ORIGINAL ARTICLE

Transfusion Timing and Postoperative Septic Complications After Gastric Cancer Surgery

A Retrospective Study of 179 Consecutive Patients

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Background: Immunosuppression associated with homologous blood transfusion was first observed in renal allograft transplantation. Clinical effects of transfusion-induced immunosuppression in surgical patients have been debated in the literature for more than a decade with contradictory results.

Objective: To investigate whether homologous blood transfusions significantly affect postoperative septic morbidity and mortality in patients undergoing elective surgery for gastric cancer.

Design: Case series.

Setting: Hospitalized care.

Patients: The hospital records of 209 patients who underwent elective surgery for gastric cancer at the Department of Surgery of the Hospital del Mar, Autonomous University of Barcelona in Spain, and at the Department of Surgery of the Catholic University of Rome in Italy from April 1984 to December 1990 were reviewed, and 179 patients were included in the study.

Main Outcome Measures: The following variables were entered into univariate and multivariate analyses to identify factors potentially affecting postoperative septic morbidity: demographic data, weight loss, preoperative serum albumin level and lymphocyte count, type and duration of operative procedure, amount and timing of blood transfusion, and stage of disease.

Results: Univariate analysis showed that a large quantity of blood transfused (>1500 mL) and transfusion in the postoperative period (group C) were associated with a worse clinical outcome. Postoperative transfusion was an independent predictor of septic morbidity in multivariate analysis.

Conclusions: Despite transfusion-induced immunomodulation, homologous blood transfusion should not be considered a risk factor for postoperative septic morbidity in patients undergoing elective major abdominal surgery. The timing-response relationship between transfusions and septic morbidity in multivariate analysis may be the effect of uncontrolled confounders such as variation of volemia induced by stress response in patients who were developing or had just developed infectious complications.

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BLOOD TRANSFUSION therapy may result in immunologic changes (immunomodulation) that are beneficial in some patients but harmful in others.[1-4]

The best-characterized clinical effect of transfusion-induced immunomodulation is improved survival of renal allografts in patients who have undergone blood transfusions.[5] The deleterious effects of transfusion-induced immunosuppression in terms of cancer recurrence and increase in postoperative infectious complications have been debated in the literature for more than a decade, with contradictory results.[6-24] Even if it has been suggested that transfusion may be a marker for other factors that contribute to cancer recurrence, many studies[4] using multivariate analysis or meta-analysis of individual retrospective studies strongly support the concept that allogenic blood products increase cancer recurrence after a potentially curative surgical resection. The few studies that failed to find significance usually analyzed small populations and were often affected by other methodological problems; however, sometimes no apparent explanation of lack of a transfusion effect can be identified.[4] The related possibility of an association of perioperative transfusion with postoperative bacterial infection was examined in

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PATIENTS AND METHODS

The hospital records of patients who underwent surgery for gastric cancer at the Department of Surgery, Hospital del Mar, Autonomous University of Barcelona, Barcelona, Spain, and at the Department of Surgery of the Catholic University of Rome, Rome, Italy, from April 1984 to December 1990 were reviewed. We excluded patients with severe organ system derangements such as cardiac disease (documented myocardial infarction within the past 6 months or New York Heart Association class IV or greater), neurologic disease (cerebrovascular accident with persistent neurologic deficit during the past 6 months or neurologic deficit necessitating confinement to a custodial environment at home or in a long-term care facility), renal disease (severe peritoneal dialysis or hemodialysis), hepatic disease (portal hypertension with gastrointestinal tract bleeding or ascites on a hepatocellular basis or hepatic encephalopathy grade II or greater or clinical diagnosis of alcoholic hepatitis), pulmonary disease (long-term supplemental oxygen required at rest), and coagulation defect (prothrombin or partial thromboplastin time ≥2 times the normal value or platelet count of 50×10^9/L or less [≤50 000/μL]).

Demographic data, percentage of weight loss, preoperative serum albumin level and lymphocyte count, type and duration of operative procedure, amount and timing of blood transfusion, stage of the disease, hospital morbidity, and mortality were recorded.

Operative procedures consisted of total or subtotal gastrectomy (GR), bypass, or explorative laparotomy.

The total amount of blood transfused was defined as low (<600 mL), intermediate (600-1500 mL), and high (>1500 mL) independently from timing. Patients who did not undergo transfusion were in group A; those who exclusively underwent preoperative and/or perioperative transfusion were in group B; and those who underwent postoperative transfusion, with or without receiving preoperative or perioperative transfusion, were in group C. All patients who underwent transfusion received exclusively whole homologous blood, and in all patients other blood products were not administered during anesthesia or in the preoperative and postoperative periods.

Staging of the disease was performed according to the TNM system.

Postoperative septic complications were classified according to the following criteria: (1) major septic complications: pneumonia, requires radiographic evidence and documentation of a pathologic organism in sputum or pleural fluid; abdominal abscess, requires clinical or instrumental (ultrasound or computed tomographic scan) evidence of an abdominal purulent collection and spontaneous or operative drainage; and septicemia, requires a temperature of 38.5°C or higher and at least 1 blood culture yielding a pathogenic organism; and (2) minor septic complications: wound infection, requires purulent exudate in the wound with or without culture growth; and urinary tract infection, requires bacteriologic confirmation of more than 100 000 organisms per 1 mL of urine.

All patients received preoperative short-term antibiotic prophylaxis (1-3 doses of second- or third-generation cephalosporins). No patients underwent chemotherapy or radiotherapy before surgery or within 30 days of hospital discharge.

Statistical analysis was carried out using a software program (Statistical Package for the Social Sciences [SPSS] for Windows, version 6.0, SPSS Inc, Chicago, Ill). The categorical variables were compared using the coded χ^2 test. $P<.05$ was considered significant. Univariate analysis was used to evaluate the postoperative septic morbidity with respect to the following variables: age (<70 or ≥70 years), sex, type of treatment (GR, bypass procedures, or explorative laparotomy), duration of surgery (<250 or ≥250 minutes), staging of the disease, nutritional parameters (albumin level, lymphocyte count, and weight loss), need for blood transfusion, and amount and timing of blood transfusion. The same variables were entered into a multivariate logistic regression model.

more than 30 observational studies and in at least 7 randomized, controlled trials. The disagreements between the stated conclusions of the randomized, controlled trials paralleled the discrepant findings of the earlier observational studies.[6]

We carried out a retrospective study to investigate whether perioperative blood transfusions significantly affect postoperative septic morbidity and mortality in patients undergoing elective surgery for gastric cancer. Particular attention was given to evaluation of the relationship between timing of transfusion and postoperative clinical outcome, which has never been focused on in any previous clinical trial.

RESULTS

A total of 209 hospital charts of patients with gastric cancer were reviewed. Of these, 30 patients were excluded because of major concurrent illness, and 179 patients entered the study. Sixty-three patients (35.2%) were women and 116 (64.8%) were men. Mean patient age was 64.6 years (range, 26-92 years). Seventeen patients (9.5%) underwent a bypass procedure, 22 (12.3%) underwent explorative laparotomy, and 140 (78.2%) underwent total or subtotal GR.

The overall septic complication rate was 41.3%. Major septic complications developed in 55 patients (30.7%), 48 of whom had undergone GR. Postoperative mortality was 10.6%; 15 patients (10.7%) in the GR group died and 4 patients (10.3%) in the explorative laparotomy and bypass procedure groups died. Postoperative morbidity and mortality are detailed in **Table 1**.

One hundred thirty-two patients (73.7%) underwent transfusion. The mean ± SD amount of blood transfused was 1204 ± 1120 mL (range, 300-9600 mL). Fifty-seven patients received a low-volume transfusion, 34 received an intermediate-volume transfusion, and 41 received a high-volume transfusion.

The timing of transfusion is reported in detail in **Table 2**. There were 47 patients in group A, 91 patients in group B, and 41 patients in group C.

Postoperative mortality and overall major septic complications were significantly higher in patients receiving blood transfusions, but the difference was no longer

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Table 1. Postoperative Morbidity and Mortality in Patients Undergoing Elective Surgery for Gastric Cancer

	No. (%) of Patients by Type of Operation		
	Gastric Resection	Bypass Procedures and Explorative Laparotomy	Total
Wound infection	11 (7.9)	3 (7.7)	**14** (7.8)
Urinary tract infection	20 (14.3)	3 (7.7)	**23** (12.8)
Pneumonia	24 (17.1)	6 (15.4)	**30** (16.8)
Abdominal abscess	18 (12.9)	0	**18** (10.1)
Sepsis	12 (8.5)	1 (2.5)	**13** (7.2)
Overall major septic complications*	48 (34.3)†	7 (17.9)†	**55** (30.7)†
Mortality	15 (10.7)	4 (10.3)	**19** (10.6)

*Include pneumonia, abdominal abscess, and sepsis.
†The total number of patients shown for major septic complications is less than the sum of patients listed as having a single complication because some patients had more than 1 major septic complication.

Table 2. Transfusion Timing in Patients Undergoing Elective Surgery for Gastric Cancer

	No. of Patients*		
Transfusion Timing	Group A (n = 47)	Group B (n = 91)	Group C (n = 41)
Never	47	. . .	. . .
Preoperative	. . .	8	. . .
Perioperative	. . .	69	. . .
Preoperative and perioperative	. . .	14	. . .
Postoperative	. . .	. . .	11
Preoperative and postoperative	. . .	. . .	3
Perioperative and postoperative	. . .	. . .	18
Preoperative, perioperative, and postoperative	. . .	. . .	9

*Ellipses indicate not applicable.

Table 3. Postoperative Morbidity and Mortality in Transfused and Nontransfused Patients Undergoing Elective Surgery for Gastric Cancer

	No. (%) of Patients		
	Transfused	Nontransfused	*P*
All patients			
Wound infection	12 (9.1)	2 (4.3)	.29
Urinary tract infection	21 (15.9)	2 (4.3)	<.05
Pneumonia	23 (17.4)	7 (14.9)	.69
Abdominal abscess	16 (12.1)	2 (4.3)	.12
Sepsis	18 (13.6)	2 (4.3)	.11
Overall major septic complications*	47 (35.6)†	8 (17.0)†	.01
Mortality	18 (13.6)	1 (2.1)	<.05
Patients undergoing gastric resection			
Wound infection	10 (8.9)	1 (3.7)	.37
Urinary tract infection	19 (16.8)	1 (3.7)	.08
Pneumonia	19 (16.8)	5 (18.5)	.83
Abdominal abscess	16 (14.2)	2 (7.4)	.34
Sepsis	12 (10.6)	1 (3.7)	.31
Overall major septic complications*	42 (37.2)†	6 (22.2)†	.14
Mortality	14 (12.4)	1 (3.7)	.19

*Include pneumonia, abdominal abscess, and sepsis.
†The total number of patients shown for major septic complications is less than the sum of patients listed as having a single complication because some patients had more than 1 major septic complication.

Table 4. Postoperative Infectious Complications and Mortality by the Amount of Blood Transfused in Patients Undergoing Elective Surgery for Gastric Cancer

	No. (%) of Patients by Amount of Blood Transfused			
	Low	Intermediate	High	*P*
All patients				
Wound infection	5 (8.8)	3 (8.8)	4 (9.7)	.76
Urinary tract infection	8 (14.0)	8 (23.5)	5 (12.2)	.08
Pneumonia	7 (12.3)	4 (11.8)	12 (29.3)	.10
Abdominal abscess	4 (7.0)	3 (8.8)	9 (21.9)	<.05
Sepsis	5 (8.8)	3 (8.8)	4 (9.7)	.67
Overall major septic complications*	14 (24.6)†	11 (32.3)†	22 (53.7)†	<.01
Mortality	5 (8.8)	1 (2.9)	12 (29.3)	<.01
Patients undergoing gastric resection				
Wound infection	4 (8.2)	3 (10.7)	3 (8.3)	.81
Urinary tract infection	8 (16.3)	6 (21.4)	5 (13.9)	.28
Pneumonia	6 (12.3)	3 (10.7)	10 (27.8)	.20
Abdominal abscess	4 (8.1)	3 (10.7)	9 (25.0)	.09
Sepsis	5 (10.2)	2 (7.1)	4 (11.1)	.54
Overall major septic complications*	13 (26.5)†	10 (35.7)†	19 (52.8)†	<.05
Mortality	4 (8.1)	0	10 (27.8)	<.01

*Include pneumonia, abdominal abscess, and sepsis.
†The total number of patients shown for major septic complications is less than the sum of patients listed as having a single complication because some patients had more than 1 major septic complication.

statistically significant when considering only those undergoing GR (**Table 3**). Patients who received larger amounts of blood showed a trend toward higher postoperative mortality and septic morbidity (**Table 4**), particularly concerning development of intra-abdominal abscesses (7.0%, 8.8%, and 21.9% for low, intermediate, and high amounts of blood, respectively; $P<.05$).

According to the timing of transfusion, postoperative mortality and major septic complication rates were significantly higher in group C (postoperative transfusion) compared with group A (no transfusion) and group B (preoperative or perioperative transfusion) (**Table 5**). Similar results were obtained considering only patients who underwent GR (Table 5).

Univariate analysis of demographic, nutritional, and treatment-related variables showed a statistically significant association of sex, duration of operative procedure, need for blood transfusion, and amount and timing of transfusion with postoperative major septic complications (**Table 6**). Of these factors, multivariate logistic regression analysis showed that only lymphocyte count less than 1.5×10^9/L (≤1500/μL) and postoperative administration of blood (group C patients) were independent predictors of septic morbidity (**Table 7**). Thirty patients (73.2%) in group C developed septic complication. All patients but 1 underwent transfusion after

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Table 5. Postoperative Infectious Complications and Mortality by Timing of Transfusion in Patients Undergoing Elective Surgery for Gastric Cancer

	No. (%) of Patients by Timing of Transfusion			
	Group A	Group B	Group C	*P*
All patients				
Wound infection	2 (4.3)	6 (6.6)	6 (14.6)	.13
Urinary tract infection	2 (4.3)	11 (12.1)	10 (24.4)	.01
Pneumonia	7 (14.9)	8 (8.8)	15 (36.6)	<.01
Abdominal abscess	2 (4.3)	5 (5.5)	11 (26.8)	<.01
Sepsis	1 (2.1)	3 (3.3)	9 (22.0)	<.01
Overall major septic complications*	7 (14.9)†	18 (19.8)†	30 (73.1)†	<.01
Mortality	1 (2.1)	6 (6.6)	12 (29.3)	<.01
Patients undergoing gastric resection				
Wound infection	1 (3.7)	5 (6.4)	5 (14.3)	.15
Urinary tract infection	1 (3.7)	9 (11.5)	10 (28.6)	<.05
Pneumonia	5 (18.5)	6 (6.6)	12 (34.3)	.05
Abdominal abscess	2 (7.4)	5 (6.4)	11 (31.4)	<.01
Sepsis	1 (3.7)	2 (2.6)	9 (25.7)	<.01
Overall major septic complications*	6 (22.2)†	16 (20.5)†	26 (72.2)†	<.01
Mortality	1 (3.7)	3 (3.9)	11 (31.4)	.01

*Include pneumonia, abdominal abscess, and sepsis.
†The total number of patients shown for major septic complications is less than the sum of patients listed as having a single complication because some patients had more than 1 major septic complication.

surgery because of postoperative anemia (hemoglobin level, <9 g/L) in the absence of clinical evidence of bleeding at any site. In most of these cases (27 patients), septic complications preceded (19 patients) or were simultaneous with (8 patients) blood transfusion.

COMMENT

Immunosuppression associated with homologous blood transfusion was first observed in renal allograft transplantation.[5] Clinical evidence of a relationship between transfusion-induced immunosuppression and development of postoperative septic complications has been reported in many series[6,7,19-24] concerning head and neck, cardiac, orthopedic, and elective and emergency abdominal surgery.

According to these commonly reported figures, results of the present study show a striking relationship between homologous blood transfusion and septic morbidity (35.6% vs 17.0%; *P*=.01) and mortality in patients who did and did not undergo blood transfusions (13.6% vs 2.1%; *P*<.05).

In this study, in univariate analysis of factors potentially affecting postoperative septic morbidity, amount and timing of transfusion were statistically significant (Table 6).

A dose-response relationship between transfusion and infection was highlighted by Nichols et al[19] and was evident in the data of Dawes et al[22] and in this series. However, this relationship may reflect the effects of an uncontrolled confounder, such as a relationship between hypovolemia and transfusion and between hypovolemia and infections.[6]

Table 6. Univariate Analysis of Factors Affecting Development of Major Septic Complications in Patients Undergoing Elective Surgery for Gastric Cancer

	No. (%) of Patients		
	Total	Infected	*P*
Age, y			
<70	112	29 (25.9)	.71
≥70	67	26 (38.8)	
Sex			
Male	116	41 (35.3)	<.05
Female	63	14 (22.2)	
Weight loss			
None or <10%	118	39 (33.0)	.13
≥10%	61	16 (26.2)	
Albumin level, g/L			
<35	38	17 (44.7)	.21
≥35	141	38 (26.9)	
Lymphocyte count, $\times 10^9$/L			
<1.5	39	19 (48.7)	.22
≥1.5	140	36 (25.7)	
Type of surgery			
Gastric resection	140	48 (34.3)	.42
Bypass procedure	17	5 (29.4)	
Explorative laparotomy	22	2 (9.1)	
Duration of surgery, min			
<250	50	19 (38.0)	.32
≥250	129	36 (27.9)	
Blood transfusion			
Yes	132	47 (35.6)	.01
No	47	8 (17.0)	
Amount of blood transfused			
Low	57	14 (24.6)	<.01
Intermediate	34	11 (32.3)	
High	41	22 (53.7)	
Timing of blood transfusion			
Group A	47	8 (17.0)	<.01
Group B	91	17 (18.7)	
Group C	41	30 (73.1)	
Stage			
I	41	17 (41.5)	.57
II	38	15 (39.5)	
III	66	19 (28.6)	
IV	34	4 (10.7)	

*Only patients with major septic complications (pneumonia, abdominal abscess, and sepsis) were included.

Stratifying patients according to timing of transfusion, postoperative mortality, and septic morbidity were similar in groups A and B and significantly lower than in group C (Table 5). Postoperative transfusion was an independent prognostic factor in multivariate analysis (odds ratio, 17.5; 95% confidence interval, 5.8-52.8; *P*=.01). However, in most group C patients, septic complications preceded or were simultaneous with transfusion, and transfusion was administered in the absence of clinical evidence of bleeding. Therefore, we conclude that extracellular fluid expansion (leading to hemodilution and a low hemoglobin value) during stress response in patients who were developing or had just developed septic complications may act as a confounder and may be considered responsible for the association between postoperative transfusion and septic morbidity. In other words, it is not blood transfusions themselves but the circumstances necessitating transfusions that are the real determinants of prognosis. This

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Table 7. Multivariate Analysis of Factors Affecting Development of Major Septic Complications in Patients Undergoing Elective Surgery for Gastric Cancer

	Odds Ratio (95% Confidence Interval)	*P*
Age, ≥70 y	2.2 (0.9-5.5)	.08
Sex, female	0.5 (0.2-1.2)	.13
Weight loss, ≥10%	0.5 (0.2-1.3)	.13
Albumin level, <35 g/L	0.6 (0.2-1.9)	.42
Lymphocyte count, $<1.5 \times 10^9$/L	0.3 (0.1-0.9)	.03
Type of surgery		
Explorative laparotomy vs bypass procedure	2.6 (0.3-25.6)	.40
Explorative laparotomy vs gastric resection	2.7 (0.4-18.4)	.31
Duration of surgery, ≥250 min	0.6 (0.2-1.5)	.24
Blood transfusion	0.4 (0.03-5.6)	.52
Timing of blood transfusion		
Group A vs group B	2.2 (0.2-23.4)	.52
Group A vs group C	17.5 (5.8-52.8)	.01
Stage		
I vs II	1.0 (0.3-3.6)	.93
I vs III	1.0 (0.3-2.9)	.95
I vs IV	0.3 (0.06-1.9)	.23

does not mean that an immunosuppressive effect of allogenic blood transfusion does not exist but only that it may not be clinically relevant with respect to postoperative infectious complications.

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The Effects of Improved Glycemic Control on Complications in Type 2 Diabetes

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Type 2 diabetes is 8 to 10 times more common than type 1 diabetes, but no single large trial has established that improved glycemic control can prevent complications in type 2 diabetes. We have reviewed the results of the existing epidemiologic and clinical trial studies and have arrived at the following conclusions: (1) Strong evidence exists that improved glycemic control is effective at lessening the risks of retinopathy, neuropathy, and nephropathy in type 2 diabetes. (2) The evidence about the effect on coronary heart disease is limited and equivocal. (3) The hypoglycemic risk from improved glycemic control is significantly less in type 2 diabetes than in type 1, and weight gain seems to be modest. In conclusion, although glycemic goals should be individualized based on several clinical factors, most patients with type 2 diabetes would probably benefit from glucose lowering to a hemoglobin A_{1c} level between 7% and 8%. (*1998;158:134-140*)

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