Treatment of Peptic Ulcer Disease in the Renal Transplant Patient

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This study reviews previous reports of peptic ulcer disease in kidney transplant recipients and includes our own experience. Between 1968–1976, 12 transplant centers reported on gastrointestinal complications occurring in 1853 renal transplant recipients. Among these are 52 patients in whom peptic ulcers developed before transplantation and 72 patients in whom peptic ulcers developed after transplantation. Included are 21 patients with peptic ulcer from 115 renal transplant recipients at VA Wadsworth Hospital. Patients who were operated upon for peptic ulcer before transplant were compared to patients with peptic ulcer before transplant but who were not operated upon. Ulcer recurrence was significantly lower in the operated group $p < .0003$. Following transplantation 59 of 68 patients with peptic ulcer disease presented with bleeding or perforation. Mortality was high: 31 deaths in 72 patients (43%). Symptoms usually occurred early, 74% in 6 months, but 19% occurred after one year. The mortality from duodenal, gastric, combined gastric and duodenal and recurrent ulcers did not differ significantly. Elective surgery is indicated for peptic ulcer when demonstrated before or after kidney transplantation.

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THERE ARE NO CLEAR guidelines to therapy for the patient who develops a peptic ulcer before or after renal transplant. Some believe the hazard of peptic ulcer is not altered by renal transplantation,[27] others routinely perform prophylactic surgery for ulcer disease in the pretransplant period.[23] The effect of a renal transplant and the drugs used for immunosuppression on the course of ulcer disease is not known.

This study reviews previous reports of peptic ulcer in the peritransplant period and includes our own experience. The data is analyzed to determine the risk of peptic ulcer in the transplant patient and establish guidelines for therapy.

Between 1968–1975, 12 transplant centers reported on gastrointestinal complications occurring in 1853 renal transplant recipients.[1,5,10–12,14,16,17,20,21,23,27] Among these were 52 patients in whom peptic ulcers developed before transplantation and 72 patients in whom peptic ulcers developed after transplantation. Some of the patients in the first group were also included in the second group when they developed an ulcer following transplantation and the results of therapy could be determined. In both groups only those patients in whom the results of therapy could be determined are included and the numbers, therefore, are less than the true incidence of peptic ulcer. Included are 21 patients with peptic ulcer from 115 renal transplant recipients at VA Wadsworth Hospital during the years 1964–1975.

In our patients peptic ulcer was diagnosed only if an ulcer crater was found on barium upper GI series or by endoscopy. It was occasionally not clear in reports by others how the diagnosis was made. We tried not to include unspecified upper gastrointestinal bleeding and cases of gastritis or stress ulceration.

Except for the standard use of azathioprine and steroids, immunosuppressive therapies varied considerably, including splenectomy, irradiation and the administration of cyclophosphamide, actinomycin C, antilymphocyte globulin, indomethacin, heparin, sodium warfarin and dipyridamole. Oral antacids were commonly given following renal transplantation although information about frequency, dose and type of antacid was not available.

Results

Data is available on 52 patients with peptic ulcer which occurred before renal transplantation and on 72 patients who developed peptic ulcer after transplant. The results of the various forms of treatment used are given in Tables 1 and 2.

Elective surgery for peptic ulcer resulted in one death in the 35 patients operated upon prior to transplantation. There were no deaths in 8 patients undergoing elective surgery after transplantation. The

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TABLE 1. *Clinical Data on 52 Patients with Peptic Ulcer before Renal Transplant*

Author, Year	No. of Patients	Type of Ulcer	Medical Treatment	Post Transplant Recurrence	Surgical Therapy		Post Transplant Recurrence
Aldrete, A. J. S., 1975	1	Duod.			Vagotomy, antrectomy	1	1
Julien, P. O., 1975	3	Unspecified	3	3			
Spanos, P. K., 1975	28	Unspecified	3	2	Vagotomy, pyloroplasty	23	5
					Vagotomy, antrectomy	2	0
Woods, J. E., 1973	2	Duod.			2		0
Hadjiyannakis, E. J. 1971	2	Duod.	1	1	1		0
Penn, I., 1968	4	Unspecified			Vagotomy, drainage	3	1
					Subtotal gastrectomy	1	0
Owens, M. L., 1976	12	Duod.	10	7	Vagotomy, pyloroplasty	1	1
					Vagotomy, antrectomy	1	0
Total	52		17	13	35		8

overall mortality rate for elective surgery was one in 43 or 2.3%.

Operations for peptic ulcer before transplant resulted in only 8 post-transplant recurrences in 35 patients. In contrast, 17 patients were managed medically before transplantation and although they were not symptomatic at the time of renal transplantation, 13 developed recurrent ulcers after transplantation. Ulcer recurrence is significantly lower in the operated group ($p < .0003$).

Peptic ulcer after transplantation presented as bleeding in 50 patients, perforation in nine patients and pain in nine. Mortality was high: 31 deaths in 72 patients (43%). Eleven deaths occurred in the 35 patients treated medically (31%), and 20 deaths among 37 surgical patients (54%). The patients treated medically and the patients treated surgically are obviously selected groups and not statistically comparable.

Peptic ulcer symptoms presented as early as 6 days and as late as 7 years following renal transplant. Symptoms usually occurred early, 61% in 3 months, 74% in 6 months, but 19% occurred after one year, (Fig. 1).[1,5,10–12,16,17,20,21,23,27]

Bleeding was the commonest and most lethal post-transplant ulcer complication and was the indication for operation in 29 of the 37 patients who were managed operatively. Emergency operation for major hemorrhage was necessary in 21 patients and resulted in 19 deaths (90%).

Perforation after transplantation was treated more successfully. operation on five patients with perforated ulcers after transplantation resulted in one death occurring in a patient with advanced peritonitis. Of the four patients not operated upon for perforated ulcer, three died. The combined mortality from perforation was 44%.

There were 43 duodenal and 9 gastric ulcers: a ratio of five to one, which is close to the usually reported ratio of duodenal and gastric ulcers in patients with normal renal function.[9,14] Compared to one another, gastric ulcers were significantly more likely to perforate ($p \leq .01$) and duodenal ulcers were more likely to bleed. The mortality from duodenal ulcers, gastric ulcers, combined gastric and duodenal ulcers and recurrent ulcers did not differ significantly and was approximately 43% (Table 3).

Discussion

Eighty-seven per cent of patients with ulcers in the post-transplant period presented with either perforation or bleeding. Frequently the patient died regardless of whether medical or surgical therapy was employed.

It may be valuable to speculate concerning the reasons peptic ulcer occurs soon after transplantation and often occurs as a lethal complication. The high incidence of peptic ulceration occurring soon after transplantation has been related to increased frequency of rejection and high dose immunosuppression in the same period.[12,14,17] It is also apparent that many patients who develop peptic ulceration also have some other transplant complication which threatens their survival.

Steroids suppress inflammation[7,25] and delay wound healing[19] possibly increasing not only the likelihood but also the severity of complications when ulcers develop. For example, the complication was not suspected until very late in all four patients who died with perforated ulcers. One patient was moribund when the diagnosis was made and three patients were diagnosed at autopsy. In a recent review Conn and

Blitzer were able to document a significant association between peptic ulceration and steroid therapy only in patients who had received a cumulative dose in excess of 1000 mg prednisone.[3] Since it is common for our patients to receive approximately 250 mg prednisone equivalent on the day of transplant, it is not surprising that all of our patients had received in excess of 1000 mg prednisone at the time of peptic ulceration. Similar large steroid doses are also used in other transplant programs and it is likely that the great majority of the patients with peptic ulcer had received in excess of 1000 mg prednisone.

Bleeding is a notably lethal complication. Contributing factors include the suppression of platelet factor III in azotemia,[26] immunosuppressive induced thrombopenia, the use of platelet inhibitors (e.g., azathioprine) and anticoagulants for the treatment of rejection, and the use of heparin for dialysis when renal function is impaired.

Since most transplanted kidneys have undergone

TABLE 2. *Clinical Data on 72 Patients with Peptic Ulcer after Renal Transplant*

Author, Year	No. of Patients	Type of Ulcer		Therapeutic Indication		Treatment: Med.	Treatment: Elect. Surg.	Treatment: Emerg. Surg.	Deaths: Med.	Deaths: Surg.
Aldrete, J. S., 1975	4	Duod.	2	Bleeding	4	0	0	2	0	0
		Gast.	1					1		1
		*Post-op	1					1		1
Spanos, P. K., 1974	4	Duod.	1	Perforation	1			1		0
		Gast.	1	Bleeding	1			1		1
		Post-op	3	Bleeding	3	2		1	1	1
Rao, M. M., 1972	2	Duod.	2	Bleeding	2	2			0	
Diethelm, A. G., 1971	2	Duod.	1	Bleeding	1		1			0
		Post-op	1	Bleeding	1			1		1
Hadjiyannakis, E. J., 1971	11	Duod.	10	Bleeding	6	1	2	3	1	3
				Perforation	1			1		0
				Unspecified	3	3			1	
		Gast.	1	Perforation	1			1		0
Minale, C., 1971	6	Duod.	2	Bleeding	2	1		1	0	1
		Gast.	4	Bleeding	3	1		2	0	2
				Perforation	1	1			0	
Gruwez, J. A., 1970	12	Not specified		Bleeding	5	2	3†		1	1
				Perforation	3	2		1	2	1
				Pain	4	2	2		0	0
Moore, T. C., 1969	9	Duod.	9	Bleeding	7		1	6		6
				Pain	2	2			0	
Penn, I., 1968	5	Duod.	3	Bleeding	2		1	1		1
				Unspecified	1		1			0
		Gast.	2	Perforation	2	1		1	1	0
Owens, M. L., 1976	17	Duod.	13	Bleeding	10	8		2	2	2
				Pain	3	3			0	
		Duod. & Gast.	2	Bleeding	2	2			1	
		Post-op	1		1	1			0	
		Gast.	1	Bleeding	1			1		0
Summary	72	Duodenal		Bleeding	32	12	5	15	3	13
				Perforation	2			2		0
				Pain	5	5			0	
		Duod.& Gast.		Unspecified	4	3	1		1	0
				Bleeding	2	2			1	
				Bleeding	5	1		4		3
		Gast.		Perforation	4	2		2	1	
		Post-op		Bleeding	6	4		2	1	3
		Unspecified		Bleeding	5	2	3†		1	1
				Perforation	3	2		1	2	1
				Pain	4	2	2		0	0
		Totals			72	35	8	26	10	21

* Patients who had ulcer operations done before renal transplantation.
† Not stated whether operations were emergency or elective.

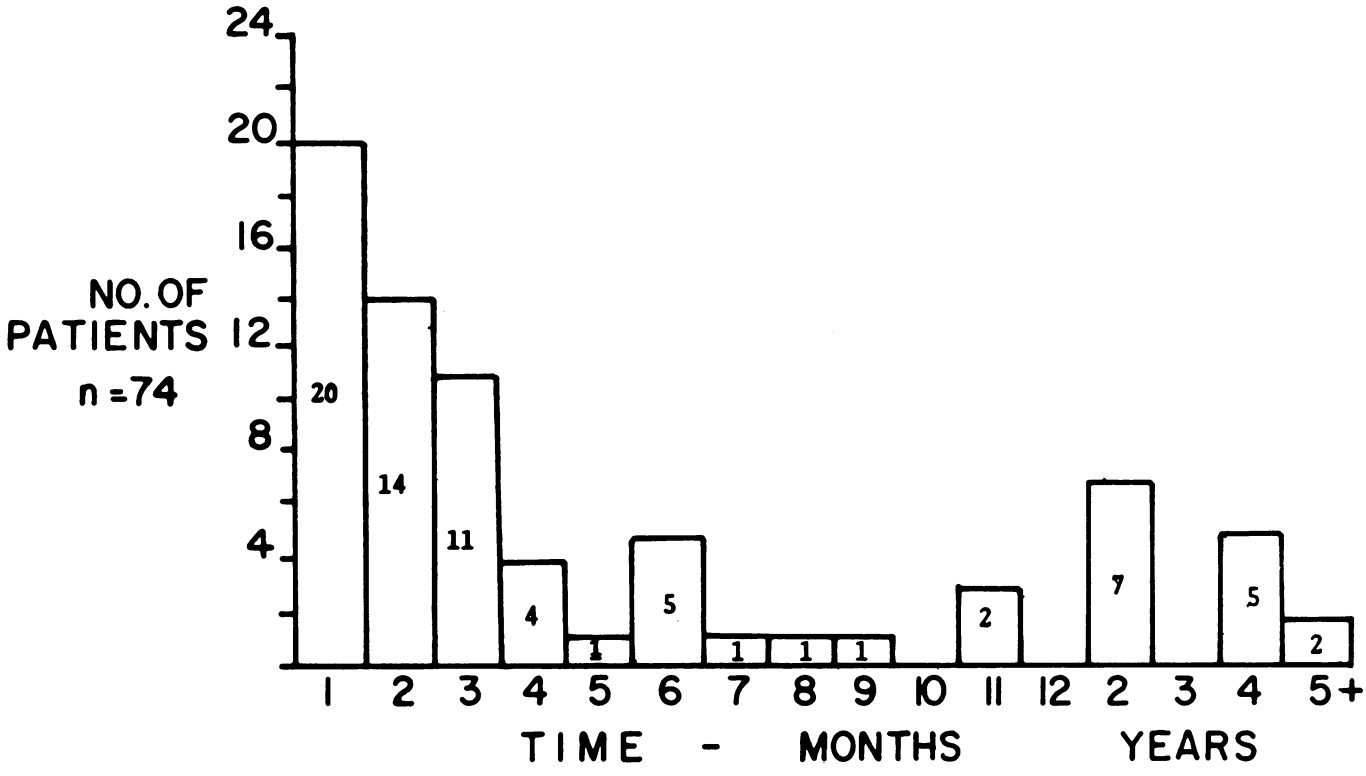

FIG. 1. Time from kidney transplantation to onset of peptic ulcer symptoms.

some degree of renal injury either as a result of ischemia during transplantation or from acute and chronic rejection afterwards, they are especially vulnerable to additional damage from reduced blood flow.[22] Reduction of renal function in a setting complicated by bleeding and hypotension probably contributes to mortality.

Since gastrin is metabolized by the renal parenchyma, impaired renal function may result in hypergastrinemia.[6,13] Stress induced epinephrine release may also increase gastrin and gastric acid.[24] Both diminished renal function and increased epinephrine may worsen peptic ulcer disease. Evidence for elevated histamine levels during rejection indicates that still another secretagogue may be increasing gastric acidity.[18] Persisting hyperparathyroidism and hypercalcemia may increase gastric acid secretion.[4]

Although the relative contributions of the various factors mentioned is largely speculative, the cumulative effect is to aggravate peptic ulcer disease. Current therapy should be prophylactic and directed at avoiding a cascade of aggravating factors.

Symptoms suggesting peptic ulceration should be reasons for prompt radiologic and endoscopic evaluation. Stool guaiac determination and hematocrits should be followed sequentially early in the post-transplant course and later if rejection or sepsis occur. Bleeding secondary to ulceration should be particularly suspected in patients receiving aspirin, indomethacin or anticoagulants. Large increases in basal and maximal gastric acid output occur in some patients following renal transplantation and results in peptic ulceration. It may be that routine BAO and MAO determinations following renal transplantation will identify those patients likely to develop peptic ulceration.[8]

Although the preventive value of antacids is not established, they have only minor side effects and should be given for 6 months following renal transplant. In the lower risk patients, antacids may be given in doses of about 75 mEq (e.g., Maalox 30 ml; Mylanta II 18 ml) one and three hours after each meal and at bedtime.

During rejection and in patients with proved or suspected ulcer disease, antacids should be given at hourly intervals during the day and evening, and a double dose should be given at bedtime. Gastric hypersecretors should receive larger doses than those who are not.

The data collected from the literature combined with our own experience indicate that *elective* surgery for peptic ulcer disease can be performed safely before or after transpllantation. The mortality rate of 2.3% differs little from the 1–2% mortality often quoted for gastric surgery in the non-transplant patient.[25] Elective operation prior to transplant signifi-

cantly reduces the likelihood of ulcer recurrence in the post-transplant period. Some patients with peptic ulcer may be too ill for elective surgery and in these patients gastric irradiation or the use of H_2 inhibitors may be considered.[2,15]

We conclude that potential transplant recipients should be carefully evaluated for peptic ulcer disease. Demonstration of a peptic ulcer on upper gastrointestinal series or endoscopy is an indication for elective surgery before transplantation. The risk of a serious complication as the presenting sign is extremely high and the opportunity for elective surgery often fails to occur after transplantation.

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