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Effect of Perioperative Allogeneic Red Blood Cell Transfusion on the Immune-Inflammatory Response After Colorectal Cancer Resection

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Abstract Cytokines play an important role in the acute-phase response to trauma. Few studies have analyzed the effects of allogeneic blood transfusion containing packed red blood cells (RBCs) on the early postoperative immune/inflammatory response after colorectal resection for cancer This study investigated whether allogeneic RBC transfusion influences the postoperative immune/inflammatory response of patients submitted to large bowel resection due to cancer. A total of 26 patients—15 men and 11 women, with a median age of 56.5 years (range 24–87 years)—were prospectively studied. Blood samples were obtained preoperatively and on the first and fourth postoperative days for C-reactive protein (CRP), interleukin-6 (IL-6), and IL-10 assays and for CD4 and CD8 lymphocyte counts. Transfused (≥3 and <3 units), and nontransfused patients were compared. Both IL-6 and IL-10 increased postoperatively in transfused patients ($p < 0.01$). The serum IL-6 level was higher in patients receiving ≥3 units of RBCs ($p < 0.01$). CRP increased postoperatively unrelated to blood transfusion. The CD8 count decreased ($p < 0.04$) in transfused subjects, whereas CD4 decreased ($p < 0.01$) only in major-transfusion patients. Perioperative allogeneic RBC transfusion enhances the inflammatory systemic response and decreased immunity in patients submitted to colorectal resection for cancer.

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Cytokines play an important role in the acute-phase response to trauma. Typically, serum levels of various cytokines increase after trauma, and the magnitude of the rise is correlated with postoperative complications [1–4]. The balance between proinflammatory [tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), IL-6] and antiinflammatory (IL-4, IL-6, IL-10) cytokines is essential for homeostasis and may define the prognosis [5]. IL-6 has both pro- and antiinflammatory characteristics, although at high levels it is an alarm indicator of the magnitude of the inflammatory response [6, 7]. The persistence of high IL-6 levels after the first postoperative day is an independent factor associated with septic postoperative complications [8–10]. Moreover, an increased IL-6/IL-10 ratio is related to a worse outcome in patients with the systemic inflammatory response syndrome (SIRS) [11].

Approximately 30% to 60% of patients with colorectal cancer are malnourished preoperatively [12, 13]. Malnutrition affects the immune response and has long been recognized as a risk factor for postoperative morbidity and mortality [12, 13]. Marked activation of the proinflammatory cytokine network is prominent in malnourished patients when they undergo intense surgical stress. These immunologic disturbances may be relevant to neutrophil activation and subsequent clinical outcome [14]. Anemia is another common feature in patients with large bowel carcinoma, and some may need blood transfusion perioperatively [15]. Anemia in patients with a malignancy increases the morbidity and mortality and weakens the therapeutic response rate [12, 15]. Untreated preoperative anemia and acute perioperative blood loss, however, may represent additional surgical risk. In contrast, allogeneic blood transfusion (ABT) may impair the immune system and enhance the acute-phase response to trauma. These effects

on the immune system caused by ABT are mostly mediated by white blood cells present in the transfused allogeneic cellular blood components [16–18]. Reported immunomodulatory effects of ABT are decreased production of T-helper cells, natural killer cells, lymphocytes, and cytotoxic-mediated cells [19].

Few studies have analyzed the effects of ABTs containing packed red blood cells (RBCs) on the early postoperative immune inflammatory response after colorectal resection for cancer [20]. We hypothesized that enhanced immunosuppressive and proinflammatory responses occur after ABT with RBCs. Therefore, a study to investigate the evolution of the proinflammatory and antiinflammatory cytokines in transfused patients could demonstrate the role of packed RBC transfusion on the acute response to operative trauma, and the data could contribute to our knowledge of postoperative immunity in patients undergoing surgery for cancer. Thus, the aim of this study was to evaluate the influence of allogeneic RBC transfusion on the systemic immune/inflammatory response after colorectal resection due to cancer.

Material and methods

Patients

The study was approved by the Ethics Committee of Julio Muller Hospital of the Federal University of Mato Grosso. Admission criteria stated that those enrolled must be elective adult patients with colorectal adenocarcinoma who were candidates for large bowel resection and who had no history of blood transfusion. Excluded from the study were patients who had had radiotherapy and/or chemotherapy before the operation; those who had used corticosteroids, cytotoxic agents, or immunosuppressive drugs within 6 months; those with an ASA (American Society of Anesthesiologists) score >3; those who had undergone recent treatment for any infection; and those who had any autoimmune or immunosuppressive disease.

Independent and outcome variables

Preoperatively, the following independent variables were recorded: sex, age, ASA score, surgical procedure, operating time, nutritional status (categorized as normal or malnourished by subjective global assessment (SGA) [21], and serum albumin level. Surgical procedures were categorized as either colectomy (right and left colectomy) or rectal resection (low anterior resection and abdominoperineal resection).

The clinical indications for blood transfusion included a pre- or perioperative hematocrit <30% or the hemodynamic status of the patient. Patients with hematocrit below 30% received the necessary amount of ABT and underwent operation only if the hematocrit reached ≥ 30%. Intraoperative ABT was given if blood loss was excessive by the surgeon's and/or anesthesiologist's judgment. The storage time of RBCs was not recorded. Patients were categorized as either group 1 (transfused) or group 2 (nontransfused). All transfusions were done using units (300 ml) of allogeneic packed RBCs. The transfused group was divided into patients who received either ≥3 units (group 1A) or <3 units (group 1B) of RBCs. We also analyzed the findings in patients receiving either preoperative or intra/postoperative ABT.

Blood samples were collected during anesthesia induction and on the first and fourth postoperative days (PODs) for a complete blood count; IL-6, IL-10, and C-reactive protein (CRP) assays; and for helper lymphocyte (CD4) and suppressor lymphocyte (CD8) counting (outcome variables). All ABTs had to be finished before the blood collection on POD 1.

Statistical analysis

Comparisons were done between the transfused (group 1) and nontransfused (group 2) patients. To analyze the influence of the magnitude of ABT, we compared the nontransfused group with group 1A (ABT with ≥3 units) and group 1B (ABT with <3 units). The timing of the transfusion (preoperative vs. intra/postoperative) was also analyzed.

The chi-squared or Fisher's exact test was used to compare categorical data. One-way analysis of variance (ANOVA) or the Kruskal-Wallis test was done for continuous variables comparison. Independent variables (sex, age, operating time, ASA score, operative procedure, and nutritional status) were tested using either logistic or linear regression analysis to identify potential associations with outcome variables (cytokines, CRP, total lymphocytes, CD4 and CD8 counts). Only nutritional status (categorized as malnourished or normal) was identified ($p < 0.20$) as having potential association with the outcome variables. Repeated-measures ANOVA (including or not including nutritional status as covariate) was used to analyze the evolution of cytokines, CRP, lymphocytes, CD4, and CD8 among groups. A multivariate ANOVA was performed to compare the differences between POD 1 and POD 0 and between POD 4 and POD 0 controlling for baseline data (POD 0) and nutritional status. Differences within or between groups were analyzed by the Wilcoxon test or Tukey's test. Statistical significance was established at 5% ($p \leq 0.05$). All analysis was done by a statistical software package (SPSS for Windows 11.0; SPSS, Chicago, IL, USA) run on a microcomputer.

Table 1 Demographic data of 26 patients undergoing colorectal resection for cancer according to allogeneic red blood cell transfusion

Parameter	Group 1 (transfused)	Group 2 (nontransfused)	*p*
No. of patients (n = 26)	14	12	
Sex (male/female)	7/7	8/4	0.45
Age (years), median and range	57 (24–87)	55.5 (23–83)	0.92
ASA			
1, 2	13	11	1.00
3	1	1	
Malnutrition (no.)	10 (71.4%)	7 (58.3%)	0.37
Hematocrit at D0 (%), median and range	36.2 (30.1–42.2)[a]	37.2 (32.4–49.9)	0.43
Operative procedure			
Colectomy	4	5	0.68
Resection of the rectum	10	7	
Duration of surgery (min), median and range	180 (125–600)	150 (110–245)	0.08
RBCs transfused (units), mean and range	3.4 (1–8)	—	<0.001
Time of the transfusion			
Preoperative	7	—	1.0
Intra/postoperative[b]	7	—	
Disease stage			
1, 2	6	7	0.69
3, 4	8	5	
Mortality (no.)	1 (7.1%)	2 (16.7%)	0.58

ASA: American Society of Anesthesiologists; RBCs: red blood cells

[a] Hematocrit at the induction of anesthesia (D0). Seven of fourteen patients in group 1 received preoperative transfusion up to adequate hematocrit status (≥30%)

[b] Intraoperative transfusion in all seven cases. In two cases transfusion continued during the immediate postoperative course

Results

In total, 26 patients entered the study. The demographic data of the patients according to groups can be seen in Table 1. No significant differences were seen in the distribution of age, sex, operative procedures, duration of surgery, ASA score, or nutritional status between the groups. The median age was 56.5 years (range 24–87 years). The tumor was localized in the right colon in 8 patients (30.8%), in the left colon in 1 (3.8%), and in the rectum in 17 (65.4%).

There were 14 patients (53.8%) who received RBC ABTs (group 1) and 12 (46.2%) who did not (group 2). Eight patients of the transfused group received ≥3units of ABT (group 1A), and six were given <3 units (group 1B). Patients in group 1 received a mean of 3.4 (range 1–8) units. The mean volume of ABT received by patients of group 1A was 4.6 units (range 3–8 units), and in subgroup 1B these figures were 1.6 units (1–2 units). Seven patients (four in group 1A, three in group 1B) were transfused preoperatively, and seven (four in group 1A, three in group 1B) were transfused intraoperatively. Intraoperative transfusion continued through the immediate postoperative course in two of them.

The clinical characteristics of the patients are in Table 1. Malnutrition was established in 65.4% (17/26) of patients: 71.4% (10/14) in group 1 and 58.3% (7/12) in group 2 (p = 0.68). Altogether, 23 (88.5%) of the patients were discharged, and 3 died (11.5%): Two patients had anastomotic dehiscence and died of multiple organ failure, and one had an acute pulmonary embolism.

Effect of blood transfusion

The results of the various outcome variables in transfused and nontransfused patients can be seen in Table 2 and Figure 1.

IL-6

Serum IL-6 levels increased after trauma in the two groups and then decreased by POD 4 ($p < 0.01$). The rise was significantly greater in the transfused group than in the nontransfused group ($p = 0.03$). The difference in the IL-6 levels between PODs 1 and 0 was greater in the transfused group ($p < 0.01$) (Fig. 1). There was no difference between POD 4 and POD 0.

IL-10

Serum IL-10 was also augmented postoperatively in the two groups, although the increase was greater in the transfused subjects (p = 0.01). The difference in IL-10 levels between POD 1 and POD 0 was higher in the transfused group ($p = 0.01$) and can be seen in Figure 2. No difference occurred between POD 4 and POD 0.

Table 2 Evolution of IL-6, IL-10, PCR, and lymphocytes in transfused and nontransfused patients undergoing colorectal resection due to cancer

Variable	Group 1 (transfused)	Group 2 (nontransfused)	*P*
IL-6 (pg/ml)			
D0	5.2 ± 3.2	4.3 ± 6.3	0.03
D1	336.5 ± 235.4*	175.0 ± 163.3*	
D4	42.5 ± 77.9	56.1 ± 102.4	
IL-10 (pg/ml)			
D0	3.3 ± 1.8	2.5 ± 1.7	0.01
D1	9.4 ± 4.4*	4.2 ± 2.1*	
D4	4.3 ± 1.9	2.1 ± 0.7	
CRP (mg/L)			
D0	5.9 ± 7.8	4.4 ± 5.3	0.62
D1	15.2 ± 7.2**	13.5 ± 6.6**	
D4	14.0 ± 8.3	13.8 ± 9.8	
Lymphocytes (/mm^3)			
D0	1518.7 ± 662.3	1731.1 ±622.5	0.12
D1	1141.9 ± 413.0***	1462.5 ± 429.4***	
D4	1161.2 ± 428.9	1442.0 ± 611.3	
CD4 (/mm^3)			
D0	510.7 ± 207.6	727.7 ± 467.3	0.21
D1	339.6 ± 86.9***	545.8 ± 516.4***	
D4	484.1 ± 237.3	591.6 ± 245.2	
CD8 (/mm^3)			
D0	267.4 ± 127.0	370.4 ± 126.7	0.04
D1	184.1 ± 68.2***	235.5 ± 107.2***	
D4	192.8 ± 107.9	273.0 ± 100.0	

IL-6: interleukin 6; IL-10: interleukin 10; CRP: C-reactive protein; CD4: helper T lymphocytes; CD8: suppressor T lymphocytes; D0: intraoperative; D1: first postoperative day; D4: fourth postoperative day

Values are the mean ± SD

*D1 > D4 > D0; $p < 0.01$

**D1 > D0; $p < 0.01$

***D1 < D0; $p = 0.04$ (for lymphocytes), $p = 0.01$ (for CD4), $p = 0.03$ (for CD8)

CRP and lymphocytes

CRP levels increased, and both total lymphocytes and CD4 counts decreased after the surgical procedure similarly in the two groups. The postoperative fall of CD8 was greater in transfused patients ($p = 0.04$). Comparisons between POD 1 and POD 0 and between POD 4 and POD 0 showed no differences for all variables.

Influence of malnutrition

There was no statistical difference between malnourished and normal subjects in any of the measurements except CD4 lymphocytes, which had a lower count in the malnourished patients than in normal subjects (730.7 ± 348.9 vs. 391.8 ± 163.6 cells/mm^3; $p < 0.01$). In a multivariate analysis that included nutritional status as a covariate, the difference seen in serum IL-6 levels between groups 1 and 2 ceased to exist. However, malnutrition did not change the findings of all other results between transfused and nontransfused patients.

Effect of the magnitude of the transfusion

The findings of the variables can be seen in Table 3 and Figure 2.

IL-6

Both groups of transfused patients had higher serum IL-6 levels than nontransfused subjects at POD 1. The increase in IL-6 between POD 0 and POD 1 was significantly greater in major-transfusion patients (≥3 units) ($p < 0.01$) than in the other two groups and was higher in patients receiving <3 units when compared to nontransfused patients ($p = 0.04$). No differences were seen in the comparisons of values on POD 4.

IL-10

The increase in serum IL-10 was significantly greater in patients who received <3 units than in nontransfused patients ($p = 0.01$). However, the difference in serum IL-10 between POD 1 and the baseline levels was higher in both transfused groups compared to the nontransfused group ($p < 0.05$). Comparisons at POD 4 were not significant.

CRP and Lymphocytes

There was no difference in the CRP level, total lymphocyte count, or CD8 count that could be related to the ABT volume. Compared with preoperative levels, on POD 1 the CD4 count was significantly lower in major-transfusion subjects [≥3 units: –302 (–444; –156) cells/mm^3] than in the other two groups [<3 units: 13 (–121; –118) cells/mm^3; nontransfused: –164 (–307; –3) cells/mm^3; $p < 0.01$]. At POD 4 there was no significant difference in any of the variables.

Effect of the timing of the transfusion

There were no statistical differences for the IL-6, IL-10, or CRP assays or for CD4 and CD8 counts (outcome variables) at POD 0, 1, or 4 in patients receiving either preoperative or intra/postoperative ABT (data not shown).

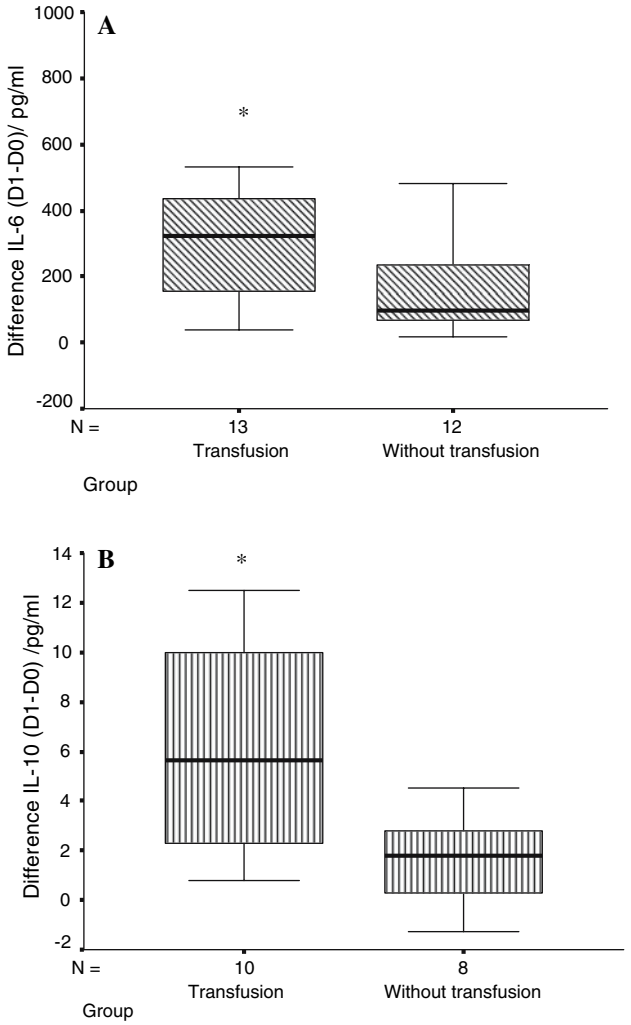

Fig. 1 Difference of serum IL-6 (**a**) and IL-10 (**b**) levels between D1 and D0 in patients undergoing colorectal resection for cancer according to the number of allogeneic red blood cells transfused. Data are the median, interquartile interval, and range. IL-6: interleukin 6; IL-10: interleukin 10; D0: intraoperative; D1: first postoperative day. *$p < 0.01$ vs. without transfusion

Discussion

Determining surgical risk is of key importance in general surgery. Various factors have been reported to play a role in the development of postoperative complications [22], including the nutritional status of the patient, magnitude of the operative procedure, experience of the surgeon, and exposure to ABT [22, 23].

High circulating levels of IL-6, IL-10, and acute-phase proteins such as CRP after trauma are predictive of postoperative complications [24, 25]. Our data showed that transfused patients had higher serum levels of both IL-6 and IL-10 than nontransfused patients. This suggests that allogeneic packed RBC transfusion may intensify the systemic inflammatory response and impair the immune re-

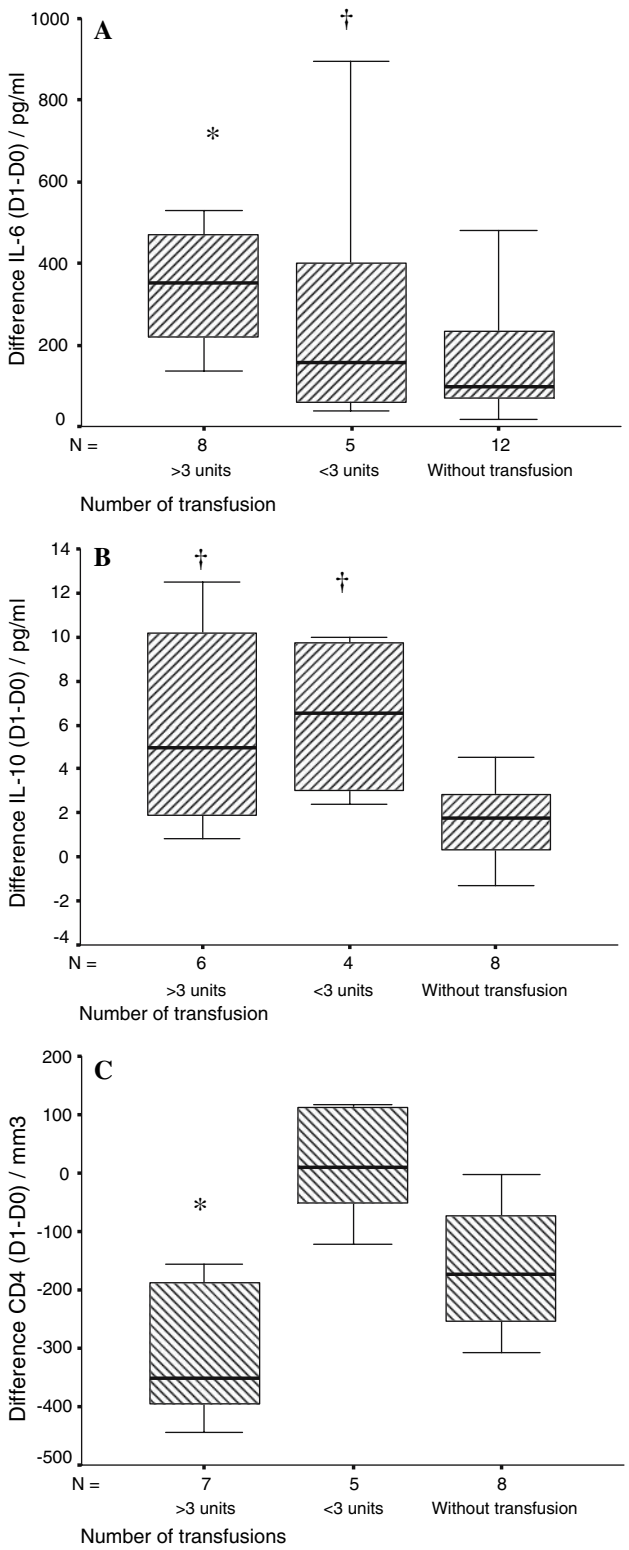

Fig. 2 Difference of serum IL-6 (**a**) and IL-10 (**b**) levels and CD4 counting (**c**) between D1 and D0 in patients undergoing colorectal resection for cancer according to the number of allogeneic red blood cells transfused. Data are the median, interquartile interval, and range. CD4: helper T lymphocytes. *$p < 0.05$ vs. both <3 units of blood and without transfusion; †$p < 0.05$ vs. without transfusion

Table 3. Evolution of IL-6, IL-10, CRP, and lymphocytes according to the number of units of red blood cells transfused in 26 patients undergoing colorectal resection for cancer

Variable	Group 1A (≥3 units transfused)	Group 1B (<3 units transfused)	*p*
IL-6 (pg/ml)			
D0	5.5 ± 3.8	4.6 ± 2.2	0.90
D1	349.6 ± 144.8*	315.2 ± 358.6*	
D4	52.0 ± 98.4	27.2 ± 27.8	
IL-10 (pg/ml)			
D0	3.3 ± 1.5	3.4 ± 2.5	0.97
D1	9.2 ± 4.6	9.7 ± 4.8*	
D4	4.8 ± 1.9	3.6 ± 2.0	
CRP (mg/L)			
D0	4.4 ± 2.7	7.8 ± 11.9	0.98
D1	16.4 ± 6.9	13.7 ± 7.9	
D4	14.8 ± 7.8	13.0 ± 9.5	
Lymphocytes (/mm^3)			
D0	1507.8 ± 406.1	1533.1 ± 953.5	0.75
D1	1048.2 ± 411.8	1266.8 ± 416.3	
D4	1067.3 ± 507.0	1286.5 ± 292.6	
CD4 (/mm^3)			
D0	656.1 ± 105.2	307.2 ± 114.8	0.55
D1	353.4 ± 108.7	406.8 ± 215.3	
D4	506.0 ± 274.6	399.1 ± 145.7	
CD8 (/mm^3)			
D0	321.8 ± 111.6	191.2 ± 115.0	0.70
D1	176.42 ± 61.2	213.4 ± 87.2	
D4	177.12 ± 107.5	202.33 ± 116.3	

Values are the mean ± SD

IL-6: interleukin 6; IL-10: interleukin 10; CRP: C-reactive protein; CD4: helper T lymphocyte; CD8: suppressor T lymphocyte, D0: intraoperative; D1: postoperative day 1; D4: postoperative day 4

*p = 0.04 (IL-6) and p = 0.03 (IL-10) versus nontransfused

sponse after surgery. In accordance with one study [26], perioperative blood transfusion was an independent risk factor for postoperative infection. The plasma supernatant of ABT products [18, 27] and even packed RBCs contain cytokines and other bioactive substances, which may cause an increase in the circulating IL-6 [28].

Interleukin-10 is an important antiinflammatory cytokine generated in response to surgical stress, and its release is related to the increased serum levels of IL-6 [29, 30]. Our findings showed that malnutrition did not modify the significant statistical association between IL-10 and ABT as it did for IL-6. This suggests that the strength of the association between ABT and IL-10 is greater than that for ABT and IL-6. High circulating levels of IL-10 impair leukocyte activation and degranulation [31]. Consequently, a potent antiinflammatory effect is expected and may predispose the patient to infection [16, 32]. Taking all this into account, the findings suggest that ABT induces a higher immunosuppressant effect than a proinflammatory effect. Although we have not assessed the incidence of postoperative complications, previous reports have consistently shown that patients receiving ABT are most prone to infections [16, 26, 32].

Circulating CRP levels are enhanced in response to various inflammatory stimuli [33–35]. However, in contrast to both IL-6 and IL-10 behavior after ABT, CRP levels increased similarly in the two groups. Serum CRP usually peaks 48 to 72 hours after stimuli; and by the second postoperative day, excessive levels may predict infection after major abdominal operations [36], Possibly, the time points of this study (PODs 1 and 4) were not the most precise to find differences in CRP levels between transfused and nontransfused subjects.

This study was focused on colorectal cancer patients, most of whom had advanced disease and were malnourished. These conditions affect the immune response [14, 37], and ABT in these circumstances may aggravate it [26, 38]. Malnutrition was assessed by SGA, which is a well validated screening tool. SGA has higher sensitivity than other methods [21] and is the screening tool recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) [39]. This may explain the high incidence of malnutrition seen in this study.

The blood transfusion volume has been related to the magnitude of the immunosuppressant effect [26, 27, 38]. Multiple ABTs cause a decrease in CD4 lymphocytes, resulting in a decreased CD4/CD8 ratio [38]. A significant decrease in CD8 lymphocytes was detected in the transfused groups, and CD4 lymphocytes decreased in major-transfusion patients. These results are relevant; they are consistent with the literature and, in conjunction with other findings, strongly suggest an immunosuppressant status after allogeneic RBC transfusion. Our data also showed that serum IL-6 increased in major-transfusion patients, although IL-10 was augmented in both minor and major ABT recipients. In contrast, the timing of transfusion did not influence the immune/inflammatory response. We could not find any previous study that compared patients receiving preooperative or intra/postoperative ABT against which to evaluate these data. However, a previous retrospective study showed that postoperative transfusion is more significantly associated with complications than perioperative (pre-/intraoperative) transfusion [40]. Thus, these findings suggest that the volume of ABT is more important than the timing of the transfusion in patients undergoing colorectal resection for cancer.

There are some weak points in this study that deserve some consideration. Although transfused and nontrans-

fused patients were comparable in terms of various demographic variables, the time of storage and the preoperative individual immunologic status due to the chronic disease were not taken into account. Blood storage time may play a significant role in blood transfusion-associated development of postoperative infectious complications [41]. Moreover, the number of patients included in the present series was small. Thus, caution is necessary when trying to understand the present findings, and further studies are mandatory.

Conclusions

Packed RBC transfusion enhances both inflammatory and immunosuppressive systemic responses in patients undergoing colorectal resection for cancer. The impairment of postoperative immunity due to ABT seems to be more marked than the enhanced proinflammatory response. The number of units transfused significantly influences the immune/inflammatory response. Thus, the current study implicates ABT as having an influence on inflammatory modulation after resection of colorectal cancer. These data emphasize the importance of avoiding unnecessary transfusions. In addition, they encourage consideration of less immunogenic alternatives to allogeneic RBC transfusion.

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