Blood Transfusion Impairs the Healing of Experimental Intestinal Anastomoses

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Blood transfusions are reported to impair the cell-mediated immune response. Because both T lymphocyte and macrophage function are important for wound repair, the authors investigated the effect of blood transfusions on anastomotic repair. Lewis rats underwent resection of both ileum and colon, followed by the construction of either an everted or an inverted end-to-end anastomosis. Immediately after operation, they received either 3 mL saline intravenously, or 3 mL heparinized blood from Lewis or Brown Norway donors. The animals were killed 3 or 7 days after operation, and anastomotic strength was assessed by measuring the bursting pressure. Anastomotic abscesses and generalized peritonitis were not found in the control group. Blood transfusions, particularly allogeneic, significantly increased the incidence of these septic complications. Three days after operation, anastomotic strength was significantly reduced in both Lewis and Brown Norway transfused groups. For instance, average bursting pressures (± standard deviation [SD]) of inverted ileal anastomoses were 79 ± 13 mmHg in the control group and 46 ± 14 and 21 ± 12 mmHg in the Lewis and Brown Norway transfused groups, respectively. Seven days after operation, the rupture site was found significantly more often within the anastomotic line in the animals that had received blood transfusions. The authors conclude that blood transfusions impair the healing of experimental intestinal anastomoses and increase susceptibility to intra-abdominal sepsis.

BLOOD TRANSFUSIONS HAVE been reported to alter the immune system. It has been known for some time that pretransplant transfusions prolong allograft survival.[1,2] Also, transfusions appear to enhance tumor growth in animal models, and to increase the recurrence rate of human colon, breast, and lung cancer.[3-7] Both experimental and clinical studies have demonstrated that blood transfusions increase susceptibility to septic complications.[8-11] Taken together, these studies suggest that blood transfusions may exert a generalized immunosuppressive effect.

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Although the precise mechanism of this transfusion-induced immunosuppression has not yet been fully elucidated, there is evidence that blood transfusions impair the cell-mediated immune response.[12-14] Cell-mediated immune reactions depend primarily on two cell types, macrophages and T lymphocytes. Although the central role of macrophages in wound healing is well established, the possible importance of lymphocytes in this process has been recognized only recently.[15-18] With this evidence in hand, it seems logical to expect a detrimental effect of blood transfusions on the wound healing sequence. Anastomotic leakage is one of the major complications of gastrointestinal surgery and is often associated with high morbidity and mortality rates.[19,20] In a number of situations, for instance, in emergency operations, chances for anastomotic failure rise.[20,21] Blood transfusions have not been recognized as a potential risk factor for anastomotic leakage. Blood transfusions are frequently required in gastrointestinal surgery to correct anemia or because of excessive blood loss from associated trauma or operative procedures. Thus, it is important to establish the effect of such transfusions on intestinal repair. Because no data are as yet available on this subject, we conducted the present study in the rat, because we have gained considerable experience with such a model for anastomotic healing.[22]

Materials and Methods

Animals

One hundred twenty adult male Lewis rats, with an average weight of 235 ± 23 (± standard deviation [SD]) g were divided into two experimental groups of 60 rats each. An additional 20 Lewis male rats and 20 Brown Norway (BN) male rats were used as donor animals. All

animals were kept in separate cages and were given food and water *ad libitum*. The animals were observed for a minimum of 1 week before initiation of the study to exclude the presence of any preexisting diseases.

Operative Procedure and Transfusions

The animals were anesthetized with intraperitoneal sodium pentobarbital and underwent a median laparotomy. One centimeter of both ileum and colon were resected at 15 cm proximal to the ileocecal junction and 3 cm proximal to the rectal-peritoneal reflection, respectively. In experiment I, everted one-layer end-to-end anastomoses were constructed microsurgically with 8 × 0 monofilament suture material (Ethicon). In experiment II, inverted anastomoses were used instead.

Blood was obtained from anesthetized Lewis and Brown Norway rats by cardiac puncture. The blood was heparinized and given through the dorsal penile vein. Within each experiment the animals were divided into three groups of 20 rats each, receiving 3 mL saline, 3 mL Lewis blood, or 3 mL Brown Norway blood, respectively. All transfusions were given immediately after the operation.

Investigations

Either 3 or 7 days after operation, the animals were anesthetized with intraperitoneal sodium pentobarbital. A second laparatomy was performed and the abdomen was inspected for the presence of abscesses and signs of generalized peritonitis. Both ileal and colonic anastomoses were prepared free, leaving surrounding tissue adherent to the anastomoses untouched, and removed. Thereafter, the animals were killed by an intraperitoneal overdose of sodium pentobarbital.

Approximately 5 cm intestinal segment containing the anastomosis was carefully cleaned from fecal content. Subsequently, the segment was attached to an infusion pump, filled with methylene-blue–stained saline solution. The pressure was increased with an infusion rate of 2.5 mL/min and recorded graphically. Both bursting pressure and site of rupture were noted.

In experiment II, the anastomotic segment was cleaned from surrounding tissue after the bursting pressure measurement, and a 0.5 cm segment, containing the anastomosis, was collected for analysis. The samples were frozen immediately and stored in liquid nitrogen until processing. After weighing, the samples were pulverized and lyophilized, and the hydroxyproline content was measured as described before.[23]

Statistical Analysis

Statistical methods are given with the results.

Results

Experiment I

Body Weight. All animals showed weight loss in the early postoperative period, followed by some weight gain later on. Average weight loss (± SD) on the third day postoperatively in the saline, Lewis, and Brown Norway transfused groups was 18.2 ± 4.6 g (n = 8), 19.4 ± 5.3 g (n = 7), and 25.6 ± 6.7 g (n = 8), respectively. Average weight gain with respect to weight at operation on the seventh day after operation in the three groups was 11.7 ± 10.6 g (n = 10), 8.4 ± 7.6 g (n = 7), and 6.3 ± 11.5 g (n = 10), respectively. The differences between groups were not statistically significant (Kruskal–Wallis test).

Mortality Rate. In the groups receiving saline or Brown Norway blood, the postoperative mortality rate was 10%, whereas animals transfused with Lewis blood exhibited a mortality rate of 30%. Two animals in the saline group died between the first and the second postoperative days, without any macroscopic evidence of anastomotic leakage or intra-abdominal infection. One rat showed signs of ileus. Animals transfused with Brown Norway blood or Lewis blood died between the second and the fourth days after operation. All of these exhibited signs of intra-abdominal sepsis, such as anastomotic abscesses or generalized peritonitis.

Intra-abdominal Sepsis. No abscesses were found at all around the anastomoses in the saline-infused group. On the contrary, high numbers of anastomotic abscesses were found after blood transfusions (Table 1). On the third day after operation, abscesses were found around 57% of the ileal anastomoses in the Lewis group, and around all anastomoses constructed in rats transfused with Brown Norway blood. A similar, although less explicit, effect was observed in colon. Next to the anastomotic abscesses, signs of generalized peritonitis and fascial abscesses were found also in 29% of the Lewis group, and 50% of the Brown

TABLE 1. *Anastomotic Abscesses and Bursting Pressures in Experiment I*

	Day 3			Day 7		
	n	Ileum	Colon	n	Ileum	Colon
Abscess						
Saline	8	0	0	10	0	0
Lewis	7	4	2	7	2	2
Brown Norway	8	8	4	10	4	2
p		0	0.07		0.08	NS
Bursting pressure						
Saline	8	31 ± 3	45 ± 11	10	325 ± 38	270 ± 23
Lewis	7	14 ± 3	32 ± 5	7	238 ± 31	166 ± 24
Brown Norway	8	13 ± 4	23 ± 9	10	207 ± 26	182 ± 26
p		0.0005	0.001		0.0001	0.0001

Bursting pressures are expressed as average (mmHg) ± SD. Differences between groups were tested for significance with a Kruskal–Wallis test.

Norway group. No such complications occurred in the saline group. Seven days after operation, abscesses still could be observed around ileal anastomoses in 29% of the animals in the Lewis group and in 40% of those in the Brown Norway group. This phenomenon was seen also around colonic anastomoses. In addition, 20% of the rats transfused with Brown Norway blood showed signs of generalized peritonitis.

Bursting Pressure and Bursting Site. The strength of the anastomoses, as assessed by the bursting pressure, was significantly impaired after blood transfusions (Table 1, Fig. 1). Three days after operation, the bursting pressure of both ileal and colonic anastomoses in the Lewis and Brown Norway transfused groups was significantly reduced as compared with the saline group. At this point, all anastomoses ruptured within the suture line. At 7 days postoperatively, similar, statistically highly significant differences were observed between the three groups. At this time, however, the bursting pressure in the saline group does not reflect anastomotic strength, because the bursting site was always outside the anastomotic area. Thus, the actual average anastomotic strength must have been even higher than the figure given in Table 1. Moreover, in the ileum of the Lewis group, rupture occurred within the anastomosis in two of seven cases. In the Brown Norway group, this happened in seven of 10 anastomoses. This constituted a statistically significant ($p = 0.004$, chi square test) shift in bursting site between groups. A similar, although statistically not significant, phenomenon was observed with regard to the colonic anastomoses (Fig. 1). Finally, it should be noted (Fig. 1) that anastomoses with abscesses always ruptured at the suture line—also at 7 days—and that their strength was always lower than that of the anastomoses without abscesses.

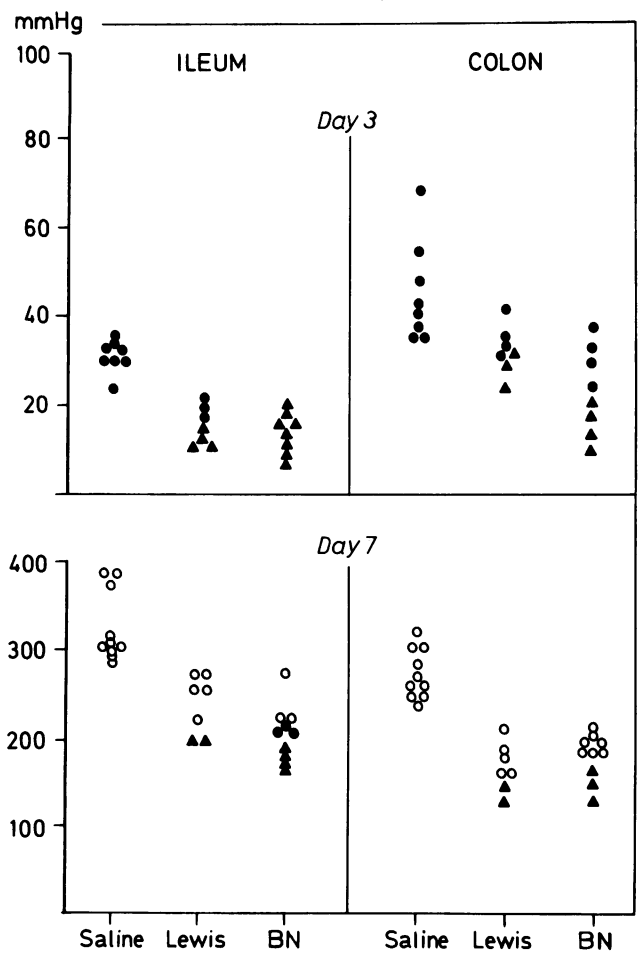

FIG. 1. Correlation between bursting pressure, bursting site, and anastomotic abscesses in experiment I. Points represent single anastomoses. Closed symbols, rupture within suture line; open symbols, rupture outside suture line; circles, no anastomotic abscess; triangles, anastomotic abscess present.

Experiment II

The results of experiment II, where inverted anastomoses were constructed instead of everted anastomoses, were similar to those of experiment I.

Body Weight. The average weight loss (±SD) on the third postoperative day was 18 ± 6 g (n = 10) in the saline group, 19 ± 4 g (n = 9) in the Lewis group, and 20 ± 6 g (n = 8) in the Brown Norway group. Seven days after the operation, all animals had gained some extra weight, with respect to their preoperative weight. The average increase (±SD) was 16 ± 12 g (n = 10) in the saline group, 8 ± 4 g (n = 8) in the Lewis group, and 6 ± 9 g (n = 10) in the Brown Norway group. Differences between groups were only significant at day 7 ($p = 0.04$, Kruskal–Wallis test).

Mortality Rate. The postoperative mortality rate appeared higher after blood transfusions. The mortality rate was 15% in the Lewis transfused group and 10% in the group transfused with Brown Norway blood. The animals died between the second and the third day after operation, exhibiting intra-abdominal septic complications. None of the animals receiving saline died before being killed.

Intra-abdominal Sepsis. Again, animals that received saline formed no abscesses at all around the anastomoses. At both 3 and 7 days after operation, an increased occurrence rate of abscesses was observed around the ileal anastomoses in both transfusion groups. This effect was more pronounced after transfusion with allogeneic—Brown Norway—blood (Table 2). In the colon, anastomotic abscesses were seen only twice 3 days postoperatively. After 7 days, however, they were found in four of eight animals transfused with Lewis blood and in six of 10 animals transfused with Brown Norway blood.

Generalized peritonitis and abdominal wall abscesses were only observed in the Brown Norway group, in 25% and 50% of the animals at 3 and 7 days after operation, respectively.

TABLE 2. *Anastomotic Abscesses and Bursting Pressures in Experiment II*

	Day 3			Day 7		
	n	Ileum	Colon	n	Ileum	Colon
Abscess						
Saline	10	0	0	10	0	0
Lewis	9	2	0	8	1	4
Brown Norway	8	7	2	10	6	6
p		0	0.07		0.005	0.01
Bursting pressure						
Saline	10	79 ± 13	97 ± 19	10	303 ± 50	241 ± 17
Lewis	9	46 ± 14	66 ± 9	8	254 ± 47	191 ± 35
Brown Norway	8	21 ± 12	47 ± 12	10	198 ± 56	183 ± 28
p		0	0		0.001	0.001

Bursting pressures are expressed as average (mmHg) ± SD. Differences between groups were tested for significance with a Kruskal–Wallis test.

Bursting Pressure and Bursting Site. The strength of the inverted anastomoses (Table 2) in the saline group was higher than the strength of the everted anastomoses (Table 1). Transfusions again induced significant loss of strength, however, both 3 and 7 days after operation. Two-by-two comparison of the experimental groups also showed that the bursting pressures of 3-day-old anastomoses were significantly lower in the Brown Norway transfused group than in the Lewis transfused group ($p = 0.005$ in ileum and $p = 0.007$ in colon, Wilcoxon one-sided test).

As in the first experiment, all 7-day-old anastomoses in the saline group were stronger than the adjacent bowel wall. In the ileum of the Lewis and Brown Norway transfused groups, rupture occurred within the suture line in 12.5% and 70% of the cases, respectively ($p = 0.001$, chi square test). For colon, these values were 50% and 60%, respectively ($p = 0.01$, chi square test). Figure 2 shows that again anastomoses with abscesses invariably ruptured within the wound area and yielded much lower bursting pressures than those healing in a peritoneal cavity without signs of infection.

Hydroxyproline Content. The hydroxyproline content is taken to be a measure for the anastomotic collagen level. Three days after operation, the hydroxyproline content of the colonic anastomoses was significantly lower in the transfusion groups than in the saline group. In the ileal anastomoses, this effect remained nonsignificant. No differences between groups were observed 7 days postoperatively, either in ileum or in colon (Table 3).

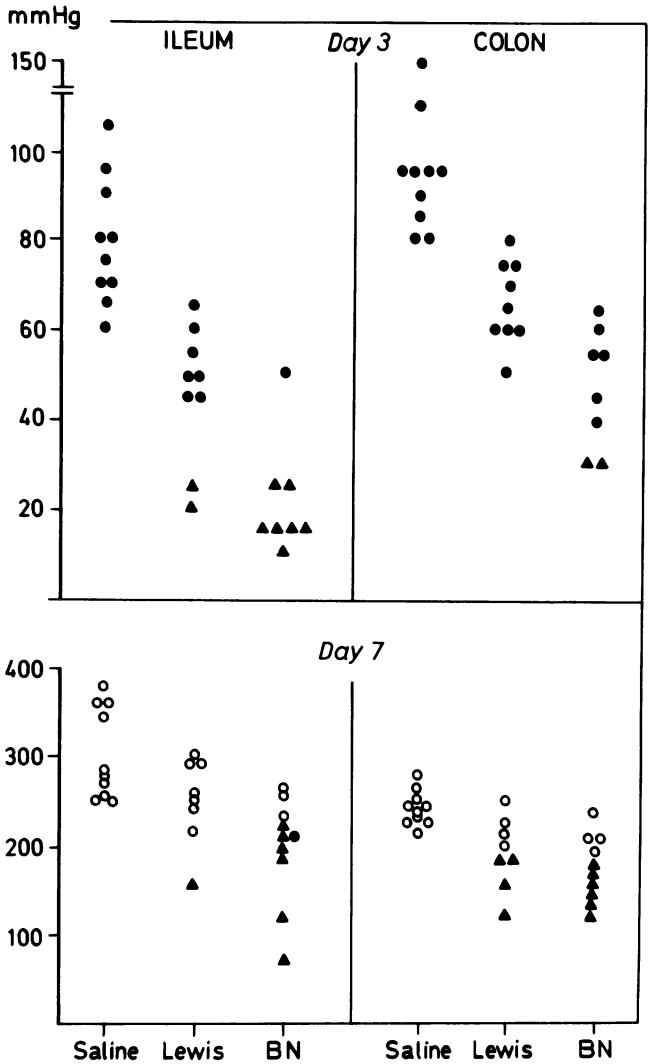

FIG. 2. Correlation between bursting pressure, bursting site, and anastomotic abscesses in experiment II. Points represent single anastomoses. Closed symbols, rupture within suture line; open symbols, rupture outside suture line; circles, no anastomotic abscess; triangles, anastomotic abscess present.

Discussion

After the discovery of the ABO groups by Landsteiner in 1900, blood transfusions have become a common treatment for correction of anemias and for the replacement of significant losses as a result of trauma of operation. During the last decade, however, increasing evidence has emerged that blood transfusions carry certain risks, previously unrecognized, for the patient, in particular with respect to immunosuppression. These include diminished cell-mediated immune response, decreased helper/sup-

TABLE 3. *Anastomotic Hydroxyproline Content in Experiment II*

	Day 3			Day 7		
	n	Ileum	Colon	n	Ileum	Colon
Saline	10	90 ± 12	176 ± 27	10	164 ± 29	244 ± 48
Lewis	9	80 ± 19	122 ± 30	8	167 ± 25	270 ± 39
Brown Norway	8	79 ± 29	121 ± 27	10	169 ± 36	301 ± 75
p		NS	0.003		NS	NS

pressor T-cell ratios, decreased natural killer cell activity, suppression of lymphocyte blastogenesis, and decreased macrophage antigen presentation.[12-14,24-26] Recently, a role has been recognized for immune regulatory cells in the wound healing process. Activated lymphocytes have been shown to secrete lymphokines, which *in vitro* alter fibroblast replication, migration, and collagen synthesis.[18] Impairment of skin wound healing was observed after *in vivo* depletion of T lymphocytes.[16] Thus, it seems likely that blood transfusions will affect the healing process. We have investigated anastomotic healing in the intestine because blood transfusions are frequently required in both elective and emergency gastrointestinal surgery, and failure of intestinal repair is a most serious complication with high morbidity and mortality rates.

To compare the effects of both syngeneic and allogeneic blood, two rat strains have been used as donors. Human transfusions are crossmatched for blood groups, but not for histocompatibility antigen mismatches. In an attempt to approach this situation, we chose the Brown Norway rat as a donor and the Lewis rat as a recipient. No hemolysis occurs in this transfusion model, but there exist histocompatibility differences, which approximate those in human transfusions.[27] In an effort to establish the consistency of the results, we performed two separate experiments using different types of anastomoses. Furthermore, no blood was taken before operation, to avoid possible effects of hemorrhage. The results of this study clearly demonstrate that blood transfusions impair the healing of intestinal anastomoses. The strength of both ileal and colonic anastomoses was significantly decreased in those rats that received either allogeneic or syngeneic blood, at both time points measured. The impairment of healing was most explicit in the allogeneically transfused rats (Brown Norway group).

Allogeneic and syngeneic blood transfusions caused an increase in the occurrence rates of anastomotic abscesses, fascial abscesses, and peritonitis. Most of the abscesses were found on the third day after operation. The morbidity rates were higher in the rats transfused with allogeneic blood than in those transfused with syngeneic blood, whereas none of the animals that received saline showed any signs of intra-abdominal sepsis. Figures 1 and 2 clearly demonstrate that the presence of anastomotic abscesses correlates with reduced anastomotic strength. These data thus confirm an increased susceptibility to septic complications after syngeneic and, particularly, allogeneic blood transfusions.

Two lines of reasoning could explain our results: blood transfusions either affect healing directly or induce intraperitoneal infections, which in turn affect healing.

In the first case, transfusions would interfere with the cellular phase of the inflammatory reaction. The role of macrophages in wound healing is well known. Macrophages release a number of cytokines and growth factors, which stimulate fibroblast proliferation (and thereby synthesis of collagen) and neovascularization.[28]

Waymack et al.[12] have demonstrated a significant impairment in the migration of macrophages into the peritoneal cavity in response to inflammatory stimuli in allogeneically transfused rats. Also, macrophages obtained from allogeneically transfused rats were found to have significant alterations in their arachidonic acid metabolism, including an increase in the production of thromboxane, prostacyclin, and prostaglandin E.[29,30] Thus, the impairment of healing could be due to alterations in macrophage migration and function. Leakage, and subsequent abscess formation, could occur as a result of inadequate development of bowel wall strength.

Another cell that appears to be involved in the wound healing process is the T lymphocyte. Although *in vivo* depletion of T lymphocytes resulted in impaired wound healing,[16] depletion of T-helper/effector cells had no effect on wound healing, and depletion of the T-suppressor/cytotoxic subset even enhanced healing.[17] Conversely, blood transfusions have been shown to diminish lymphocyte blastogenesis in response to mitogen stimulation and to increase suppressor cell activity.[24,25] In addition, blood transfusions exert a negative influence on the generation of interleukin-2,[26,31] which compound has been reported to enhance wound healing in rats.[32]

A second line of reasoning would be that blood transfusions primarily cause intraperitoneal infection, which then affects the healing of intestinal anastomoses. Tartter et al.[8] reported increased rates of infectious complications after colon surgery in patients given blood transfusions in the perioperative period. The presence of peritonitis or abscesses has been known to result in increased leakage and reduced strength of intestinal anastomoses.[20,33] Waymack et al.[10] reported decreased resistance to *Escherichia coli* peritonitis challenges, and impaired macrophage bactericidal function[34] in allogeneically transfused rats.

The higher incidence of abscesses around ileal anastomoses as compared with colonic anastomoses, however, might argue against the second explanation. If transfusions impaired healing primarily because of induction of intraperitoneal infection, more anastomotic abscesses should have been found in colon than in ileum, because of the lower concentration of microorganisms in ileum.

It should be noted that, although differences were found between groups with regard to the average hydroxyproline content of anastomoses, these reached significance only in colon (on day 3). Also, at 7 days after operation, the average anastomotic hydroxyproline content in the colons of animals transfused with either Lewis or Brown Norway blood tended to be higher in comparison with the saline group. These findings suggest that blood transfusions not so much affect the quantity of the anastomotic collagen,

but possibly even more its quality, which might very well decide eventual anastomotic strength.

At this time, it remains unexplained why syngeneic blood also suppresses the healing of intestinal anastomoses. This finding is similar to results of other studies, however. Waymack et al. also found that syngeneic transfusions increase susceptibility to infections,[9,29] and impair lymphocyte blastogenesis.[25] One possible explanation would be that the animals in the syngeneic group, although littermates of the recipients, were not identical twins. This phenomenon could also mean that there are other—as yet unknown—factors that may contribute to the effect of blood transfusions on wound healing.

In conclusion, the present data clearly demonstrate that—in our model—blood transfusions impair the healing of intestinal anastomoses, and increase susceptibility to intra-abdominal septic complications, possibly as the result of an alteration of the local or systemic immune response to the traumatic injury of the intestine caused by the surgical procedure. Further research in this area is certainly required because of the possible clinical consequences of these findings.

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