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

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Abstract

Objectives—To determine if a higher blood transfusion threshold would prevent new or worsening delirium symptoms in the hospital after hip fracture surgery.

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Design—Ancillary study to a randomized clinical trial.

Setting—Thirteen hospitals in United States and Canada.

Participants—One-hundred-thirty-nine hospitalized hip fracture patients, age ≥50, with cardiovascular disease or risk factors, and hemoglobin<10 g/dL within 3 days of surgery, recruited in an ancillary study of "Transfusion Trigger Trial for **F**unctional **O**utcomes in **C**ardiovascular Patients **U**ndergoing **S**urgical Hip Fracture Repair (FOCUS) trial."

Intervention—Treatment groups: 1) Liberal: received one unit of packed red blood cells and as much blood as needed to maintain hemoglobin >10 g/dL; 2) Restrictive: received transfusions if developed symptoms of anemia or hemoglobin fell below 8 g/dL.

Measurements—Delirium assessments performed pre-randomization and up to three times post-randomization. Primary outcome: Severity of delirium using Memorial Delirium Assessment Scale (MDAS) scale. Secondary outcome: presence or absence of delirium defined by Confusion Assessment Method Diagnostic Algorithm (CAM).

Results—Mean age was 81.5 (SD=9.1). Liberal group received a median 2 units and Restrictive group 0 units of blood. Hemoglobin concentration on day 1 post randomization was 1.4 g/dL higher in the Liberal group. Treatment groups did not significantly differ at any time point or over time on either MDAS delirium severity (p=0.28) or CAM delirium presence (p=0.83).

Conclusion—Blood transfusion to maintain hemoglobin >10 g/dL alone is unlikely to influence delirium severity or rate in postoperative hip fracture patients with hemoglobin concentration <10 g/dL.

Trial Registration—ClinicalTrials.gov identifier: NCT00071032 http://clinicaltrials.gov/ct2/show/NCT00071032

Keywords

Delirium; Hip Fracture; Blood Transfusion

INTRODUCTION

Delirium is a serious illness of disrupted brain physiology that results in symptoms of acute confusion, reduced attention, and/or reduced consciousness.[1, 2] Delirium is identified in 10–62% of all hospitalizations[1, 3–5] and is more prevalent in elderly patients.[1, 6] It is especially common in hip fracture patients (35–62%),[5–10] in whom delirium 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]

Hip fracture patients are frequently anemic (about 75% have postoperative hemoglobin <10 g/dL[14–16]) and commonly receive blood transfusion.[17] Observational studies have shown an association between postoperative hemoglobin<10g/dL and subsequent incidence of delirium.[18] Transfusion was one component of two multi-factorial geriatric consultation interventions shown to reduce delirium; blood was administered to maintain hematocrit at 30% or greater (equivalent to hemoglobin of 10 g/dL). [19, 20] However, it is unknown if transfusion 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 hip fracture patients designed to test whether a higher blood transfusion threshold improved functional recovery, morbidity and mortality.[21] Patients were randomly allocated to receive blood transfusion to keep the hemoglobin concentration >10 g/dL (Liberal strategy) versus

transfusion only if hemoglobin concentration was <8 g/dL or when symptoms of anemia developed (Restrictive strategy). We report results from the FOCUS Cognitive Ancillary Study that assessed the presence and severity of delirium during hospitalization in 139 FOCUS participants. We hypothesized that the Liberal transfusion strategy would prevent new or worsening delirium symptoms.

METHODS

FOCUS

Patients were eligible for FOCUS if they were 50 years of age or older, undergoing surgical repair of hip fracture, had a hemoglobin <10 g/dL within three days after surgery, and had clinical evidence for cardiovascular disease or cardiovascular disease risk factors. [17, 21] Patients were excluded if they were unable to walk without human assistance prior to hip fracture; declined blood transfusions; suffered multiple trauma; had pathologic hip fracture, clinically recognized acute myocardial infarction within 30 days prior to randomization, 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 hemoglobin >10 g/dL. The Restrictive group received transfusion if they developed symptoms of anemia or if, at study physician's discretion, hemoglobin was below 8 g/dL. Symptoms of anemia that were indications for transfusion were: 1) chest pain thought to be cardiac in origin; 2) congestive heart failure; 3) unexplained tachycardia or hypotension unresponsive to fluid replacement. Blood was administered one unit at a time and the presence of symptoms was 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).

Both the FOCUS and Cognitive Ancillary Study protocols were approved by the Institutional Review Boards or Ethics Committees at participating institutions. There was an independent Data and Safety Monitoring Board. Informed consent was obtained from study participants or proxies. FOCUS methods and results were 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. One additional exclusion criterion for this study was non-English speaking due to 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 were performed pre-randomization (at the time of consent, some done pre-surgery) and multiple times within five days following randomization or up to hospital discharge (if hospital stay was shorter). All post-surgical assessments were done at least 12 hours after surgery in order 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:

1. 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 0–30 scale (30 is most severe). MDAS scores of 0–4 are indicative of no delirium, 5–9 mild delirium, 10–14 moderate delirium, and ≥15 severe delirium severity.[23, 29]

2. Confusion Assessment Method Diagnostic Algorithm (CAM) was the secondary outcome. This short 4-item algorithm operationalizes Diagnostic and Statistical Manual of Mental Disorder criteria of delirium[30] including presence of acute onset/fluctuating course and inattention, with either disorganized thinking or altered level of consciousness.

This combination of measures, administered by trained research assistants, has been found to have high 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 both in-person and web-based training, and their competence was tested.

In addition to the clinical characteristics and transfusion variables collected in the main study[22], we recorded the number of years of formal education, marital status, and history of dementia as documented in the medical record on admission. We determined pre-fracture cognition from proxies using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).[31, 32] This 16-item measure was collected in-person or by telephone, and 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 prior to hip fracture. Using a cut-off point of >3.44, the IQCODE questionnaire has a 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 (AHFS)[35] coding for class 28:XXX.XX, including subgroups of antipsychotics (28:16.08), antidepressants (28:16.04), opiates (28:08.08), other analgesics (28:08.04 and 28:08.92), and sedative-hypnotics (28:24). Medications were coded as use of any medication within the class during the pre-randomization time frame (excluding the day of randomization).

Statistical Analyses

Analyses examined differences in the severity of delirium (MDAS) over time by treatment groups. There was 1 pre-randomization measure and up to 3 post-randomization assessments. Generalized Estimating Equations (GEE)[36] were used to evaluate the longitudinal patterns comparing the two groups of hip fracture patients using all measurement time points. There were 2–4 measurement points available for the MDAS measure [pre-randomization and inhospital measures up to 3 times post-randomization (day 1 to day 5 post-randomization)]. The Stata 9 procedure XTGEE was used, which allows for robust standard error estimates, explicit modeling of covariance matrices, and is relatively tolerant of missing data.[36] An independent covariance structure was specified in order to avoid problems resulting from non-random patterns of missing data. Robust standard error estimates were obtained using a technique described by Huber.[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 pre-randomization serving as the reference to allow for non-linear 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 zero. 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 n=100 per group, assuming 2 time points (1 pre, 1 post), a correlation of r=0.5 over time, and α=0.01. Previous work[38] has found a clinically meaningful difference of 2.5 points on the MDAS and a medium effect size[39] difference (0.5 SD) of 2.7 (previous data showing SD=5.5). With a sample size n=139 and over-time correlation (r=0.62), we 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 S.D. (2.9 MDAS points).

RESULTS

Of the 222 FOCUS subjects approached, informed consent was obtained from 176 (79%) subjects and 139 were randomized (Figure 1). Failure to randomize was due to 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 pre-randomization assessment (88% in each group, missing due to unavailability of staff) or number of post-randomization assessments [Liberal group mean=2.4 (SD=1.4), Restrictive group mean=2.5 (SD=1.2)]. Most pre-randomization assessments were done before surgery (62%) with an average 1.4 days between surgery and randomization and did not differ by group.

The two treatment arms' characteristics were similar (Table 1), except that the Liberal group had more females (81%) compared to Restrictive (65%; p=0.03). Pre-randomization use of two classes of psychoactive medications was greater in the Liberal group vs. the Restrictive group: sedative hypnotics: 38% vs. 24%, p=.07, and antidepressants: 33% vs. 19%, p=.06. Dementia was present in over 25% of the sample based on medical record review, with an additional 14–15% in each group having dementia detected from the proxy informant interview. The groups did not differ on hemoglobin levels pre-surgery (mean=11.9, SD=1.5) nor pre-randomization (mean=8.9, SD=0.9). The hemoglobin concentration on post-randomization day 1 was on average 1.4 g/dL higher (p<0.001) in the Liberal group (mean=10.2, SD=1.1) compared to the Restrictive group (mean=8.8, SD=0.9). The median number of units transfused was 2 in the Liberal group and 0 in the Restrictive group; 54.2% of Restrictive patients did not receive any transfusion after randomization.

Although the two groups did not differ on timing of randomization after surgery, there was a significant association of days from surgery with MDAS delirium severity scores over time (p=0.04). The MDAS averaged below 5 points before surgery and peaked at 8–10 points on the day after surgery.

For the primary outcome (MDAS score), neither the unadjusted means (Table 2), nor the results from the GEE models (Figure 2) showed statistically significant differences between the two treatment arms over time or at any time point. Before randomization, the Restrictive transfusion group had a similar MDAS delirium severity score to the Liberal group (difference=−0.66, 95% Confidence Interval: −2.50 to 1.18). On post-randomization day 1, there was virtually no difference between the two groups (difference=−0.05, 95% Confidence Interval: −1.67 to 1.58). Thereafter, differences remained small (post-randomization day 2 difference=0.98, 95% Confidence Interval: −1.11 to 3.07; post-randomization day 3 difference=0.88, 95% Confidence Interval: −1.24 to 2.99; post-randomization day 4/5 difference =1.20, 95% Confidence Interval: −0.93 to 3.32). Notably, all of the observed MDAS differences were smaller than the 2.5 points shown to be clinically meaningful, but the confidence intervals for post-randomization days 2–5 do include 2.5 in the upper boundary.

There were also no significant differences for the presence of delirium as defined by CAM (secondary outcome) between the groups at any time point or in the trend over time. The largest difference in magnitude was seen at post-randomization day 1 (unadjusted percentage Restrictive=40% delirium vs. Liberal=31%; Relative Risk=1.26, 95% Confidence Interval=0.76–2.08 in GEE models, Figure 3).

Sensitivity analyses

We adjusted for baseline differences in gender, use of sedative hypnotics and anti-depressants, and the effect of days from surgery on delirium over time. 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 post-randomization between-treatment differences in MDAS delirium severity scores reported in Figure 2 is p=0.23; in the sensitivity analyses these p values ranged from 0.26 to 0.31.

Also, since 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, but did decrease the magnitude of the difference in CAM delirium at the first randomization day (Relative Risk=1.13, 95% Confidence Interval=0.64–1.86).

CONCLUSION

Administration of blood transfusion to maintain hemoglobin concentration greater than 10 g/dL did not significantly reduce the severity or frequency of in-hospital delirium compared to 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 among hip fracture patients 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, as compared with a restrictive strategy, did not improve functional recovery or reduce mortality or in-hospital morbidity, in elderly patients with cardiovascular disease or risk factors. [21]

Consistent with other studies, we observed a peak in delirium severity one day after surgery.[40] The naturally occurring peak of delirium severity on postoperative day one 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), we waited at least 12 hours after surgery ended to begin our delirium assessments; however, this amount of time may not have been sufficient to allow for anesthesia effects to fully clear. Time from surgery to

randomization or assessment did not differ between the two groups and thus we do not believe it influenced our overall conclusions.

Interventions to prevent delirium may differ from those to treat delirium.[41] Other studies have shown that geriatric consultation reduced the incidence and severity (prevention) but not duration of delirium (treatment).[19, 20] A trial of low dose haloperidol (given as prophylaxis) in patients with hip fracture and elective hip replacement found a reduction in delirium duration and severity but not in the incidence of delirium.[42] In contrast, a study evaluating olanzapine (given as prophylaxis perioperatively) in elective total hip and knee replacement patients showed decreased incidence of delirium but increased severity in the patients who got delirious.[43] Our study did not find an effect of transfusion in preventing delirium or improving delirium symptoms.

It is also possible that a single intervention strategy such as transfusion may be ineffective for a multi-factorial geriatric syndrome such as delirium. Previous work showed that a multi-faceted delirium intervention, which included transfusion for hemoglobin < 10 g/dl, did prevent delirium incidence[19] and a geriatrics intervention in Sweden, which also included transfusion, found improvement in symptoms among patients with delirium. [20] The Swedish study[20] had a different threshold for those already delirious (11 g/dL) than to prevent delirium (10 g/dL) as part of the multi-factorial intervention. Our 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 multi-component interventions. The Hospital Elder Life Program[44] did not include transfusions, but is another multi-component intervention that has been shown to prevent delirium in general medical and surgical patients.[44, 45]

The frequency of delirium was lower (not significant) day 1 post-randomization in the Liberal group but higher on days 2 and 3 compared to 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),[46] and melatonin treatment (12% melatonin vs. 31% placebo). [47]

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 surprising. Models adjusting for dementia attenuated the small, non-significant effect of transfusion seen on post-randomization day 1.

There were some potential limitations to our study. Even though we were not able to achieve the target sample size, we still had good power (>80%) for detecting moderate-sized differences in the primary outcome.[39] We chose the MDAS severity measure as the primary outcome for this trial because it predicts the long-term outcomes of delirium[3, 21], and a large proportion of hip fracture patients have symptoms of delirium (including subsyndromal delirium) in the absence of full diagnostic criteria.[3, 23] We had pre-specified 2.5 points on the MDAS as a clinically meaningful difference[38], and this difference was not observed between treatment groups at any time point, although confidence intervals on some days did include this value. We did not have three full days of post-randomization assessments for many of the subjects, which could also limit the power for many of these comparisons, although 61.6% had at least 2 post-randomization assessments. There was an imbalance between the two arms of age, sedative-hypnotic, and antidepressant use, although our sensitivity analyses did not find that it substantially altered our findings.

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

This study did have a number of strengths. Our study was conducted in the context of a rigorous, multi-site randomized trial. This ancillary trial showed substantial differences in post-randomization hemoglobin concentrations and the quantity of blood administered in the two arms. [21] Pre-surgery (baseline) hemoglobin values (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[48], and with recently published transfusion guidelines[49]. In addition, the FOCUS Cognitive Ancillary Study utilized rigorous, state-of-the-art delirium measures (MDAS and CAM), including extensive training and oversight of all delirium assessments. Finally, only 1 subject was excluded from analyses because there was no inhospital assessments.

In conclusion, transfusion of hip fracture patients after surgery to maintain hemoglobin above 10 g/dL does not appear to prevent or reduce the severity of delirium. These results suggest it is reasonable to withhold blood transfusion in post-surgical patients unless the patient develops symptoms from anemia, or if hemoglobin concentration falls below 8 g/dL.

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The NHLBI conducted the independent DSMB but had no direct role in the design, methods, subject recruitment, data collections, analysis and preparation of paper. No other sponsors had a direct role in design, methods, subject recruitment, data collections, analysis and preparation of paper.

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Conflict of Interest

Dr. Magaziner received support from the following companies to conduct research through his institution, provide academic consultation, or serve on an advisory board: Amgen, Eli Lilly, Glaxo SmithKline, Merck, Novartis, and Sanofi Aventis. Dr. Roffey reports working as a consultant for Palladian Health. Dr. Carson reports receiving grant support to his institution from Amgen.

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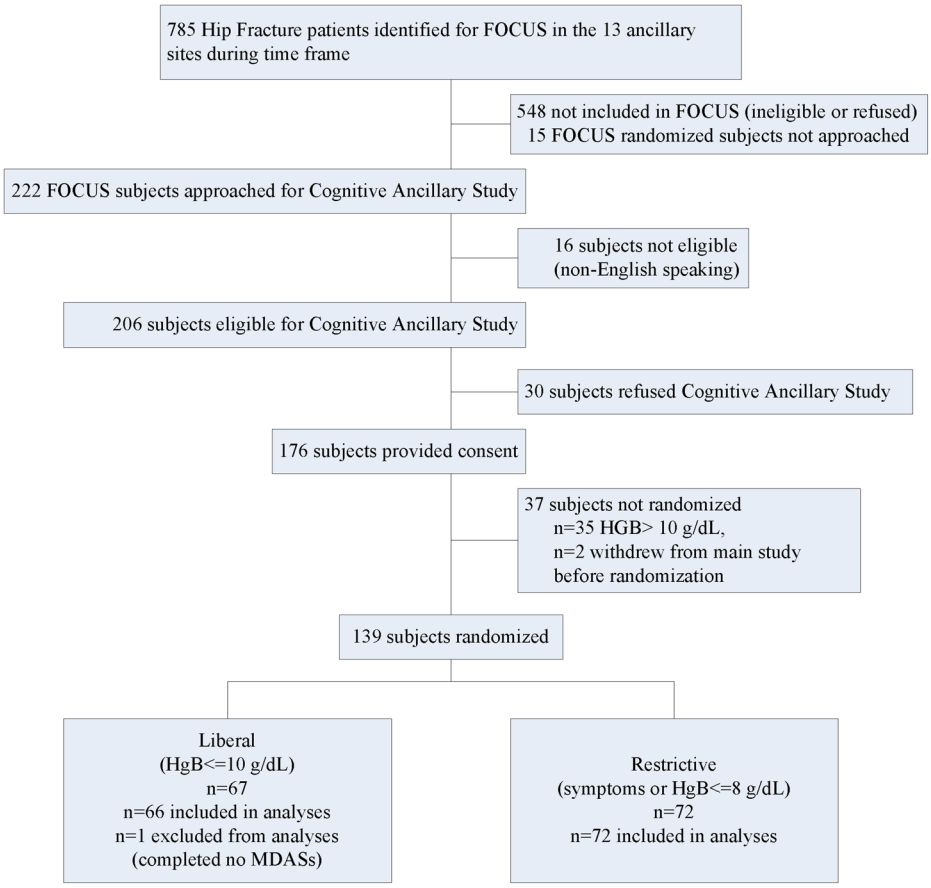

Figure 1.
Flow of Participants Through the Trial. Legend: MDAS Memorial Delirium Assessment Scale (primary outcome); HGB Hemoglobin

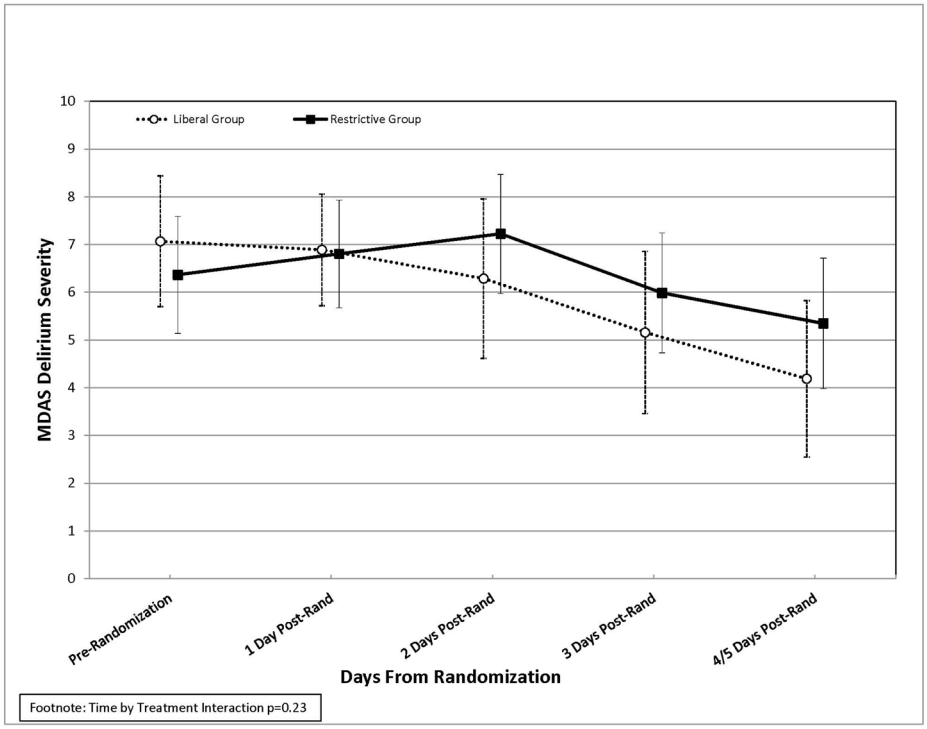

Figure 2.
Primary Outcome: MDAS Delirium Severity Score (Estimated Mean and 95% CI From GEE) by Days Relative to Randomization by Treatment Group. Footnote: Time by Treatment Interaction p=0.23

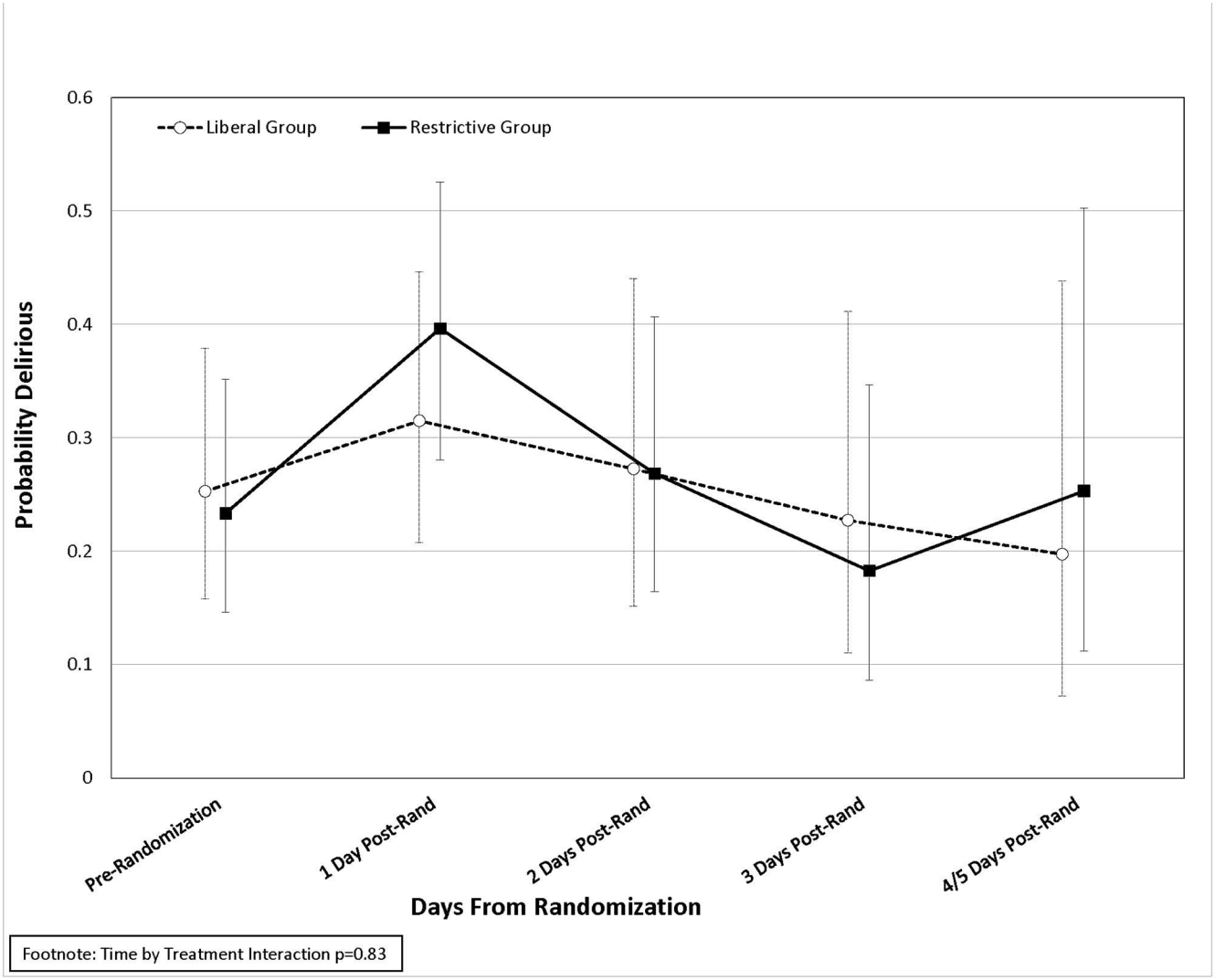

Figure 3.
Secondary Outcome CAM Delirium (Estimated Probability and 95% CI From GEE) by Days Relative to Randomization by Treatment Group. Footnote: Time by Treatment Interaction p=0.83

Table 1

Sample Description by Treatment Group

Baseline Variable	Liberal (n=66)	Restrictive (n=72)
Age (years), mean (std. dev.)	82.4 (7.4)	80.6 (10.4)
Sex		
Female	54 (81.8%)	47 (65.3%)
Male	12 (18.2%)	25 (34.7%)
Race		
White	59 (89.4%)	66 (91.7%)
Black	7 (10.6%)	5 (6.9%)
Unspecified	0 (0.0%)	1 (1.4%)
Education (years), mean (std. dev.)	12.3 (3.4)	12.4 (3.1)
Marital Status		
Married	23 (36.5%)	25 (34.7%)
Widowed	30 (47.6%)	30 (41.7%)
Divorced/Separated	3 (4.8%)	8 (11.1%)
Never Married	7 (11.1%)	8 (11.1%)
Unspecified	0 (0.0%)	1 (1.4%)
Pre-admission residence		
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		
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%)
per Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE>3.44) but not chart or significant other	9 (13.6%)	6 (8.3%)
Comorbidities (History from chart):		
Stroke or Transient Ischemic Accident (TIA)	5 (7.6%)	12 (16.7%)
Chronic lung disease	16 (24.4%)	13 (18.1%)
Cancer	10 (15.2%)	12 (16.7%)
Diabetes	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/deaf	10 (15.2%)	15 (20.8%)
Visual problems/blind	7 (10.6%)	9 (12.5%)
Alcohol abuse or withdrawal	2 (3.0%)	5 (6.9%)

Baseline Variable	Liberal (n=66)	Restrictive (n=72)
Malnourished or cachectic at admission	2 (3.0%)	3 (4.2%)
Labs		
White Blood Count, mean (std. dev.)	10.8 (4.6)	10.1 (3.7)
Sodium, mean (std. dev.)	137.1 (4.1)	137.0 (4.3)
Blood Urea Nitrogen (BUN), mean (std. dev.)	22.1 (13.8)	23.3 (13.7)
Glucose, mean (std. dev.)	124.7 (48.5)	127.9 (36.3)
Albumin, mean (std. dev.)	3.7 (0.5)	3.7 (0.5)
Creatinine, mean (std. dev.)	1.1 (0.5)	1.1 (0.8)
BUN/creatinine ratio ≥18	40 (61.5%)	43 (59.7%)
Type of hip fracture		
Femoral neck	33 (50.0%)	30 (41.7%)
Intertrochanteric/Subtrochanteric	33 (50.0%)	42 (58.3%)
Anesthesia Type		
General or Combined General/Regional/Spinal	38 (57.6%)	42 (58.3%)
Regional/Spinal only	28 (42.4%)	30 (41.7%)
American Society of Anesthesiologists Physical Status score, mean (std. dev.)	2.8 (0.5)	3.0 (0.5)
Length of surgery (minutes), mean (std. dev.)	131.3 (55.2)	140.0 (44.7)
Hospital Length of Stay, mean (std. dev.)	6.6 (3.9)	6.7 (3.6)
Prerandomization Assessment Time[a]		
Before surgery	35 (61.4%)	38 (60.3%)
After surgery	22 (38.6%)	25 (39.7%)
Days between surgery and randomization, mean (std.)	1.4 (0.7)	1.4 (0.8)
Hemoglobin value, mean (std. dev.)		
Pre-surgery	11.9 (1.3)	11.9 (1.7)
Pre-randomization	8.9 (0.8)	8.9 (0.7)
1 day post-randomization	10.2 (1.1)	8.8 (0.9)
2 days post-randomization[ab]	10.4 (0.9)	8.7 (0.9)
3 days post-randomization[c]	10.8 (0.8)	8.7 (0.9)
4 days post-randomization[d]	10.8 (1.0)	9.3 (0.8)
5 days post-randomization[e]	10.9 (1.1)	9.3 (1.0)
Number of units of blood transfused post-randomization		
None	3 (4.5%)	39 (54.2%)
1 unit	27 (40.9%)	22 (30.6%)
2 units	24 (36.4%)	9 (1.4%)
3 units	8 (12.1%)	0 (0.0%)

Baseline Variable	Liberal (n=66)	Restrictive (n=72)
4+ units	4 (6.1%)	2 (2.8%)
Total units of blood transfused post-randomization[f]	115	53
Pre-transfusion Hemoglobin (if transfused post-randomization), mean(g/dL) (std. dev.) [g]	8.9 (0.8)	7.7 (0.4)
Medications given pre-randomization		
Any psychoactive	57 (86.4%)	63 (87.5%)
Antipsychotic medications	6 (9.1%)	6 (8.3%)
Antidepressants	22 (33.3%)	14 (19.4%)
Opiates	52 (78.8%)	54 (75.0%)
Other Analgesics	45 (68.2%)	44 (61.1%)
Sedative-hypnotics	25 (37.9%)	17 (23.6%)
Post-randomization Complications		
Infections	3 (4.6%)	3 (4.2%)
Pulmonary Embolism	2 (3.0%)	0 (0.0%)
Congestive Heart Failure	1 (1.5%)	2 (2.8%)
Hemorrhaging (>100cc)	6 (9.1%)	4 (5.6%)

Footnotes:

[a] Only if MDAS administered, numbers will not add up to all subjects in group.

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

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

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

[e] Total n includes only those still in hospital 5 days post-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).

Table 2

Means (standard deviations) or Number (percentages) for FOCUS CAS Outcomes by Measurement Timepoint

Measures	Pre-randomization		Post-rand day 1		Post-rand day 2		Post-rand day 3		Post-rand day 4		Post-rand day 5	
	Liberal (n=57)	**Restr. (n=63)**	**Liberal (n=53)**	**Restr. (n=55)**	**Liberal (n=36)**	**Restr. (n=46)**	**Liberal (n=23)**	**Restr. (n=31)**	**Liberal (n=9)**	**Restr. (n=9)**	**Liberal (n=5)**	**Restr. (n=3)**
Primary Outcome												
Memorial Delirium Assessment Scale, Mean (SD)	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 from t-tests)		p=0.72		p=0.93		p=0.69		p=0.87		p=0.23		p=0.28
Secondary Outcome												
Confusion Assessment Method, n (% delirium)	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 from chi-squares)		p=0.92		p=0.29		p=0.51		p=0.37		p=0.53		p=0.41