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Prophylaxis with ranitidine against peptic ulcer disease after liver transplantation

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Abstract. Upper gastrointestinal bleeding resulting from peptic ulcer disease is a potentially life-threatening situation. There are several reports on the association of ulcer disease and corticosteroid treatment, especially when high doses (>40 mg/day) are used. Some categories of patients are prone to ulcer disease under steroid treatment. Prophylaxis in this situation therefore seems reasonable. We compared 23 consecutive liver transplant patients who received ranitidine prophylaxis with 33 previously transplanted patients who had no prophylaxis. In the control group there were 13 patients who had an ulcer, seven of whom bled. In the treated group two ulcers without upper GI bleeding were found. The results indicate that ranitidine can effectively reduce peptic ulcer disease in liver transplantation patients, despite the use of very high doses of corticosteroids.

Key words: Orthotopic liver transplantation – Peptic ulceration – Ranitidine prophylaxis.

Peptic ulcer disease is a dangerous complication in liver transplant patients, since every peptic ulcer is a potential bleeding site. In our first patients who had a liver transplantation there was a high incidence of peptic ulceration. Three patients exsanguinated despite proper therapy; sometimes peptic ulceration worsened an already poor clinical condition, for instance, in patients with chronic rejection.

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Liver transplantation patients are prone to develop a peptic ulcer because of the preexisting cirrhosis [2], perioperative stress, and the use of high doses of corticosteroids for immunosuppression. Acid secretion is likely to play a major role in peptic ulceration. Inhibition of acid secretion in the initial postoperative period seems appropriate, for instance, with an H2-antagonist. Ranitidine is a potent inhibitor of acid secretion. In liver transplant patients the additional advantages of ranitidine are that (1) it has minimal affinity to cytochrome P-450; (2) liver blood flow does not seem to be influenced by ranitidine, which could be of vital importance for the graft; and (3) there is no evidence of immune modulatory effects of ranitidine on subsets of lymphocytes (no receptors for ranitidine), but this is probably of little clinical significance [12].

We analyzed retrospectively the frequency and severity of steroid-induced peptic ulceration in orthotopic liver transplant (OLT) patients not treated prophylactically with ranitidine, studied prospectively the effect of ranitidine prophylaxis on the same category of patients, and compared the results.

Patients and methods

This report concerns all adult patients who underwent transplantation between March 1979 and June 1988. All patients were selected for OLT according to criteria which have been published elsewhere [8]. The patients were divided into two groups:

Group 1 was the control group and consisted of 33 adult patients (24 women and 9 men) who received no ulcer prophylaxis. Twenty-three patients had an upper GI endoscopy within

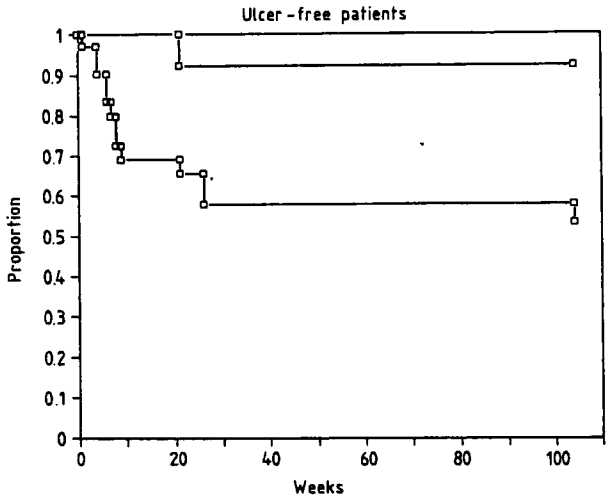

Fig. 1. Proportion of ulcer-free patients after orthotopic liver transplantation. *Upper line* represents group 2 (prophylaxis), *lower line* represents group 1 (no prophylaxis)

Table 1. Data of patients prophylactically treated with ranitidine (group 2) and historical control group (group 1)

	Historical control (group 1), $n=33$	Prophylaxis group (group 2), $n=23$
Azathioprine (125 mg/day)	33	23
Cyclosporin A	-	18
Corticosteroids		
- mean dose/day (30 days)	77.4 mg[a]	77.2 mg (NS)
- mean dose/day (8 weeks)	62.5 mg[a]	60.4 mg (NS)
Ranitidine	-	23
Ulcer	13	2 $P=0.025$[b]

[a] Expressed in equivalents of milligrams prednisolone
[b] Log rank test

8 weeks after transplantation and 15 patients had at least one endoscopy preoperatively. Endoscopy in this group was done only when clinical signs raised the suspicion of peptic ulceration, which resulted in an underestimation of peptic ulcer disease. The strikingly high incidence of peptic ulcer disease in group 1 prompted us to prospectively study the effect of prophylactic ranitidine treatment on the development of peptic ulcer disease in group 2.

Group 2 received ranitidine prophylaxis and included 23 patients (17 women and 6 men) who initially received ranitidine 50 mg t.i.d. intravenously, followed by 150 mg b.i.d. orally for a total period of 4 weeks. All patients had an upper GI endoscopy less than 2 months before transplantation, 4 weeks after OLT, and in case of clinical problems. Preoperatively, the gastric pH was measured to demonstrate gastric acid secretion. Immunosuppression in group 1 and group 2 consisted of prednisolone and azathioprine. Prednisolone was started at a dose of 200 mg/day and gradually tapered; the azathioprine dose was 125-150 mg/day, lifelong. In addition, 18 patients in group 2 received cyclosporin A, aiming at trough levels of 150-250 ng/ml measured by high-performance liquid chromatography (HPLC). Rejection episodes in the first 3 weeks were treated with methylprednisolone, 1000 mg/day intravenously for 3 days. If rejection occurred after 3 weeks, the daily dose of prednisolone was increased to 100 mg/day for 5 days and subsequently tapered.

Peptic ulcer disease was diagnosed as upper GI blood loss or fecal blood loss with ulceration visualized on endoscopy or at autopsy. To compare differences in ulcer incidence, we studied the time between transplantation and the development of a peptic ulcer (i.e., interval free of peptic ulcer disease) and compared the results in groups 1 and 2 (Fig. 1), using the log rank test [7]. To facilitate direct comparison of both groups, the boluses of methylprednisolone administered were converted to equivalents of prednisolone and included in the mean dose per day. Statistical analysis of differences in diagnosis and Child-Pugh classification was performed with a 2×2 table; all other parameters were tested for differences with a Wilcoxon test, $P<0.05$ being significant.

Results

Table 1 shows patient data concerning immunosuppression, use of ranitidine, and ulcer incidence. It reveals no statistically significant differences in average and cumulative corticosteroid dosages at 4 and 8 weeks. Age, sex, Child-Pugh classification, total time in the operating room, and blood loss during transplantation, together with postoperative stay in intensive care, are shown in Table 2. The severity of cirrhosis was quite similar in both groups. Though groups 1 and 2 differ with regard to Child A and B patients, the mean Child score is equal in both groups. The operative procedures were similar in the treated and control groups. Group 2 differed from group 1 with a longer total operation time and more days spent in intensive care, but total blood loss did not differ statistically. If anything, the differences between both groups are to the disadvantage of group 2 (prophylaxis).

In group 1 (no prophylaxis) 13 of 33 patients had a peptic ulcer. Four of these were gastric ulcers, two of which bled, and nine were duodenal ulcers, five of which bled. Three patients died as a direct result of the bleeding. In four patients the bleeding exacerbated an already poor clinical condition.

In group 2 two ulcerations were observed in 23 patients, 2 and 5 months after transplantation. The first patient had *Pneumocystis* pneumonia in a state of chronic rejection; the other had chronic rejection. Two patients had a slight gastritis. The ulcer-free interval in group 1 differed significantly from that in group 2 (proportion of ulcer-free pa-

Table 2. Comparison of recipient diagnosis, Child-Pugh classification, and some peroperative parameters of group 1 (no prophylaxis) and group 2 (prophylaxis)

	Group 1 ($n=33$)	Group 2 ($n=23$)	P-value
Age (mean/range)	36.8 (17-54)	42.5 (18-58)	NS
Male/female	9/24	6/17	NS
Diagnosis:			
- cirrhosis			
primary biliary (PBC)	15	9	NS
chronic active/inactive	12	4	NS
secondary biliary	1	2	NS
- primary sclerosing cholangitis	-	3	NS
- hepatocellular carcinoma	1	2	NS
- Budd-Chiari	1	1	NS
- giant cavernous hemangioma	1	-	NS
- alpha-1-antitrypsin deficiency	1	1	NS
- erythropoietic protoporphyria	1	-	NS
- anomalous liver veins and cirrhosis	-	1	NS
Preoperative Child-Pugh classification:			
- class A	13	3	$P<0.02$
- class B	12	18	$P<0.02$
- class C	8	2	NS
Mean total operating time in min	376	457	$P<0.05$
Mean total blood loss in liters	11.4	14.2	NS
Mean no. of days in intensive care after transplantation	4.3	8.5	$P<0.007$

tients at 2 years 61% vs 91.15%, log rank test [7], $P<0.025$). Follow-up in group 1 ranged from 2 to 7 years, in group 2 from 10 months to 4 years.

Discussion

Since significantly less ulcer disease occurred in the ranitidine group, we conclude that ranitidine provides adequate prophylaxis for peptic ulcer disease during high-dose steroid treatment after OLT. In contrast, the incidence and severity of peptic ulcer disease in the control group was striking. Figure 1 clearly shows that 4 weeks of ranitidine prophylaxis results in prevention, but not postponement, of peptic ulceration.

Upper GI complications like ulcers and bleeding were found predominantly in the first months after OLT, comparable to kidney transplantation [3, 5]. In the first weeks after liver transplantation, immunosuppression is maximal and high-dose corticosteroid treatment is given (Table 1). There is convincing evidence that >40 mg per day of prednisolone for more than 1 month is a risk factor for developing an upper GI ulcer [1, 6].

Only a few studies have been done on the prophylactic use of H2 receptor antagonists under corticosteroid treatment in kidney transplant patients, and there are no such reports on liver transplant patients [4, 5, 9-11]. Most studies concern cimetidine prophylaxis in renal transplant patients [3-5, 9-11], but the results are not consistent [10].

Since we did not perform a double-blind study, factors other than ranitidine treatment might be considered to explain our results.

First, immunosuppression was somewhat different in group 2, as 18 patients also received cyclosporin A and - during the first 10 days - cyclophosphamide, together with conventional prednisolone and azathioprine treatment. However, the average dosage per day of corticosteroids during the study period and the way the corticosteroids were administered did not differ between the two groups.

Second, the diagnostic approach for establishing peptic ulcer disease differed between the two groups. In group 1 (control group) no systematic upper-GI endoscopy was performed, while in group 2 the treatment protocol included pre- and postoperative endoscopy. If anything, this difference would have led to an underestimation of the incidence of peptic ulcer disease in group 1. The frequency of peptic ulcer disease in group 2 contrasts markedly with the high incidence of ulcer disease after OLT in the control group. This cannot be attributed to patient selection, since the criteria were the same for all patients.

Third, the operative procedure was the same in both groups. The perioperative complications did not differ between the treated and the control groups. Blood loss in group 1 and group 2 was not statistically different. The statistical differences in Child-Pugh classification, time spent in the operating room, and time in intensive care are all to the disadvantage of group 2 (Table 2). The clinical significance of these statistical differences, i.e., the impact on ulcer incidence, is not easily explained. One may assume that the operative stress in group 2 (prophylaxis) equaled the operative stress in group 1 (no prophylaxis). If these differences should reflect more perioperative stress in group 2, this would emphasize the need for peptic ulcer prophylaxis in liver transplant patients.

As our results show, ranitidine provides adequate protection against peptic ulcer disease in liver

transplant patients under high-dose corticosteroid treatment. We therefore recommend ulcer prophylaxis with an H2 antagonist such as ranitidine in this category of patients.

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