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The effect of preoperative blood transfusion on morbidity and survival in colorectal malignancy

Ameliyat öncesi kan transfüzyonunun kolorektal kanserde morbidite ve sağkalıma etkisi

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Background/aims: *It is believed that blood transfusions adversely affect colorectal cancer surgery. However, intra- and postoperative blood transfusions represent urgent interventions, and immeasurable confounding factors may affect the short- and long-term outcome. Therefore, we compared colorectal cancer patients who had received preoperative blood transfusion with patients who did not receive transfusions with regard to postoperative complications and long-term outcome.* ***Methods:*** *The records of 333 patients who were operated for colorectal malignancy between 1980 and 1995 were evaluated.* ***Results:*** *Sixty-one patients (18.3%) received preoperative blood transfusions. Wound infection rate was higher (14.2% vs 1.9%) in the no-transfusion group. Disease-free survival was not different between the groups (p=0.134). Cumulative survival was adversely affected in the preoperative transfusion group (p=0.012). However, preoperative blood transfusion did not emerge to be an independent factor for wound infection or for death on follow-up when the confounding factors were corrected.* ***Conclusion:*** *Preoperative transfusion during surgery for colorectal malignancy does not result in an increase in postoperative complications, long-term failure or death rates.*

Key words: Colorectal cancer, complications, blood transfusion, survival

Amaç: *Kolorektal kanser cerrahisinde kan transfüzyonunun hastayı olumsuz etkilediği düşünülmektedir. Ancak ameliyat sırasında ve sonrasında yapılan transfüzyonlar acil kabul edilen girişimler olup transfüzyon dışında birçok ölçülemeyecek etken kısa ve uzun dönem sonuçlarda etkili olabilir. Bu nedenle kolorektal kanserli hastalarda daha elektif bir girişim olan ameliyat öncesi kan transfüzyonunun ameliyat sonrası komplikasyonlara ve uzun dönem sağkalıma etkisini araştırdık.* ***Yöntem:*** *1980-1995 yılları arasında kolorektal kanser nedeniyle ameliyat edilen 333 hastanın kayıtları geriye dönük olarak incelendi.* ***Bulgular:*** *Altmışbir hastaya (%18.3) ameliyat öncesi kan transfüzyonu yapıldı. Yara enfeksiyonu kan transfüzyonu yapılmayan grupta daha fazla idi (%14.2'ye karşı %1.9). Hastalıksız sağkalım iki grup arasında farklı değildi (p=0.134). Toplam sağkalım ameliyat öncesi transfüzyon yapılan grupta daha kötü idi (p=0.012). Ancak etkisi olabilecek diğer etkenlerin düzeltilmesinden sonra ameliyat öncesi kan transfüzyonunun yara enfeksiyonu ve uzun dönemde ölüm riskine etkisi olmadığı gösterildi.* ***Sonuç:*** *Serimizde ameliyat öncesi kan transfüzyonunun kolorektal kanser cerrahisinde komplikasyon artışına, hastalık yinelemesine ve ölüm oranına etkili olmadığı belirlenmiştir.*

Anahtar kelimeler: Kolorektal kanser, komplikasyon, kan transfüzyonu, sağkalım

INTRODUCTION

Blood transfusion in colorectal cancer surgery has long been a topic of debate. Over 100 retrospective and at least three prospective randomized trials have been published in the literature (1). It was proposed that immuno- suppressive effects of blood transfusion might adversely affect the postoperative outcome and long-term survival (2). In fact, in many of the retrospective studies a negative effect was documented. However, some of the authors who reported detrimental effects hypothesized that not blood transfusion per se, but circumstances that necessitate transfusion, are responsible for the adverse outcome (3). Furthermore, some studies could not demonstrate any untoward effects of perioperative blood transfusion (1, 4, 5).

Blood transfusion during or after the surgical procedures is usually an urgent intervention resulting from worsening condition of the patient.

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Conversely, preoperative transfusion is usually an elective maneuver aimed at optimally preparing the patient for the oncoming surgical trauma. In most of the studies, these separate interventions are pooled together, which may be a reason for the inconsistent results. In an effort to homogenize the groups, we compared the non-transfused patients with only preoperatively transfused patients in terms of postoperative complications and long-term outcome.

MATERIALS AND METHODS

The records of the 812 patients with the diagnosis of colorectal malignancy, who were managed between January 1980 and December 1995 at the Department of General Surgery, were analyzed retrospectively. Of these patients, 713 (87.8%) underwent surgical exploration or polypectomy for early lesions. Polypectomy cases and the patients with malignant lesions other than carcinomas were excluded. Of the remaining patients, 333 patients were either preoperatively transfused or did not receive any kind of transfusion during the hospitalization. Blood transfusions were whole blood or packed red cells; leukocyte or buffy-coat reduction was not done. Patient demographics, admission biochemistry panel, complete blood count, tumor markers (CEA, CA 19-9, AFP), admission symptoms, duration of symptoms, results of the imaging/endoscopic studies, length of stay, type of surgery, number and timing of blood transfusions, ASA score, postoperative complications, histological type, tumor size, and Duke's stage (Astler-Coller modification) were recorded. The follow-up data was compiled from the patient records, posted questionnaires and telephone calls requesting the

Table 1. General characteristics of the patients

Parameters**	Preoperative transfusion (n=61)	No transfusion (n=272)	P (univariate)	P (regression for wound infection)¶	P (regression for death on follow-up)¶
Age (years [SD]) (n=332)	55.3 [14.8]*	53.0 [14.0]	0.260	-	-
Sex (M/F) (n=333)	32/29	167/105	0.198	-	-
Intestinal obstruction † (n=306)	3/53 (5.7%)	47/253 (18.6%)	0.021	0.570	0.385
Presence of weight loss (n=288)	35/52 (67.3%)	124/236 (52.5%)	0.053	0.924	1.0
Mass on abdominal examination (n=305)	24/49 (49.0%)	65/256 (25.4%)	0.001	0.624	0.213
LOS (days) ‡ (n=330)	24.9 [16.7]	20.8 [12.4]	0.030	0.495	0.065
Hb (g/dl) (n=329)	8.9 [2.4]	12.9 [1.8]	<0.001	0.899	0.121
Albumin (g/dl) (n=314)	3.5 [0.7]	3.9 [0.7]	<0.001	0.970	0.990
Duration of symptoms (months) (n=312)	10.9 [10.6]	7.7 [11.3]	0.049	0.707	0.624
ASA score (n=329)	2.6 [0.8]	1.6 [0.7]	<0.001	0.372	0.946
Tumor located in rectum/sigmoid (n=333)	13/61 (21.3%)	107/272 (39.3%)	0.008	0.083	0.304
Invasion to adjacent organs (n=154)	21/33 (63.6%)	48/121 (39.7%)	0.046	0.386	0.557
Perforation at surgery (n=333)	1/61 (1.6%)	6/272 (2.2%)	0.623	-	-
Surgery with curative intent (n=329)	35/60 (58.3%)	188/269 (69.9%)	0.083	-	-
Ostomy (n=333)	13/61 (21.3%)	98/272(36.0%)	0.028	0.404	0.111
Add. Intervention § (n=333)	10/61 (16.4%)	27/272 (9.9%)	0.146	-	-
Pathological tumor size (cm) (n=153)	7.5 [3.9]	5.1 [2.6]	0.001	0.387	0.656
Duke's stage			0.139	-	-
A		14 (5.1%)			
B	25 (41.0%)	110 (40.4%)			
C	10 (16.4%)	64 (23.5%)			
D	25 (41.0%)	81 (29.8%)			
Unknown	1 (1.6%)	3 (1.1%)			
Metastatic lymph nodes (n=281)	1.5 [2.9]	1.7 [3.4]	0.640	-	-
Total lymph nodes (n=164)	17.6 [13.1]	13.9 [10.3]	0.185	-	-
Total complications (n=316) ††	13/55 (23.6%)	81/261 (31.0%)	0.275	-	-
Pulmonary	1	6	0.653		
Anastomotic	0	5	0.388		
Wound infection	1 (1.9%)	37 (14.2%)	0.011		
Urinary	0	10	0.147		
Cardiac	1	9	0.465		
Other	10 (18.5%)	22 (8.4%)	0.025		
Postoperative death (n=315)	3/54 (5.6%)	11/261 (4.2%)	0.441	-	-
Loco-regional recurrence (n =175)	4/26 (15.4%)	23/149 (15.4%)	0.630	-	-
Distant metastasis (n=183)	7/30 (23.3%)	31/153 (20.3%)	0.716	-	-
Death on follow-up (n=265)	17/43 (39.5%)	59/222 (26.6%)	0.085	-	-
Preoperative transfusion				0.322	0.781

*Figures in brackets are standard deviation values, **Figures in parenthesis represent the available patient numbers for the specific analysis, † Symptoms that point to partial or complete obstruction, †† Some patients have more than one complication, therefore the numbers do not total properly. ‡ Length of stay, § Additional interventions during primary surgery, ¶ Significance of factors for wound infection and mortality on logistic regression analysis

last clinically documented status, and health security databases. Overall, 278 patients (83.5%) had a mean follow-up of 58.6 months (range: 1-257 months).

Chi-square analysis with Spearman's correlation analysis when necessary was used for comparison of categorical variables. For continuous variables, Student's t-test or its nonparametric counterpart, Mann Whitney-U test, was used. Logistic regression analysis with forward stepwise inclusion of the independent variables was used for analyzing the multivariate effects of the variables on binary outcomes of wound infection and death on follow-up. Life-table method with Gehan statistic was used for survival analysis. For all analyses, a probability value of less than 0.05 was accepted as significant.

RESULTS

Of the 333 patients, 199 (59.8%) were male. The mean (standard deviation-SD) age of the patients was 53.5 (14.2) years. Rectosigmoid tumors were present in 36.0% (n=120) of the patients. Sixty-one patients (18.3%) received a mean of 2.2 units (range: 1-9 units) of preoperative blood transfusion. Pathological types were adenocarcinoma (83.0%), mucinous carcinoma (12.7%) or undifferentiated carcinoma (4.2%). The main characteristics of the groups are depicted in Table 1.

There was no difference regarding the total complication rate and postoperative deaths between the groups. However, the wound infection rate was higher in the no-transfusion group. Preoperative transfusion did not emerge to be a significant factor when the factors that were significantly different between the groups in the univariate analysis were entered in the logistic regression model (Table 1). None of the factors that were significantly different between the groups in the univariate analysis was correlated with an increased rate of wound infection or death on follow-up in the regression model.

Similarly, the rates of patients with recurrence, distant metastasis, and death on follow-up were not significantly different between the groups. In the patients who were operated with curative intent (n=223, 66.9%), disease-free survival was not significantly different between the groups (p=0.134). However, the overall crude survival was adversely effected in the preoperatively transfused patients (p=0.012) (Figures 1, 2). This effect

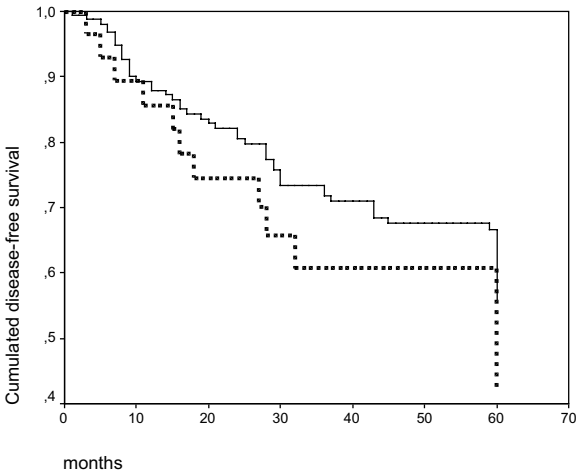

Figure 1. Cumulated disease-free survival of patients who received preoperative blood transfusion (dotted line) or no transfusion (straight line). Life-table plot with Gehan statistic; p=0.134

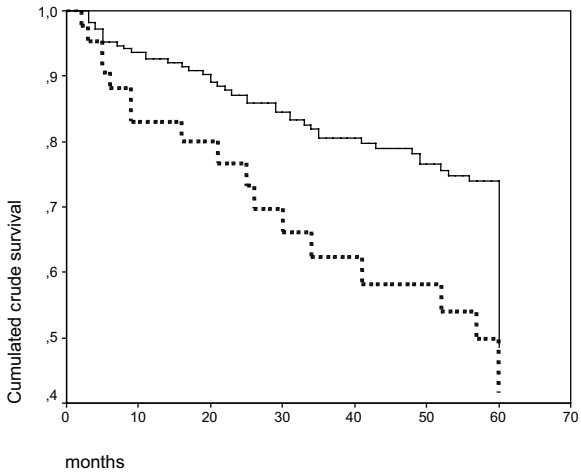

Figure 2. Cumulated crude survival of patients who received preoperative blood transfusion (dotted line) or no transfusion (straight line). Life-table plot with Gehan statistic; p=0.012

of preoperative blood transfusion was pronounced in the Duke's stage C group. In stage C patients, five-year survival rate for the no-transfusion group was 72.9% versus 34.3% in the preoperatively transfused patients (p=0.005). There was no significant difference in five-year survival rates between groups in other Duke's stages (data not shown).

DISCUSSION

After the initial report documenting a beneficial effect of graft survival in renal transplantation patients who received blood transfusion, many

authors investigated the effects of transfusion on patients with different cancer types (6). Colorectal cancer is the most frequently studied type. Effects of blood transfusion in the surgery of colorectal cancer were investigated mainly under two headings as postoperative complications and long-term survival.

Most of the studies to date have demonstrated a detrimental effect of perioperative transfusion in terms of postoperative complications, especially infectious complications, in colorectal cancer surgery (1, 7). Although no difference could be detected between leukocyte-depleted transfusion and buffy-coat depleted transfusion in terms of wound infection, an increased risk due to any kind of blood transfusion was documented in prospective randomized studies (4, 8). Adverse effects of blood transfusion were documented in other cancer types. In patients undergoing gastric cancer surgery, postoperative transfusion led to an increased incidence of postoperative septic complication (9).

It was suggested that adverse effects of blood transfusion might last years, which is also reflected in the increased incidence of recurrence (2). However, increased risk of infection was documented with only postoperative transfusion and has led to the conclusion that the effects of blood transfusion are short-lived (7, 9). This suggests that preoperative transfusion may not be detrimental after all. In line with this, it was reported that preoperative transfusion did not increase surgical site infections after elective colorectal resections in a large series (10). The patients who were preoperatively transfused in our series were in a poorer condition than their counterparts as reflected by a lower hemoglobin and albumin level, higher ASA score, and increased incidence of weight loss. And yet there was no increased incidence of general postoperative complications. Interestingly, the wound infection rate was even lower in the pre-transfused group. However, when the mentioned confounding variables were corrected between the groups, no effect of transfusion on wound infection remained (Table 1). Although the main reason for morbidity was wound infection, other serious complications also occurred in this series. Anastomotic failure may be a fatal complication. In fact, one of our patients with anastomotic failure (20%) died in the hospital. Colostomy, either diverting or permanent, may help to decrease the rate of intra-abdominal catastrophes caused by anastomotic failures. However, colostomy complications occur frequently. In our series, colostomy complications (necrosis or prolapsus) resulted in morbidity in five patients (4.5% of patients with stoma). There was no significant difference between groups regarding these complications.

The claimed adverse effects of blood transfusion on long-term outcome such as recurrence or death due to the disease were mainly the immunosuppressive effects of blood transfusion (2). Parrott et al. reported an increased rate of recurrence and mortality in 517 patients undergoing curative surgery for colorectal cancer with perioperative blood transfusion (11). However, other studies have not supported this conclusion (5). Although over 100 retrospective studies have been published regarding the long-term outcome of colorectal cancer patients, only one-fourth of them had sufficient qualified data to be included in a recent meta-analysis (12). Furthermore, most of the studies did not even include a measure of the general health status such as ASA score (1). Therefore, inconsistent conclusions are present even between the several meta-analyses (12, 13). In order to overcome the limitations of the retrospective studies, several prospective studies that compared different transfusion protocols in which less immunosuppressive effect is aimed in the treatment arms were designed. In these studies, no adverse effects were demonstrated between different transfusion protocols (3, 4). However, an adverse effect on recurrence and survival was documented in patients receiving transfusions of any type. Thus, it was claimed that not blood transfusions but the circumstances that necessitate transfusions are deleterious (3, 14). A crude but general measure of the general status of the patients is the ASA score. Although it is deduced that ASA score may be an important determinant in colorectal surgery, in our series the ASA score did not seem to affect complications nor the long-term outcome (1).

Palliative or curative surgery is a principal option in locoregional recurrence. Seventeen patients with locoregional recurrence (62.9%) underwent surgical exploration. The median survival of these patients was 35 months. Of the patients with distant metastasis, liver was the only affected organ in 22 patients (57.9%). In this group, salvage surgery in the form of wedge or formal liver resection augmented with chemotherapy may result in extended survival. In our group, liver resection was possible in only three patients. The small number prevented any statistical analysis.

Unfortunately, there are only a small number of studies investigating the timing of perioperative transfusion in relation with recurrence and survival rates in colorectal cancer. Francis and Judson reported that transfusion during surgery was associated with a worse prognosis (14). However, the same relation could not be demonstrated by others (11, 15). In our series, preoperative transfusion did not cause an increase in the recurrence rate or disease-free survival compared to the non-transfused patients. Although there was no difference in the rate of patients who died during follow-up, overall survival was less in the preoperatively transfused patients (Figure 2). Interestingly, in only Duke's stage C patients, preoperative transfusion was associated with a poorer overall survival. Transfusion might have accelerated the disease process, which was in an advanced stage in this group. In Duke's D patients, however, the disease is so advanced that it is probably not possible to further speed up the progression by transfusion. Conversely, in early stage cancers, other clinicopathological variables are dominant in determining the overall survival, and transfusion probably does not have enough impact on prognosis.

Patients transfused during or after the operation represent an urgent clinical status, which inherently presents difficulties for measuring confounding factors such as transient hypotension and decreased perfusion of the organs. Some of these factors are probably unknown at the present time and they may even be immeasurable. Therefore, in an effort to homogenize the study population, we included only the preoperatively transfused patients that represent an elective intervention in terms of transfusion protocols and clinical status.

In conclusion, preoperative blood transfusion in this retrospective series did not cause an increase in postoperative complications, in local or distant failure rates or in disease-free survival. Although overall survival was adversely affected in preoperatively transfused patients, preoperative transfusion is a safe practice and should not be withheld in anemic patients who present with an increased operative risk.

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