The Effect of Blood Transfusions on the Rate of Anastomotic Leakage After Gastric Resections for Carcinoma

KANSER NEDENİYLE YAPILAN MİDE REZEKSİYONLARINDAN SONRA GÖRÜLEN ANASTOMOZ KAÇAKLARINA KAN NAKİLLERİNİN ETKİSİ

Mehmet Ali YERDEL****, Cüneyt KÖKSOY**, Masahiro AOYAMA***, Kaihara AKIHIKO***, Nakayama FUMIYO***, Akira GOUCHI***, Kıınzo ORITA***

* Dept. of General Surgery, Medical School of Ankara University,
** Ankara Oncology Hospital, Ankara, TURKEY
*** 1st Dept. of Surgery, Medical School of Okayama University, Okayama, JAPAN

Summary

Experimental studies reported association between blood transfusion and impaired healing of intestinal anastomosis. To date no clinical study has addressed this issue in particular and this study was undertaken in order to assess to probable effects of blood component therapy on the rate of anastomotic leakage after gastric resections for carcinoma. Records of419 patients who had undergone curative gastric resections for carcinoma during a 10 year period were reviewed with special reference to the perioperative transfusion status. All variables that may have a probable role in anastomotic leakage were recorded. Statistical analysis was done by chi-square and student t tests as appropriate. Simultaneous adjustment of the effects of all variables on leakage was done using multivariate stepwise logistic regression analysis. Postoperative upper gastrointestinal contrast studies documented 20 leakages (4.7 percent). Among all variables studied by multivariate analysis; perioperative blood transfusion, was found to be the only independent risk factor that is significantly associated with higher leakage rates ($p<0.05$). In conclusion; as the clinical consequences of leakage are well known, surgeons can be advised to be more cautious when using blood products.

Key Words: Blood transfusion, Anastomotic healing, Leakage, Complications

T Klin J Med Res 1997; 15:128-132

Özet

Deneysel çalışmalar kan nakilleri ve bağırsak anastomozu iyileşmesi arasında bir ilişki olduğuna dikkat çekmişlerdir. Zamanımıza dek; özel olarak bu konuya değinen hiçbir klinik çalışma yapılmamıştır ve bu çalışmada, mide kanseri nedeniyle yapılan rezeksiyonlardan sonraki anastomoz kaçağı ile kan ürünü tedavisi arasında muhtemel bir ilişki olup olmadığı araştırılmıştır. On yıl süre içinde kanser nedeniyle küratif rezelcsiyon geçiren 419 hastanın kayıtları, özellikle kan transfüzyonu durumları dikkate alınarak incelendi. Anastomoz kaçağına etki edebileceği düşünülen tüm değişkenler kaydedildi. İstatistiksel analizler ki kare ve stıident t testleri ile yapıldı. Anastomoz kaçağına etki edebilecek değişkenlerin birbirleri üzerine olan etkisinin ayarlanabilmesi için multivaıyant regresyon analizi yapıldı. Ameliyat sonrası kontrastlı üst gastvintestinal seriler 20 kaçak saptadılar (%4.7). Multivaıyant analiz sadece ameliyat, dönemindeki kan iransfüzyonunun, diğer değişkenlerden bağımsız biçimde anastomoz kaçağı riskini anlamlı ölçüde arttırdığını belirledi ($p<0.05$). Sonuç olarak, anastomoz kaçaklarının yol açabileceği klinik problemler iyi bilindiğinden, cerrahların kan ürünlerini kullanırken daha temkinli olmaları önerilebilir.

Anahtar Kelimeler: Kan nakilleri, Anastomoz iyileşmesi, Anastomoz kaçağı, Komplikasyonlar

TKlin Araştırma 1997, 15:128-132

Blood transfusions, by altering the immune system are known to be associated with prolonged allograft survival (1), increased tumor recurrence rates (2) and increased rate of postoperative septic complications (3). Although the precise mechanism of transfusion related immunosuppression is yet to be defined (4), there is evidence that blood transfusions impair the cell mediated immune reactions that depend on primarily two cell types namely macrophage and T lymphocyte (5-7). Since both macrophages and T lymphocytes have an important role in wound healing (8-11), it is quiet reasonable

Correspondence: Mehmet Ali YERDEL
İlgaz Sok. 7/10
06700 Gaziosmanpaşa
Ankara, TURKEY

to expect a detrimental of blood transfusions on wound and anastomotic healing. Recently Tadros et al showed that; blood transfusion impairs the healing of experimental intestinal anastomosis (12). Their effort, although providing evidence regarding possible association between blood transfusions and anastomotic leakage, certainly deserves further assessment in clinical series. In this report we retrospectively analyzed the risk factors that may be responsible from the gastrointestinal anastomotic leakage after 419 gastric resections performed for carcinoma with special reference to the transfusion effect. To date no previous study has particularly addressed to this issue.

Patients and Methods

The files of all patients who had undergone relative or absolute curative resection for gastric carcinoma between 1980 and 1990 were retrospectively analyzed. Inclusion criteria for "relative" and "absolute" curative resections were established according to the Japanese Rules for Gastric Cancer Study (13). A11 operations were performed by the same surgical team consisting of the consultant surgeon and the staff surgeons using standard techniques and no surgical resident or trainee was primarily involved in any of the operations. The following data were obtained from the records of each patient: Age, gender, blood type, hematocrit-total protein-albumin levels on admission, presence of obesity-diabetes, duration of operation, surgical technique (total-subtotal-proximal-extended gastrectomy), types of dissection performed according to the Japanese Rules for Gastric Cancer Study (13) (D0-Dl-D2-D3-Dx), concomitant operations performed (cholecystectomy, appendectomy, colon resection, splenectomy, hepatic resection), tumor diameter and grade (poor, moderate, well differentiated), microscopical stage, early or advanced gastric carcinoma status, aim of the operation (relative or absolute curative), blood loss during the operation, presence/absence of blood transfusion and total unit of blood component transfused and early postoperative complications.

Follow-up time was defined as the period between the operation and the discharge from the hospital, the day before a subsequent operation or in-hospital death. Collection of information regarding the blood transfusion status was limited with the first ten days after the operations in patients without leakage. In patients with leakage, transfusion status before the diagnosis of leakage was recorded and any form of blood component therapy after the diagnosis of leakage was omitted for the purpose of the study. During the follow-up, all patients were undergone upper gastrointestinal series with contrast medium 9 to 13 days after surgery as a part of our routine clinical practice.

Anastomotic leakage was defined as extragastrointestinal visualization of the contrast material in close vicinity to the anastomotic area and/or clinically apparent anastomotic failure which is defined as intraabdominal sepsis followed by X-ray confirmation of the leak and/or drainage of gastrointestinal fluid from the drains.

Statistical analysis was done by chi-square test with Yates correction and student t test as appropriate utilizing the software program SPSS (Statistical Package for Social Services, SPSS for windows, Release 5.0.1., SPSS Inc.). Furthermore we carried out simultaneous adjustment of the effects of all variables available on leakage using multivariate stepwise logistic regression analysis. P values smaller than 0.05 is accepted as statistically significant.

Results

Among all operations (n:651) performed for gastric carcinoma during the study period, 419 were curative or relative curative gastric resections, and these 419 patients were the subject of this study. Palliative operations were excluded for standardization. Leakage occurred in 20 patients (4.7 percent) and this complication was diagnosed by routine postoperative X-ray examination of the upper gastrointestinal tract in 11 patients and was clinically apparent in 9 within four to den days postoperatively. Mean hospital stay in leakage group (66.5±23 days) was significantly longer than that in non-leakage group (37.5±15 days) ($p<0.001$). Mortality was also higher in leakage group (19:1) in comparison to the rest of the series (396:3) ($p=0.056$). Patient characteristics and the different factors studied in probable relation to leakage is presented in Table 1. Univariate analysis

Table **1.** Comparison of patients with or without leakage

Leakage	No	Yes	p values
Number	399	20	
Age	59.8(12)	59(12)	NS
Gender (Male:Female)	277:12	17:3	NS
Hematocrit %	39.8(20.6)	41.2(53)	NS
Albumin (g/dL)	3.95(0.5)	3.9(0.3)	NS
Total proteins (g/dL)	6.71(0.68)	6.6(0.68)	NS
Obesity (no:yes)	390:9	19:1	NS
Diabetes mellitus (no:yes)	350:49	17:3	NS
Duration of operation (minutes)	225(64)	242(61)	NS
Stage of tumor (I:II:III:lV)	243:62:64:30	13:3:3:1	NS
Early gastric cancer: Advanced gastric cancer	210:189	12:8	NS
Grade (well: moderate: poor)	122:61:216	7:4:9	NS
Diameter of tumor (cm)	4:49(3.2)	4.15(3)	NS
Blood type (A:B:0:AB)	192:69:87:51	10:3:3:4	NS
Surgical technique*	285:87:3:24	13:7:0:0	NS
Absolute vs. relative curative resection	358:41	18:2	NS
Nodal dissection (DO:DI:D2:D3)	7:59:197:138	1:3:10:6	NS
Concomitant surgical procedure (yes:no)	81:318	4:16	NS
Postoperative complications (yes:no)	52:347	4:16	NS
Blood loss (mL)	555(260)	585(220)	NS
Blood transfusion (yes:no)	216:183	16:4	0.02
Blood transfusion (0-2:3-7:>8 units)	215:60:124	4:6:10	0.01

^Surgical techniques: Distal subtotal gastrectomy (1); Total gastrectomy (2); proximal subtotal gastrectomy (3); extended gastrectomy (4).

of this data revealed that only blood transfusion have a significant role in the occurrence of leakage. Patients who received blood component therapy had significantly higher risk of leakage in comparison to patients without any form of blood transfusion ($p<0.05$). Regarding the amount of blood component therapy, there was association between the units of blood components and rate of leakage ($p=0.01$). According to the multiple logistic regression analysis of all the parameters listed in Table 1, the presence of transfusion was found to be the only independent risk factor which is associated with significantly higher rate of leakage ($p<0.05$) (Table 2). In other words: when the effect of each variable on leakage was corrected according to a possible intervariablc influence, none of the variables except the presence of blood transfusion was found to be significantly associated with higher rates of leakage.

Discussion

It is well known that anastomotic failure after gastrointestinal anastomosis is associated with high morbidity and mortality. The presented scries documented a leakage rate of 4.7 per cent after curative gastric carcinoma operations. It is noteworthy that, we were also able to document even the subclinical leakages as postoperative upper gastrointestinal series is a part of routine clinical practice in our Department. Our univariate analysis of numerous factors (Table 1) which may have a probable role in the occurrence of leakage pointed out blood transfusion as a significant factor that led to anastomotic disruption. More importantly, this significance was maintained when all parameters were re-investigated by multivarite regression analysis. In the light of this finding we may speculate that "other" mechanisms, rather than "indication for transfusion" accounts for this association. In other words, conditions which led to increased rate of blood transfusion in the present series were not associated with higher leakage rates.

Table **2.** Multivariate logistic regression analysis of parameters in Table 1*

Variable	ß (Beta)	Standard error of coefficient	Wald	p values	R**	Regression coefficient
Transfusion (yes:no)	4081	0.5810	5.8729	0.0154	0.1557	4.0882
Constant	-3.5843	0.5131	48.7994	0.0000		

*Only the significant parameter is listed

**A measure of the partial correlation between the dependent variable and independent variable

We are aware that validity of our findings is based on the assumption that surgeons maintained consistent standards of technical excellence and that a large series of cases is internally controlled when all operations are performed by a few experienced surgeons. Considering the fact that all operations in the present series were performed by a consultant surgeon (KO) or under his supervision by a senior staff surgeon and all operations were relatively standard "curative" resections, variables which correlate statistically with high rates of leakage may be related in some way to impaired anastomotic healing.

During the last decades, after the beneficial effect of blood transfusion induced immunosuppression on allograft survival became apparent (1), many reports including our own experience (14) pointed out detrimental effects of blood transfusions such as: increased tumor recurrence rates (2,14-16) and increased infectious complications (3,17,18). Recently, Tadros et al showed impairment of intestinal anastomotic healing by allogenic transfusions in a rat model (12,19). According to their study, impairment of healing at the anastomotic site was a direct effect rather than an infection induced effect. Although the causative mechanisms remains unclear, transfusions were thought to interfere with the cellular phase of inflammatory reactions which have a key role in wound healing (5-7). Waymack et al reported clear association between allogenic transfusions and decreased macrophage immigration and function (5). Furthermore another cell type that appears to have a role in wound healing is the T lymphocyte (8-11) and it is also known that blood transfusions diminish lymphocyte blastogenesis and increase suppressor cell activity (20-21). Facts such as; in vivo depletion of T cells impairs wound healing (9) and depletion of suppressor subtypes even may enhance healing (10), may explain the adverse effect of blood transfusions on wound healing. Furthermore, the production of IL-2, a compound which has been shown to enhance wound healing in rats (22,23), is decreased by blood transfusions (23-25) and recently Tadros et al showed that exogenous IL-2 reverses the negative effects of blood transfusions on anastomotic repair (26). Therefore; blood transfusions, by adversely affecting the both macrophage and T cell populations may interfere with the healing of gastrointestinal anostomoses. As previously shown experimentally (12,19,26), this may also lead to clinical consequences as demonstrated in this present series. We also have to admit that the validity of our findings can be further criticised because of the retrospective nature of this study, in line with relatively low number of leakage cases which coupled with high number of parameters per patient studied making the statistical comparisons rather complicated. However, as the effect of blood transfusion on any clinical consequence can not be studied in a prospective randomized fashion, we think that results presented herein deserves attention although we failed to document a very high statistical significance.

To date three previous studies reported association between blood transfusion and higher rate of anastomotic leakage (27-29). Two of these investigations were carried out concerning colonic anastomoses (27,28) and differing from our study, none of these studies were concentrated on transfusion effect and more importantly, their results were not controlled by multivariate logistic regression analysis to confirm blood transfusion as an independent risk factor. More recently, Galub et al reported a heterogenous series of 813 intestinal anastomoses in which they identified several risk factors including perioperative blood transfusion as an independent risk factor for anastomotic leakage using multivariate analysis (29). It is noteworthy that, differing from our series their study population included colonic, small bowel and different anastomotic locations. The assessment of transfusion effect on anastomotic leakage in clinical practice is intentionally carried out in gastric operations in the present series since the well known natural habitants of the colonic lumen may give rise to higher rate of infectious complications, 'Seriously interfering the leakage rates.

In conclusion; the present study revealed a significantly increased rate of leakage in patients who are transfused in comparison to patients who did not receive any form of blood component after curative gastric carcinoma surgery. Although the statistical significance is not very high ($p<0.05$), as the consequences of leakage are well known after an otherwise successful major operation, surgeons may be advised to be more cautious when using blood products.

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