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Perioperative Allogeneic Blood Transfusion Is Associated With Surgical Site Infection After Abdominoperineal Resection—a Space for the Implementation of Patient Blood Management Strategies

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Allogeneic blood transfusion (ABT) has been reported as a major risk factor for surgical site infection (SSI) in patients undergoing colorectal surgery. However, the association of ABT with SSI in patients undergoing abdominoperineal resection (APR) and total pelvic exenteration (TPE) still remains to be evaluated. Here, we aim to elucidate this association. The medical records of all patients undergoing APR and TPE at our institution in the period between January 2000 and December 2012 were reviewed. Patients without SSI (no SSI group) were compared with patients who developed SSI (SSI group), in terms of clinicopathologic features, including ABT. In addition, data for 262 patients who underwent transabdominal rectal resection at our institution in the same period were also enrolled, and their data on differential leukocyte counts were evaluated. Multivariate analysis showed that intraoperative transfusion was an independent predictive factor for SSI after APR and TPE ($P = 0.004$). In addition, the first–operative day lymphocyte count of patients undergoing APR, TPE, and transabdominal rectal resection was significantly higher in nontransfusion patients compared with transfusion ones ($P = 0.026$). ABT in the perioperative period of APR and TPE may have an important immunomodulatory effect, leading to an increased incidence of SSI. This fact should be carefully considered, and efforts to avoid allogeneic blood exposure while still achieving adequate patient blood management would be very important for patients undergoing APR and TPE as well.

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Postoperative surgical site infection (SSI) is one of the most frequent complications associated with various surgical procedures, and it results in adverse outcomes, including longer hospital stay, higher health care costs, and increased surgical mortality.[1] It is one of the most frequent nosocomial complications, accounting for almost one fifth of all health care–associated infections.[2] Colon surgery and rectal surgery are associated with higher SSI rates compared with most other abdominal procedures, with 5% to 25% of colon and rectal surgery patients developing incisional and organ/space SSI.[3–5] Moreover, the incidence of overall SSI was reported to be higher in rectal surgery patients (17%–28%) than in colonic surgery patients (9%–23%),[3,5,6] with especially higher overall SSI rates observed in patients undergoing abdominoperineal resection (APR; 12%–51%).[7–9] These are attributed to the high infection rates of the perineal wound, reported to be as high as 21%.[10] Thus, the incidence of SSI associated with APR should be the highest among the various abdominal operative procedures.

Various risk factors for postoperative SSI in colorectal surgery were reported previously. Open surgery,[10–12] perioperative allogeneic blood transfusion (ABT),[4,10,12] and prolonged operation time[4,9] have been found to be risk factors for SSI in a number of studies. Although several preceding reports have investigated the risk factors for SSI associated with APR, the reported independent risk factors varied among the studies. Although a number of studies have reported on the role of ABT as a strong risk factor for incisional SSI in colorectal surgery,[13,14] only one study has investigated on its relevance to the onset of incisional SSI after APR procedure; but this study failed to demonstrate a significant association. Presently, therefore, the role of ABT as a potential risk factor for incisional SSI in APR remains to be elucidated, and doing so will be very important for the implementation of measures to achieve patient blood management in this group of patients.

In this study, we aimed to elucidate the risk factors for SSI in patients receiving APR, especially focusing on ABT.

Materials and Methods

Medical records were retrospectively reviewed for 150 consecutive patients undergoing APR or total pelvic exenteration (TPE) in the Department of Surgical Oncology, University of Tokyo, in the period between January 2000 and December 2012. Patients without SSIs (no SSI group) were compared with patients with postoperative SSIs (SSI group). Wound infections were detected according to the Centers for Disease Control and Prevention (CDC) classification of SSI.[15] The diagnosis of SSI was made by the clinical signs, including the presence of erythema, induration, pain, and contaminated discharge of the wound. In addition, laboratory data indicative of inflammation, and the presence of abscess accompanied by opacity of the adjacent tissue in the abdominal computed tomography scan were used as parameters to confirm SSI.

Patients' characteristics include age, sex, body mass index, American Society of Anesthesiologists physical status, presence of diabetes mellitus, smoking habit, and neoadjuvant therapy. Serologic data include preoperative total protein, albumin, carcinoembryonic antigen, and carbohydrate antigen. Blood cell counts include preoperative white blood cell, hemoglobin, and platelet counts. Operative details include intraoperative blood transfusion, preoperative diagnosis, operative procedure, infusion volume, urination volume, estimated blood loss, ABT volume, and operation time. Neoadjuvant therapy includes both preoperative radiotherapy and preoperative chemoradiotherapy. The radiotherapy regimen usually consisted of a total dose of 50.4 Gy administered by a 3-field technique fractionated over a 5-week period (28 fractions of 1.8 Gy), and the chemoradiotherapy regimen consisted of dosing tegafur/uracil and folinate (with or without weekly CPT-11) simultaneously with 50.4 Gy/28 fraction radiation. Among the 150 patients included in the study, 128 patients received a diagnosis of primary rectal cancer. These patients were histopathologically reviewed, and pathologic TNM classification was determined according to the classification established by the American Joint Committee on Cancer.

We also evaluated the association between preoperative or postoperative leukocyte subsets and ABT in rectal surgery patients. Because data for differential leukocyte count in the first postoperative day (POD1) were available for only 44 patients undergoing APR or TPE, all consecutive patients who underwent transabdominal rectal resection, including APR and TPE, during the same period were

retrospectively investigated. Among the 812 patients investigated, 507 were excluded because the differential leukocyte count in the POD1 was not measured, and another 72 were excluded because of the precedent neoadjuvant therapy, which could affect the leukocyte subset count. Finally, 233 patients were included in this evaluation and were divided into two groups, namely, the transfused and the non-transfused groups. The number of preoperative neutrophils and lymphocytes, and those at POD1 were assessed, and the differences between the groups were evaluated using a Mann-Whitney *U* test.

Statistical analysis was performed using JMP software (SAS Institute Inc, Cary, North Carolina). The univariate correlation between each independent variable and incisional SSI was evaluated using a Mann-Whitney *U* test for continuous variables and a Pearson χ^2 test for categoric variables. Independent variables with a *P* value <0.1 in the univariate analysis were entered into the multivariate logistic regression model, using a Wald statistic backward stepwise selection. The Kaplan-Meier method and the log-rank test were used to estimate long-term survival. Cox proportional hazard model was also used for multivariate analysis. *P* values <0.05 were considered to be statistically significant. Our study protocol was approved by the ethics committee of the University of Tokyo.

Results

Univariate analysis

During the study period, 150 patients underwent APR or TPE, and among them, 57 patients (38%) developed SSI. The differences in patient background characteristics, serologic data, blood cell count, and operative details between the groups (no SSI group and SSI group) are shown in Table 1. No differences between groups were observed in any of the parameters investigated, except for intraoperative ABT and ABT volume. The incidence of SSI was significantly higher in patients who underwent intraoperative ABT ($P = 0.006$), and the ABT volume was significantly higher in the SSI group ($P = 0.008$).

The pathologic features of the patients with primary rectal cancer are shown in Table 2. In total, 128 patients received a diagnosis of primary rectal cancer, and 50 of them (39%) developed SSI. Absence of lymph node metastasis or vascular invasion was associated with higher incidences of SSI ($P = 0.024$ and $P = 0.036$, respectively). Absence of lymphatic invasion also showed a tendency toward association with higher SSI incidence ($P = 0.060$).

Multivariate analysis

Based on the results of univariate analysis, multivariate logistic regression analysis was performed using variables with *P* values lower than 0.1, namely, intraoperative ABT, lymph node metastasis, lymphatic invasion, and vascular invasion. Table 3 shows the results of multivariate analysis. Only intraoperative ABT was found as an independent factor in predicting the onset of SSI after APR and TPE ($P = 0.004$).

Associations between SSI or ABT and cancer prognosis

Of the 128 patients with primary rectal cancer, 28 died and 56 experienced disease recurrence, including 18 local recurrences. We evaluated the association of SSI and ABT with prognosis in rectal cancer patients. As shown in Fig. 1a and 1b, neither the disease-free survival (DFS) nor the overall survival (OS) was significantly different between the SSI and the non-SSI groups. In contrast, patients with perioperative ABT showed a significantly shorter DFS compared with those without ABT ($P = 0.002$). We also evaluated the multivariate analysis using Cox proportional hazard model, but we failed to demonstrate the independency of ABT in DFS after surgery (Table 4).

Neutrophil and lymphocyte count before and after operation

To elucidate the mechanism of the association between blood transfusion and postoperative SSI development, we focused on the perioperative changes in leukocyte subsets. Because the leukocyte subset was available in only 44 of the APR or TPE patients, we alternatively investigated all patients who underwent rectal surgery during the same period and had leukocyte subsets of preoperation and POD1 available, excluding those who received neoadjuvant chemotherapy.

Finally, a total of 233 patients were divided into two groups, namely, those without (n = 197) and those with (n = 36) intraoperative blood transfusion. Both preoperative neutrophil and lymphocyte counts were not significantly different between these groups (3720 ± 1386 versus 3890 ± 1736, $P = 0.517$; 1622 ± 584 versus 1452 ± 542, $P = 0.106$, respectively), and there was also no significant difference in neutrophil count at POD1 between the groups (7472 ± 2402 versus 7122 ± 2310; $P = 0.415$). However, patients receiving intraoperative blood transfusion showed a markedly lower lymphocyte count in the POD1 than those without

Table 1 Clinicopathologic features of patients undergoing APR or TPE, according to the presence or absence of SSI

Variable	No SSI (n = 93)	SSI (n = 57)	*P* value
Age, y, median (range)	65 (31–89)	66 (32–87)	0.227
Sex, n (%)			0.604
Male	61 (65.6)	35 (61.4)	
Female	32 (34.4)	22 (38.6)	
BMI, median (range)	21.9 (15.0–31.2)	21.5 (15.8–38.3)	0.870
ASA physical status, n (%)			0.287
I	27 (29.0)	23 (40.4)	
II	61 (65.6)	30 (52.6)	
III	5 (5.4)	4 (7.0)	
Diabetes mellitus, n (%)			0.196
Absent	82 (87.5)	45 (78.9)	
Present	11 (12.5)	12 (21.1)	
Smoking, n (%)			0.449
Absent	55 (56.8)	37 (64.9)	
Present	38 (43.2)	20 (35.1)	
Alcohol consumption, n (%)			0.940
Absent	43 (46.7)	27 (47.4)	
Present	49 (53.3)	30 (52.6)	
Neoadjuvant therapy, n (%)[a]			0.163
Absent	40 (43.0)	18 (31.6)	
Present	53 (57.0)	39 (68.4)	
TP, g/dL, median (range)	6.8 (5.3–8.3)	6.7 (5.4–7.7)	0.370
Alb, g/dL, median (range)	3.8 (2.5–4.8)	3.8 (2.0–4.4)	0.657
CEA, ng/mL, median (range)	5.0 (1.1–1417)	5.1 (1.5–256.3)	0.817
CA19-9, U/mL, median (range)	14 (1–1830)	14 (1–1164)	0.968
WBC, ×1000/μL, median (range)	5.7 (2.6–12.4)	5.7 (2.7–28.2)	0.369
Hb, g/dL, median (range)	12.5 (7.2–16.8)	11.9 (7.7–16.1)	0.451
Plt, ×10,000/μL, median (range)	25.5 (8.9–56.6)	25.4 (10.0–58.1)	0.696
Intraoperative ABT, n (%)			0.006
Absent	54 (58.1)	20 (35.1)	
Present	39 (41.9)	37 (64.9)	
Diagnosis, n (%)			
Primary rectal cancer	78 (83.9)	50 (87.7)	0.518
Recurrent rectal cancer	12 (12.9)	5 (8.8)	0.439
Other	3	2	0.925
Surgical procedure, n (%)			0.908
APR	86 (92.5)	53 (93.0)	
TPE	7 (7.5)	4 (7.0)	
Infusion volume, mL, median (range)	4400 (570–15,250)	4550 (1670–18,400)	0.619
Urination volume, mL, median (range)	775 (0–5400)	708 (18–5210)	0.674
Estimated blood loss, mL, median (range)	885 (10–17,140)	1070 (146–14,490)	0.404
ABT volume, mL, median (range)	0 (0–12,800)	390 (0–12,400)	0.008
Operation time, min, median (range)	370 (194–1035)	411 (145–1270)	0.444

Alb, albumin; ASA, American Society of Anesthesiologists; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; Hb, hemoglobin; Plt, platelet; TP, total protein; WBC, white blood cell.

[a]Neoadjuvant therapy includes radiotherapy and chemoradiotherapy.

transfusion (1184 ± 512 versus 982 ± 445; $P = 0.026$; Fig. 2).

Discussion

The rate of SSI after APR has been reported to range between 12% and 51%,[7–9] and in the present study it was found to be 38.0%. Although several studies have been conducted to evaluate the risk factors of postoperative SSI in APR, even the definition of SSI varies among reports,[7–9,16] possibly because perineal wound infection was also observed in most cases, and it was often difficult to distinguish superficial perineal wound infection from pelvic dead space infection, which should be classified as deep/organ space SSI. Therefore, in this study we did not divide SSI into superficial, deep, or organ space, but analyzed them together.

Table 2 Histologic features of patients with primary rectal cancer associated with SSI

Variable	No SSI (n = 78)	SSI (n = 50)	*P* value
Tumor stage, n (%)			
T1 and T2	18 (23.1)	18 (36.0)	0.113
T3 and T4	60 (76.9)	32 (64.0)	
Lymph node metastasis, n (%)			0.024
Absent	44 (56.4)	38 (76.0)	
Present	34 (43.6)	12 (24.0)	
Distant metastasis, n (%)			0.632
Absent	65 (83.3)	40 (80.0)	
Present	13 (16.7)	10 (20.0)	
Lymphatic invasion, n (%)			0.060
Absent	54 (69.2)	42 (84.0)	
Present	24 (30.8)	8 (16.0)	
Vascular invasion, n (%)			0.036
Absent	26 (33.3)	26 (52.0)	
Present	52 (66.7)	24 (48.0)	
Histologic classification, n (%)			0.142
Well- and moderately differentiated type	72 (92.3)	42 (84.0)	
Poorly differentiated and mucinous type	6 (7.7)	8 (16.0)	

Our study reviewed 150 patients, which was a sample size comparable with those of precedent studies.[8,16,17] Further large database studies from multiple institutions should be conducted to validate our result, but we are confident of the clinical importance of a study from a single institution, because it is well known that large interinstitution variation in the incidence of SSI exists, which may have different etiologies.

The reported risk factors of SSI in APR largely vary among the studies. Some studies demonstrated that preoperative radiotherapy or chemoradiotherapy was associated with higher incidence of perineal wound complications, including SSI,[8,18] whereas others failed to show this association.[7,16] In the present study, no association was observed between adjuvant radiotherapy or chemoradiotherapy and SSI. Similarly, body mass index,[7] alcohol consumption,[17] and delayed primary wound closure[17] were reported to be risk factors of perineal wound complication, including SSI. However, we failed to demonstrate the association between these factors and SSI, possibly because of the small sample size of the study.

In previous reports related to SSI after general surgery, several other risk factors have been reported. History of diabetes,[19–22] American Society of Anesthesiologists physical status,[19,20,22] smoking habit,[19,20] worse wound classification,[19,20] and perioperative ABT[20,22] are the reported risk factors for SSI in general surgery, but in our study none of them, except for blood transfusion, showed an association with the onset of SSI.

A number of studies also showed the correlation between perioperative ABT and increased postoperative infection in both general surgery[20,22] and colorectal surgery.[4,10,12] Bernard *et al*[13] analyzed the records for more than 100,000 general surgery patients and reported that the intraoperative ABT of red blood cells, even 1 U, strongly correlated with SSI, increased 30-day mortality, pneumonia, and sepsis. Recently, a meta-analysis to investigate the effect of ABT in colorectal surgery patients demonstrated that perioperative ABT was associated with increased mortality, recurrence, metastasis, death, postoperative infection, and surgical reintervention.[14] Although these reports suggest that the perioperative ABT for APR or TPE patients could also increase the incidence of SSI, only a few reports have investigated ABT as a risk factor for SSI in patients undergoing these specific operations, and all of them failed to demonstrate a correlation.[7,17] Thus, the present study was conducted, focusing especially on the correlation between ABT and SSI in APR or TPE cases, and it demonstrated that ABT was the only independent factor for SSI in the multivariate analysis.

Transfusion-related immunomodulation has been considered to be one of the major mechanisms of these blood transfusion–induced SSI developments.

Table 3 Univariate and multivariate analysis of variables associated with SSI

Variable	Univariate analysis *P* value	Multivariate analysis		
		Odds ratio	95% CI	*P* value
Intraoperative transfusion	0.006	3.05	1.41–6.91	0.004
Lymph node metastasis	0.024	0.43	0.17–1.03	0.059
Vascular invasion	0.036	0.54	0.23–1.23	0.144
Lymphatic invasion	0.060	0.61	0.21–1.70	0.345

CI, confidence interval.

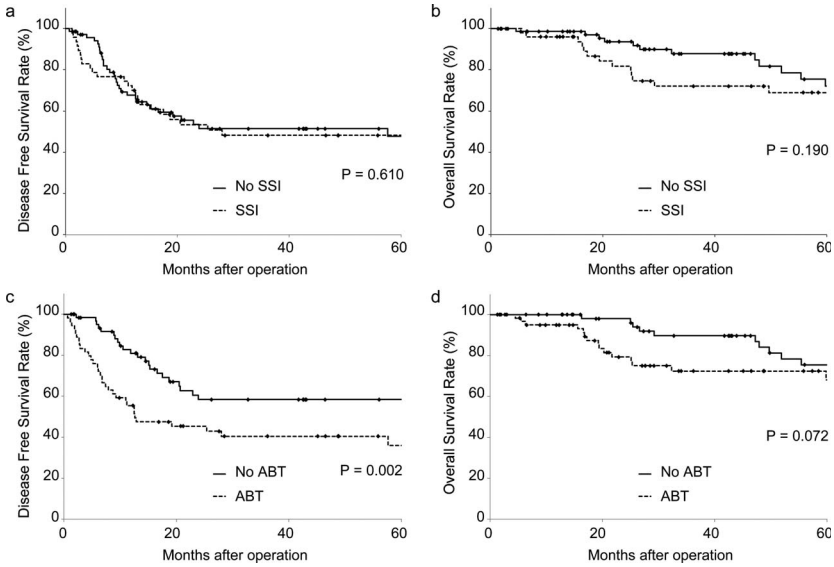

Fig. 1 No significant difference was observed in the DFS rates (a) and the OS rates (b) of the non-SSI and the SSI groups. When comparing the DFS rates (c) and the OS rates (d) of the non-ABT and ABT groups, the non-ABT group had a significantly improved DFS rate.

Both proinflammatory and immunosuppressive effects were reported to be simultaneously induced by ABT, and they were mediated by allogeneic mononuclear cells; soluble biologic response modifiers released from white blood cell granules, red blood cells, or platelets during storage; and soluble human leukocyte antigen class I peptides that circulate in allogeneic plasma. Although ABT is supposed to induce tolerance in the host immune system, which results in an increase in postoperative infection and cancer recurrence, the detailed mechanisms are still to be completely elucidated.[23–25]

Several reports have demonstrated the postoperative increase of peripheral blood interleukin-6 and interleukin-10 concentrations in patients who underwent colorectal cancer resection and received a transfusion,[26–28] which could be one explanation for ABT-induced immunosuppression. ABT also has been reported to prolong the elevation of serum immunosuppressive acidic protein level after surgery.[29] However, no study has reported a change in the number of circulating lymphocytes induced by ABT in APR and TPE. In our series involving 147 patients undergoing rectal resection, we found a significantly lower POD1 lymphocyte count in the ABT compared with the non-ABT group, whereas the POD1 peripheral blood neutrophil count was not significantly different between these groups. Because interleukin-10 is supposed to exert an immunosuppressive effect on lymphocytes, the ABT-induced increase of interleukin-10 may be a possible explanation of this phenomenon.[26,28]

Moreover, because postoperative lymphocyte counts on POD1 and POD3 have been reported to correlate with the extent of surgical trauma,[30] we are confident of the strong clinical value of our novel finding of the significant reduction in postoperative leukocyte count caused by the intraoperative blood transfusion.

Table 4 Univariate and multivariate analysis of variables associated with DFS

	Univariate analysis	Multivariate analysis		
Variable	*P* value	Odds ratio	95% CI	*P* value
SSI: absent versus present	0.610			
Distant metastasis: absent versus present	<0.001	0.28	0.13–0.60	0.002
Tumor stage: T1, T2 versus T3, T4	<0.001	0.35	0.14–0.76	0.007
Lymph node metastasis: absent versus present	<0.001	0.61	0.34–1.13	0.118
Intraoperative transfusion: absent versus present	0.002	0.70	0.36–1.33	0.277
Estimated blood loss: ≤1000 mL versus >1000 mL	0.018	0.71	0.37–1.39	0.317
Operation time: >360 min versus ≤360 min	0.027	0.75	0.38–1.47	0.399
Lymphatic invasion: absent versus present	0.043	0.76	0.41–1.46	0.402

CI, confidence interval.

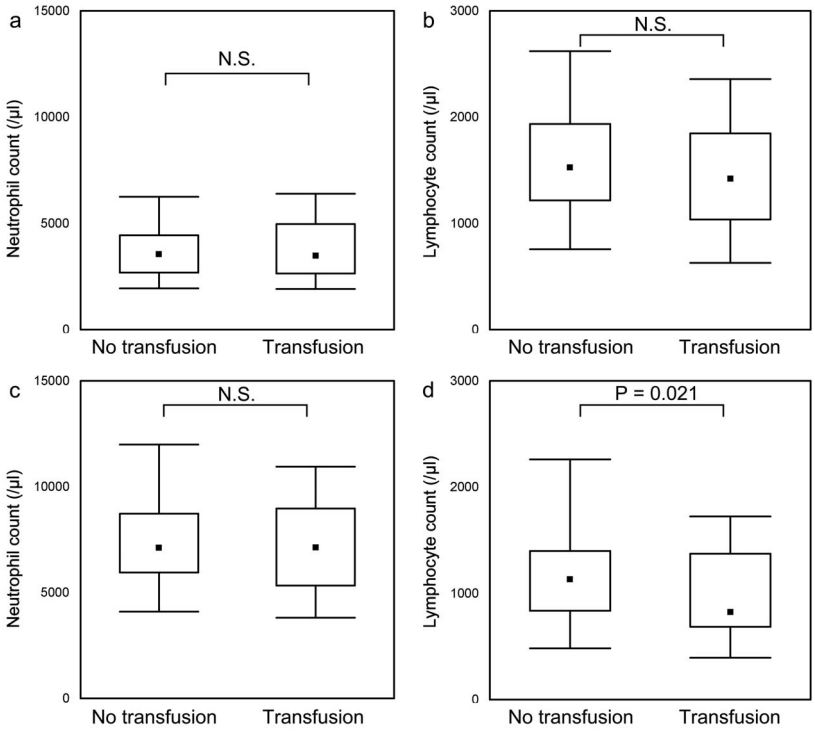

Fig. 2 Perioperative neutrophil and lymphocyte counts in 233 rectal surgery patients. Patients were divided into non-ABT and ABT groups, and the preoperative neutrophil counts (a) and lymphocyte counts (b), as well as the POD1 neutrophil counts (c) and lymphocyte counts (d), were analyzed. The POD1 lymphocyte counts (d) were significantly lower in the ABT group compared with the non-ABT group. There was no significant difference between ABT and non-ABT related to preoperative neutrophil (a) and lymphocyte (b) counts, or the POD1 neutrophil counts (c).

In conclusion, perioperative ABT during APR and TPE, by modulating and suppressing the host immune system, especially circulating lymphocytes, may increase the incidence of SSI. Thus, efforts should be made to implement measures to avoid unnecessary ABT, such as the preoperative control of anemia; the use of restrictive transfusion triggers; the minimization of intraoperative blood loss, hemostasis, and coagulation management; and the use of autologous blood options, in an attempt to achieve patient blood management.[31]

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