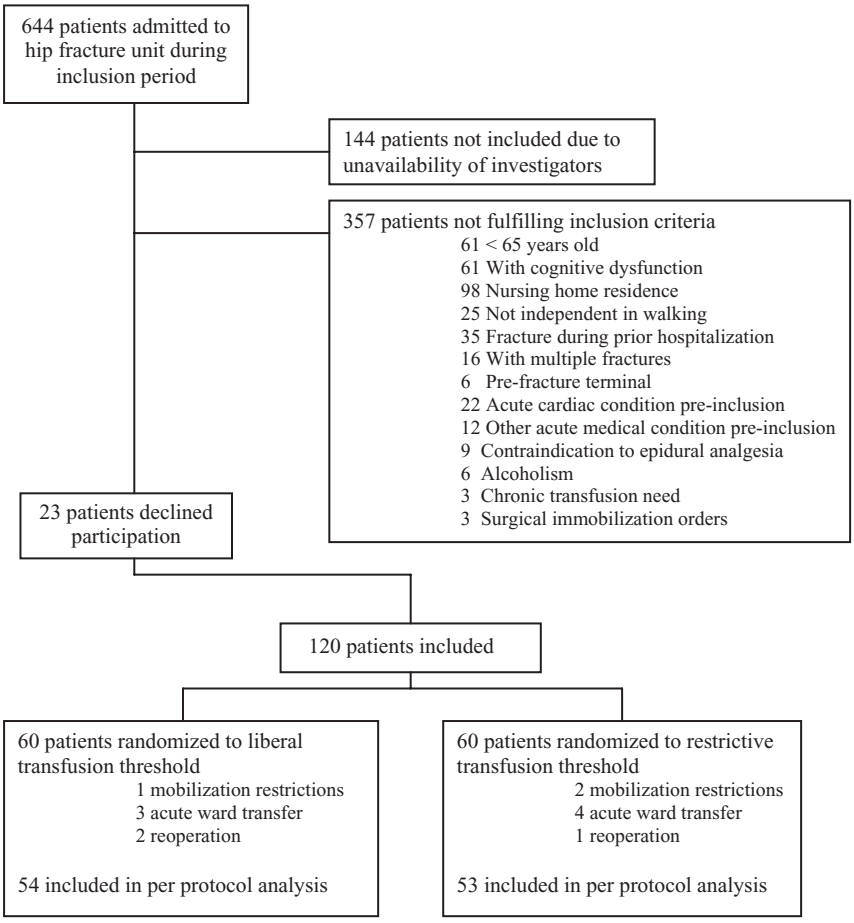

Fig. 2. Inclusion of 120 hip fracture patients in study of liberal versus restrictive transfusion thresholds.

there were a higher number of patients in the restrictive group with an ASA rating of 3 than in the liberal group ($p = 0.02$). This was, however, not reflected in a higher number of patients with cardiovascular disease ($p = 0.19$). The overall distribution of types of surgery was not different between the two groups ($p = 0.18$) but there were fewer patients ($p = 0.05$) with pins/screws (Hansson Hookpins/Olmed screws) in the liberal transfusion group. In the per-protocol analysis there was a significantly higher number of patients ($p = 0.02$) in the liberal group who had either a sliding hip screw (SHS) or an intermedullary hip screw (IMHS) procedure—predictive of higher perioperative blood loss.[1]

More patients received transfusions in the liberal transfusion group (44 [74%]) than in the restrictive group (22 [37%]); the difference was significant (<0.01). Patients in the liberal transfusion group received significantly more transfusions ($p < 0.0001$) than those in the restrictive group (median, 2 [interquartile range, 1-2] units vs. 1 [1-2] units). Perioperative Hb values are shown in Fig. 3.

The per-protocol analysis of rehabilitation outcomes and anemia symptoms is shown in Table 2. There were no significant differences between the two groups apart from higher reported fatigue values in the restrictive transfusion group on the second postoperative day ($p = 0.04$). There were significant intergroup differences in the CAS between the different types of surgery ($p = 0.02$), with screws/pins and arthroplasty having the highest numbers (i.e., best rehabilitation scores); to elucidate these differences the per-protocol analysis were performed on each type of surgery separately (Table 3). There was a trend toward improved CAS in patients with arthroplasty in the liberal transfusion group, although this was not significant ($p = 0.07$).

Outcomes are shown in Table 4. There were no differences in rehabilitation outcome on an intention-to-treat basis. There was a higher rate of cardiovascular complications in the restrictive transfusion group (2% vs. 10%; $p = 0.05$) and a higher 30-day mortality (0% vs. 8%; $p = 0.02$; relative risk, 2.1 [1.5-2.5]); there was no significant difference between infectious complications in the two groups, although there was a trend toward a higher incidence of wound infections ($p = 0.08$) in the liberal group. Of the five patients who died in the restrictive group none had any known prefracture cardiovascular disease; three had cardiovascular conditions as primary cause of death, one died suddenly during the night, and one died of general exhaustion (age 98).

DISCUSSION

In this randomized trial we did not find a decreased rehabilitation potential in patients treated with a restrictive transfusion therapy, in the form of decreased postoperative ambulation, length of stay in hospital, or number of patients achieving independent ambulation. We did, however, find an increased morbidity in the form of cardiovascular events and an increased mortality in the restrictive transfusion group.

We previously found postoperative anemia after hip fracture surgery to be an independent predictor of postoperative inability to walk independently and postoperative Hb level was also positively correlated with the ambulation score.[10] Hb level has been found to be an independent predictor for distance walked at discharge, and anemia on discharge has been found to be predictive of readmission.[8-9,17] The only previous randomized study of

TABLE 1. Demographic data in 120 hip fracture patients randomly assigned to liberal or restrictive transfusion thresholds*

	Liberal transfusion threshold (n = 60)	Restrictive transfusion threshold (n = 60)	p Value
Age (years)	81 (6.8)	81 (7.3)	0.95
Sex (female)	46 (77)	46 (77)	1.00
ASA (I/II/III/IV)	9/39/12/0 (15/65/20/0)	2/35/23/0 (4/58/38/0)	0.02
Weight (kg)	64 (16)	63 (13)	0.66
Height (cm)	165 (7.6)	166 (7.6)	0.60
New mobility score (0-9)	8 (6-9)	7 (5-9)	0.37
Mental score (0-9)	9 (8-9)	9 (8-9)	0.78
Surgical procedure			
Screws/pins	2 (3)	8 (13)	
Arthroplasty	22 (37)	24 (40)	0.18
SHS	25 (42)	21 (35)	
IMHS	11 (18)	7 (12)	
Surgical procedure (per-protocol)			
Screws/pins	2 (4)	8 (15)	
Arthroplasty	16 (30)	22 (42)	0.06
SHS	25 (46)	17 (32)	
IMHS	11 (20)	6 (11)	
Cerebrovascular disease	2 (3)	6 (10)	0.14
Cardiovascular disease	21 (35)	28 (47)	0.19
Ischemic heart disease	4 (7)	10 (17)	0.09
Congestive heart disease	5 (8)	3 (5)	0.46
Atrial fibrillation	3 (5)	3 (5)	1.0
Hypertension	14 (23)	20 (33)	0.22
COPD	8 (13)	9 (15)	0.79
Diabetes	5 (8)	4 (7)	0.73
Chronic renal failure	1 (2)	2 (3)	0.56
Intraoperative blood loss (mL)	298 (270)	276 (247)	0.65

* Values given are median (25th-75th percentiles) for nonparametric numeric data, mean (SD) for continuous numeric data, and number (%) for categorical data.
COPD = chronic obstructive pulmonary disease.

TABLE 2. Ambulation, functional outcome, and anemia symptoms in 107 hip fracture patients randomly assigned to liberal or restrictive transfusion thresholds*

	Liberal transfusion threshold (n = 54)	Restrictive transfusion threshold (n = 53)	p Value
Ambulation score (0-6)			
Day 1	3 (3-4)	3 (2.25-3.75)	0.75
Day 2	3 (3-5)	3 (3-4.75)	0.35
Day 3	3 (3-6)	3 (3-5)	0.67
CAS (0-18)†	9 (9-15)	9 (9-13.5)	0.46
Patients regaining functional independence during hospitalization	29 (54)	30 (57)	0.76
Length of hospitalization	18.1 (14.6)	16.3 (11.8)	0.48
Fatigue score (0-4)			
Day 1	1 (1-2)	1 (1-2)	0.37
Day 2	1 (1-2)	2 (1-3)	0.04
Day 3	1 (1-2)	2 (1-2)	0.11
Cumulated fatigue score (0-12)	4 (3-6)	5 (3-7)	0.46
Dizziness score (0-4)			
Day 1	0 (0-1)	0 (0-1)	0.94
Day 2	0 (0-1)	0 (0-1)	0.48
Day 3	0 (0-1)	0 (0-1)	0.82
Cumulated dizziness score	0 (0-1)	0 (0-1)	0.64

* Ambulation score is a composite score evaluating independence in walking or getting up from chair. Fatigue and dizziness scores are verbal rating scale 0-4. Cumulated scores are the cumulated values from Days 1-3. Values given are median (25-75 percentiles) for ordinal scales, mean (SD) for continuous numeric data, and number (%) for categorical data.
† High score indicates good ambulation.

transfusion thresholds after hip fracture surgery found no difference in the ability to walk independently at discharge.[11] The major advantage of this study is that perioperative setup was standardized. Patients received a multimodal rehabilitation program,[3] including regional anesthesia and analgesia, standardized fluid therapy, nutrition support, supplemental oxygen, and intensive physical therapy as well as day to day nurse care plans.[18] Similar programs have been shown to improve physical capacity in other types of surgery compared to conventional care.[18] Pain is associated with poor ambulation and rehabilitation outcomes and regional analgesia has been shown to reduce pain as a limiting factor in rehabilitation.[13,19,20] As such, our setup should optimize conditions to define and isolate the influence of transfusion thresholds on rehabilitation. Unfortunately our randomization resulted in a significant higher proportion of patients with either SHS or IMHS in the liberal transfusion group. These types of surgery that are used in pertrochanteric and subtrochanteric fractures have been shown to be independent predictors of increased perioperative blood loss; they are associated with higher pain levels, a decreased ability to independent ambulation, poorer rehabilitation outcome, and increased mortality.[1,16,20-23] In the restrictive group, there also were a significantly higher number of patients receiving screws/pins—the procedure associated with the least blood loss.[1] This could explain the fact that despite a higher number of transfusions in the liberal group, mean Hb values were actually very close in the perioperative period, confounding the impact of the liberal transfusion therapy. A continued blood loss into the postoperative period was evident, as patients in the liberal transfusion group continued to become anemic despite transfusions, as documented in previous studies.[1]

Moderate anemia has been associated with increased mortality in patients over 65 years old undergoing noncardiac surgery, but no effect of RBC

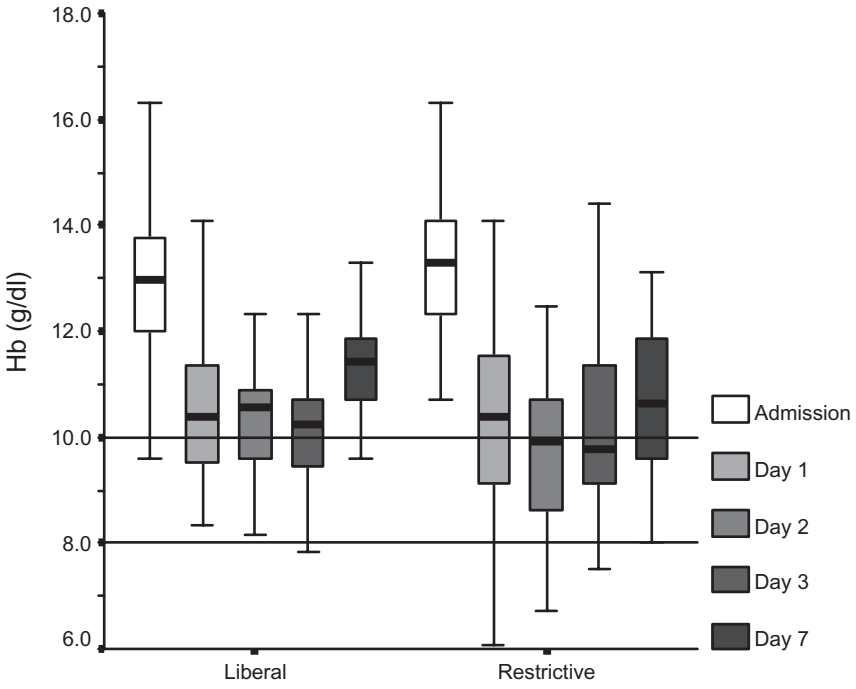

Fig. 3. Perioperative Hb values in 120 hip fracture patients randomly assigned to liberal versus restrictive transfusion thresholds. Liberal group were transfused with RBCs at a threshold of 10.0 g per dL, and restrictive at 8.0 g per dL. Day 1 indicates first day postsurgery, and so forth.

TABLE 3. Ambulation in 107 hip fracture patients randomly assigned to liberal or restrictive transfusion thresholds stratified according to type of surgery*

CAS (0-18)†	Number	Liberal transfusion threshold	Number	Restrictive transfusion threshold	p Value
Screws or pins	2	14 (10-14)	8	11.5 (9-16.75)	0.53
Arthroplasty	16	15 (9-16)	22	11 (8-15)	0.07
SHS	25	9 (8.5-12.5)	17	11 (9-13)	0.67
IMHS	11	9 (8-9)	6	9 (7-9)	0.46

* Ambulation score is a composite score evaluating independence in walking or getting up from chair from Days 1 to 3. Values given are median (25-75 percentiles).
† High score indicates good ambulation.

transfusion on mortality has been found in hip fracture patients with a Hb level of more than 80 g per L.[4,17] The previous randomized study of transfusion thresholds in hip fracture patients compared a threshold of a Hb level of less than 100 g per L with a threshold of less than 80 g per L or "symptomatic anemia," and showed a similar trend toward improved survival with the liberal transfusion trigger—a relative risk of 2.5, compared to 2.1 in the present study.[11] Despite a significantly higher mortality in the restrictive transfusion group, the findings should be interpreted with caution both due to the fact that the skewed distribution of patients with an ASA score of 3 between groups may have confounded the result and due to the fact that mortality was a secondary outcome measure, which the study was not initially powered to detect.

Existing cardiovascular disease has been shown to increase the risk of perioperative anemia.[3] Regional analgesia with epidural local anesthetics reduces preoperative cardiac complications and minimizes postoperative ischemia, and as such, our perioperative setup should theoretically decrease the risk of cardiac complications.[13,24,25] We found a significantly higher rate of cardiac complications in the restrictive threshold group compared to the liberal group, despite no significant difference in existing cardiovascular disease. All fatalities occurred in patients *without* known cardiac disease. Age is a proxy for comorbidity, and elderly patients have reduced organ reserves compared to younger. Since it is not known to which extent cardiovascular disease is underdiagnosed in this group of patients, the decision to transfuse should probably reflect this.[26] It is also of importance to note that the hip fracture population included in a study such as this represents the fittest part of the population and that any negative effects seen will potentially be amplified if implemented in the general hip fracture population where the degree of medical comorbidity is even higher. As such, restrictive transfusion triggers in elderly hip fracture patients without known cardiac comorbidity should be used cautiously until further evidence exists.

Transfusions can be immunosuppressive and have been linked to increased risk of bacterial infections in hip fracture patients, although this is controversial.[27-29] We did find a tendency toward an increased incidence of wound infections in the liberal group, but no difference in overall incidence of infectious complications was found; this outcome is most likely not influenced by the distribution of surgical procedures between the groups.[30]

The present data do not allow us to conclude finally on the safety of restrictive transfusion thresholds in the elderly hip fracture patient with or without cardiac comorbidity thereby calling for larger well-designed randomized studies with mortality as a primary outcome measure. Such studies should stratify patients according to type of surgery to avoid the confounding effects of pain and

TABLE 4. Outcome data in 120 hip fracture patients randomly assigned to liberal or restrictive transfusion thresholds*

Outcome	Liberal transfusion threshold (n = 60)	Restrictive transfusion threshold (n = 60)	p Value
Cerebrovascular event	1 (2)	1 (2)	1.00
Acute myocardial infarction	0 (0)	1 (2)	0.32
Pulmonary edema/congestive heart failure	0 (0)	2 (3)	0.15
Acute arrhythmia	1 (2)	3 (5)	0.31
Any cardiovascular event	1 (2)	6 (10)	0.05
Pneumonia	2 (3)	1 (2)	0.56
Sepsis	1 (2)	1 (2)	1.00
Wound infection	3 (5)	0 (0)	0.08
Any infectious complication	11 (18)	6 (10)	0.19
Thromboembolic event	2 (3)	1 (2)	0.56
Delirium	5 (8)	6 (10)	0.75
30-day mortality	0 (0)	5 (8)	0.02
Cardiovascular event or death (30 days)	1 (2)	11 (18)	<0.01
Hospitalization (days)	18.4 (14.4)	17.0 (12.9)	0.61
Discharged directly to own home	46 (77)	42 (70)	0.58
Readmissions in 30 days	11 (18)	9 (15)	0.31

* Values given are mean (SD) for continuous numeric data and number (%) for categorical data.

increased blood loss, to more accurately assess the effects of transfusion thresholds on rehabilitation. Until such data are available, the clinical application of restrictive transfusion thresholds should be applied cautiously in hip fracture patients.

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