

Risk Factors for Hyperamylasemia After Hepatectomy Using the Pringle Maneuver

Randomized Analysis of Surgical Parameters

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Objectives: To determine whether the increased portal venous pressure caused by use of the Pringle maneuver contributes to inducing posthepatectomy hyperamylasemia and, subsequently, to evaluate risk factors for its development.

Design: Randomized study.

Setting: University hospital.

Patients: Forty patients who were going to undergo hepatectomy were assigned prospectively to either a superior mesenteric artery clamp (n=20) or a nonclamp (n=20) group by the random-block method.

Interventions: The Pringle maneuver was used during hepatectomy, and in the superior mesenteric artery clamp group the superior mesenteric arteries were clamped simultaneously.

Main Outcome Measures: Amylase activity, isozyme, and creatinine levels in the blood and urine samples were measured before and after surgery, and the amylase creatinine clearance ratio was estimated.

Results: The serum amylase activity levels of the superior mesenteric artery clamp and nonclamp groups did not differ significantly during the 7 postoperative days. The serum amylase activity levels exceeded 250 U/L in 14 patients (group 1) and remained below this level in 26 (group 2). The salivary-type isozyme levels of group 1 increased significantly compared with those of group 2, and the levels of group 2 remained normal. The total amount of amylase excreted in the urine samples of group 1 patients also increased significantly, with the salivary-type isozyme predominating. All the mean amylase creatinine clearance ratios before and after surgery remained normal. The mode χ^2 of the logistic model including the indocyanine green retention rate at 15 minutes and the ratio of the resected liver weight to the whole liver volume showed a significantly increased risk ($P=.01$).

Conclusion: It is not the increased portal venous pressure caused by use of the Pringle maneuver but the liver function and the extent of liver resection that are considered risk factors for inducing posthepatectomy salivary-type hyperamylasemia.

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ALTHOUGH posthepatectomy hyperamylasemia has been reported increasingly as the number of patients undergoing surgical procedure for hepatocellular carcinomas and metastatic lesions increases, the mechanism responsible remains to be clarified.¹⁻⁴ During hepatectomy, the Pringle maneuver,⁵ ie, total occlusion of the liver vasculature at the hepatoduodenal ligament, is used in most patients,^{6,7} and it induces not only stagnation of the portal venous blood, thereby increasing portal venous pressure (PVP), but also ischemic liver damage. Increased PVP may induce pancreatitis and contribute to mortality.^{3,4,8} At present, amylase metabolism has not been fully clarified: about 24% to 26% of the serum amylase is excreted by the kidney,⁹ whereas most

of the remainder is thought to be removed by the reticuloendothelial system in the body, and the liver is suspected to be a major organ for amylase removal.¹⁰⁻¹³ Therefore, ischemic liver damage is also suspected to play an important role in inducing hyperamylasemia.¹²

In this study, the effect of increased PVP caused by using the Pringle maneuver on postoperative serum amylase activity levels was investigated prospectively by comparing patients who underwent hepatectomy using the Pringle maneuver with those whose PVP increase was reduced by clamping the superior mesenteric arteries (SMAs) simultaneously. Then, risk factors for hyperamylasemia induction were investigated by univariate and multivariate analyses.

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PATIENTS AND METHODS

DESIGN AND PATIENTS

This study was done at the Second Department of Surgery, Faculty of Medicine, University of Tokyo, Tokyo, Japan, from February 1996 to October 1996. Forty patients who were going to undergo hepatectomy using the Pringle maneuver entered this prospective study. Preoperatively, hepatocellular carcinoma was diagnosed in 30 patients with chronic hepatitis or liver cirrhosis, metastatic lesions were diagnosed in 6 patients with normal liver function, and other diagnoses were assigned to 4 patients with normal liver function. To examine the effect of increased PVP on serum amylase activity levels, 40 patients were assigned prospectively to either the SMA clamp (n=20) or the nonclamp (n=20) group by the random-block method. Clamping of the SMA is considered to reduce the magnitude of the PVP increase caused by using the Pringle maneuver. The Pringle maneuver was performed using Fogarty forceps for 15 minutes, followed by a 5-minute release period. This schedule was repeated until hepatectomy was accomplished. The SMAs of the patients in the SMA clamp group were occluded simultaneously using Fogarty forceps at the caudal side of the mesocolon. Hepatectomy was performed using the standard technique of our department, as described elsewhere.^{6,7}

BLOOD AND URINE SAMPLING

The amylase activity and creatinine levels in the blood and urine samples were measured before surgery and on the first, second, third, fifth, and seventh days after surgery. Amylase activity levels were measured using a blocked-type substrate, 2-chloro-4-nitrophenyl 65-azido-65-deoxy- β -maltopentaoside (Dai-ichi Chem Co, Tokyo, Japan), and the levels were expressed in units per liter (normal range in the serum, <156 U/L). The salivary- (S; normal range in the serum, 34.6%-63.4%) and pancreatic-type (P; normal range in the serum, 25.8%-61.5%) amylase isozymes were stained by the blue starch method (Neo Amylase Test, Dai-ichi Chem Co). If the serum amylase activity level exceeded 250 U/L, the patient was considered to have significant hyperamylasemia.

AMYLASE CREATININE CLEARANCE RATIO (ACCR)

The ACCR was estimated using the following formula: $ACCR = [(Am)u \times (Cr)s] / [(Am)s \times (Cr)u]$, where [Am]u indicates urinary amylase activity (expressed in units per liter); [Am]s, serum amylase activity (expressed in units per liter); [Cr]s, serum creatinine concentration (expressed in milligrams per deciliter); and [Cr]u, urinary creatinine concentration (expressed in milligrams per deciliter). Ratios of 2.0 to 4.2 were considered normal.

ESTIMATION OF LIVER FUNCTION AND WHOLE LIVER VOLUME

Liver function was evaluated by determining the indocyanine green (0.5 mg/kg) retention rate at 15 minutes (ICG15; normal range, <10%). Whole liver volume was estimated using computed tomography. The serial abdominal transverse computed tomographic scans taken at 0.8- or 1.0-cm intervals, including the segment between the dome and the most inferior part of the liver, were used to calculate the liver volume (expressed in milliliters) by the method of Heymsfield et al,¹⁴ with minor modifications. The ratio of the weight of the resected liver to the whole liver volume was termed the resection ratio (Rr), which was expressed as a percentage.

VARIABLES FOR UNIVARIATE AND MULTIVARIATE ANALYSES

Superior mesenteric artery clamping, operation duration, total duration of the Pringle maneuver, total blood loss, ICG15, Rr, sex, and age were included as variables for univariate and multivariate analyses for risk factors for post-hepatectomy hyperamylasemia.

STATISTICAL ANALYSIS

The SMA clamp and nonclamp groups were compared using the unpaired Student *t* test and the χ^2 test, and differences at $P < .05$ were considered significant. The variables listed in the paragraph above were evaluated by univariate and multivariate analyses using a logistic model. The data are expressed as mean \pm SD.

RESULTS

CHARACTERISTICS OF SMA CLAMP AND NONCLAMP GROUPS

There were no significant differences among the operation duration, the total duration of the Pringle maneuver, total blood loss, ICG15, Rr, operative procedures, sex, or age values of the SMA clamp and nonclamp groups (**Table 1**). No patient received a blood transfusion or showed clinical signs of pancreatitis or sialadenitis.

ALTERATIONS OF THE SERUM AMYLASE ACTIVITY AND ISOZYME LEVELS

The amylase activities of the SMA clamp and nonclamp groups peaked on the first postoperative day and then

decreased slightly during the remaining 6 postoperative days (**Table 2**). Although the postoperative values of the SMA clamp group tended to be higher than those of the nonclamp group, the values did not differ significantly on any of the 7 postoperative days. The serum amylase activity levels of 9 patients in the clamp group and 5 patients in the nonclamp group exceeded 250 U/L. Overall, the serum amylase activity levels exceeded 250 U/L in 14 patients (group 1, 35%) (**Figure 1**) and remained below this level in the remaining 26 (group 2, 65%). During the first 7 postoperative days, group 1 and 2 values differed significantly ($P < .05$). In group 1, S-type isozyme proportions increased significantly on the first and second postoperative days ($P = .0001$), and as the serum amylase activity levels decreased, so did the proportion of the S-type isozymes, which was normal by the third day. In group 2, both the S- and P-type

isozyme proportions were normal throughout. The S-type isozyme proportions of these 2 groups differed significantly during the first 7 days ($P<.05$).

ALTERATIONS OF THE TOTAL AMOUNTS OF AMYLASE AND ITS ISOZYMES IN THE URINE

The total amount of amylase excreted in the urine samples of group 1 patients increased significantly on the first, second, third, and seventh postoperative days, and the values for groups 1 and 2 on the first 3 postoperative days differed significantly ($P<.05$) (**Table 3**). The proportions of the S-type isozyme in the urine samples of group 1 patients also increased significantly on the first and second postoperative days

($P<.05$), and as the urinary amylase activity level decreased, so did the S-type isozyme proportion, whereas neither the urinary amylase activity level nor the S-type isozyme proportion of group 2 patients increased significantly at any time. There were significant differences between the S-type isozyme proportions of the 2 groups on each of the first 7 postoperative days ($P<.05$).

ALTERATIONS OF ACCRs

All the mean ACCRs remained within the normal range, and there were no significant differences among the values for the 2 groups on any of the first 7 postoperative days (**Table 4**).

Table 1. Characteristics of the SMA Clamp and Nonclamp Groups*

Characteristic	SMA Clamp Group	Nonclamp Group
Sex, male:female	17:3	12:8
Age, y	61.7±9.1	64.8±9.7
Operation duration, min	379.7±107.7	392.6±122.9
Total duration of the Pringle maneuver, min	55.8±38.9	68.5±37.5
Total blood loss, mL	665.0±387.0	615.6±470.8
Indocyanine green retention rate at 15 min, %	13.5±10.0	9.4±5.9
Resection ratio, %	24.5±22.3	22.5±22.4
No. with operative procedures		
Systematic subsegmentectomy	8	11
Limited resection	5	5
Lobectomy	7	4

*Data are given as mean±SD unless noted otherwise. SMA indicates superior mesenteric artery.

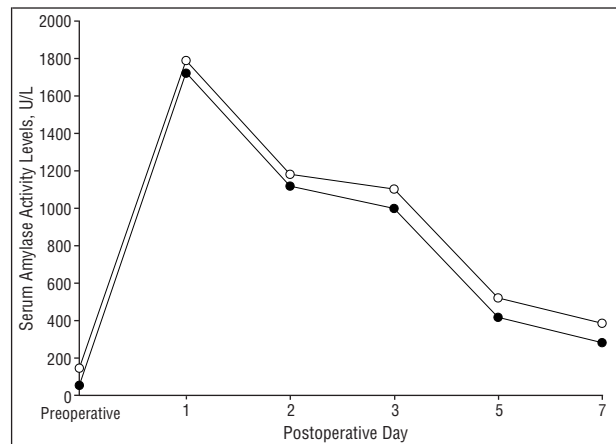


Figure 1. Alteration of serum amylase activity levels in a patient with posthepatectomy hyperamylasemia. The serum amylase activity levels (open circles) were increased the first postoperative day and remained high during the first 7 postoperative days. Amylase isozyme analysis showed that salivary-type amylase (closed circles) was predominant during this period.

Table 2. Alterations of Serum Amylase Activity Levels and Salivary-Type Amylase Proportions in the SMA Clamp Group, Nonclamp Group, Group 1, and Group 2*

Group	Preoperative Day	Postoperative Day				
		1	2	3	5	7
SMA clamp group (n=20)	118.4±43.2 (48.3%±15.2%)	298.5±408.5 (62.8%±26.9%)	205.8±251.3 (60.8%±22.7%)	194.4±232.6 (51.2%±22.7%)	254.9±291.7 (48.1%±24.2%)	194.1±114.9 (43.8%±22.1%)
Nonclamp group (n=20)	98.2±29.6 (49.2%±11.6%)	234.8±342.1 (61.5%±18.5%)	154.1±204.7 (53.6%±20.8%)	143.2±142.9 (42.0%±22.5%)	161.6±110.1 (37.2%±19.6%)	151.3±77.6 (39.3%±22.5%)
Group 1 (n=14)	115.1±36.1 (50.4%±12.8%)	564.4±516.2 (78.3%±18.3%)	356.4±319.8 (73.7%±18.9%)	305.4±280.8 (62.2%±24.4%)	360.2±324.8 (55.2%±28.2%)	251.9±118.8 (54.4%±23.9%)
Group 2 (n=26)	103.1±39.0 (48.0%±13.7%)	106.3±49.7 (53.4%±20.3%)	85.6±31.0 (48.3%±17.9%)	96.0±26.0 (38.3%±17.1%)	126.4±50.9 (35.9%±15.3%)	†130.0±51.0 (34.7%±18.1%)

*Data are given as mean±SD. (Data in parentheses indicate the proportions of salivary-type amylase in the serum expressed in units per liter.) SMA indicates superior mesenteric artery.

† $P<.05$.

Table 3. Alterations of Total Amounts of Amylase and the Proportion of Salivary-Type Amylase in the Urine*

Group	Preoperative Day	Postoperative Day				
		1	2	3	5	7
1 (n=14)	326.8±135.3 (35.4%±9.2%)	3152.6±3400.2 (69.4%±22.4%)	1574.3±1359.4 (63.1%±22.8%)	1401.6±1039.4 (51.0%±28.6%)	1509.1±2141.2 (42.2%±26.1%)	624.9±299.2 (41.8%±21.1%)
2 (n=26)	329.7±200.6 (31.9%±12.1%)	685.9±363.4 (38.6%±18.4%)	533.8±310.6 (34.1%±15.9%)	563.9±279.5 (25.4%±11.8%)	683.6±477.8 (22.8%±17.7%)	575.3±328.0 (22.1%±13.6%)

*Data are given as mean±SD. (Data in parentheses indicate the proportions of salivary-type amylase in the urine expressed in units per liter.)
†P<.05.

Table 4. Alterations of Amylase Creatinine Clearance Ratios*

Group	Preoperative Day	Postoperative Day				
		1	2	3	5	7
1 (n=14)	2.6±0.9	2.7±1.2	3.0±1.6	3.7±1.6	2.8±1.2	2.8±1.3
2 (n=26)	2.9±1.5	3.2±1.0	3.5±1.5	3.5±1.0	3.7±1.8	3.3±1.3

*Data are given as mean±SD.

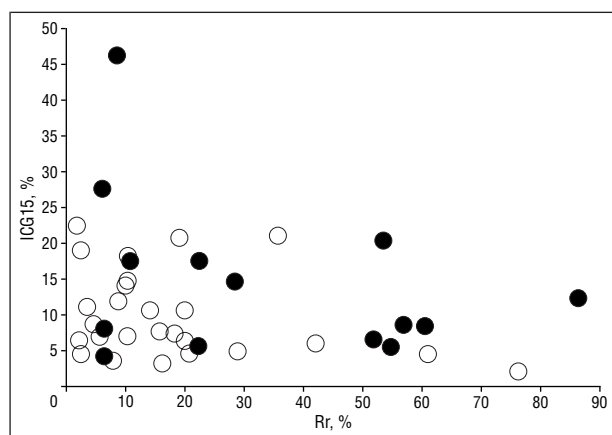


Figure 2. Distribution of 40 patients in terms of the indocyanine green retention rate at 15 minutes (ICG15) and the ratio of the weight of the resected liver to the whole liver volume (Rr). The closed circles indicate the 14 patients with posthepatectomy hyperamylasemia, and the open circles indicate the 26 without hyperamylasemia. As the ICG15 and the Rr increased, the patients tended to show posthepatectomy hyperamylasemia.

RISK FACTORS FOR POSTHEPATECTOMY HYPERAMYLASEMIA

Univariate analysis revealed no significant risk factors. After performing variable selection, a logistic model ($df=2$) including ICG15 and Rr was chosen, and the mode χ^2 test of the logistic model revealed a significantly increased risk ($P=.01$), with P values for ICG15 and Rr of .07 (odds ratio, 1.09) and .02 (odds ratio, 1.05), respectively (**Figure 2**).

CLINICAL OUTCOMES

None of the 40 patients experienced either mortality or morbidity related to posthepatectomy hyperamylasemia, and they all recovered uneventfully.

COMMENT

Recently, hyperamylasemia after hepatectomy has been noted.¹⁻⁴ Tsuzuki et al² observed hyperamylasemia in 70 (39.5%) of 177 patients who had undergone hepatectomy for hepatocellular carcinoma or metastatic lesions, but they could not elucidate the mechanism responsible. Miyagawa and colleagues^{3,4} suggested that prolonged complete occlusion of the portal vein during hepatectomy in patients with chronic liver disease has a serious effect on serum amylase levels. Many factors, such as increased PVP, ischemic liver damage, and reduced functional liver volume, may affect amylase metabolism after hepatectomy.^{3,4,8,15,16}

It has been reported that the portal venous stasis associated with liver disease may predispose patients to develop pancreatitis.⁸ Use of the Pringle maneuver is, therefore, considered to promote portal venous stasis, to affect the exocrine pancreas, and to induce pancreatitis.^{3,4} In this study, to elucidate the effect of increased PVP induced by use of the Pringle maneuver on the serum amylase activity level, 40 patients were randomly assigned to either the SMA clamp or the nonclamp group. Establishment of SMA stenosis was shown to reduce PVP by

reducing the inflow blood volume to the small intestine.^{17,18} Therefore, SMA clamping is considered to have the same effect on PVP and is used clinically to reduce portal venous stagnation when the portal vein is clamped completely during surgical procedures. Although PVP was not measured in our 40 patients, SMA clamping was considered to have reduced the increase in PVP during the Pringle maneuver compared with that during the maneuver alone. There were no significant differences among any of the variables in our 2 groups preoperatively, which indicated that the patients had been randomly assigned successfully. During the 7 postoperative days, the serum amylase activity levels of both groups did not differ significantly, indicating that SMA clamping does not have any effect on serum amylase activity level alterations, and, therefore, increased PVP would seem to have little effect on posthepatectomy hyperamylasemia.

DURING the first 7 postoperative days, the serum amylase activity levels of 14 patients exceeded 250 U/L, and amylase-isozyme analysis revealed a significant increase in mean S-type isozyne levels and a decrease in mean P-type isozyne levels. As the serum amylase level decreased with every passing postoperative day, the proportion of the S-type isozyne also decreased and that of the P-type isozyne increased, finally reaching the standard ranges. No patients had clinical signs of sialadenitis, and, therefore, abnormal S-type amylase metabolism was considered to have contributed to posthepatectomy hyperamylasemia.

The kidney plays an important role in removing serum amylase,¹⁹ which seems to be filtered by the glomerus at a rate of at least 3% of the glomerular filtration rate and, perhaps, far more rapidly if amylase is catabolized by the renal tubule. The P-type isozyne is cleared about 1.6 times faster than the S-type isozyne by the baboon kidney,⁹ and this difference may be as great as 2-fold in man.²⁰ If the kidney does not remove sufficient serum amylase, this would explain why the serum amylase level increases after hepatectomy. In fact, reduced amylase clearance has been suggested to be a cause of hyperamylasemia in patients with chronic liver diseases.^{15,16} However, in our patients, as the serum amylase activity level increased, the total amount of amylase excreted in the urine increased significantly, with a high proportion of the S-type isozyne. Furthermore, the postoperative ACCR values did not increase significantly compared with the preoperative values, and the postoperative ACCR values of the patients with and without hyperamylasemia did not differ significantly. These findings indicate that hyperamylasemia was induced neither by renal dysfunction nor by pancreatitis and suggest that some other mechanism does not function adequately after hepatectomy, resulting in S-type-predominant hyperamylasemia.

Amylase metabolism has been suggested to be altered as a result of liver dysfunction: Bhutta and Rahman²¹ reported that serum amylase activity levels were related to the degree of liver dysfunction. There are 2 possible mechanisms of serum amylase removal

by the liver. One is the excretion of intact amylase into the bile^{11,13}: Donaldson et al¹¹ found there was no significant difference among the amylase activity levels of 32 paired serum and bile samples from humans. The other mechanism is amylase removal by the hepatocytes or reticuloendothelial system: Hiatt and Bonorris¹⁰ carried out an experiment in dogs and demonstrated that amylase was removed from the serum by deposition in the hepatocytes, probably through the reticuloendothelial system, and Murata et al¹² showed that in rabbits, glycoprotein-S-type amylase was taken up into the hepatocytes and excreted. Impairment of this process may cause S-type hyperamylasemia in patients with chronic liver diseases.

Multivariate analysis of the data from our patients showed that ICG15 and Rr correlated significantly with the induction of posthepatectomy S-type hyperamylasemia. This result corresponds well with results from a previous study showing that as the liver function deteriorated the serum amylase activity increased²² and suggests that the liver plays an important role in removing serum amylase, particularly the S type.¹² A poorly functioning liver will probably be prone to suffer ischemic damage due to use of the Pringle maneuver. However, if liver function alone predisposes to the occurrence of posthepatectomy hyperamylasemia, then hyperamylasemia in patients with normal livers cannot be explained. Our results also suggest that the extent of hepatic resection contributes to the induction of hyperamylasemia by reducing the functional liver volume for serum amylase removal. Thus, liver function and resection volume seem to be risk factors for posthepatectomy hyperamylasemia development.

In conclusion, the increased PVP caused by use of the Pringle maneuver may not be related to posthepatectomy S-type hyperamylasemia. Liver function and the extent of liver resection are considered to contribute to the induction of such hyperamylasemia, and the liver is suspected to play an important role in removing serum amylase, particularly the S type. Clinically, we have been treating such patients as we do those with pancreatitis. As far as this type of hyperamylasemia resolves postoperatively, it may not be related to any mortality or morbidity, as observed in our patients, and, therefore, patients with it only require careful observation without special treatment.

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