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Perioperative Transfusion Associated With Increased Morbidity and Mortality in Geriatric Patients Undergoing Hip Fracture Surgery

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Abstract

Introduction: Both conservative and liberal transfusion thresholds, in regard to hematocrit and hemoglobin levels, have been widely studied with varying outcomes. The aim of this study was to evaluate if transfusion administered peri- (anytime during the admission), pre-, intra-, or postoperatively an its association with morbidity and mortality in the geriatric population undergoing hip surgery. **Methods:** This study was an institutional review board approved retrospective analysis of data collected from 841 patients at a single urban institution who underwent surgical repairs for hip fractures from 2008 to 2010. **Results:** Our analysis included data from 841 surgical patients. Mean patient age was 83, 74% were female, 48% received spinal anesthesia while 52% underwent general anesthesia. Out of 841 patients, 425 were transfused during the perioperative period. Most transfusions occurred postoperatively. Perioperative, intraoperative and postoperative transfusion was associated with an increase in post-operative AKI. Intraoperative blood transfusion was associated with an increase in morbidity (11.6% increased to 22.2%) by 1.9 fold, AKI (3.9% increased to 11.1%) by 2.8 fold, as well as an increase in mortality (5.2 increased to 15.6%) within 60 days by 3 fold. **Conclusions:** This may suggest that patients transfused prior to surgery, despite having met a specific trigger hemoglobin level earlier, may have been treated before deteriorating to a point that would cause future systemic implications.

Keywords

ASA, geriatric medicine, morbidity, mortality, transfusion

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Introduction

Hip fractures are a common injury with an annual incidence of about 1.3 million worldwide.[1] With hip fractures accounting for 72% of osteoporotic related fractures, the economic burden is significant and greatly impacts Medicare related expenditure.[2] Both the direct cost of surgery and the indirect costs associated with unplanned complications and associated morbidities are contributory when calculating the overall burden of this disease. More so, hip fractures represent a major public health concern in the elderly population due to substantial pre-existing co-morbidities and subsequent difficulty in achieving favorable outcomes. Hip fractures can be devastating in terms of functional and economic loss, quality of life, and mortality. In-hospital mortality rates have been estimated at up to 10%,[2] with 1-year mortality as high as 27.3%.[3] Long-term, approximately 50% require ambulation assistance and up to 25% require long term physical care.[2] Multiple patient variables have been proven to directly affect patient morbidity and mortality following hip surgery. These variables include patient age, gender, delay in surgery, congestive heart failure, pulmonary disease, renal failure, fluid and electrolyte imbalances, and perioperative anemia.[4,5] Increased blood loss, represented by decreases in hematocrit

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and hemoglobin, have been suggested as surrogate markers of increased morbidity and mortality.[6] Thus, perioperative transfusions are often employed in an attempt to improve the patient's hemodynamic status and mitigate the impact of blood loss on postoperative complications.[7]

The ideal hematocrit before surgery and whether or not to transfuse has not been determined. Transfusion related immune modulation is a well-established phenomenon in which allogenic blood transfusion can cause clinically significant immunosuppression, thus leading to increased risk of post-operative infections and organ dysfunction.[2,8] Therefore, both conservative and liberal transfusion thresholds, in regard to hematocrit and hemoglobin levels, have been widely studied with varying outcomes[9,10,11] The aim of this study was to evaluate if transfusion administered peri- (anytime during the admission), pre-, intra-, or post-operatively is associated with increased morbidity and mortality in the geriatric population undergoing hip surgery. Our study sought to evaluate the following questions:

1. Does transfusion increase mortality, morbidity, and length of stay (LOS) in geriatric hip fracture patients?
2. Is this compounded by sex, age, or American Society of Anesthesiologist physical classification system (ASA) status?
3. Is there an optimal time for transfusion?

Methods

This study was an institutional review board approved retrospective analysis of data collected from 841 patients at a single urban institution who underwent surgical repairs for hip fractures from 2008 to 2010. Descriptive statistics were generated for any continuous variables, including the mean and standard deviation. Data transformations were performed to evaluate specific categories. The patients were separated into groups including no transfusion or as having received allogenic blood transfusion in the following periods: pre-operative, intra-operative, post-operative, or perioperative (Tables 1, 2 & 3). Each subset was analyzed for the development of specific post-operative morbidities and mortality within 60 days (Tables 2 & 3, respectively). Patients were also analyzed according to the American Society of Anesthesiologist physical classification system (ASA). In terms of ASA measurements, patients were categorized into 1 of 3 groups: ASA 1 and 2, ASA 3, or ASA 4.

Post-operative complications evaluated included the following: myocardial infarction (MI), cerebral vascular events (CVA), acute kidney injury (AKI), pulmonary embolism (PE), pneumonia (PNA), and post-operative cognitive dysfunction (POCD). AKI was defined as an increase in serum creatinine (SCr) by $\geq$ 0.3mg/dl within 48 hours or an increase in SCr to $\geq$ 1.5 times baseline within 7 days. Underlying chronic kidney disease was adjusted for using the MDRD (Modification of Diet in Renal Disease) formula (estimated glomerular filtration rate = 186 x serum creatinine-1.154 x age-0.203 x [1.210 if black] x [0.742 if female]). Statistical analysis was performed using Fischer's Exact 2-sided test.

Statistical significance of complications and 2 month mortality with respect to time of transfusion (peri-, pre-, intra-, and post- operatively) was further evaluated by possible confounding factors: age, sex, American Society of Anesthesiologist physical status classification (ASA), and type of anesthesia (general versus spinal). Statistical significance was determined using multi-variable logistic regression analysis.

Statistical analysis was performed using the Kruskall Wallis test (or 1-way ANOVA on ranks). Post-hoc analysis involved the Bonferroni-adjusted significance tests for pairwise

Table 1. Transfusion Associated Morbidity and Mortality: Statistical Significance was Determined using Multi-Variable Logistic Regression Analysis.

	Perioperative			Preoperative			Intraoperative			Postoperative		
Morbidity	NO**	YES**	p =	NO	YES	P =	NO	YES	P =	NO	YES	P =
MI	1.90% 8	1.90% 8	0.213	1.90% 16	0% 0	1.000	1.70% 13	3.30% 3	0.240	1.80% 8	2.00% 8	0.806
CVA	1.00% 4	0.20% 1	0.213	0.60% 5	0% 0	1.000	0.70% 5	0.00% 0	1.000	0.90% 4	0.30% 1	0.378
POCD	3.60% 15	5.20% 22	0.314	4.50% 37	0.00% 0	1.000	3.90% 29	8.90% 8	0.049	3.80% 17	5.10% 20	0.402
PE	0.05% 2	0.90% 4	0.686	0.70% 6	0.00% 0	1.000	0.80% 6	0.00% 0	1.000	0.40% 2	1.00% 4	0.427
PNA	4.30% 18	4.50% 19	1.000	4.40% 36	5.60% 1	0.559	3.70% 28	10.00% 9	0.012	4.70% 21	4.10% 16	0.737
AKI	2.70% 10	6.80% 29	0.003*	4.60% 38	5.60% 1	0.578	3.90% 29	11.10% 10	0.005*	2.90% 13	6.60% 26	0.013
2 month Mortality	4.80% 20	7.80% 33	0.089	6.40% 53	0.00% 0	0.621	5.20% 39	15.60% 14	0.001*	5.40% 24	7.40% 29	0.257
Any Morbidity	11.30% 47	14.10% 60	0.255	12.60% 104	16.70% 3	0.491	11.60% 87	22.20% 20	0.007*	11.90% 53	13.70% 54	0.468

Differences were consider statistical significance if $p < 0.01$, (*). (**) = answer to the question if the patient was transfused during the described period.

Table 2. Changes in acute kidney injury associated with transfusion, gender, and ASA classification 4.

	Perioperative				Preoperative				Intraoperative				Postoperative			
AKI	OR	Lower	Upper	P =	OR	Lower	Upper	P =	OR	Lower	Upper	P =	OR	Lower	Upper	P =
Transfusion	3.22	1.51	6.88	0.002*	0.85	0.10	6.89	0.876	2.39	1.09	5.26	0.031*	2.85	1.40	5.80	0.004*
Male	3.89	1.96	7.73	0.000*	3.38	1.73	6.63	0.000*	3.25	1.65	6.37	0.001*	4.00	2.01	7.97	0.000*
ASA 4	4.55	1.28	16.14	0.019*	5.29	1.50	18.66	0.010*	4.95	1.40	17.53	0.013*	4.85	1.37	17.14	0.014*

Odds of acute kidney injury (AKI): Statistical significance was determined using multi-variable logistic regression analysis. Differences were consider statistical significance if $p < 0.05$, (*).

Table 3. Changes in 2-month mortality associated with transfusion, gender, and ASA classification 4.

	Perioperative				Preoperative				Intraoperative				Postoperative			
2 Month Mortality	OR	Lower	Upper	P =	OR	Lower	Upper	P =	OR	Lower	Upper	P =	OR	Lower	Upper	P =
Transfusion	1.62	0.90	2.91	0.110				0.998	2.70	1.38	5.30	0.004*	1.47	0.83	2.62	0.188
Male	1.97	1.09	3.57	0.025*	1.90	1.06	3.43	0.032*	1.79	0.99	3.23	0.055	1.98	1.09	3.58	0.025*
ASA 4	4.00	1.45	11.03	0.007*	4.32	1.57	11.90	0.005*	3.89	1.41	10.76	0.009*	4.13	1.50	11.35	0.006*

Odds of 2 month mortality: Statistical significance was determined using multi-variable logistic regression analysis. Data was considered statistical significance for $p < 0.05$, (*).

Table 4. Demographics.

Category	Number (%)	Category	Number (%)
Average age (yrs)	83 ± 10 (X ± SD)		
Age < 70	92 (11%)	ASA 1 or 2	209 (25%)
Age = 70-79	152 (18%)	ASA 3	433 (51%)
Age ≥ 80	597 (71%)	ASA 4	199 (24%)
Female	624 (74%)	Male	217 (26%)
Spinal	400 (48%)	General	441 (52%)
Total	841 (100%)		

ASA status and demographics of the patients in the study. A total of 841 patient's charts were included in the study. Patients that were admitted for a second hip fracture, only the first admission was included in the study.

Table 5. Number of Patients Transfused.

Transfusion	Patients
Preoperative	18 (2.1%)
Intraoperative	90 (10.7%)
Postoperative	394 (46.8%)
Perioperative	425 (50.5%)

Number of patients transfused. Perioperative: anytime during the admission for hip fracture. Some patients were transfused multiple times at different stages of their hospital stay.

comparisons. Odds ratios for risk factors such as age group (<70, 70-79, and ≥ 80), sex, and type of anesthesia (general versus spinal/neuraxial) were obtained using logistic regression models with independent variables (ASA and preoperative days) and time of transfusion as the dependent variable. Statistical Analysis was generated using SAS Version 9.4 and SPSS version 23.

Results

Our analysis included data from 841 surgical patients. Mean patient age was 83, 74% were female, 48% received spinal anesthesia while 52% underwent general anesthesia. Descriptive statistics and frequencies are found in Table 4.

Out of 841 patients, 425 were transfused during the perioperative period (Table 5). Most transfusions occurred postoperatively. 70 patients were transfused in more than 1 perioperative period. Of interest, 13 out of 18 patients transfused preoperatively had more than one perioperative period transfusion. The choice of anesthetic technique (spinal vs. general) or age of patient was not associated with an increase in morbidity or mortality after blood transfusion. There was no statistical difference in patients transfused perioperatively compared to non-transfused patients with respect to MI, CVA, PE, PNA or POCD (Table 1). However, perioperative, intraoperative and postoperative transfusion was associated with an increase in post-operative AKI ($p = 0.003$, $p = 0.005$, $p = 0.013$, respectively: Table 1). Using multi-variable logistic regression, AKI was still significantly increased when accounting for ASA status and sex. Males and ASA4 were correlated with an increased odds ratio of developing AKI and 2 month mortality if transfused at any point during the hospital course (Table 2 and Table 3). Only intraoperative transfusion was associated with increased mortality (Table 1, $p < 0.001$).

Intra-operative blood transfusion associated with in an increase in morbidity (11.6% increased to 22.2%) by 1.9 fold, AKI (3.9% increased to 11.1%) by 2.8 fold, as well as an increase in mortality (5.2 increased to 15.6%) within 60 days by 3 fold. ($p = 0.007$, $p < 0.005$ and $p = 0.001$, respectively: Table 1).

Discussion

Hip fractures are continuously placed among the top ten causes of disability worldwide. The global estimated annual number of hip fractures is projected to be over 6 million by the year 2050,[12] In the United States alone, over 300,000 persons are hospitalized each year with hip fractures.[13] The aggregated hospital costs nationally associated with hip fractures exceed 4.5 billion dollars. The incidence of hip fractures is largely skewed toward the geriatric population with the peak number of fractures arising in patients between the ages of 75 and 79.[1] Within the geriatric population, women account for nearly 70% of all fractures. As the population ages, these estimates are expected to rise, with one study indicating a nearly 4% increase in the number of fractures occurring in 2015.[2] Additionally, the resultant functional decline and decrease in overall quality of life place a burden on patients, their families, and the health care system. Accordingly, the morbidity and mortality associated with hip fractures are compounded in the geriatric population by concurrent comorbidities. Thus, these patients typically have multiple medical co-morbidities that complicate the management of their hip fractures. As a result, hip fractures have been found to carry a 4.0-5.3% 30-day mortality, and a 19%-36% one-year mortality.[3,14,15]

Multiple variables are associated with the increased risk of morbidity and mortality in geriatric patients undergoing hip fracture surgery. Overall, these fractures are associated with a significant post-operative morbidity and mortality rate. In an effort to identify strategies to improve outcomes for patients undergoing surgical repair, numerous studies have investigated a wide range of factors such as socioeconomic status, post-surgical placement, advanced age, ASA classification, delay in surgery, and cognitive status.[3,8,16] Other coexisting medical conditions that have been shown to negatively impact survival rates and 30-day mortality include preexisting renal disease, cardiac failure, ischemic heart disease, and urinary tract infections.[17]

In this elderly and sick population, blood transfusion is typically considered during the perioperative period. Hidden blood loss (that is not observed intra-operatively) during hip fracture fixation has been found to vary between 547 ml and 1473 ml, depending on the type of fixation utilized.[11] The mean drop in hemoglobin after hip fracture surgery has been reported at 2.8 g/dL.[18] The same study found that higher postoperative hemoglobin was associated with decreased length of stay and lower 60 day readmission rates, suggesting that intraoperative transfusion can be beneficial in this patient population.

However, conflicting data exists with regard to the post-operative morbidity and mortality following hip surgery in those receiving blood transfusions.[19] Transfusion related adverse events, most commonly related to immune modulation, a well-established phenomenon in allogenic blood transfusions, may cause recipients to experience an increase in morbidity and mortality. Specifically, patients may experience clinically significant immunosuppression leading to an increased risk of infections and organ dysfunction. Thus, allogenic blood transfusions in surgical candidates have been shown to increase post-surgical infections, respiratory complications, and admission rates to intensive care units.[20] However, withholding or delaying transfusions with sequential perioperative anemia has been associated with a decrease in survival and has been shown to be inversely related to operative mortality.[20]

The finding that allogenic blood transfusions are associated with adverse outcomes is supported by a prospective analysis of patients undergoing surgery for hip fractures conducted by Koval et al. In a cohort of 687 patients undergoing surgery, the post-operative rate of urinary tract infection was 26.8% in those who received an allogenic erythrocyte blood transfusion (EBT) compared with 14.9% in non-transfused patients.[21] Another study found transfusion to be associated with an increased rate of postoperative infection, but not with mortality.[22] Engoren et al,[23] in a study examining 229 patients of which 90 received EBT, examined patients at 30, 90, and 120 days follow-up. Immediate post-op through 90 days of follow-up found no association of increased mortality. However, the risk of increased mortality began after 90 days and persisted throughout the remainder of follow-up. The increased risk was not associated with an increased number of units transfused.[23] However, another retrospective study by Everhart et al.[24] examined 6,788 cases of knee and hip arthroplasties to determine if allogenic blood transfusion was associated with an increased risk of surgical site infection. Findings indicated a dose dependent relationship between the units of blood transfused and the risk of infection.[24]

Other studies have shown that perioperative blood transfusion in hip fracture patients has not been associated with an increased risk of infection or mortality.[25] Another study found that post-operative transfusion did not affect mortality, length of stay, or complication rate in patients with hemoglobin levels between 8.0 and 9.5 g/dl.[26]

In contrast, evidence exists that demonstrates the safety and efficacy of employing blood transfusions as needed in patients undergoing hip surgery. More recent studies have sought to determine the risks vs. benefits of utilizing a liberal or conservative transfusion protocol when treating perioperative blood loss and anemia. Carson et al.[9] studied 8,787 patients over the age of 60 who underwent hip fracture surgery in United States hospitals. The study found no evidence that those receiving transfusions at a hemoglobin level greater than 8.0g/dL had improved survival rates. A later randomized controlled study performed by Carson et al.[10] assigned patients to one of 2 treatment groups: a liberal transfusion group with a hemoglobin transfusion trigger of 10.0g/dL, or a more conservative group with a hemoglobin cut off of 8.0 g/dL.[10] A total of 2016 patients were included with 1007 and 1009 in each group respectively. Median follow up was 3.1 years and suggested no difference in long-term mortality between the groups. Further, there was no difference in the underlying cause of death.[10] As a low perioperative hemoglobin is a well-established surrogate marker for morbidity and mortality in hip fracture patients, as well as in all surgical patients, the use of a more liberal transfusion protocol may help treat these patients before their

hemoglobin reaches a critical level.[6,20] Will et al.[27] examined postoperative morbidity and mortality in patients undergoing non-cardiac surgery and received transfusions to determine postoperative hemoglobin levels that were most indicative of adverse outcomes. A postoperative hemoglobin level of less than 7.5 or greater than 11.5 were associated with longer hospitalizations compared to patients whose hemoglobin levels were in less extreme ranges. Correspondingly, the authors recommended a final hemoglobin level of 7.5 to 11.5 as a target metric for patients undergoing intraoperative transfusion. More so, targeting the lower end of the metric at 7.5 prevented overshooting final postoperative hemoglobin levels and avoided hemoglobin levels of 11.5. This suggests that restrictive transfusion protocols are more efficacious and underlines the need for identifying patients at risk for perioperative falling hemoglobin levels.[27]

In order to better understand the risks and controversy associated with perioperative transfusions, we stratified the patients into having received allogenic blood transfusions during the peri-operative (any transfusion), pre-operative, intra-operative, or post-operative periods. To our knowledge, few current studies have broken down the transfusion period in order to better assess the impact of transfusions on post-operative outcomes. Our study also analyzed specific post-operative morbidities, which are otherwise not well discussed in the current literature with regard to hip fractures. Specifically, 60 day post-operative myocardial ischemia (MI), cerebral vascular accident (CVA), post-operative cognitive dysfunction (POCD), pulmonary embolism (PE), pneumonia (PNA), and acute kidney injury (AKI) were studied. As patients receiving transfusions are often more critical, have more co-morbidities, and are of higher ASA status, we controlled for age, sex, ASA status classification and type of anesthesia administered. Our findings demonstrated that there was no statistical difference between patients that were transfused perioperatively compared to non- transfused patients with regard to 60-day adverse events other than AKI. 60-day post-operative AKI was significantly more common in patients transfused at any point perioperatively, but specifically during the intra-operative and post-operative periods. This finding was even more pronounced in males and in patients with an ASA classification of 4. This may have been a consequence of blood products frequently being held in the clinical setting until patients became hemodynamically unstable. The subsequent decrease in cardiac output and renal perfusion results in pre-renal azotemia and kidney injury, as well as in possible renal failure. Studies substantiate these findings and have shown that AKI is common in hospital settings, especially after surgery, and that blood transfusions increase the risk of post-operative AKI.[28] Therefore, blood transfusions pre-operatively may be of benefit, specifically in male patients or in those with an ASA classification of 4.

Further analysis of the transfusion time period subsets demonstrated that intra-operative EBT associated with in a 1.9-fold increase in overall morbidity and 3-fold increase in 60-day mortality. Specifically, intra-operative transfusion was correlated with increased incidence of post-operative AKI and 60-day mortality. However, preoperative transfusions were not associated with any morbidity or 60-day mortality. This may suggest that patients transfused prior to surgery, despite having met a specific trigger hemoglobin level earlier, may have been treated before deteriorating to a point that would cause future systemic implications. Several studies lend to the current restrictive hemoglobin trigger practice of 8.0g/dL for patients undergoing orthopedic surgery.[7,9,10] This is often adhered to in the preoperative setting. However, if a patient's level acutely drops during the intra or postoperative time frame, or there is acute bleeding, symptomatic anemia, or acute coronary syndrome, a more liberal trigger of 10g/dL may be used with the treating clinician's discretion.[29] Therefore, this supports the theory that patients treated preoperatively are less likely to experience an acute drop in hemoglobin requiring a more urgent transfusion, while patients receiving blood products intraoperatively have already been adversely affected.

Limitations/Future Studies

There are several limitations in our study. As this was a single center investigation, specific practices and intrinsic characteristics of the primary demographic treated may differ from other centers. Additionally, as the analysis was retrospective, only relationships can be identified and we cannot comment on causality. Furthermore, the data was collected from 2008 to 2010. Further studies investigating the relationship between blood transfusions and post-operative morbidity and mortality in which the transfusion time period is broken down will assist in the understanding of how to prophylactically identify and treat patients at risk for downstream adverse events.

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