Delirium Outcomes in a Randomized Trial of Blood Transfusion Thresholds in Hospitalized Older Adults with Hip Fracture

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OBJECTIVES: To determine whether a higher blood transfusion threshold would prevent new or worsening delirium symptoms in the hospital after hip fracture surgery.

DESIGN: Ancillary study to a randomized clinical trial.

SETTING: Thirteen hospitals in the United States and Canada.

PARTICIPANTS: One hundred thirty-nine individuals hospitalized with hip fracture aged 50 and older (mean age 81.5 ± 9.1) with cardiovascular disease or risk factors and hemoglobin concentrations of less than 10 g/dL within 3 days of surgery recruited in an ancillary study of the Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair.

INTERVENTION: Individuals in the liberal treatment group received one unit of packed red blood cells and as much blood as needed to maintain hemoglobin concentrations at greater than 10 g/dL; those in the restrictive treatment group received transfusions if they developed symptoms of anemia or their hemoglobin fell below 8 g/dL.

MEASUREMENTS: Delirium assessments were performed before randomization and up to three times after randomization. The primary outcome was severity of delirium according to the Memorial Delirium Assessment Scale (MDAS). The secondary outcome was the presence or absence of delirium defined according to the Confusion Assessment Method (CAM).

RESULTS: The liberal group received a median two units of blood and the restrictive group zero units of blood. Hemoglobin concentration on Day 1 after randomization was 1.4 g/dL higher in the liberal group. Treatment groups did not differ significantly at any time point or over time on MDAS delirium severity ($P = .28$) or CAM delirium presence ($P = .83$).

CONCLUSION: Blood transfusion to maintain hemoglobin concentrations greater than 10 g/dL alone is unlikely to influence delirium severity or rate in individuals with hip fracture after surgery with a hemoglobin concentration less than 10 g/dL. **J Am Geriatr Soc 61:1286–1295, 2013.**

Key words: delirium; hip fracture; blood transfusion

Delirium is a serious illness of disrupted brain physiology that results in symptoms of acute confusion, poor attention, and lack of consciousness.[1,2] Delirium is identified in 10% to 62% of all hospitalizations[1,3–5] and is more prevalent in elderly adults.[1,6] It is especially common in individuals with hip fracture (35–62%),[5–10] in whom it is associated with longer hospital length of stay, greater risk of death, more nursing home placements, and poorer functional and cognitive recovery.[1,6,7,9,11–13]

Individuals with hip fracture frequently have anemia (~75% with postoperative hemoglobin concentrations <10 g/dL[14–16]) and commonly receive blood transfusions.[17] Observational studies have shown an association between postoperative hemoglobin concentrations of less than 10 g/dL and subsequent incidence of delirium.[18] Transfusion was one component of two multifactorial geriatric con-

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sultation interventions shown to reduce delirium; blood was administered to maintain hematocrit at 30% or greater (equivalent to hemoglobin of 10 g/dL),[19,20] but it is unknown whether transfusions contributed to the improved outcome.

The Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) was a randomized clinical trial of 2,016 individuals with hip fracture designed to test whether a higher blood transfusion threshold improved functional recovery and reduced morbidity and mortality.[21] Participants were randomly allocated to receive blood transfusion to keep their hemoglobin concentration at greater than 10 g/dL (liberal strategy) or to receive transfusion only if hemoglobin concentration was less than 8 g/dL or when symptoms of anemia developed (restrictive strategy). Results are reported from the FOCUS Cognitive Ancillary Study, which assessed the presence and severity of delirium during hospitalization in 139 FOCUS participants. It was hypothesized that the liberal transfusion strategy would prevent new or worsening delirium symptoms.

METHODS

FOCUS

Individuals were eligible for FOCUS if they were aged 50 and older, were undergoing surgical repair of hip fracture, had a hemoglobin concentration of less than 10 g/dL within 3 days after surgery, and had clinical evidence of cardiovascular disease or cardiovascular disease risk factors.[17,21] Individuals were excluded if they had been unable to walk without human assistance before hip fracture, declined blood transfusions, had multiple traumas, had pathological hip fracture, had clinically recognized acute myocardial infarction within 30 days before randomization, had previously participated in the trial, had symptoms associated with anemia (e.g., ischemic chest pain), or were actively bleeding at the time of potential randomization.[14,20]

Subjects were randomized using an automated central telephone randomization system to the liberal transfusion arm or restrictive arm. The liberal group received one unit of packed red blood cells and as much blood as needed to maintain a hemoglobin concentration of greater than 10 g/dL. The restrictive group received a transfusion if they developed symptoms of anemia or if, at the study physician's discretion, their hemoglobin concentration was below 8 g/dL. Symptoms of anemia that were indications for transfusion were chest pain thought to be cardiac in origin, congestive heart failure, and unexplained tachycardia or hypotension unresponsive to fluid replacement. Blood was administered one unit at a time, and symptoms were reassessed after each unit. Subjects with dementia were transfused when their hemoglobin concentrations fell below 8 g/dL because they might not be able to report their symptoms. Delirium or altered mental status was not considered an indication for transfusion.

Delirium was initially considered as an outcome for the larger study, but it was recognized that recorded delirium in the medical records alone would miss many cases of unrecognized delirium. The resources required to study this outcome adequately, including daily interviews, were not available to the main study. Thus, the Cognitive Ancillary Study was proposed (and subsequently funded).

The institutional review boards or ethics committees at participating institutions approved the FOCUS and Cognitive Ancillary Study protocols. There was an independent data and safety monitoring board. Informed consent was obtained from study participants or proxies. FOCUS methods and results have been previously reported.[17,19,21,22]

FOCUS Cognitive Ancillary Study

The enrollment period for this ancillary study was April 2008 to February 2009. Subjects were recruited from 13 clinical sites (see Appendix 1). One additional exclusion criterion for this study was non-English speaking because of the lack of equivalent non-English versions of many cognitive measures. All eligible FOCUS subjects at each participating site were approached for the ancillary study during this time frame.

Delirium Assessments

Delirium assessments were performed before randomization (at the time of consent, some before surgery) and multiple times within 5 days after randomization or up to hospital discharge (if hospital stay was shorter). All postsurgical assessments were performed at least 12 hours after surgery to avoid the effects of anesthesia. Research staff members conducting the delirium assessments were not blinded to treatment status except at one site.

Delirium presence and severity were determined using a battery of assessments from prior delirium studies,[23,24] including the Mini-Mental State Examination,[25] Digit Span,[26] and Delirium Symptom Interview,[27] which were then used to score the following.

Memorial Delirium Assessment Scale. The Memorial Delirium Assessment Scale (MDAS)[28] was the primary outcome. This 10-item scale rates the severity of delirium.[23,29] Each item is rated from 0 (not present) to 3 (severe) to generate a scale from 0 to 30 (30 is most severe). MDAS scores of 0 to 4 are indicative of no delirium, 5 to 9 mild delirium, 10 to 14 moderate delirium, and 15 or greater severe delirium.[23,29]

Confusion Assessment Method Diagnostic Algorithm. Confusion Assessment Method (CAM) Diagnostic Algorithm was the secondary outcome. This short, four-item algorithm operationalizes *Diagnostic and Statistical Manual of Mental Disorders* criteria of delirium,[30] including presence of acute onset or fluctuating course and inattention along with disorganized thinking or altered level of consciousness.

This combination of measures, administered by trained research assistants, has been found to have high bb inter-rater agreement (kappa > 0.87 for all components of the assessment; kappa = 0.94 for MDAS, kappa = 0.95 for CAM) and validity.[24] All delirium assessors underwent in-person and Web-based training, and their competence was tested.

Other Measures

In addition to the information on clinical characteristics and transfusion variables collected in the main study,[22] the

number of years of formal education, marital status, and history of dementia as documented in the medical record on admission were recorded. Prefracture cognition was determined by asking proxies using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[31,32] Information for this 16-item measure was collected in-person or over the telephone, and it correlates well with direct cognitive assessments to evaluate the presence of dementia.[33] The family member or significant other most knowledgeable about the subject rated the items, reporting change over the 10 years before hip fracture. Using a cutoff point of 3.44, the IQCODE questionnaire has sensitivity of 100% and specificity of 86% for diagnosing dementia in a hospitalized sample.[34] Proxies also reported whether the subject had a previous diagnosis of dementia.

Use of psychoactive medications was abstracted from the medical chart using American Hospital Formulary Service[35] coding for class 28, including subgroups of antipsychotics (28:16.08), antidepressants (28:16.04), opiates (28:08.08), other analgesics (28:08.04, 28:08.92), and sedative-hypnotics (28:24). Medications were coded as use of any medication within the class during the prerandomization time frame (excluding the day of randomization).

Statistical Analyses

Analyses examined differences in the severity of delirium (MDAS) over time according to treatment group. There was one prerandomization measure and up to three postrandomization assessments. Generalized Estimating Equations (GEE)[36] were used to evaluate the longitudinal patterns, comparing the two groups of individuals with hip fracture using all measurement time points. There were two to four measurement points available for the MDAS measure (before randomization and in-hospital measures up to three times after randomization (Day 1 to Day 5 after randomization)). The Stata 9 procedure XTGEE was used, which allows for robust standard error estimates and explicit modeling of covariance matrices and is tolerant of missing data.[36] An independent covariance structure was specified to avoid problems resulting from nonrandom patterns of missing data. Robust standard error estimates were obtained using a technique described previously.[37]

The independent variables included a main effect term for the transfusion intervention. Binary indicator (dummy) variables were used to indicate the time points, with prerandomization serving as the reference to allow for nonlinear trajectories over time. Interactions between these dummy variables and the intervention term were included as fixed effects in the longitudinal model. This model was used to estimate the mean and standard error of the outcome measure at each time point for each of the two treatment groups. A global *P*-value for the differences in longitudinal trajectories between the two groups was obtained from a test of the null hypothesis that all the treatment by time interaction coefficients in the model were simultaneously 0. Time-specific between-group contrasts were tested at the 5% level using Wald statistics derived from the linear combination of model coefficients used to estimate the difference in means and its standard error.

The FOCUS Cognitive Ancillary Study was powered at 90% to detect a 2.6-point difference between groups on the MDAS with 100 participants per group, assuming two time points (1 before, 1 after), a correlation coefficient (r) of 0.5 over time, and $\alpha = 0.01$. Previous work[23] has found a clinically meaningful difference of 2.5 points on the MDAS and a medium effect size[38] difference (0.5 standard deviation (SD)) of 2.7 (previous data showing a SD of 5.5). With a sample size of 139 and over-time correlation ($r = 0.62$), the study had 80% power to detect a difference of 0.46 SD (2.5 MDAS points) and 90% power to detect a difference of 0.53 SD (2.9 MDAS points).

RESULTS

Informed consent was obtained from 176 (79%) of the 222 FOCUS subjects approached, and 139 were randomized (Figure 1). Failure to randomize was because of hemoglobin concentration not falling below 10 g/dL ($n = 35$) or the subject withdrawing consent ($n = 2$). Eleven of the 13 participating sites enrolled subjects; the remaining two sites consented one subject each, but neither was randomized. There was one subject in the liberal group not included in the analyses because delirium assessment was not performed in the hospital.

The groups did not differ in presence of prerandomization assessment (88% in each group, missing due to unavailability of staff) or number of postrandomization assessments (liberal group mean 2.4 ± 1.4, restrictive group mean 2.5 ± 1.2). Most prerandomization assessments were done before surgery (62%) than after, with an average 1.4 days between surgery and randomization, and did not differ according to group.

The characteristics of the two treatment arms were similar (Table 1), except that the liberal group had more women (81%) than the restrictive group (65%) ($P = .03$). Prerandomization use of two classes of psychoactive medications was greater in the liberal group than in the restrictive group (sedative hypnotics, 38% vs 24%, $P = .07$; antidepressants, 33% vs 19%, $P = .06$). Dementia was present in more than 25% of the sample based on medical record review, with dementia detected from the proxy informant interview in an additional 14% to 15% in each group. The groups did not differ in hemoglobin concentrations before surgery (mean 11.9 ± 1.5) or randomization (mean 8.9 ± 0.9). Hemoglobin concentration on postrandomization day 1 was on average 1.4 g/dL higher ($P < .001$) in the liberal group (mean 10.2 ± 1.1) than in the restrictive group (mean 8.8 ± 0.9). The median number of units transfused was two in the liberal group and zero in the restrictive group; 54.2% of restrictive participants did not receive any transfusion after randomization.

Although the two groups did not differ in timing of randomization after surgery, there was a significant association between days from surgery and MDAS delirium severity scores over time ($P = .04$). The MDAS averaged less than 5 points before surgery and peaked at 8 to 10 points on the day after surgery.

For the primary outcome (MDAS score), there were no statistically significant differences between the two treatment arms over time or at any time point in the unadjusted means (Table 2) or the results from the GEE models

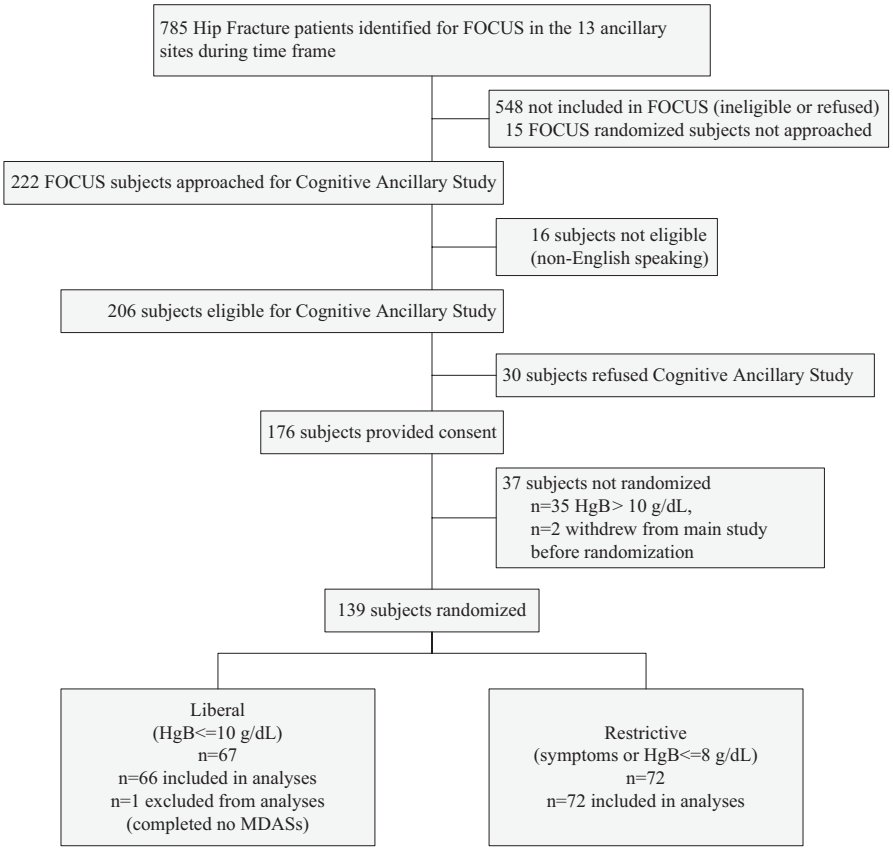

Figure 1. Flow of participants through the trial. FOCUS = Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair; MDAS = Memorial Delirium Assessment Scale (primary outcome); HgB = hemoglobin.

(Figure 2). Before randomization, the restrictive transfusion group had a similar MDAS delirium severity score to that of the liberal group (difference −0.66, 95% confidence interval (CI) = −2.50 to 1.18). On postrandomization day 1, there was virtually no difference between the two groups (difference −0.05, 95% CI = −1.67 to 1.58). Thereafter, differences remained small (postrandomization day 2 difference 0.98, 95% CI = −1.11 to 3.07; postrandomization day 3 difference 0.88, 95% CI = −1.24 to 2.99; postrandomization day 4/5 difference 1.20, 95% CI = −0.93 to 3.32). All of the observed MDAS differences were smaller than the 2.5 points shown to be clinically meaningful, although the CIs for postrandomization days 2 to 5 include 2.5 in the upper boundary.

There were also no significant differences for the presence of delirium as defined using CAM (secondary outcome) between the groups at any point or in the trend over time. The largest difference in magnitude was seen on postrandomization day 1 (unadjusted percentage: restrictive, 40%; liberal, 31%; relative risk = 1.26, 95% CI = 0.76–2.08 in GEE models, Figure 3).

Sensitivity Analyses

Baseline differences in sex, use of sedative hypnotics and antidepressants, and the effect of days since surgery on delirium over time were adjusted for. The estimated effects and statistical significance did not change substantially when any or all of these variables were included in the models. For example, the *P*-value for the postrandomization between-treatment differences in MDAS delirium severity scores reported in Figure 2 was .23; in the sensitivity analyses, these *P*-values ranged from .26 to .31.

Because dementia is a known risk factor for delirium, and there was an absolute difference of 9% in dementia prevalence between the groups, models adjusting for dementia were also tested. These did not affect the overall results, although they decreased the magnitude of the difference in CAM delirium on the first randomization day (relative risk = 1.13, 95% CI = 0.64–1.86).

DISCUSSION

Blood transfusions to maintain hemoglobin concentration greater than 10 g/dL did not cause a significant difference in the severity or frequency of in-hospital delirium from that of a blood transfusion threshold of 8 g/dL. There was a clinically significant difference in amount of blood transfused between the treatment arms. These results suggest that liberal transfusion alone does not reduce the risk of postoperative delirium in individuals with hip fracture with hemoglobin concentrations less than 10 g/dL. This finding supports the overall conclusions of the main FOCUS trial, which found that the liberal transfusion strategy did not improve functional recovery or reduce mortality or in-hospital morbidity in elderly adults with cardiovascular disease or risk factors over the effects of the restrictive strategy.[21]

Table 1. Sample Characteristic According to Treatment Group

Baseline Characteristic	Liberal, n = 66	Restrictive, n = 72
Age, mean ± SD	82.4 ± 7.4	80.6 ± 10.4
Sex, n (%)		
Female	54 (81.8)	47 (65.3)
Male	12 (18.2)	25 (34.7)
Race, n (%)		
White	59 (89.4)	66 (91.7)
Black	7 (10.6)	5 (6.9)
Unspecified	0 (0.0)	1 (1.4)
Education, years, mean ± SD	12.3 ± 3.4	12.4 ± 3.1
Marital status, n (%)		
Married	23 (36.5)	25 (34.7)
Widowed	30 (47.6)	30 (41.7)
Divorced or separated	3 (4.8)	8 (11.1)
Never married	7 (11.1)	8 (11.1)
Unspecified	0 (0.0)	1 (1.4)
Preadmission residence, n (%)		
Home	59 (89.4)	56 (77.8)
Retirement home	4 (6.1)	8 (11.1)
Nursing home	3 (4.6)	7 (9.7)
Unspecified	0 (0.0)	1 (1.4)
History of dementia, n (%)		
Any	18 (27.3)	26 (36.1)
From chart	8 (12.1)	16 (22.2)
From significant other but not chart	1 (1.5)	4 (5.6)
According to Informant Questionnaire on Cognitive Decline in the Elderly (>3.44) but not chart or significant other	9 (13.6)	6 (8.3)
Comorbidities (history from chart), n (%)		
Stroke or transient ischemic attack	5 (7.6)	12 (16.7)
Chronic lung disease	16 (24.4)	13 (18.1)
Cancer	10 (15.2)	12 (16.7)
Diabetes mellitus	14 (21.2)	14 (19.4)
Atrial fibrillation	21 (31.8)	23 (31.9)
Parkinson's disease	2 (3.0)	2 (2.8)
Hearing problems or deaf	10 (15.2)	15 (20.8)
Visual problems or blind	7 (10.6)	9 (12.5)
Alcohol abuse or withdrawal	2 (3.0)	5 (6.9)
Malnourished or cachectic at admission, n (%)	2 (3.0)	3 (4.2)
Laboratory tests		
White blood count ($\times 10^3$), mean ± SD	10.8 ± 4.6	10.1 ± 3.7
Sodium, mEQ/L, mean ± SD	137.1 ± 4.1	137.0 ± 4.3
BUN, mg/dL, mean ± SD	22.1 ± 13.8	23.3 ± 13.7
Glucose, mg/dL, mean ± SD	124.7 ± 48.5	127.9 ± 36.3
Albumin, g/dL, mean ± SD	3.7 ± 0.5	3.7 ± 0.5
Creatinine, mg/dL, mean ± SD	1.1 ± 0.5	1.1 ± 0.8
BUN/creatinine ratio ≥18	40 (61.5)	43 (59.7)
Type of hip fracture, n (%)		
Femoral neck	33 (50.0)	30 (41.7)
Intertrochanteric or subtrochanteric	33 (50.0)	42 (58.3)
Anesthesia type, n (%)		
General or combined general, regional, spinal	38 (57.6)	42 (58.3)
Regional or spinal only	28 (42.4)	30 (41.7)
American Society of Anesthesiologists Physical Status score, mean ± SD	2.8 ± 0.5	3.0 ± 0.5
Length of surgery, minutes, mean ± SD	131.3 ± 55.2	140.0 ± 44.7
Hospital length of stay, days, mean ± SD	6.6 ± 3.9	6.7 ± 3.6
Prerandomization assessment time, n (%)[a]		
Before surgery	35 (61.4)	38 (60.3)
After surgery	22 (38.6)	25 (39.7)
Days between surgery and randomization, mean ± SD	1.4 ± 0.7	1.4 ± 0.8
Hemoglobin value, g/dL, mean ± SD		
Before surgery	11.9 ± 1.3	11.9 ± 1.7
Before randomization	8.9 ± 0.8	8.9 ± 0.7
1 day after randomization	10.2 ± 1.1	8.8 ± 0.9
2 days after randomization[ab]	10.4 ± 0.9	8.7 ± 0.9
3 days after randomization[c]	10.8 ± 0.8	8.7 ± 0.9
4 days after randomization[d]	10.8 ± 1.0	9.3 ± 0.8
5 days after randomization[e]	10.9 ± 1.1	9.3 ± 1.0
Number of units of blood transfused after randomization, n (%)		
0	3 (4.5)	39 (54.2)
1	27 (40.9)	22 (30.6)
2	24 (36.4)	9 (1.4)
3	8 (12.1)	0 (0.0)
≥4	4 (6.1)	2 (2.8)
Total units of blood transfused after randomization, n[f]	115	53
Pretransfusion hemoglobin, g/dL (if transfused after randomization), mean ± SD[g]	8.9 ± 0.8	7.7 ± 0.4
Medications given after randomization, n (%)		
Any psychoactive	57 (86.4)	63 (87.5)
Antipsychotic	6 (9.1)	6 (8.3)
Antidepressant	22 (33.3)	14 (19.4)
Opiate	52 (78.8)	54 (75.0)
Other analgesic	45 (68.2)	44 (61.1)
Sedative-hypnotic	25 (37.9)	17 (23.6)
Postrandomization complications, n (%)		
Infection	3 (4.6)	3 (4.2)
Pulmonary embolism	2 (3.0)	0 (0.0)
Congestive heart failure	1 (1.5)	2 (2.8)
Hemorrhage (>100 mL)	6 (9.1)	4 (5.6)

SD = standard deviation; BUN = blood urea nitrogen.

[a] Only if Memorial Delirium Assessment Scale administered; numbers will not sum to all subjects in group.

[b] Total n includes only those still in hospital 2 days after randomization (L, n = 48; R, n = 58).

[c] Total n includes only those still in hospital 3 days after randomization (L, n = 34; R, n = 45).

[d] Total n includes only those still in hospital 4 days after randomization (L, n = 21; R, n = 28).

[e] Total n includes only those still in hospital 5 days after randomization (L, n = 12; R, n = 15).

[f] Raw number of units across all subjects within group.

[g] Values per transfusion and only if transfused (L, n = 63; R, n = 33 transfusions).

(Continued)

Table 2. Functional Outcomes in Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair Cognitive Ancillary Study Outcomes According to Measurement Time Point

Measures	Before Randomization		Postrandomization Day 1		Postrandomization Day 2		Postrandomization Day 3		Postrandomization Day 4		Postrandomization Day 5	
	Liberal, n = 57	Restrictive, n = 63	Liberal, n = 53	Restrictive, n = 55	Liberal, n = 36	Restrictive, n = 46	Liberal, n = 23	Restrictive, n = 31	Liberal, n = 9	Restrictive, n = 9	Liberal, n = 5	Restrictive, n = 3
Primary outcome: Memorial Delirium Assessment Scale score, mean±standard deviation	6.7 ± 5.3	6.4 ± 5.2	6.8 ± 4.4	6.9 ± 4.6	6.9 ± 5.5	7.4 ± 4.9	5.7 ± 4.8	6.0 ± 5.0	3.0 ± 1.9	5.0 ± 4.3	5.2 ± 4.3	2.7 ± 1.5
Time-specific *P*-value from *t*-test		.72		.93		.69		.87		.23		.28
Secondary outcome: delirium (Confusion Assessment Method), n (%)	14 (24.6)	15 (23.8)	16 (30.2)	22 (40.0)	12 (33.3)	12 (26.7)	6 (26.1)	5 (16.1)	1 (11.1)	2 (22.2)	1 (20.0)	0 (0.0)
Time-specific *P*-value from chi-square test		.92		.29		.51				.53		.41

Consistent with other studies, a peak in delirium severity was observed 1 day after surgery.[39] The naturally occurring peak of delirium severity on postoperative day 1 and subsequent decline highlights the importance of including an appropriate control group in all delirium intervention trials. Because of concern about residual effects of anesthesia (one potential explanation for a peak in delirium after surgery), delirium assessments were not begun until at least 12 hours after surgery, although this amount of time may not have been sufficient to allow for the effects of anesthesia to clear completely. Time from surgery to randomization or assessment did not differ between the two groups, and thus it is unlikely that it influenced the overall results.

Interventions to prevent delirium may differ from those to treat delirium.[40] Other studies have shown that geriatric consultation reduces the incidence and severity (prevention) but not duration of delirium (treatment).[19,20] A trial of low-dose haloperidol (given as prophylaxis) in individuals with hip fracture and elective hip replacement found shorter delirium duration and lower severity but not lower incidence of delirium.[41] In contrast, a study evaluating olanzapine (given as prophylaxis perioperatively) in individuals undergoing elective total hip and knee replacement showed lower incidence of delirium but greater severity in the individuals who became delirious.[42] The current study did not find an effect of transfusion in preventing delirium or reducing delirium symptoms.

It is also possible that a single intervention strategy such as transfusion may be ineffective for a multifactorial geriatric syndrome such as delirium. Previous work showed that a multifaceted delirium intervention, which included transfusion for hemoglobin concentrations less than 10 g/dL, prevented delirium incidence,[19] and a geriatrics intervention in Sweden that also included transfusion found improvement in symptoms in individuals with delirium.[20] The Swedish study[20] had a different threshold for those who were already delirious (11 g/dL) than to prevent delirium (10 g/dL) as part of the multifactorial intervention. The current study's threshold did not differentiate between prevalent and incident delirium and was lower than their higher threshold. It is possible that a higher threshold would have been beneficial or it may be that that transfusion does not make any difference in the multicomponent interventions. The Hospital Elder Life Program[43] did not include transfusions but is another multicomponent intervention that has been shown to prevent delirium in general medical and surgical patients.[43,44]

The frequency of delirium was lower (not significantly) 1 day after randomization in the liberal group but higher on Days 2 and 3 than in the restrictive transfusion group. These observed differences were smaller (largest 30% liberal vs 40% restrictive) than seen in many other successful interventions, including geriatrics consultation (32% in intervention vs 50% usual care),[19] anesthesia sedation reduction (19% light vs 40% deep sedation),[45] and melatonin treatment (12% melatonin vs 31% placebo).[46]

There were more subjects with dementia, a known risk factor for delirium,[3–5] (9% point difference, not statistically significant) in the restrictive group such that the slightly higher delirium rates in this group were not

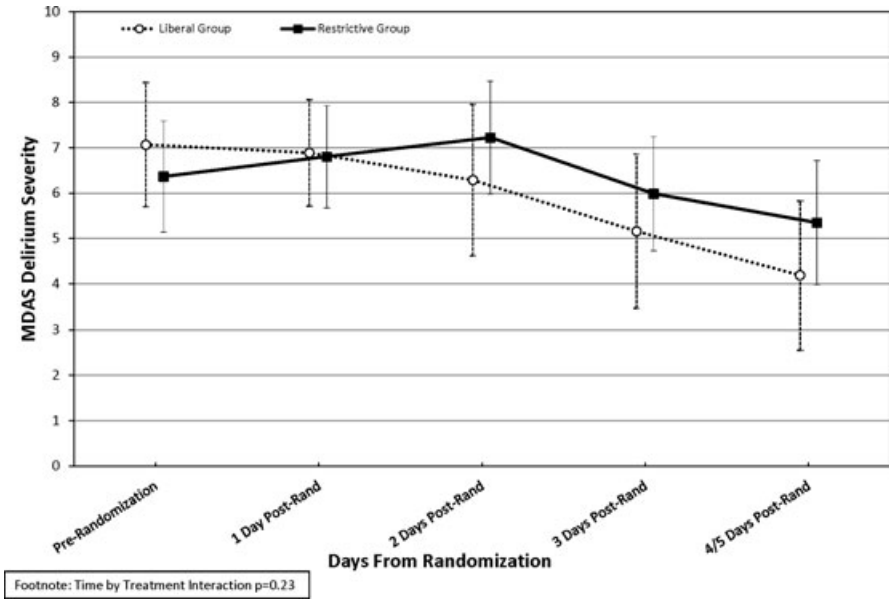

Figure 2. Primary outcome: Memorial Delirium Assessment Scale (MDAS) delirium severity score (estimated mean and 95% confidence interval from generalized estimating equation) according to day relative to randomization according to treatment group. Time by treatment interaction $P = .23$.

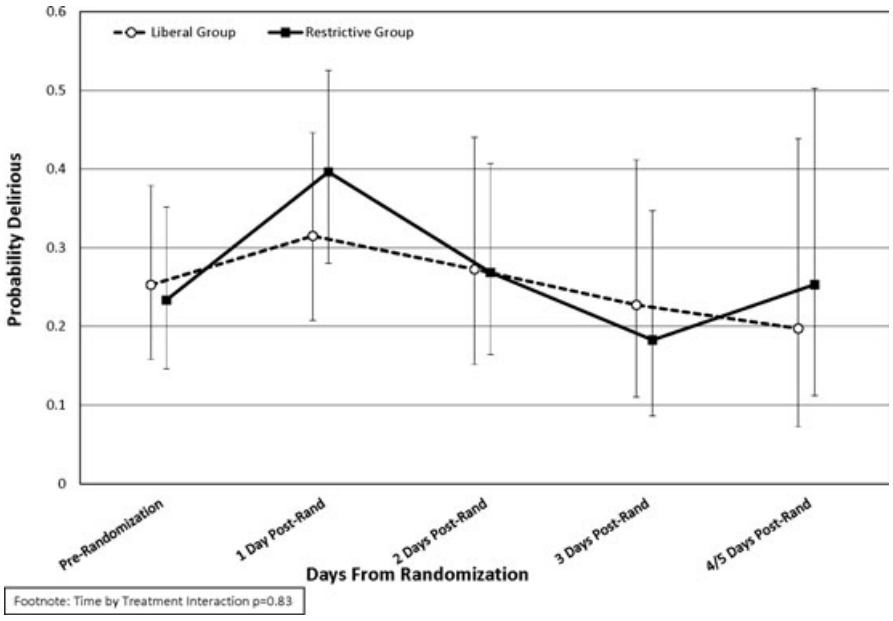

Figure 3. Secondary outcome: Confusion Assessment Method delirium (estimated probability and 95% confidence interval from Generalized Estimating Equation) according to day relative to randomization according to treatment group. Time by treatment interaction $P = .83$.

surprising. Models adjusting for dementia attenuated the small, nonsignificant effect of transfusion seen on postrandomization day 1.

There were some potential limitations to this study. Even though it was not possible to achieve the target sample size, there was still good power (>80%) for detecting moderate-sized differences in the primary outcome.[38] The MDAS severity measure was chosen as the primary outcome for this trial because it predicts the long-term outcomes of delirium,[3,21] and a large proportion of individuals with hip fracture have symptoms of delirium (including subsyndromal delirium) in the absence of full diagnostic criteria.[3,23] Two and a half points on the MDAS had been prespecified as a clinically meaningful difference,[23] and this difference was not observed between treatment groups at any time, although CIs on some days included this value. Three full days of postrandomization assessments were not available for many of the subjects,

which could also limit the power for many of these comparisons, although 61.6% had at least two postrandomization assessments. There was an imbalance between the two arms of age, sedative-hypnotic, and antidepressant use, although the sensitivity analyses did not find that it substantially altered the findings.

Another limitation of the study was that the delirium evaluators were not blind to treatment (although the investigators were). To overcome this, objective delirium assessment measures were used, and more importantly, the interviewers did not calculate any summary scores or the final CAM determinations. Only one site was blinded (n = 24 subjects), so it was not possible to test the effect of blinding on the results. It would have been ideal if assessments could have been blinded, but this was not feasible because of inadequate staffing. The evaluators also could not be fully blinded because they might have been present when blood was being given.

This study had a number of strengths. It was conducted in the context of a rigorous, multisite, randomized trial. This ancillary trial showed substantial differences in postrandomization hemoglobin concentrations and the quantity of blood administered in the two arms.[21] Presurgery (baseline) hemoglobin levels (11.9 g/dL in both groups) suggest that most participants had primarily acute blood loss and not severe chronic anemia. The results are consistent with the larger FOCUS trial that liberal transfusion did not improve function, mortality, or morbidity;[21] with previous literature;[47] and with recently published transfusion guidelines.[48] In addition, the FOCUS Cognitive Ancillary Study used rigorous, state-of-the-art delirium measures (MDAS and CAM), including extensive training and oversight of all delirium assessments. Finally, only one subject was excluded from analyses because there were no in-hospital assessments.

In conclusion, transfusion of individuals with hip fracture after surgery to maintain hemoglobin above 10 g/dL does not appear to prevent or reduce the severity of delirium. These results suggest that it is reasonable to withhold blood transfusion after surgery unless the individual develops symptoms of anemia or hemoglobin concentration falls below 8 g/dL.

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Author Contributions: Gruber-Baldini, Marcantonio, Orwig, Magaziner, Terrin, Barr, Hebel, Carson: study concept and design. Gruber-Baldini, Marcantonio, Orwig, Magaziner, Terrin, Barr, Brown, Paris, Zagorin, Roffey, Zakriya, Blute, Carson: acquisition of subjects and data. Gruber-Baldini, Marcantonio, Orwig, Magaziner, Terrin, Barr, Brown, Paris, Zagorin, Roffey, Zakriya, Blute, Hebel, Carson: analysis and interpretation of data. Gruber-Baldini, Marcantonio, Magaziner, Brown, Paris, Zagorin, Roffey, Zakriya, Blute, Hebel, Carson: preparation of manuscript.

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APPENDIX

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