

Original Research Article

The effect of peroperative erythrocyte transfusion on infectious complications in patients with gastric cancer undergoing curative gastrectomy

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ABSTRACT

Background: In this study, the effect of perioperative blood transfusion on infectious complications in patients undergoing curative surgery for gastric adenocarcinoma was investigated.

Methods: The clinicopathological results of 312 patients who underwent curative gastrectomy were retrospectively analyzed. The effect of blood transfusion on the development of postoperative infectious complications were statistically analyzed.

Results: In the subgroup of patients with intraoperative transfusion, surgical site infection incidence was found to be significantly higher in patient with 2U above ES transfusions. ($p=0.014$). In the subgroup of patients with postoperative transfusion, hospital stay ($p<0.001$), postoperative CRP values ($p<0.001$), surgical site infection incidence ($p=0.049$) and anastomosis leakage incidence ($p<0.001$) were found to be significantly higher in patient with 2U above ES transfusions. In the subgroup of patients with both intraoperative and postoperative transfusion, SSI, anastomotic leakage and any infective complication incidences were found to be significantly higher in patients with 2U and above transfusions. In multivariate analysis, age ($p=0.015$), BMI ($p=0.011$), intraoperative transfusion ($p=0.011$) and both intraoperative and postoperative transfusion ($p=0.045$) were found to be independent risk factors for infective complications.

Conclusions: It was found that performing peroperative ES transfusion is associated with increased rates of infectious complications in patients undergoing curative gastrectomy for gastric cancer by causing immunomodulation.

Keywords: Blood transfusion, Infection, Immunomodulation, Peroperative complications, Stomach neoplasm

INTRODUCTION

Gastric cancer is the fourth most common cancer in the world.¹ In our country, patients diagnosed with stomach cancer are generally diagnosed at an advanced stage. The gold standard treatment of advanced gastric cancer is radical gastrectomy and D2 lymph node dissection. Anemia that may develop due to tumor bleeding, gastrectomy or lymph node dissection is a common condition in patients with advanced gastric cancer. Peroperative blood transfusion may be inevitable in some

cases. However, there is an inverse proportion between the surgical experience and the need for blood transfusion.¹

There are many studies reporting that blood transfusion, which is frequently used to improve the general condition of the patient in the intraoperative and postoperative period, has a negative effect on long-term survival in cancer patients. In studies conducted, this negative effect on long-term survival was explained by transfusion-related immunomodulation.²⁻⁴ Experimental studies have

shown that allogeneic blood transfusion has suppressive effects on primary and secondary immunity. It is stated that it may have synergistic effect with immunosuppression resulting from surgical stress and anesthesia.⁵⁻⁷ Considering the literature, studies on infectious complications associated with blood transfusion in stomach cancer patients are limited.

The aim of the study was to reveal the relation between the timing of blood transfusion and the development of post-operative infective complications in patients undergoing gastrectomy for gastric adenocarcinoma.

METHODS

Patient selection

In the study, 312 patients who underwent gastrectomy at Ankara University Faculty of Medicine Surgical Oncology Department with a diagnosis of gastric malignant neoplasm between January 2017 and January 2019 were retrospectively reviewed. Patients with metastatic disease, palliative surgery, additional organ resection, emergency surgery, patients with hematological disease, patients with active infection, patients with preoperative blood product replacement, patients with synchronous tumors, non-adenocarcinoma malignant gastric tumor patients and patients with additional comorbidity that would impair wound healing were excluded from the study. 127 patients who met the criteria were included in the study. The study was planned after the approval of Ankara University Faculty of Medicine Ethics Committee.

Surgery procedure

All cases were done by the same surgical team. Informed consent was obtained from the patients in the preoperative period. One day before the operation, bowel cleansing was performed using laxatives and enemas. The patients were operated after 8 hours of fasting. Cefazolin was administered as a prophylactic antibiotics preoperatively 1g I.V. infusion and the second dosage form perioperative. Intraoperative normothermia was provided by anesthesiologists and all surgical procedures were performed in accordance with routine asepsis and antisepsis rules. Patients undergoing laparoscopic surgery were given Lloyd-Davies position, and patients undergoing conventional surgery were supine. Total/subtotal gastrectomy + D2 lymph node dissection surgery was performed according to the localization of the tumor with an open or laparoscopic approach. Inpecially laparoscopic patients, all incisions were standardized by removing them from the abdomen through the median incision on the navel.

Data collection

Transfusion timing and total amount of transfused erythrocyte suspension (ES) were documented in patients

who needed erythrocyte suspension transfusion during or after surgery. The replacement limit was generally considered to be below the hemoglobin concentration of 8 g/L. However, in order to provide hemodynamic stabilization, patients with higher hemoglobin concentrations needed replacement. The hemoglobin value above 10 g/L was accepted as the criteria on for replacement of the replacement.⁸ In the postoperative period, all infective complications that developed during the hospitalization of the patient were documented. demographic data of all patients, ASA (American Society of Anesthesiologists) scores, preoperative hemoglobin and albumin values, co-morbid diseases, duration of surgery and type of surgery, TNM stage of tumor, need for erythrocyte suspension in intraoperative and postoperative period and amount of replacement, level of white blood cell, 48. hour C-reactive protein levels (CRP), blood and body fluid cultures, PA chest X-ray findings, images of patients undergoing abdominal imaging were documented. All data were collected and processed by the general surgery specialist and data collection assistants.

Statistical analysis

Statistical analyzes were performed using IBM SPSS statistics for Windows (Ver. 23.0, NY: IBM Corporation). Continuous data are given as mean value \pm SD and student T test was used in the data with normal distribution. X² or Fisher Exact Test was used to evaluate categorical data. Univariate analyzes were performed in subgroup analyzes between infectious complications and risk factors, and p values were calculated to be considered as <0.05 significance by performing multivariate analyzes among significant parameters.

RESULTS

In this study, retrospective observational evaluation of the relationship between intraoperative or postoperative erythrocyte suspension replacement and postoperative infectious complications in patients undergoing curative surgery due to gastric adenocarcinoma. 65 of 127 patients included in the study consist of male patients. The average age of the patients was calculated as 55.5 \pm 14.5.

The patients were grouped as patients receiving intraoperative and postoperative blood transfusions. When evaluated according to intraoperative transfusions, patients were divided into subgroups as patients who underwent ES transfusion under 2 units (U) and those who underwent 2 U and above. There were 103 patients undergoing ES transfusion below 2U. When age, body mass index (BMI), TNM stage, preoperative hemoglobin and albumin values, tumor localization and neoadjuvant treatment were compared between patients grouped according to the need for intraoperative transfusion, there was no significant difference.

Table 1: Comparison of clinicopathological variables according to intraoperative and postoperative transfusion administration.

Variables	Intraoperative transfusion		P value	Postoperative transfusion		P value
	<2 units or none	≥2 units		<2 units or none	≥2 units	
Age	55.75±13.84	54.96±14.74	0.804	52.20±11.40	63±16.17	0.001>
Gender (male)	57 (55.3)	8 (33.3)	0.043	45 (51.7)	20 (50)	0.504
BMI	26.54±4.06	25.69±3.47	0.345	27.1±3.44	24.6±4.48	0.001
T Stage						
T1	3 (2.9)	0 (0)	0.231	3 (3.4)	0 (0)	0.001>
T2	31 (30.1)	3 (12.5)		33 (37.9)	1 (2.5)	
T3	46 (44.7)	13 (54.2)		35 (40.2)	24 (60.0)	
T4	23 (22.3)	8 (33.3)		16 (18.4)	15 (37.5)	
N Stage						
N0	29 (28.2)	3 (12.5)	0.217	31 (35.6)	1 (2.5)	0.001>
N1	67 (65)	20 (83.3)		51 (58.6)	36 (90)	
N2	7 (6.8)	1 (4.2)		5 (5.7)	3 (7.5)	
TNM						
Stage 1	28 (27.2)	3 (12.5)	0.275	30 (34.5)	1 (2.5)	0.001>
Stage 2	51 (49.5)	13 (54.2)		40 (46)	24 (60.0)	
Stage 3	24 (23.3)	8 (33.3)		17 (19.5)	15 (37.5)	
Preoperative Hg	13.34±2.51	12.53±2.20	0.152	14.10±2.25	11.15±1.49	0.001>
Preoperative albumin	35.83±6.87	33.34±6.18	0.107	37.39±6.50	30.94±5.18	0.001>
Neoadjuvant treatment	21 (20.4)	4 (16.7)	0.464	15 (17.2)	10 (25)	0.215
Tumor localizations						
Distal	69 (67)	13 (54.2)	0.172	54 (62.1)	28 (70)	0.253
Other	34 (33)	11 (45.8)		33 (37.9)	12 (30)	
Operative approach						
Laparoscopy	68 (66)	11 (45.8)	0.056	60 (69)	19 (47.5)	0.017
Laparotomy	35 (34)	13 (54.2)		27 (31)	21 (52.5)	
Operasyon						
DG	69 (67)	13 (54.2)	0.172	54 (62.1)	28 (70)	0.253
TG	34 (33)	11 (45.8)		33 (37.9)	12 (30)	

Table 2: Comparison of preoperative outcomes according to intraoperative and postoperative transfusion administration.

Variables	Intraoperative Tx		P value	Postoperative Tx		P value
	<2 units or none	≥2 units		<2 units or none	≥2 units	
Operation Time	169.45±24.72	167.34±26.19	0.857	168.73±25.55	167.94±26.24	0.732
Hospital stay	16.98±6.86	16.92±7.27	0.968	14.94±4.87	21.38±8.53	0.001>
Postoperative WBC	10.25±3.15	10.50±3.49	0.728	10.16±3.00	10.57±3.62	0.507
Postoperative CRP	221.9±61.27	229.5±63.17	0.589	207.1±59.89	258.6±49.29	0.001>
SSI	12 (11.7)	8 (33.3)	0.014	10 (11.5)	10 (25)	0.049
Anastomotic leakage	15 (14.6)	5 (20.8)	0.315	6 (6.9)	14 (35)	0.001>
Pneumonia	14 (13.6)	5 (20.8)	0.272	11 (12.6)	8 (20)	0.206

In case of male gender ($p=0.043$) and open surgery approach in operative procedure, the need for blood transfusion was significantly higher. ($p=0.056$). When the patients who received ES transfusions postoperatively were evaluated, there was no significant difference between the groups undergoing ES replacement below 2U and the groups undergoing ES replacement at 2U and

above, according to gender ($p=0.804$), neoadjuvant therapy ($p=0.464$) and tumor localization ($p=0.172$). There was a significant difference between the two groups in the age ($p<0.001$), BMI ($p=0.001$), TNM staging ($p<0.001$), preoperative hemoglobin ($p<0.001$), preoperative albumin ($p<0.001$), open surgical approach. ($p=0.017$) (Table 1).

Table 3: Comparison of postoperative infective complications in the subgroup of patients have been administered both intraoperative and postoperative treatment.

Variables	Total (n=127)	Intraoperative and Postoperative Tx (Peroperative Tx) (n=9)	P value
SSI	20 (15.7)	4 (44.4)	0.034
Anastomotic leakage	20 (15.7)	4 (44.4)	0.034
Pneumonia	19 (15)	2 (22.7)	0.402
Any infective complications	43 (33.9)	6 (66.7)	0.040

Table 4: Univariate and multivariate analysis of risk factors of any infective complications after curative gastrectomy for gastric adenocarcinoma.

Variables	Univariate analysis		Multivariate analysis	
	OR (%95 CI)	P value	Adjusted OR (%95CI)	P value
Age (>65)	10.2 (4.19~25.1)	0.001>	1.06 (1.01~1.12)	0.015
Gender (male)	-	-	-	-
BMI(>25)	0.32 (0.15~0.69)	0.003	1.06 (1.01~1.12)	0.011
Operative Approach (laparotomy)	2.10 (0.94~4.27)	0.050	-	-
Operation Time (>180mn)				
Neoadjuvant Treatment				
Intraoperative Tx	2.32 (0.94~5.73)	0.050	4.76 (1.42~15.8)	0.011
Postoperative Tx	3.84 (1.73~8.49)	0.001		
Peroperative Tx	4.37 (1.03~18.4)	0.040	4.62 (1.03~20.8)	0.045

When the peroperative outcomes of the patients with intraoperative transfusion were compared, each other surgical site infection incidence was found to be significantly higher in patient with 2U above ES transfusions. (p=0.014).

When the peroperative outcomes of the patients with postoperative transfusion, were compared, each other hospital stay (p<0.001), postoperative CRP values (p<0.001), surgical site infection incidence (p=0.049) and anastomosis leakage incidence (p<0.001) were found to be significantly higher in patient with 2U above ES transfusions (Table 2).

In the subgroup analysis of patients who underwent ES transfusion intraoperatively and postoperatively, infectious complications were significantly increased. It is observed that 4 (p=0.034) of 20 patients with wound infection, 4 (p=0.034) of 20 patients with anastomosis leakage and 2 of 19 patients with respiratory infections are in this group (Table 3).

Univariate analysis was performed for the effect of risk factors which are expected to be effective on the development of infective complications and evaluated separately. As a result of the analysis, age>65 (p<0.001), body BMI>25 (p=0.003), selection of laparotomy as a surgical method (p=0.050), intraoperative ES transfusion (p=0.050), postoperative ES transfusion (p=0.001) and ES transfusion in the intraoperative plus postoperative period (p=0.040) were statistically significant with the risk of surgical complications (Table 4). When

performing multivariate analysis, the age>65 (p=0.015), BMI>25 (p=0.011), intraoperative transfusion (p=0.011) or intraoperative and postoperative transfusion (p=0.045) statistically on surgical complications. It was found to be significantly effective (Table 4).

DISCUSSION

Today, it is known that there is a significant relationship between ES transfusion and pneumonia, surgical site infections and perioperative mortality in non-traumatic and non-cardiothoracic abdominal operations.⁹ In a study published in 1992, in patients undergoing elective gastrointestinal cancer surgery, it has been shown that peroperative 1000 ml ES transfusion increases the risk of developing postoperative infectious complications.¹⁰

In studies conducted, peroperative transfusion was found to be an important negative prognostic factor associated with decreased disease-free survival and overall survival, regardless of transfusion timing or number of units transfused.³ In addition to its effect on relapse and survival, numerous studies have shown that peroperative transfusion is a risk factor for postoperative complications after gastric resection, especially infectious and septic complications.^{9,11} Although the immunosuppression mechanism developed after transfusion cannot be fully revealed, the decrease in TNF- α level, IL10 induction, natural killer lymphocytes and macrophages loss, relative increase in T helper 2 lymphocyte and decrease in IL2 amount are shown as responsible.^{6,11-13}

The relationship between peroperative ES transfusions and infectious complications is not clear in gastric cancer patients undergoing curative gastrectomy. In the studies conducted, although the results in our study are generally similar, some findings have also been encountered in some studies.

There are studies on the effect of erythrocyte transfusions on peroperative results and early complications, especially in colorectal surgery. There are studies on colorectal surgery where multiple ES transfusions are detected as an independent risk factor for anastomosis leakage in the perioperative period.¹⁴ However, in patients operated for left colon cancer and undergoing colorectal anastomosis, a relationship has been demonstrated between multiple ES transfusions and the frequency of anastomosis leakage.¹⁵

In multivariate analyzes performed in a multicentre retrospective study in which data of 765 patients were examined, peroperative ES transfusion was determined as an independent variable associated with decreased disease-free survival and decreased overall survival regardless of timing.³ In another study published in 2002, the ES transfused group reported a statistically significant lower survival and negative dose-response relationship between the amount of transfused ES and the prognosis.¹⁶

In patients undergoing esophagectomy, there was no statistically significant relationship between ES transfusion and postoperative major infectious complications.¹⁷ In contrast, in the study of gastroesophageal junction tumors, there was a significant relationship between ES transfusion after surgery and leakage in esophagoenterostomy anastomosis, but no increase in anastomosis leaks with increased transfusion amount.¹⁸

In the study conducted in Japan in 2014, where risk factors for pulmonary complications after gastrectomy were investigated, pneumonia, surgical site infection and mortality were significantly increased in patients undergoing ES transfusion.¹⁹

This study generally gives similar results to the literature. Nevertheless, it is considered as a deficiency in the study because it was planned as a single-center study, the peroperative mortality was not added, the number of patients was not high, it was planned as a retrospective study and that the group of patients who were not given any transfusion and the groups that received transfusion could not be compared as a subgroup.

As a result, in our study, it was observed that peroperative ES transfusion in patients who underwent curative surgery due to gastric cancer was associated with increased infectious complications due to immunomodulation. Surgical site infection was the most common infectious complication. These findings are compatible with the literature.

CONCLUSION

It was found that performing peroperative ES transfusion is associated with increased rates of infectious complications in patients undergoing curative gastrectomy for gastric cancer by causing immunomodulation.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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