

**Title:**

Hyperamylasemia and pancreatitis following posterior spinal surgery

**Running title**

Hyperamylasemia after spinal surgery

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1 Hyperamylasemia and pancreatitis following posterior spinal surgery

2

### 3 **Abstract**

4 **Background:** Postoperative pancreatitis has primarily been reported as a complication of  
5 abdominal surgery, but there are some case reports of postoperative pancreatitis after spinal  
6 surgery. The objective of this study was to investigate a case series of hyperamylasemia and  
7 pancreatitis following posterior spinal surgery.

8 **Methods:** The serum amylase level was measured following posterior spinal surgery in the  
9 prone position. Patients were divided into groups with a normal serum amylase level (0-125  
10 IU/L) and with hyperamylasemia (>125 IU/L), based on the upper limit of normal of 125  
11 IU/L in our institution. Relationships among preoperative factors, perioperative factors, and  
12 the serum amylase level were investigated.

13 **Results:** Hyperamylasemia (serum amylase >125 IU/L) following posterior spinal surgery  
14 was found in 92 cases (35%). Among perioperative factors, intraoperative estimated blood  
15 loss (EBL) and operating time were significantly higher in patients with high serum amylase  
16 than in patients with normal serum amylase ( $P < 0.01$ ). In a multivariate regression model,  
17 intraoperative EBL (OR 1.001, 95% CI 1.000-1.002;  $p=0.001$ ) and operation time (OR 1.006,  
18 95% CI 1.003-1.009;  $p=0.006$ ) were significantly associated with postoperative pancreatitis.  
19 Serum amylase levels of  $\geq 5$  times the upper limit of normal were found in 6 cases. Five of  
20 these cases were asymptomatic and one was caused by severe pancreatitis.

21 **Conclusions:** In our case series, intraoperative blood loss caused a rise in the serum amylase  
22 level following posterior spinal surgery. Thus, this level should be carefully monitored after  
23 spinal surgery with significant blood loss. Clinical symptoms of pancreatitis, such as  
24 abdominal pain and vomiting, should also be monitored following spinal surgery.

25

26

1 **Introduction**

2 Pancreatitis is a life-threatening systemic disease involving multisystem organ failure.  
3 Postoperative pancreatitis has a high mortality rate (10-45%) and has primarily been reported  
4 as a complication of abdominal or anterior spine surgery [1-3], but has also recently been  
5 identified as a complication of scoliosis surgery [4]. The serum amylase level is currently  
6 used for diagnosis of pancreatitis, with a finding of hyperamylasemia suggesting a diagnosis  
7 of acute pancreatitis [5]. However, the association of hyperamylasemia with spinal surgery  
8 has not been previously investigated.

9

10 **Materials and Methods**

11 A total of 352 spinal surgeries were performed in our institution from January 2010 to  
12 December 2012, including 23 with an anterior or lateral approach and 329 with a posterior  
13 approach in the prone position. After exclusion of 67 cases in which amylase was not  
14 measured, the study was performed as a retrospective review of 262 cases of spinal surgery  
15 with a posterior approach in the prone position. A chest roll with a gel cushion was used in  
16 cervical spine surgery with a head pin, and a prone frame with a four-mount cushion was  
17 used for thoracic and lumbar spine surgery.

18 Data were abstracted from electronic medical records and included preoperative factors of  
19 age, gender, BMI, and comorbidities (diabetes mellitus, hyperlipidemia, and hypertension);  
20 perioperative factors of estimated blood loss (EBL), operating time, intraoperative diastolic  
21 pressure, and allogeneic RBC (red blood cell) transfusion; and outcomes including  
22 occurrence of postoperative pancreatitis, and serum levels of amylase, glutamic oxaloacetic  
23 transaminase (GOT), glutamic pyruvic transaminase (GPT), lactate dehydrogenase, and  
24 creatine phosphokinase (CPK) on postoperative day (POD) 1.

25 Patients were divided into two groups based on the presence of a serum amylase level  
26 within the normal range (0-125 IU/L, normal group) or greater than the normal range (>125  
27 IU/L, hyperamylasemia group). Preoperative factors, perioperative factors, and outcomes

1 were compared between the two groups. Results were also examined for cases in which the  
2 amylase level was  $\geq 5$  times the upper normal serum value, since this is the diagnostic  
3 criterion used by White et al. [6] to define postoperative pancreatitis.

4 Statistical significance was assessed by Student t-test, chi-square test, and Fisher exact test,  
5 with a significance level of  $P < 0.05$ . Odds ratios (ORs) and their 95% confidence interval  
6 (CI) were estimated with multivariate logistic regression models to evaluate the association of  
7 hyperamylasemia with preoperative factors, comorbidities, perioperative factors, and  
8 outcomes. All analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA).

9 At study entry, all subjects gave written informed consent before examination. All aspects  
10 of the study were approved by the institutional review board.

11

## 12 **Results**

13 Preoperative serum amylase levels were within the normal range (upper limit of normal of  
14 125 IU/L in our institution) in all 262 patients. Postoperatively, 92 patients (35%) had serum  
15 amylase levels  $>125$  IU/L and were placed in the hyperamylasemia group. The surgical lesion  
16 sites in these cases were cervical (n=19), thoracic (n=37), and lumbar (n=36). There were no  
17 significant differences in preoperative factors (age, gender, BMI, and comorbidities) between  
18 the 92 patients with hyperamylasemia and the 170 patients with normal postoperative  
19 amylase levels. Among perioperative factors, EBL was significantly higher in the  
20 hyperamylasemia group ( $835 \pm 938$  vs.  $323 \pm 556$  g,  $P < 0.01$ ) and operating time was longer  
21 in the hyperamylasemia group ( $324 \pm 154$  vs.  $234 \pm 145$  min,  $P < 0.01$ ). On POD1, GOT  
22 ( $42.4 \pm 3.9$  vs.  $30.3 \pm 1.7$  IU/L,  $P < 0.01$ ) and CPK ( $1501.5 \pm 202.2$  vs.  $823.6 \pm 116.8$  IU/L,  $P$   
23  $< 0.01$ ) levels were significantly higher in the hyperamylasemia group (Table 1).

24 In multivariate logistic regression using perioperative factors, intraoperative EBL (OR  
25 1.001, 95%CI 1.000-1.002;  $p=0.001$ ) and operation time (OR 1.006, 95%CI 1.003-1.009;  
26  $p=0.006$ ) were significantly associated with hyperamylasemia (Table 2).

27 There were six patients with a serum amylase level  $\geq 5$  times the upper limit of normal

1 (Table 3). In three of these cases, the serum amylase level was >1000 IU/L, which is 8 times  
2 the upper limit of the normal range, but lipase was only elevated in one of these cases.  
3 Nausea, vomiting and abdominal pain, hyperamylasemia and hyperlipasemia occurred in one  
4 case. Finally, this case was diagnosed as acute pancreatitis and required prompt treatment.

5 Increased intraoperative EBL was associated with an increased postoperative serum  
6 amylase level and hyperamylasemia (Table 4). EBL  $\geq$  1000 g occurred in 35 cases, of which  
7 25 had hyperamylasemia (71%). In addition, hypertension was significantly associated with  
8 hyperamylasemia ( $p=0.03$ ) in these 35 cases.

9

## 10 **Discussion**

11 Pancreatitis usually results from alcoholism, bile stones, exacerbation of chronic  
12 pancreatitis, or idiopathic causes [6], and has also occasionally been reported after abdominal  
13 surgery, primarily in association with gastroduodenal surgery [1,6]. In contrast, pancreatitis  
14 and hyperamylasemia after spinal surgery are relatively rare. Leichtner et al. first reported a  
15 case series of pancreatitis following scoliosis surgery in children and young adults [4]. Sasaki  
16 et al. reviewed 56 patients who underwent spine surgery in the prone position, and identified  
17 14 patients with hyperamylasemia, including one who underwent posterior lateral fusion [23].  
18 In a retrospective study of 355 patients who underwent spine fusion for neuromuscular  
19 scoliosis due to cerebral palsy, Borkhuu et al. found 109 cases (30.1%) of postoperative  
20 pancreatitis [10]. To the best of our knowledge, the current study is the largest to examine  
21 hyperamylasemia and pancreatitis after posterior spinal surgery (Table 5).

22 An amylase blood test is commonly requested in cases of abdominal pain, and particularly  
23 for a patient with acute abdominal pain. Postoperative blood tests are routinely conducted for  
24 anemia and infection, but serum amylase is often neglected in these tests. The diagnostic  
25 criteria for pancreatitis reported by White et al. include an amylase level  $\geq$ 5 times the upper  
26 normal serum value [6], and serum amylase levels >1000 IU/L are highly suggestive of  
27 pancreatitis [5]. In this study, hyperamylasemia was detected in 92 patients (35%) and this

1 relatively high rate suggests that serum amylase should be measured in postoperative blood  
2 tests. However, hyperamylasemia does not always cause pancreatitis and an increase in serum  
3 amylase may be a nonspecific phenomenon without clinical implications. Some instances of  
4 asymptomatic hyperamylasemia, such as salivary hyperamylasemia, may also be unrelated to  
5 pancreatic diseases [11,12].

6 In a study of 44 patients undergoing single-stage surgery for scoliosis, Leichtner found  
7 that 6 (14%) developed hyperamylasemia and 4 (9%) developed pancreatitis [4]. In our study,  
8 derotation for scoliosis was performed in 33 patients, of whom 21 (61%) had  
9 hyperamylasemia and none had postoperative pancreatitis. In addition, among 135 fusion  
10 surgeries with instrumentation, excluding cases of scoliosis, 53 patients (39%) had  
11 hyperamylasemia ( $p=0.01$ ). Leichtner found no significant differences with regard to age,  
12 surgical technique, degree of initial or residual deformity, or length of surgery. However, we  
13 believe that scoliosis surgery is likely to lead to hyperamylasemia because of stress on the  
14 abdominal blood vessels due to strong vertebral body rotation and correction in this surgery.

15 The etiology of postoperative hyperamylasemia and pancreatitis after spinal surgery is not  
16 established, but poor general health, intraoperative positioning, and hypotensive anesthesia  
17 have been suggested as potential risk factors [10,14-17]. In our cases, all surgeries were  
18 performed using a posterior approach and the surgical site was distant from the pancreas. In  
19 cervical surgery, patients were positioned using a chest roll with a gel cushion, and in thoracic  
20 and lumbar surgery patients were positioned prone on a frame with a four mount cushion that  
21 supported the thorax and pelvis, but not the abdomen. Such an apparatus may decrease  
22 abdominal pressure. However, hyperamylasemia occurred after cervical spine surgery, in  
23 which a frame was not used, as well as after thoracic or lumbar spine surgery. Thus, in this  
24 series, hyperamylasemia occurred regardless of the surgical lesion.

25 Pancreatic ischemia may also be a cause of acute pancreatitis [4,18]. Tauchi et al. found  
26 that pancreatitis after spinal posterior lumbar interbody fusion (PLIF) occurred as a result of  
27 hypoperfusion of the pancreas due to increased intraoperative blood loss [19]. Relton et al.

1 suggested that use of so-called hypotensive anesthesia to maintain intraoperative blood  
2 pressure is a risk factor for ischemia in scoliosis surgery [20], and Warshaw et al. confirmed  
3 the effects of ischemic injury on the pancreas in autopsy examinations [21]. In the current  
4 study, the mean intraoperative blood loss and operative time were significantly higher in  
5 patients with postoperative hyperamylasemia compared to those with normal amylase, and  
6 the levels of muscle enzymes such as GOT and CPK were also significantly higher in patients  
7 with hyperamylasemia. Postoperative hyperamylasemia also increased in patients with high  
8 EBL, and hypertension was significantly associated with hyperamylasemia in patients with  
9 intraoperative EBL >1000 g. These observations are all related to surgical invasiveness; thus,  
10 serum amylase elevation reflects reduced pancreatic blood flow due to increased EBL, and  
11 characteristics of longer invasive surgery (such as increased EBL) may lead to  
12 hyperamylasemia. These results are consistent with previous findings that pancreatic  
13 ischemia is caused by increased EBL and may lead to pancreatitis [4,18,19]. However, blood  
14 transfusion has not previously been linked to hyperamylasemia. The relationship between  
15 RBC transfusion and hyperamylasemia is uncertain, but we routinely use intraoperative blood  
16 recovery and autologous blood transfusion in cases with increased EBL. Therefore, cases  
17 with allogeneic RBC transfusion are rarely associated with hyperamylasemia.

18 In abdominal surgery, White et al. suggested that postoperative pancreatitis might be due  
19 to loss of blood flow and hypovolemic shock during surgery [6]. In spine surgery, Leichtner  
20 et al. showed that greater blood loss was associated with postoperative pancreatitis in cases  
21 with scoliosis [4]. In contrast, Borkhuu et al. found no association between blood loss during  
22 surgery and postoperative pancreatitis in spine fusion with cerebral palsy [10]. In our series,  
23 we examined postoperative pancreatitis and hyperamylasemia, and we found a significant  
24 dependence of hyperamylasemia on EBL and operative time. However, the odds ratios were  
25 low (EBL: 1.001, operation time:1.006). The series included many different surgeries,  
26 including some with low EBL and a long operative time, such as surgery for spinal cord  
27 tumor. In addition, the hyperamylasemia group (n=92) had a considerable range of serum

1 amylase levels (237-2907 IU/L), and these factors may explain why the correlations are  
2 relatively weak.

3 In one of our cases of pancreatitis, the patient had continuous abdominal pain and vomiting  
4 for 2 hours postoperatively. Thus, pancreatitis should be suspected in cases with these  
5 symptoms from the early postoperative period. Changes in the serum amylase level and  
6 clinical symptoms should also be carefully monitored in cases with significant blood loss.

7 One limitation of this study was that serum amylase isoenzymes (pancreatic and salivary  
8 type) and lipase were not examined in all cases because there were no abdominal symptoms.

9 These tests are only required for definite diagnosis of pancreatitis in cases with abdominal  
10 symptoms, but are also useful for diagnosis of pancreatitis.

11 In our series, hyperamylasemia was observed in 35% of cases on the day after spinal  
12 surgery and pancreatitis occurred in one patient. Surgery with a large amount of bleeding may  
13 be a risk for development of hyperamylasemia. In such cases, postoperative monitoring is  
14 needed to identify additional symptoms of pancreatitis, such as abdominal pain and vomiting.

15

#### 16 **Conflict of Interest**

17 The authors declare that they have no competing interests.

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**Table 1.** Demographics, operative details, POD1 data, and serum amylase levels in groups of patients with hyperamylasemia and with normal serum amylase levels.

	Hyperamylasemia (n=92) (>125 IU/L)	Normal (n=170) (0-125 IU/L)	<i>P</i> value
<b>Demographic</b>			
Age (years)	51.7 (22.8)	55.6 (20.5)	0.08
Sex (females)	54	96	0.64
BMI (kg/m <sup>2</sup> )	22.2 (7.0)	22.8 (4.9)	0.45
<b>Comorbidities</b>			
Diabetes mellitus	14	21	0.07
Hyperlipidemia	11	15	0.52
Hypertension	19	32	0.90
<b>Serum Amylase (IU/L)</b>			
Preoperative	66.1 (22.7)	62.7 (24.4)	0.13
<b>POD1</b>	306.4 (350.6)	73.0 (27.4)	<0.01
<b>Data on POD1</b>			
<b>GOT</b> (IU/L)	42.4 (3.9)	30.3 (1.7)	<0.01
GPT (IU/L)	20.4 (4.2)	20.1 (1.2)	0.08
LDH (IU/L)	236.7 (9.8)	217.9 (7.4)	0.14
<b>CPK</b> (IU/L)	1501.5 (202.2)	823.6 (116.8)	<0.01
<b>Perioperative factors</b>			
<b>EBL</b> (g)	835 (978)	323 (556)	<0.01
EBL $\geq$ 1000 (cases)	25	10	<0.01
<b>Operation time</b> (min)	324 (154)	234 (145)	<0.01
Intraoperative diastolic pressure (mmHg)	49 (8)	50 (8)	0.11
Allogeneic RBC transfusion	10	6	0.14

Data are shown as means with the standard deviation in parentheses.

BMI: body mass index

POD: postoperative day

EBL: estimated blood loss

RBC: red blood cell

**Table 2.** Multivariate logistic prediction model of risk for perioperative factors of hyperamylasemia

	Odds Ratio	95%CI	<i>p</i>
<b>Estimated Blood Loss</b>	1.001	1.000-1.002	0.001
<b>Operation time</b>	1.006	1.003-1.009	0.006

All variables were treated as continuous variables. The odds ratio is the increase in odds per unit increase in the predictor. Regression coefficients have been zero corrected.

**Table 3.** Summary of data for six patients with postoperative serum amylase levels  $\geq 5$  times the upper limit of normal serum values.

	Age / Sex	Diagnosis (Operation)	BMI (kg/ m <sup>2</sup> )	Comorbidities	Serum Amylase on POD1 (IU/L)	Serum Lipase on POD1 (IU/L)	EBL (RBC transfusion) (g)	Operation time (min)	Abdominal pain	Pancreatitis
1	53/ F	Spondylolisthesis (L3-5 PLIF)	27	DM/HT	2907	343	1096 (4-U, allo)	246	+	+
2	72/ F	LCS (L3-S PLIF)	25	HT	1509	38	735 (2-U, allo)	350	-	-
3	68/ F	C1-2 subluxation (C1-2 fixation)	30	HL/HT	1021	15	476	149	-	-
4	57/ F	CSM (C3-6 fixation)	29	DM	894	27	360	275	-	-
5	61/ F	Th-OPLL (Th5-9 fixation)	27	DM/ HT	821	19	651 (2-U, allo)	300	-	-
6	73/ F	LCS (L2-5 PLIF)	23	HT	818	40	1610 (4-U,auto)	306	-	-

PLIF: posterior lumbar interbody fusion

LCS: lumbar canal stenosis

OPLL: ossification of the posterior longitudinal ligament

DM: diabetes mellitus

HL: hyperlipidemia

HT: hypertension

U: unit

Allo: allogeneic

Auto: autologous

**Table 4.** Relationship of serum amylase level and hyperamylasemia in groups with different estimated blood loss (EBL).

	EBL: <100 g (n=82)	EBL 100-500 g (n=96)	EBL 501-1000 g (n=49)	EBL >1000 g (n=35)
Serum Amylase (IU/L)				
Preoperative	71.2 (25.9)	66.1 (25.0)	76.5 (68.3)	70.0 (24.5)
POD1	123.8 (143.9)	122.5 (138.4)	197.2 (235.1)	294.8 (491.7)
Hyperamylasemia (>125 IU/L)	20% (n=17)	27% (n=26)	49% (n=24)	71% (n=25)

Data are shown as means with the standard deviation in parentheses.

POD: postoperative day

EBL: estimated blood loss

**Table 5.** Previous studies related to hyperamylasemia, pancreatitis, and spine surgery

Author	Year	Number of patients	Average age (y)	Surgical procedure	Hyper amylasemia (>125 IU/L)	Hyper amylasemia (>625 IU/L)	Pancreatitis
Leichtner et al.	1991	44	15	Posterior or anteroposterior fusion	10	NA	4
Sasaki et al. (in Japanese)	2005	56	57	Posterior fusion or laminectomy	14	4	1
Borkhuu et al.	2009	355	14	Posterior or anteroposterior fusion	NA	NA	109
Present study	2014	262	53	Posterior fusion or laminectomy	92	6	1

NA: not available

## 題名：脊椎術後の高アミラーゼ血症・膵炎の検討

【背景】脊椎術後の高アミラーゼ血症は、腹部手術だけでなく腹臥位による脊椎手術でも起こりうる合併症とされている。また膵炎まで発症した場合には重篤な状態になりうる。これまでに脊椎術後の膵炎については、側彎症や前方固定など1例報告や、また小児CPで側弯矯正固定をした際に、膵炎を30%に認めた報告などがあるが、まとまった報告は少ない。そこでわれわれは脊椎手術後の高アミラーゼ血症と膵炎について、自験例をふまえ調査した。

【方法】対象は、2010年1月から当施設で行われた脊椎手術のうち、血清アミラーゼ値を測定し得た262例（男性121例、女性141例）。平均年齢は53.9歳であった。

【結果】術翌日の血清アミラーゼ値が当院の正常値にあたる125IU/L以上の値を示したものは、92例（37%）であった。術後アミラーゼ値を正常群（125IU/L以下）と上昇群（125IU/L以上）の2群にわけて検討を行ったところ、年齢、性別、基礎疾患（糖尿病、高脂血症、高血圧）BMIでは2群間に有意な差はみられなかった。術中出血量・手術時間については上昇群では正常群に比べ有意に高かった（いずれも $P<0.01$ ）。採血データのうちGOT、GPT、LDH、CKについて検討を行ったところ、上昇群では正常群に比べGOTとCKが有意に高かった（いずれも $P<0.01$ ）。さらに正常値の5倍以上の高アミラーゼ血症（625IU/L以上）を示したものは、6例（3%）であった。そのうち5例は無症状であったが、1例は重症膵炎を発症し、内科的治療を要した。

【結論】脊椎術後のアミラーゼ高値の原因として、①腹臥位による腹部臓器の圧迫、②基礎疾患（糖尿病・慢性膵炎）の存在、③術中の麻酔、④手術侵襲が上げられる。今回の検討では、手術侵襲に当たる手術時間と術中出血量が術後高アミラーゼ血症となりうる因子であった。また術後GOT、CKなど骨格筋逸脱酵素の有意な上昇と高アミラーゼ血症に関連をみとめた。手術侵襲とくに出血による膵血流の低下がアミラーゼ上昇をおこした原因と考えた。出血量が多い場合、術後に腹痛・嘔吐など膵炎を疑わせる臨床症状に注意する必要がある。