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Clinical Outcomes Associated With Allogeneic Red Blood Cell Transfusions in Spinal Surgery: A Systematic Review

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Abstract

Study Design: Systematic review.

Objectives: The objectives of this systematic review were to report the available clinical evidence on patient outcomes associated with perioperative allogeneic red blood cell (RBC) transfusions in adult patients undergoing spinal surgery and to determine whether there is any evidence to support an association between transfusion timing and clinical outcomes.

Methods: A systematic review of the PubMed, EMBASE, and Cochrane Library databases was performed to identify all articles examining outcomes of adult spinal surgery patients who received perioperative allogeneic RBC transfusions. The level of evidence for each study was assessed using the "Oxford Levels of Evidence 2" classification system. Meta-analysis was not performed due to the heterogeneity of reports.

Results: A total of 2759 unique citations were identified and 76 studies underwent full-text review. Thirty-four studies were selected for analysis. All the studies, except one, were retrospective. Eleven studies investigated intraoperative or postoperative transfusions. Only one article compared outcomes related to intraoperative versus postoperative transfusions.

Conclusions: Perioperative transfusion is associated with increased rates of postoperative complications, especially infectious complications, and prolonged length of stay. Some evidence suggests that a dose-response relationship may exist between morbid events and the number of RBC units administered, but these findings are inconsistent. Because of the heterogeneity of reports and inconsistent findings, the incidence of specific complications remains unclear. Limited research activity has focused on intraoperative versus postoperative transfusions, or the effect of transfusion on functional outcomes of spine surgery patients. Further research is warranted to address these clinical issues.

Keywords

spine surgery, allogeneic red blood cell transfusion, transfusion timing, intraoperative period, postoperative period, complications

Introduction

Reconstructive spine surgery is associated with an increased risk of significant intraoperative and postoperative blood loss. Total blood loss of 1 to 2 L or more is common and patients are at risk of developing perioperative anemia, which has been shown to increase postoperative morbidity and mortality in a variety of clinical settings.[1-5] Because the mainstay of treatment for blood loss and perioperative anemia is transfusion, the incidence of transfusion in adult spine fusion surgery has been estimated to be as high as 50% to 81%.[6] Advancements in blood testing have markedly improved the safety of allogeneic blood products, but transfusions are not without risks.[7] Hemolytic transfusion reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, bacterial

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contamination, or allergic reactions may occur after transfusion.[8] Exposure to allogeneic blood has also been reported as an independent risk factor for increased postoperative morbidity and mortality in the settings of cardiac and noncardiac surgery.[9-12] As a result, current evidence-based guidelines support the use of "restrictive" transfusion practices and recommend against allogeneic red blood cell (RBC) transfusions in the absence of symptoms of anemia or a hemoglobin level of $\leq$8 g/dL.[13] However, spine surgery is associated with significant muscular trauma that may increase the risk of hypoxia and tissue death in the setting of anemia, and it is currently unknown whether spine surgery patients would benefit from more aggressive intraoperative resuscitation practices.

Despite the high rate of transfusions in reconstructive spine surgery, little is known about the association between transfusion timing and postoperative patient outcomes, and it is uncertain whether outcomes differ for patients receiving intraoperative or postoperative transfusions. Transfusion timing may be an important factor in the management of perioperative anemia in the setting of intraoperative and postoperative blood loss through surgical drains. Therefore, the goal of this systematic review is 2-fold: to report the available clinical evidence on patient outcomes associated with perioperative allogeneic RBC transfusions in adult patients undergoing spinal surgery, and to determine whether there is any evidence to support an association between transfusion timing and clinical outcomes.

Methods

The PubMed, EMBASE, and Cochrane Library databases were searched for literature published before July 31, 2017. Literature searches were developed, tested, and executed in PubMed, which includes MEDLINE (1946 to present), EMBASE.com (1974 to present), and the Cochrane Library's (John Wiley & Sons) Cochrane Database of Systematic Reviews (Issue 1, January 2017) and Cochrane Central Register of Controlled Trials (CENTRAL; Issue 11, November 2016). Controlled vocabularies (ie, MeSH, EMTREE terms), specific title/abstract/keyword searches, and Boolean operators were used to identify all articles describing allogeneic RBC transfusions in spine surgery. Only English-language articles were retrieved. The PubMed search strategy is included in its entirety in the supplementary material.

The titles and abstracts of all retrieved references were independently reviewed by 2 authors (CWB, KLM). Articles were included if they assessed outcomes of adult spinal surgery patients who received perioperative allogeneic RBC transfusions. Articles were excluded if they focused on pediatric patients, included nonspine surgery patients, or if they did not compare transfused patients with nontransfused patients. Other exclusions included reviews, editorials, case reports, abstracts, and animal studies. Any disagreements between the reviewers were reconciled independently by a third author (JET). After this preliminary screen, the full-text articles of the remaining references were retrieved and reviewed using the inclusion and exclusion criteria previously described. Once a preliminary list of selected articles was established, the references cited by those articles were retrieved and screened in an identical manner. This process was performed iteratively until no new articles were identified.

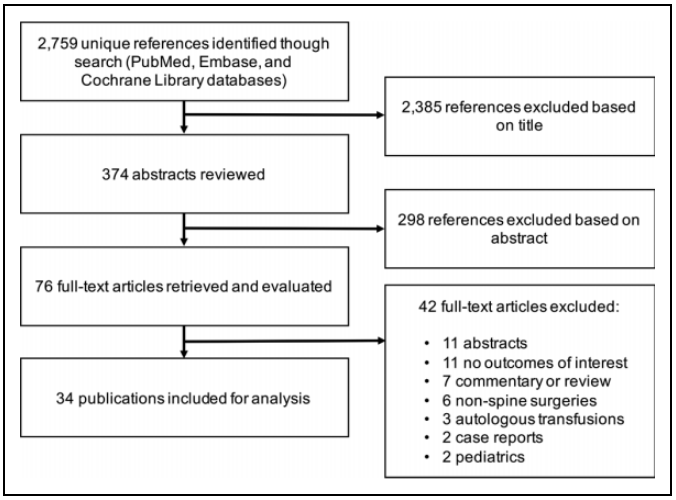

Figure 1. Flowchart of the literature search.

Two reviewers (CWB, KLM) independently conducted data extraction from the 34 articles included in this review, and the datasets were compared to confirm the accuracy of information. Publication year, sample size, transfusion type, surgery type, primary outcome, incidence of outcomes, odds ratios, and conclusions were extracted from each report. Transfusions were categorized as perioperative, preoperative, intraoperative, or postoperative. Studies that failed to define the transfusion period were classified as perioperative. The level of evidence for each study was assessed using the "Oxford Levels of Evidence 2" classification system.[14] Meta-analysis could not be performed because of the heterogeneity of reports.

Results

The initial database search identified 2,759 unique citations (Figure 1). Of these articles, most were excluded on the basis of title or abstract and 76 studies underwent full review. Thirty-four studies were ultimately selected for analysis (Table 1). All the studies included in this review, except one, were retrospective.[15] The majority of studies investigated perioperative transfusions, with only 11 studies investigating intraoperative or postoperative transfusions.[16-26] Only 1 article specifically compared outcomes related to intraoperative and postoperative transfusions in spine surgery.[16]

Perioperative Transfusions

Composite Morbidity. Three retrospective cohort studies investigated the relationship between perioperative transfusions and composite rates of morbidity, broadly defined as all complications (Table 2). All the studies reported significant rates of morbidity among transfused patients. Two studies reported

Table 1. Studies Identified by Systematic Literature Review.

First Author (Year)	Type of Study (LOE)	No. of Patients	Type of Surgery	Transfusion Period	Primary Outcome(s)
Johnson (2017)	RCS (III)	963	VAR	PERI	Various
Choy (2017)	RCS (III)	1474	LUM	PRE	Composite morbidity
Di Capua (2017)	CCS (IV)	7761	LUM[a]	PRE	Major complications
Elsamadicy (2017)	ACS (III)	160	VAR[a]	PERI	30-day readmission
Fisahn (2017)	RCS (III)	56	VAR[b]	PERI	Infection and LOS
Purvis (2017)	RCS (III)	6931	VAR	PERI	Composite morbidity
Zaw (2017)	RCS (III)	247	META	PERI	Cancer survival
Aoude (2016)	RCS (III)	13 695	LUM/THOR	PERI	Various
Haleem (2016)	CCS (IV)	272	VAR	PERI/INT/POST	Surgical site infection
Jiang (2016)	CCS (IV)	451	VAR	INT	Postoperative delirium
Paulino Pereira (2016)	RCS (III)	649	META	PERI	Cancer survival
Janssen (2015)	RCS (III)	3721	LUM	PERI	Infection
Kato (2015)	RCS (III)	84 650	LUM[a]	PERI	Infection and mortality
Khanna (2015)	RCS (III)	1187	VAR	PERI	30-day readmission and LOS
Kimmell (2015)	CCS (IV)	22 430	VAR	PRE	Composite morbidity
Osterhoff (2015)	RCS (III)	244	THOR	PRE	Surgical site infection
Wang (2015)	RCS (III)	1346	VAR	INT	Deep vein thrombosis
Wang (2015)	RCS (III)	1346	VAR	INT	Myocardial infarction
Woods (2015)	CCS (IV)	1799	LUM	PERI	Surgical site infection
Yaldiz (2015)	CCS (IV)	540	LUM	PERI	Surgical site infection
Yang (2015)	CSX (IV)	995	LUM	PERI	Deep vein thrombosis
Basques (2014)	RCS (III)	1861	LUM	INT	LOS
Claussen (2014)	RCS (III)	170	META	PERI	Cancer survival
Seicean (2014)	RCS (III)	36 901	VAR[a]	PERI/INT	Morbidity and mortality
Gruskay (2013)	CSE (IV)	103	LUM	PERI	LOS
Abdul-Jabbar (2012)	CCS (IV)	6628	VAR	PERI	Surgical site infection
Pull ter Gunne (2010)	CCS (IV)	300	VAR	POST/INT	Morbidity, mortality, and LOS
Schwarzkopf (2010)	CCS (IV)	132	LUM/THOR	PERI	Surgical site infection
Gao (2008)	CCS (IV)	549	VAR	INT[c]	Postoperative delirium
Olsen (2008)	CCS (IV)	273	VAR	PERI	Surgical site infection
Apisarnthanarak (2003)	CCS (IV)	60	VAR	POS/INT	Surgical site infection
Olsen (2003)	CCS (IV)	219	VAR	PERI/POST/INT	Surgical site infection
Nahtomi-Shick (2001)	CSE (IV)	103	VAR	INT	ICU LOS
Triulzi (1992)	PCS (II)	109	VAR	PERI	Infection

Abbreviations: LOE, level of evidence; ACS, ambispective cohort study; CCS, case-control study; CSE, case series; CSX, cross-sectional study; PCS, prospective cohort study; RCS, retrospective cohort study; VAR, lumbar, thoracic, and cervical surgeries; LUM, lumbar surgery; META, metastatic spine surgery; THOR, thoracic surgery; PERI, perioperative transfusions; PRE, preoperative transfusions; INT, intraoperative transfusions; POST, postoperative transfusions; ICU, intensive care unit; LOS, length of stay.

[a] Elective surgery.

[b] Major deformity surgery (>8 levels fused).

[c] Intraoperative blood transfusion $\geq$800 mL.

increased rates of morbidity after exposure to allogeneic RBCs (odds ratio [OR] =2.39, 95% confidence interval [CI] 1.61-3.56, $P < .0001$ and OR = 1.6, 95% CI 1.4-1.9).[20,27] The latter study demonstrated comparable results after stratifying patients by major (OR = 1.7, 95% CI 1.4-2.0) and minor complications (OR = 1.6, 95% CI 1.2-2.0).[20] The third study reported a dose-dependent increase in morbidity following allogeneic RBC transfusion (OR = 1.183 per unit transfused, 95% CI 1.103-1.274, $P < .0001$). The authors identified a threshold of $\geq$3 units of RBCs at which morbidity increased significantly ($P < .05$); transfusions of 1 to 2 RBC units were not associated with a change in morbid event rates.[28]

Infection. Four retrospective studies and one prospective study investigated associations between perioperative transfusions and composite rates of infection (Table 3). Of the retrospective studies, 2 articles demonstrated significant increases in rates of infection following exposure to allogeneic RBCs (OR = 3.82, 95% CI 1.70-8.58, $P = .001$ and OR = 2.6, 95% CI 1.7-3.9, $P < .001$), and a third article reported a dose-dependent increase in infection (OR = 1.182 per unit, 95% CI 1.077-1.332, $P = .0002$).[27-29] Triulzi et al,[15] in the only prospective study included in this review, reported a strong association between allogeneic transfusion and rates of in-hospital infection (20.8% vs 4.0%, $P = .0185$). Exposure to allogeneic RBCs during hospitalization ($P = .0157$) or at any time in the past ($P = .0043$) were both found to be significant predictors of in-hospital infection. The authors also reported a dose-response relationship for in-hospital transfusions ($P = .012$) and total lifetime transfusions ($P = .005$).[15] In an analysis of patients

Table 2. Key Findings of Studies Assessing Transfusions and Composite Morbidity.

First Author (Year)	Type of Study (LOE)	Conclusion(s)/Limitation(s)
Perioperative period		
Johnson (2017)	RCS (III)	Transfusion was associated with a dose-dependent increase in morbidity (OR 1.183 per unit, 95% CI 1.103-1.274, $P < .0001$). A dose of $\geq$3 RBC units was the threshold at which morbidity increased significantly
Purvis (2017)	RCS (III)	Transfusion was independently associated with perioperative morbidity among all transfused patients (OR = 2.39, 95% CI 1.61-3.56, $P < .0001$), as well as patients with a whole hospital hemoglobin nadir of 8-10 g/dL (OR = 2.12, 95% CI 1.24-3.64, $P = .006$)
Seicean (2014)	RCS (III)	Transfusion was significantly associated with all postoperative complications (OR = 1.6, 95% CI 1.4-1.9), major complications (OR = 1.7, 95% CI 1.4-2.0), and minor complications (OR = 1.6, 95% CI 1.2-2.0)
Preoperative period		
Choy (2017)	RCS (III)	Preoperative transfusion of >4 units was associated with surgical complications (OR = 7.12, 95% CI 1.43-35.37, $P = .016$), but not medical complications. The most common surgical complication was SSI (83% of complications)
Di Capua (2017)	CCS (IV)	Transfusion within 72 hours of surgery was associated with rates of developing $\geq$1 major complication (OR = 3.04, 95% CI 1.24-7.49, $P = .016$), but not $\geq$2, or $\geq$3 major complications. The most common complication was intra-/postoperative transfusion (23.2% patients)
Kimmell (2015)	CCS (IV)	Transfusion was independently associated with postoperative complications (OR = 13.41, 95% CI 8.19-21.95, $P < .001$)
Intraoperative period		
Seicean (2014)	RCS (III)	Major complications were associated with transfusion of $\geq$4 units (OR = 1.5, 95% CI 0.9-2.4), or 2-3 units (OR = 1.7, 95% CI 1.1-2.6), but not with 1 unit. Transfusion of $\geq$4 units (OR = 3.0, 95% CI 0.9-2.4), 2-3 units (OR = 1.7, 95% CI 1.1-2.6), or 1 unit (OR = 2.4, 95% CI 1.3-4.3) increased the odds for minor complications

Abbreviations: LOE, level of evidence; CCS, case-control study; RCS, retrospective cohort study; RBC, red blood cells; OR, odds ratio; 95% CI, 95% confidence interval.

undergoing major deformity surgery ($\geq$8 levels fused), Fisahn et al[30] reported comparable rates of infection among transfused patients (36% vs 10%, $P = .03$), but the association was not significant after controlling for smoking status and estimated blood loss. However, this study was limited by a small sample size (N = 56).[30]

Three retrospective cohort studies and 3 case-control studies reported independent associations between perioperative transfusions and surgical site infection (SSI; Table 4).[29,31-35] Schwarzkopf et al[35] demonstrated the most dramatic effect in a case-control study of 132 thoracic and lumbar patients, reporting an OR of 8.02 (95% CI 2.28-28.2, $P = .0001$). One retrospective cohort study and 4 case-control studies could not support an independent relationship between perioperative transfusion and SSI.[23,26,30,36,37] However, all these studies reported greater rates of infection in transfused patients than nontransfused patients, and a possible association cannot be ruled out.

Three cohort studies reported statistically significant associations between perioperative transfusions and urinary tract infections (UTI; Table 3). Two of the articles reported significant findings after multivariable analysis (OR = 2.5, 95% CI 1.5-4.2, $P < .001$ and OR = 2.6, 95% CI = 1.7-3.9, $P = .004$).[29,31] The third study reported a 3-fold increase in the rate of UTI after perioperative transfusion ($P = .0065$), but this result was based on a univariable analysis not controlling for potential confounding variables.[38]

Two studies investigated the association between perioperative transfusion and pneumonia (Table 3).[29,38] Although one article reported higher rates of pneumonia among transfused patients, neither study demonstrated significant results on multivariable analysis.[29] Similarly, a third report demonstrated higher rates of respiratory tract infection and sepsis among transfused patients, but the relationships were not sustained after matching.[31]

Hospital Course. Eight studies assessed perioperative transfusion and length of stay (LOS; Table 5).[15,20,27,30,32,38-40] Seven articles demonstrated a significant relationship between the variables, although only 4 of those reports confirmed their results with multivariable analysis.[15,20,32,40] Two studies investigated the rates of readmission associated with perioperative transfusions during spine surgery.[38,40] Only one of these articles reported a significant result ($P = .0052$).[38] Finally, 1 article assessed the possible relationship between perioperative transfusion and return to operating room following spine surgery, reporting an independent association between the variables (OR = 1.7, 95% CI 1.3-2.2).[20]

Thrombotic and Ischemic Events. Five studies investigated perioperative transfusions and thrombotic events (Table 6). All the studies, except 1, reported significant findings. Purvis et al[27] found perioperative transfusion to be an independent predictor of the rate of deep vein thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulopathy (DIC), reported as a single composite variable (OR = 2.04, 95% CI

Table 3. Key Findings of Studies Assessing Perioperative Transfusions and Postoperative Infection, Excluding Surgical Site Infection.

First Author (Year)	Type of Study (LOE)	Conclusion(s)/Limitation(s)
Composite infection		
Johnson (2017)	RCS (III)	Transfusion was associated with a dose-dependent rate of infection (OR = 1.182, 95% CI 1.077-1.332, $P = .0002$)
Fisahn (2017)	RCS (III)	Transfusion was associated with infection on univariable analysis (36.1% vs 10%, $P = .03$), but not significant when smoking and estimated blood loss were included in the logistic regression model. Results limited by small sample size (N = 56)
Purvis (2017)	RCS (III)	Transfusion was independently associated with higher rates of infection (OR = 3.82, 95% CI 1.70-8.58, $P = .001$)
Janssen (2015)	RCS (III)	Transfusion was independently associated with infection (OR = 2.6, 95% CI 1.7-3.9, $P < .001$). However, the evidence did not support a dose-response relationship between the number of blood units transfused and infection
Triulzi (1992)	PCS (II)	Exposure to allogeneic blood during hospitalization ($P = .0157$) or at any time in the past ($P = .0043$) were significant predictors of in-hospital infection. A possible dose-response relationship was reported between the number of units transfused and rates of infection for in-hospital transfusions ($P = .012$) and total lifetime transfusions ($P = .005$)
Urinary tract infection (UTI)		
Elsamadicy (2017)	ACS (III)	The rate of UTIs was 3-fold higher in patients receiving perioperative blood transfusions than those who did not (18.00% vs 5.00%, $P = .0065$). Multivariate analysis was not performed
Janssen (2015)	RCS (III)	Transfusion was independently associated with UTI (OR = 2.6, 95% CI 1.7-3.9, $P = .004$). However, the evidence did not support a dose-response relationship between the number of blood units transfused and UTI
Kato (2015)	RCS (III)	Transfusion was independently associated with UTI (OR = 2.5, 95% CI 1.5-4.2, $P < .001$)
Pneumonia		
Elsamadicy (2017)	ACS (III)	Transfusion was not associated with pneumonia. Limited by a small event rate (8 total)
Janssen (2015)	RCS (III)	Transfusion was associated with pneumonia on univariable analysis, but significance not sustained on multivariable analysis. Evidence did not support dose-response relationship between the number of units transfused and pneumonia
Kato (2015)	RCS (III)	Transfusion was associated with "respiratory tract infection" on univariable analysis, but the relationship was not maintained after matching
Other infections		
Kato (2015)	RCS (III)	Transfusion was significantly associated with sepsis on univariable analysis, but relationship not maintained after matching

Abbreviations: LOE, level of evidence; ACS, ambispective cohort study; PCS, prospective cohort study; RCS, retrospective cohort study; OR, odds ratio; 95% CI, 95% confidence interval.

1.07-3.91, $P = .031$). Aoude et al[32] reported significant associations between perioperative transfusion and DVT (OR = 2.69, 95% CI 1.77-4.09, $P < .001$) and PE (OR = 3.55, 95% CI 2.23-5.66, $P < .001$) in patients undergoing lumbar fusion, but not in patients undergoing thoracic fusion. Two additional studies reported a possible dose-dependent relationship between allogeneic RBCs and thrombotic events. Johnson et al[28] demonstrated increased odds of composite thrombotic events equal to 1.104 per RBC unit (95% CI 1.032-1.194, $P = .0035$). Similarly, Yang et al[41] reported that large blood transfusions were associated with increased rates of postoperative DVT in lumbar fusion patients ($P = .04$). The only inconclusive report among these studies was limited by a small rate of events (3 in 160 patients).[38]

Four of these authors also evaluated rates of ischemic events among transfused patients and reported similar findings (Table 6). Purvis et al[27] reported a significant relationship between perioperative transfusion and myocardial infarction (MI), transient ischemic attack, and stroke, reported as a single composite variable (OR = 7.02, 95% CI 1.22-40.34, $P = .029$). Aoude et al[32] demonstrated that transfusion was independently associated with rates of MI in lumbar spine patients (OR = 2.85, 95% CI 1.41-5.78, $P = .004$), but not in thoracic spine patients. Johnson and colleagues[28] reported a tendency for composite ischemic events to increase with increasing doses of allogeneic RBCs, suggesting a possible dose-response relationship, but the relationship was not statistically significant. Elsamadicy et al[38] found no statistical evidence supporting a relationship between transfusion and stroke, but these findings were limited by a small event rate (5 in 160 patients).

Table 4. Key Findings of Studies Assessing Transfusions and Surgical Site Infection.

First Author (Year)	Type of Study (LOE)	Conclusion(s)/Limitation(s)
Perioperative period		
Fisahn (2017)	RCS (III)	5 SSIs observed, all in transfusion group, but rate of SSIs was not significant. Limited by small sample size (N = 56) and event rate
Aoude (2016)	RCS (III)	Transfusion was associated with DSSI (OR = 2.44, 95% CI 1.55-3.83, $P < .001$) and SSSI (OR = 1.52, 95% CI 1.03-2.26, $P < .037$) in patients undergoing lumbar fusion, but not with DSSI or SSSI in patients undergoing thoracic fusion
Haleem (2016)	CCS (IV)	Transfusion was associated with SSI on bivariable analysis (OR = 3.0, 95% CI 1.4-6.6, $P = .004$), but not on multivariable analysis. Results limited by small event rate (2.3 per 100 procedures)
Janssen (2015)	RCS (III)	Transfusion was associated with SSI (OR = 2.6, 95% CI 1.3-5.3, $P = .007$). Evidence did not support a dose-response relationship
Kato (2015)	RCS (III)	Transfusion was independently associated with SSI (OR = 1.88, 95% CI 1.40-2.50, $P < .001$)
Yaldiz (2015)	CCS (IV)	Transfusion was independently associated with SSI (OR = 2.654, 95% CI 1.401-5.028, $P = .003$). Transfusions were also associated with increased severity of infection (92.9% transfusion rate in DSSI group vs 42.9% in SSSI group, $P = .003$)
Woods (2015)	CCS (IV)	Transfusion volume was significantly associated with SSI (OR = 4.0, 95% CI 1.96-8.15). However, there was no significant difference in the number of patients who received transfusions between the infection and control groups
Abdul-Jabbar (2012)	CCS (IV)	Transfusions showed strong significance with SSI ($P < .001$), but association was not sustained on multivariable analysis
Schwarzkopf (2010)	CCS (IV)	Transfusion was strongly and significantly associated with infection (OR = 8.02, 95% CI 2.28-28.2, $P = .0001$)
Olsen (2008)	CCS (IV)	Transfusion was associated with SSI on univariable analysis ($P < .001$), but not on multivariable analysis
Olsen (2003)	CCS (IV)	Transfusion was associated with SSI on univariable analysis (P = .001), but not on multivariable analysis
Preoperative period		
Osterhoff (2015)	RCS (III)	Transfusion within 48 hours of surgery was independently associated with SSI (OR = 2.7, 95% CI 1.1-6.4, $P = .024$)
Intraoperative period		
Haleem (2016)	CCS (IV)	Transfusion was associated with increased rates of SSI on bivariable analysis, but not on multivariable analysis
Pull ter Gunne (2010)	CCS (IV)	No association demonstrated between intraoperative transfusion and SSI
Apisarnthanarak (2003)	CCS (IV)	No association demonstrated between intraoperative transfusion and SSI. Limited by small sample size (N = 60)
Olsen (2003)	CCS (IV)	Transfusion was associated with SSI on univariable analysis ($P = .002$), but not on multivariable analysis
Postoperative period		
Haleem (2016)	CCS (IV)	Transfusion was associated with increased rates of SSI on bivariable analysis, but not on multivariable analysis
Pull ter Gunne (2010)	CCS (IV)	PRBC use after surgery not significantly associated with clinical infection on multivariable analysis (OR = 1.22, 95% CI 0.98-1.52). After stratifying SSI into DSSI and SSI, a significant association was shown between postoperative transfusion and DSSI (3.75 units vs 1.85 units, $P = .002$). Because no other factors were significantly associated, multivariable analysis was not performed
Apisarnthanarak (2003)	CCS (IV)	No association demonstrated between intraoperative transfusion and SSI. Limited by small sample size (N = 60)
Olsen (2003)	CCS (IV)	Transfusion was associated with SSI on univariable analysis ($P < .001$), but not on multivariable analysis

Abbreviations: LOE, level of evidence; CCS, case-control study; RCS, retrospective cohort study; SSI, surgical site infection; DSSI, deep surgical site infection; SSSI, superficial surgical site infection; PRBC, packed red blood cells; OR, odds ratio; 95% CI, 95% confidence interval.

Mortality. Four retrospective cohort studies investigated perioperative transfusions and mortality.[20,27,31,32] Three articles reported increased rates of mortality among transfused patients, but none of the studies demonstrated a statistically significant relationship on multivariable analysis.

Table 5. Key Findings of Studies Assessing Transfusions and Hospital Course.

	First Author (Year)	Type of Study (LOE)	Conclusion(s)/Limitation(s)
Perioperative period	Length of stay		
	Elsamadicy (2017)	ACS (III)	Transfusion was associated with increased LOS (8.88 vs 6.41 days, $P = .02$). Based on univariable analysis
	Fisahn (2017)	RCS (III)	Transfusion was associated with increased LOS (9.1 vs. 5.9 days, $P = .01$). Based on univariable analysis
	Purvis (2017)	RCS (III)	Transfusion was associated with increased LOS (median [IQR], 7 [5-10] vs 3 [2-5], $P < .0001$). Univariable analysis
	Aoude (2016)	RCS (III)	Transfusion was independently associated with prolonged LOS ($\geq$5 days) in lumbar spine surgery (OR = 3.06, 95% CI 2.77-3.27, $P < .001$), and in thoracic spine surgery (OR = 1.90, 95% CI 1.22-2.97, $P = .004$)
	Khanna (2015)	RCS (III)	Transfusions were found to increase the length of hospital stay by 60% ($P < .001$)
	Seicean (2014)	RCS (III)	Transfusions were independently associated with prolonged LOS (>4 days) (OR = 2.6, 95% CI 2.3-2.9)
	Gruskay (2013)	CSE (IV)	Transfusions were not associated with increased LOS ($\geq$5 days)
	Triulzi (1992)	PCS (II)	Transfusion was a significant predictor of LOS after multivariable analysis, although the data was not reported. The authors also found a possible dose-response relationship between transfusion and LOS ($P = .0037$)
	Readmission		
	Elsamadicy (2017)	ACS (III)	Transfusion was independently associated with unplanned readmission within 30 days of discharge ($P = .0052$)
	Khanna (2015)	RCS (III)	Transfusions were not associated with increased rates of readmission
	Return to operating room		
	Seicean (2014)	RCS (III)	Transfusions were independently associated with return to operating room (OR = 1.7, 95% CI 1.3-2.2)
Intraoperative period	Length of stay		
	Basques (2014)	RCS (III)	Intraoperative transfusion was independently associated with extended LOS ($P <= .001$)
	Seicean (2014)	RCS (III)	Patients who received $\geq$4 units (OR = 13.1, 95% CI 5.4-31.4), 2-3 units (OR = 3.3, 95% CI 2.3-4.8) or 1 unit (OR = 2.0, 95% CI 1.5-2.6) were more likely to experience a prolonged LOS (>4 days) than those who were not transfused
	Pull ter Gunne (2010)	CCS (IV)	No associations demonstrated between intraoperative transfusion and ICU days, ward days, or discharge to home
	Nahtomi-Shick (2001)	CSE (IV)	Intraoperative blood administration was not predictive of ICU LOS, but total intraoperative crystalloid administration ($P = .000$) was predictive of ICU LOS
Postoperative period	Length of stay		
	Pull ter Gunne (2010)	CCS (IV)	Transfusions in the first 24 hours after surgery were positively associated with increased ICU LOS (0.25 days per unit, $P = .001$). Use of transfusions after surgery until discharge was also associated with increased ward LOS (0.36 days per unit, $P = .001$). No association was demonstrated between postoperative transfusions and discharge to home

Abbreviations: LOE, level of evidence; ACS, ambispective cohort study; CCS, case-control study; CSE, case series; PCS, prospective cohort study; RCS, retrospective cohort study; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range.

Cancer Survival. Three retrospective cohort studies investigated overall rates survival in metastatic spine tumor surgery.[42-44] None of the reports demonstrated a significant relationship between perioperative transfusion and survival. One of these studies also investigated progression-free survival but did not demonstrate any significant association.[42]

Other Outcomes. Two studies investigated the association between perioperative transfusion and rates of kidney injury and respiratory events. While rates of kidney injury and respiratory events were higher among transfused patients in both studies, none of the relationships were significant on multivariable analysis.[27,28]

Only 1 article investigated the relationship between transfusion and patient-reported outcomes. Elsamadicy et al[38] evaluated functional status (Oswestry Disability Index), neck, back, and leg pain (visual analogue scale), physical health (Short Form–36 health survey physical component summary [SF-36 PCS]), and mental health (SF-36 mental component summary [SF-36 MCS]) before surgery, as well as 3, 6, and 12 months after surgery. No significant relationships were reported.[38]

Table 6. Key Findings of Studies Assessing Transfusions and Thrombotic/Ischemic Events.

	First Author (Year)	Type of Study (LOE)	Conclusion(s)/Limitation(s)
Perioperative period	Thrombotic events		
	Elsamadicy (2017)	ACS (III)	No association was reported between transfusion and PE. Results limited by small event rate (3 total)
	Johnson (2017)	RCS (III)	Transfusion was associated with a dose-dependent increase (OR = 1.104, 95% CI 1.032-1.194, $P = .0035$) in thrombotic events[a]
	Purvis (2017)	RCS (III)	Transfusion was independently associated (OR = 2.04, 95% CI 1.07-3.91, $P = .031$) with increased rate of thrombotic events[a]
	Aoude (2016)	RCS (III)	Transfusion was independently associated with DVT (OR = 2.69, 95% CI 1.77-4.09, $P < .001$) and PE (OR = 3.55, 95% CI 2.23-5.66, $P < .001$) in lumbar spine patients, but not in thoracic spine patients
	Yang (2015)	CSX (IV)	Large blood transfusions were associated with increased rates of DVT ($P = .04$)
	Ischemic events		
	Elsamadicy (2017)	ACS (III)	No association demonstrated between transfusion and stroke. Results limited by small rate of events (5 total)
	Johnson (2017)	RCS (III)	Reported higher rates of ischemic complications among transfused patients, but the difference was not significant. Results limited by a small number of events (4 total)
	Purvis (2017)	RCS (III)	Transfusion was an independent predictor of ischemic events[b] (OR = 7.02, 95% CI 1.22-40.34, $P = .029$)
	Aoude (2016)	RCS (III)	Transfusion was independently associated with MI in lumbar spine patients (OR = 2.85, 95% CI 1.41-5.78, $P = .004$), but not in thoracic spine patients
Intraoperative period	Thrombotic events		
	Wang (2015)	RCS (III)	Transfusion was not associated with DVT in all spine cases or in cases of emergent surgery, but a significant relationship was reported in nonemergent surgeries (OR = 1.91, 95% CI 0.38-9.55, $P = .037$)
	Ischemic events		
	Wang (2015)	RCS (III)	Transfusion was associated with postoperative MI in all spine cases (OR = 4.17, 95% CI 1.79-9.73, $P < .01$) and when stratified by nonemergent surgery (OR = 4.19, 95% CI 1.44-12.23, $P = .01$). No relationship demonstrated when stratified by emergent surgery

Abbreviations: LOE, level of evidence; ACS, ambispective cohort study; CSX, cross-sectional study; RCS, retrospective cohort study; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; 95% CI, 95% confidence interval; IQR, interquartile range; DVT, deep vein thrombosis; PE, pulmonary embolism; MI, myocardial infarction.

[a] Defined as DVT, PE, and disseminated intravascular coagulopathy.

[b] Defined as myocardial infarction, transient ischemic attack, and stroke.

Preoperative Transfusions

Four studies investigated the relationship between preoperative transfusions and patient outcomes in spine surgery. Di Capua et al[45] reported that preoperative transfusion is associated with an increased rate of developing ≥1 major complication (OR = 3.04, 95% CI 1.24-7.49, $P = .016$), but not ≥2 major complications, or ≥3 major complications, following elective posterior lumbar fusion. The most common major complication reported was intra- or postoperative transfusion (23.2%).[45] Choy et al[46] found preoperative transfusion of >4 units of packed red blood cells (pRBCs) to be a significant predictor of developing surgical complications (OR = 7.12, 95% CI 1.43-35.37, $P = .016$), but not medical complications, following single-level anterior lumbar interbody fusion (ALIF). Importantly, the authors reported that transfusion may have been acting as a proxy for preoperative anemia, which was not sufficiently corrected for in the study. Finally, Kimmel et al[47] found a strong and significant association between preoperative transfusion and postoperative complications (OR = 13.41, 95% CI 8.19-21.95, $P < .001$). The final article investigating preoperative transfusions found RBC transfusion within 48 hours prior to surgery was independently associated with SSI (OR = 2.7, 95% CI 1.1-6.4, $P = .024$).[48]

Intraoperative Transfusions

Eleven studies investigated the relationship between intraoperative transfusion and outcomes in spine surgery. In a matched analysis, Seicean et al[20] reported that intraoperative transfusion was significantly associated with prolonged LOS and increased rates of major and minor complications, but not mortality or 30-day return to operating room. In addition, the authors reported a possible dose-response relationship between transfusion and morbidity, finding intraoperative transfusion of 1 unit of blood to be associated with prolonged LOS (OR = 2.0, 95% CI 1.5-2.6) and increased rates of postoperative complications (OR = 2.4, 95% CI 1.3-4.3).[20]

One study investigated the association between intraoperative transfusion and MI in spine surgery. Intraoperative

transfusion was reported to be a significant predictor of postoperative MI in all spine surgery patients (OR = 4.17, 95% CI 1.79-9.73, $P < .01$). When stratified by nonemergent surgery, the association was sustained (OR = 4.19, 95% CI 1.44-12.23, $P = .01$). When stratified by emergent surgery, however, transfusions were not found to be a significant predictor of MI.[17]

One study assessed intraoperative transfusion and DVT. Transfusion was not associated with DVT in all spine cases, but a significant relationship was reported in nonemergent surgeries (OR = 1.91, 95% CI 0.38-9.55, $P = .037$). Transfusion was not associated with DVT in emergent surgery, including trauma and neoplastic cases.[18]

Two studies considered intraoperative transfusion as a risk factor for postoperative delirium.[21,25] Only 1 of these studies reported a significant result, finding intraoperative transfusion of ≥800 mL to be independently associated with postoperative delirium (OR = 2.537, 95% CI 0.819-7.856, $P = .107$). However, the level of significance of transfusion within the logistic regression model ($P = .107$) was less than traditional measures of significance (ie, $P = .05$).[21]

Four studies investigated intraoperative transfusion and SSI.[16,22,23,26] None of these articles reported significant findings on multivariable analysis. A second pair of studies evaluated possible associations between intraoperative transfusions and intensive care unit (ICU) LOS.[16,24] Neither study reported significant findings, although a significant relationship between intraoperative transfusion and overall LOS was reported by 2 different articles.[19,20]

Postoperative Transfusions

Only 4 studies investigated postoperative transfusion in spine surgery (Table 5). Pull ter Gunne et al[16] reported increased rates of deep SSI ($P = .002$), but not superficial SSI, and prolonged LOS ($P = .001$) in patients receiving postoperative transfusions. The association with deep SSI was based on univariable analysis, not controlling for confounding variables. The authors also found transfusion in the first 24 hours after surgery to increase ICU LOS by 0.25 days per RBC unit ($P = .001$), and transfusion after surgery until discharge to increase ward LOS by 0.36 days per RBC unit ($P = .001$).[16] This study was the only one included in this review to directly compare intraoperative and postoperative outcomes; and the authors reported no association between intraoperative transfusion and SSI or LOS. The remaining 3 studies reported higher rates of SSI among transfused patients, but none of the relationships were sustained on multivariable analysis.[22,23,26]

Discussion

The objectives of this systematic review were to report the available clinical evidence on patient outcomes associated with perioperative allogeneic RBC transfusions in adult patients undergoing spinal surgery, and to determine whether there is any evidence to support an association between transfusion timing and clinical outcomes. The preponderance of literature reviewed assessed rates of complications, especially infectious complications, associated with perioperative transfusions. Exposure to allogeneic RBCs was positively associated with increased postoperative morbidity, as well as all-cause infection, SSI, UTI, DVT, PE, and MI. Perioperative transfusions were also associated with increased rates of reoperation, hospital readmission, and prolonged LOS. While not all of these findings were consistent across the literature, these trends are supported by observational research from outside the field of spine surgery.[9-12,49] Evaluations of composite variables, such composite rates of morbidity, infection, thrombotic events, and ischemic events, were more frequently significant than those of any specific complications, suggesting that insufficient statistical power may be one of the factors contributing to the mixed results of the available clinical research.

Exposure to allogeneic RBCs was not independently associated with mortality, pneumonia, sepsis, or decreased cancer survival. However, possible relationships between allogeneic RBCs and these complications cannot be ruled out. Increased rates of mortality, pneumonia, and sepsis were reported among transfused patients, but failed to be significant after adjusting for confounding variables. The consistent lack of conclusive evidence (from 4 independent studies) to support a relationship between allogeneic RBC transfusion and mortality is remarkable, however, as significant associations have been found by observational studies in the settings of cardiac surgery and noncardiac surgery.[9-11,50]

The results of this systematic review produced very little data on the association between transfusions and the clinical outcomes specific to spine surgery. Spine surgery is associated with significant muscular trauma that may increase the risk of hypoxia and tissue death in the setting of anemia. As a result, the interplay of perioperative anemia and transfusions may have an impact on the postoperative functional status and recovery of spine surgery patients. Despite this possibility, only 1 observational study reported an assessment of postoperative functional status, health status, mental status, or pain.[38] Further research is warranted to determine whether patient recovery and long-term functional outcomes are benefited by a more liberal approach to perioperative resuscitation.

The preponderance of literature included in this review assessed perioperative transfusions, bundling together pre-, intra-, and postoperative transfusions into a single variable. Only 1 report explicitly compared intraoperative and postoperative transfusions. In a retrospective analysis of three hundred patients, Pull ter Gunne et al[16] found that low postoperative hemoglobin levels and postoperative pRBC transfusions were associated with increased rates of SSI. Intraoperative transfusions of pRBCs were not associated with increased rates of SSI and use of intraoperative fresh frozen plasma was associated with decreased rates of SSI. The authors also found a positive correlation between LOS (ICU LOS and ward LOS) and postoperative transfusion, but not intraoperative transfusion. As a result, the authors speculated that a more liberal approach to intraoperative resuscitation with pRBCs and fresh frozen plasma could decrease postoperative

morbidity and LOS among spine patients.[16] Corroborating these findings is difficult because of the paucity of literature focusing specifically on intraoperative- and postoperative-only transfusions. Haleem et al[26] reported increased rates of SSI among patients receiving intraoperative transfusions, as well as those receiving postoperative transfusions. However, neither association was sustained on multivariate analysis and the authors did not elaborate on the results.[26] Other reports from Olsen et al[23] and Apisarnthanarak et al,[22] which evaluated intraoperative and postoperative transfusions, found no statistical evidence for a relationship between either time period and rates of SSI.

Studies evaluating intraoperative transfusions, but not postoperative transfusions, demonstrated increased morbidity and prolonged LOS among patients receiving intraoperative resuscitation, demonstrating that intraoperative transfusion is not "risk-free." Seicean et al,[20] for example, reported significant associations between intraoperative transfusion and postoperative morbidity and prolonged LOS in a propensity-score matched analysis. Similarly, Wang and colleagues[17,18] found intraoperative transfusion to be an independent predictor postoperative DVT and PE. Further research is needed to clarify the impact of transfusion timing on patient outcomes.

All the studies included in this review, except one, were retrospective, the results of which have an increased risk of being influenced by unmeasured confounding variables. Blood transfusion may be a proxy for intraoperative blood loss, longer surgical times, increased surgical trauma, perioperative anemia, or other chronic diseases, making it difficult to isolate the adverse effects of transfusion on postoperative morbidity. In clinical practice, the decision to transfuse is often determined by the severity of illness demonstrated by the patient's symptoms. Retrospective studies are inherently unable to control for these subtle clinical signs which often influence transfusion decisions. While strict adherence to transfusion thresholds (eg, <8 g/dL) can minimize these effects, differences in transfusion protocols between institutions can be difficult to determine from national databases and the threshold for transfusions was unclear in the majority of studies included in this review. Therefore, the associations reported in this review are likely to be biased by the lack of standardization of transfusion decisions and the level of evidence supporting the associations reported in this review must be interpreted cautiously. The significant heterogeneity of the literature prevented a meta-analysis of the collective data, the lack of which is a limitation of the present study. As a result, the trends reported in this review cannot be interpreted as conclusive evidence of the effects of transfusions in spine surgery.

The gold standard of determining the efficacy of any treatment is the randomized clinical trial. Random allocation of patients into control and experimental groups increases the probability that known and unknown risk factors are distributed equally between the cohorts. To date, there have been 2 large, randomized, controlled trials assessing the impact of allogeneic blood transfusions on patient outcomes. In 1999, the TRICC (Transfusion Requirement in Critical Care) trial compared liberal (<10 g/dL) and restrictive (<7 g/dL) transfusion practices in critical ill patients.[51] Thirty-day mortality was similar between the groups, but subgroup analysis demonstrated significantly lower mortality associated with restrictive transfusion practices in younger patients (<55 years; $P = .02$) and less acutely ill patients (Acute Physiology and Chronic Health Evaluation Score ≤ 20; $P = .03$). Restrictive transfusions were also associated with lower rates of MI ($P = .03$), pulmonary edema ($P < .01$), and multiple-organ dysfunction ($P = .03$), but not infections, duration of ventilator support, or length of ICU or hospital stay. More recently, the FOCUS (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Repair) trial compared liberal (<10 g/dL) and restrictive (<8 g/dL) triggers in patients with a history of cardiovascular disease undergoing hip fracture surgery.[52,53] Liberal transfusions were not correlated with increased mortality at 60 days or on long-term follow-up (median follow-up, 3.1 years). In addition, liberal transfusions were neither associated with an inability to walk unaided on 60-day follow-up, nor were they associated with increased rates of MI, infection, or in-hospital complications. The findings from these 2 randomized clinical trials do not confirm many of the findings reported in this review, or those from observational studies outside the field of spine surgery, increasing our suspicion that the retrospective studies comprising the preponderance of the spine literature may be unduly influenced by unmeasured confounding variables. This observation underscores the need for randomized trials to assess the impact of transfusions in the setting of spinal surgery.

Conclusion

The available clinical research describing the use of allogeneic RBCs in spine surgery supports the conclusion that transfusion is associated with postoperative complications, especially infectious complications, and prolonged LOS. Some evidence demonstrates that a possible dose-response relationship may exist between morbid events and the number of RBC units administered, but these findings are inconsistent across the literature. The incidence and relative risks of specific complications remain unclear, because of the heterogeneity of reports, inconclusive findings of many of the studies, and the inherent limitations of retrospective analysis. Randomized clinical trials are required to clarify the impact of transfusions on patient outcomes in spinal surgery. Finally, 2 important gaps in the literature were identified: (*a*) the effect of liberal transfusion practices on patient recovery and long-term functional status and (*b*) the effect of transfusion timing on clinical outcomes. Further research is warranted to clarify these important clinical issues.

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Supplemental Material

The supplemental material is available in the online version of the article.

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