Drain amylase monitoring for early diagnosis of anastomotic leakage in sleeve gastrectomy

An animal study

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BACKGROUND: *Sleeve gastrectomy(SG) is a popular bariatric surgery procedure with rare but dreaded complications. Although drain amylase levels are a reliable early predictor of anastomosis leakage in oesophagectomy and pancreatico-duodenectomy, for SG have not yet been studied. We aimed to monitor drain amylase levels to ascertain their applicability for early diagnosis of gastric leakage in SG.*
METHODS: *Twenty-four rats were randomly divided into three groups: Group A: only laparotomy and abdominal drain; Group B: laparotomy, SG, and drain; Group C: laparotomy, SG with fistula,and drain. On postoperative days 0,1,2,3, and 4, drain lavage samples were collected to measure amylase.*
RESULTS: *Groups were compared in pairs. Preoperative weights were not significantly different in any comparison. On postoperative days 0,1,2,3, and 4, drain amylase levels were found to be significantly lower in Group A than in Group B as well as in Group A than in Group C but were significantly higher in Group C than in Group B. For postoperative day 1, a receiver operating characteristic curve was done. Drain amylase levels over 1514 IU were statistically significant for leakage.*
CONCLUSIONS: *Drain amylase levels were significantly high in sleeve gastrectomy with fistula. This indicates that drain amylase level monitoring might be an easy and cheap alternative for determining staple-line leakage for high risk patients with Body Mass Index(BMI)>50kg/m^2 in whom we cannot use radiological imaging.*

KEY WORDS: Animal Experimental Study, Bariatric Surgery, Drain amylase, Sleeve gastrectomy, Staple-line leakage

Introduction

Obesity and its related co-morbidities are the most rapidly spreading epidemic diseases [1]. Medical treatment has limited success in obese patients and no success in morbidly obese patients. In the medium and long term only bariatric surgery is successful in the treatment of morbidly obese patients' comorbidities [2-4].
The very first sleeve gastrectomy (SG) was performed in 1993 as a first step of duodenal switch surgery on high-risk superobese patients [5]. In the past decade SG has been used stand-alone as a major bariatric surgery procedure [6]. Even SG alone is more effective than medical treatment in patients with metabolic syndrome and diabetes mellitus. Besides, SG has comparative outcomes to a Roux-en-Y gastric bypass (RNY) [7].
Unfortunately, SG might cause undesired complications [8,9]. Minor complications of SG are gastro-oesophageal reflux

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ABBREVIATIONS

BMI: Body Mass Index
SG: Sleeve Gastrectomy
ROC: Receiver Operating Characteristic
RNY: Roux-en-Y gastric bypass
CT: Computer tomography
ERAS: Enhanced Recovery After Surgery

disease, stricture or dilation of the gastric tube, and insufficient weight loss [10,11]. Major complications of SG are bleeding and staple-line [12]. Staple-line leakage after SG occurs in 0–8% of cases [13]. Although staple-line leakage is not a common complication, it leads to severe morbidity and is the second-most common reason of death after SG [14].

Staple-line leakages may be the result of various etiologies such as tissue ischemia especially at the His angle, tissue injury, stapler misfire, wrong staple size for the tissue, distal stenosis, twisted gastric pouch, narrowing at the angularis incisures or hematoma [15,16]. Whatever the reason, staple-line leakage is a very serious complication due to its morbidity and mortality. Intraoperative staple-line leakage tests such as methylene blue dye insufflation from the esophagus or intraoperative gastroscopy are being performing by many surgeons. However, the use of intraoperative staple-line leakage tests is controversial in the literature, with some studies suggesting to use these tests and some others saying these tests have 0% sensitivity [17-19]. In the literature some postoperative leakage tests as drinking methylene blue dye or video fluoroscopy have been defined, but it should be considered that methylene blue test has more than 50% and video fluoroscopy has 20-30% false negative prediction [20,21]. Although routine intraoperative and postoperative staple-line leakage tests are controversial, patients with a clinical suspicion of staple-line leakage should be examined in detail. Unexplained tachycardia is the first clinical finding in these [22]. Patients with tachycardia, fever, and leucocytosis must be checked for staple-line leakage. Computer tomography (CT) is the best choice for leakage diagnosis with 95% positive prediction [22]. At this point, there are some difficulties regarding the patient's weight. Standard CTs cannot be used for patients over 200 kilograms. An alternative test with high sensitivity and specificity is required to diagnose staple-line leakage in morbidly superobese patients.

We therefore monitored drain amylase levels to ascertain their usefulness for early diagnosis of gastric leaks in SG.

Methods

This study was approved by the Animal Experiments Local Ethics Committee of Istanbul University Institute of Experimental Medicine (Process number 2016/57). The experiments were performed at the Laboratory of Surgical Physiopathology, adhering to the International guidelines for the care and use of laboratory animals. 24 Male Wistar rats (250-300 g) were purchased from the Istanbul University Institute of Experimental Medicine. Male rats were preferred, because the menstrual cycle might affect the laboratory test results.

All rats were stored in metal cages and maintained under a 12-hour dark/light (lights on at 09:00 am) cycle at a controlled temperature of 22°C (±1). All rats were fed a diet comprising 15% protein, 50% fat and 35% carbohydrates (Nucleon, Bil-Yem, Ivedik, Ankara, Turkey) and fresh tap water for four weeks to induce obesity. After four weeks model rats reached a mean weight of 420 ± 9.27 g. Rats were not fed only one day before surgery. All cages were cleaned daily. Before surgery rats were housed four together in a cage; after surgery all rats were put in a cage alone.

Anaesthesia and surgical protocol

Before the surgery night, rats were fasted for nine hours. Rats were subsequently anesthetized with ketamine hydrochloride 50 mg/ml and xylazine hydrochloride 20 mg/ml given intraperitoneally with a dosage of 0.1 ml/100 g. Following this, the rats were fixed in the supine position on a regularly disinfected and surgically draped operating table. After shaving the rat's abdominal wall, it was sterilized with povidone–iodine solution and wrapped with Ioban drape. All surgical instruments were sterile.

In Group A (n = 8) a 3 cm upper median laparotomy incision was made. A 1.7 mm 16G intravenous cannula (I.V.) (Bicakcilar, Sisli, Istanbul, Turkey) was placed from the left side of the median laparotomy through the abdominal wall. The I.V. cannula was placed to the left side of the greater curvature and its apex was fixed with 2/0 silk suture (Ethicon US, LLC). The abdominal wall was subsequently closed with 3/0 polypropylene (Ethicon US, LLC) suture. The skin was closed with 3/0 vicryl rapide (Ethicon US, LLC) suture intracutaneously.

In Group B (n = 8) a 3 cm upper median laparotomy incision was made. The stomach was located and dissected from the liver and spleen from the greater curvature side. The stomach was placed on the Ioban drape outside the abdomen. It was cut 3 mm from the pylorus and an 8G aspiration catheter (Bicakcilar, Sisli, Istanbul, Turkey) was placed through the stomach from the lesser curvature up to the oesophagus. The stomach was cut guided by the aspiration catheter and sutured with 4/0 vicryl (Ethicon US, LLC) utilizing a gambee suture pattern. A 1.7 mm 16G intravenous cannula (I.V.) (Bicakcilar, Sisli, Istanbul, Turkey) was placed from the left side of the median laparotomy through the abdominal wall. The I.V. cannula was placed to the left side of the greater curvature and its apex was fixed with 2/0 silk suture (Ethicon US, LLC). The abdominal wall was subsequently closed with 3/0 polypropylene (Ethicon US, LLC) suture. The skin was closed with 3/0 vicryl rapide (Ethicon US, LLC) suture intracutaneously.

In Group C (n = 8) a 3 cm upper median laparotomy incision was made. The stomach was located and dissected from the liver and spleen from the greater curvature side. The stomach was placed on the Ioban drape outside the abdomen. It was cut 3 mm from the pylorus and an 8G aspiration catheter (Bicakcilar, Sisli, Istanbul, Turkey) was placed through the stomach from the lesser curvature up to the oesophagus. The stomach was cut guided by the aspiration catheter and sutured with 4/0 vicryl (Ethicon US, LLC) utilizing agambee suture pattern, but a 3 mm fistula was left on the proximal side. A 1.7 mm 16G intravenous cannula (I.V.) (Bicakcilar, Sisli, Istanbul, Turkey) was placed from the left side of the median laparotomy through the abdominal wall. The I.V. cannula was placed to the left side of the greater curvature and its apex was fixed with 2/0 silk suture (Ethicon US, LLC). The abdominal wall was subsequently closed with 3/0 polypropylene (Ethicon US, LLC) suture. The skin was closed with 3/0 vicryl rapide (Ethicon US, LLC) suture intracutaneously.

After surgery all rats were fasted for six hours and to avoid dehydration 10 ml saline solution was administered subcutaneously. After six hours all rats were fed with normal chow diet. All animals were in close care for eight hours postoperatively and then rats were visited twice a day for four days.

All rats were sacrificed at day 4 with a high dose of ketamine and examined for the last time.

Experimental Protocol

The test subjects were randomly enrolled into one of the three study groups.

GroupA (n = 8): Laparotomy and drain fixation were done. Perioperative peritoneal lavage was made and 2 cc samples were collected. On days 1, 2, 3, and 4 postoperatively peritoneal lavage was made through the I.V. cannula with 10 cc saline solution and 2 cc samples were collected.

GroupB (n = 8): Laparotomy, sleeve gastrectomy and drain fixation were done. Perioperative peritoneal lavage was made and 2 cc samples were collected. On days 1, 2, 3, and 4 postoperatively peritoneal lavage was made through the I.V. cannula with 10 cc saline solution and 2 cc samples were collected.

GroupC (n = 8): Laparotomy, sleeve gastrectomy, drain fixation, and a 3 mm fistula were done. Perioperative peritoneal lavage was made and 2 cc samples were collected. On days 1, 2, 3, and 4 postoperatively peritoneal lavage was made through the I.V. cannula with 10 cc saline solution and 2 cc samples were collected.

All rats were sacrificed on day 4 with a high dose of ketamine and examined for the last time.

Amylase Analysis

We measured levels of amylase by the colorimetric method using the BIOLABO SAS kit (REF: 80123) (Lot No: 0715522D, Maizy, France) and a Saturno 300 autoanalyzer (Crony Instruments Srl, Rome, Italy, 2008). We checked the analytical performance of the method by testing two levels of control material within a run. We measured each sample once.

Performance characteristics of the amylase assay kit

The assay was linear up to 2000 IU/L for the kit that we used. The minimal detection limit was 6 IU/L. Reported intra-assay and inter-assay values for the coefficient of variation were 3.3% and 3.5%, respectively. The tested concentrations of bilirubin, hemoglobin and lipids did not interfere with α-amylase activity determination.

Statistical Analysis

Data were analyzed with IBM SPSS Statistics 15. Two-group comparisons were performed by using the Mann–Whitney U test; for comparisons involving three or more groups, the Kruskal–Wallis H test was used. The correlation between the variables was calculated with Fisher's Exact Test. A value of $p \leq 0.05$ was taken as significant.

Results

Rats gained half of their body weight during four weeks on a high-caloric diet and reached 420.25 ± 9.27 g. The summary statistics of all rats is given in Table II.

A gastric fistula was determined during post-scarification examination in GroupB (rat no. 7) and this rat was added to GroupC. All statistical analyses were made with these new groups (GroupA: n = 8; GroupB: n = 7; GroupC: n = 9). Group statistics are given in Table II. Groups were compared in pairs to distinguish the differences.

GroupA compared to GroupB: Drain amylase levels were significantly lower in GroupA on days 0, 1, 2, 3 and 4 postoperatively and preoperative weights were not significantly different (Table III).

TABLE I - *General summary of all rats.*

Rat Number	Group	Weight (gram)	Amylase PO[1] day 0 (IU/L)	Amylase PO day 1 (IU/L)	Amylase PO day 2 (IU/L)	Amylase PO day 3 (IU/L)	Amylase PO day 4 (IU/L)	Fistula*
1	A	413	25	21	14	64	36	0
2	A	420	30	121	24	47	40	0
3	A	435	34	15	7	62	30	0
4	A	429	23	23	13	28	87	0
5	A	410	18	15	47	18	33	0
6	A	412	9	7	12	31	18	0
7	A	422	21	18	7	39	80	0
8	A	431	18	20	9	26	20	0
1	B	413	333	302	24	31	84	0
2	B	432	921	1062	32	33	30	0
3	B	418	636	462	45	32	91	0
4	B	427	999	130	13	31	60	0
5	B	429	295	566	15	35	85	0
6	B	415	122	467	17	39	42	0
7	B	412	418	394	323	1039	3413	1
8	B	407	203	195	27	29	39	0
1	C	406	1493	1514	1797	1530	1250	1
2	C	419	677	1572	1886	2800	6540	1
3	C	435	764	1514	1937	1913	7810	1
4	C	436	181	1544	1944	2165	3233	1
5	C	413	652	1825	1512	1890	8000	1
6	C	418	456	1580	4240	4531	7740	1
7	C	417	1753	1889	1156	1480	4520	1
8	C	417	617	1873	1508	1920	7900	1

PO: Postoperative; *0: No fistula; 1: fistula

GroupA compared to GroupC: Drain amylase levels were significantly lower in GroupA on days 0, 1, 2, 3, and 4 postoperatively and preoperative weights were not significantly different (Table IV).
GroupB compared to GroupC: Drain amylase level on postoperative day 0 and preoperative weights were not significantly different. Drain amylase levels on days 1, 2, 3, and 4 postoperatively were statistically higher in GroupC (Table V).
For postoperative day 1, a receiver operating characteristic curve was obtained with 0.889 sensitivity, 1 specificity and 0.938 accuracy between GroupB and GroupC. Drain amylase levels over 1514 IU were statistically meaningful for gastric leakage (Table VI).

Discussion

Might monitoring drain amylase be the optimum test for diagnosing staple-line leakage after SG for high risk patients?
In the past decade, from 2003 to 2013, the prevalence of SG operations among all bariatric procedures increased from 0 to 37% [3,22]. Data from the IFSO-European Chapter Centre of Excellence program shows that SG has now become the bariatric procedure used most [23]. We believe that this increase in the prevalence of SG is related to the easy technique and short learning curve. SG is accepted as a first-step operation in bariatric surgery and is mostly chosen by inexperienced surgeons. It is also well known that SG has effects comparable to RNY [8,9]. However, although SG is an easy procedure compared to RNY, the complication and mortality rates are higher in SG [23]. The incidence of staple-line leakage with SG reported in the literature is between 0% and 8% and the second common reason for death [12,14]. Staple-line leaks are usually located in the proximal third of the stomach, so we also included a 3 mm fistula in the proximal stomach in our animal model in accordance with this knowledge [24]. We started monitoring drain amylase on postoperative day 0 to monitor surgical stress and leakage from the pancreatic capsule. Recent studies have shown that the surgical area over the pancreas may cause drain amylase elevation [25]. During SG, the gastric antrum over the pancreatic capsule is dissected [26]. In GroupA drain amylase levels were significantly lower on postoperative day 0 than in Groups B or C but in GroupB comparing with GroupC there was no statistical difference, so these results show us that surgical stress is not an important factor for drain amylase levels but that SG increases drain amylase levels on postoperative day 0. From another perspective, the increase

TABLE II. *Weight and Amylase levels of rats.*

Group		Weight (gram)	Amylase PO[1] day 0 (IU/L)	Amylase PO day 1 (IU/L)	Amylase PO day 2 (IU/L)	Amylase PO day 3 (IU/L)	Amylase PO day 4 (IU/L)
A	Mean	421.50	22.25	30.00	16.63	39.38	43.00
	SD	9.46	7.74	37.10	13.43	16.95	26.15
	Min	410.00	9.00	7.00	7.00	18.00	18.00
	Max	435.00	34.00	121.00	47.00	64.00	87.00
B	Mean	420.14	501.29	454.86	24.71	32.86	61.57
	SD	9.32	352.55	310.27	11.27	3.29	25.20
	Min	407.00	122.00	130.00	13.00	29.00	30.00
	Max	432.00	999.00	1062.00	45.00	39.00	91.00
C	Mean	419.22	779.00	1522.78	1811.44	2140.89	5600.66
	SD	10.05	512.80	451.19	1046.65	1020.75	2546.37
	Min	406.00	181.00	394.00	323.00	1039.00	1250.00
	Max	436.00	1753.00	1889.00	4240.00	4531.00	8000.00
Total	Mean	420.25	445.75	713.71	692.04	825.54	2132.54
	SD	9.27	480.30	731.76	1079.66	1202.38	3128.30
	Min	406.00	9.00	7.00	7.00	18.00	18.00
	Max	436.00	1753.00	1889.00	4240.00	4531.00	8000.00
P value		0.867					

PO: postoperative; SD: standard deviation; Min: minimum; Max: maximum; p<0.05 is statistically significantly

TABLE III - *Comparison of Group A (laparotomy and drain fixation) with Group B (laparotomy, sleeve gastrectomy and drain fixation).*

	Group A	Group B	*P* value
Body weight (gram)	421.5 ± 9.45	420.14 ± 9.31	0.673
Amylase PO day 0 (IU/L)	22.25 ± 7.74	501.28 ± 352.54	0.000
Amylase PO day 1 (IU/L)	30 ± 37.09	454.85 ± 310.26	0.000
Amylase PO day 2 (IU/L)	16.62 ± 13.42	24.71 ± 11.26	0.000
Amylase PO day 3 (IU/L)	39.37 ± 16.95	32.85 ± 3.28	0.000
Amylase PO day 4 (IU/L)	43 ± 26.147	61.57 ± 25.19	0.000

PO: Postoperative; *P* values calculated with the Mann–Whitney *U* test. p<0.05 is statistically significantly.

TABLE IV - *Comparison of Group A (laparotomy and drain fixation) with Group C (laparotomy, sleeve gastrectomy, drain fixation and 3 mm fistula).*

	Group A	Group C	*P* value
Body weight (gram)	421.5 ± 9.45	419.22 ± 10.04	0.673
Amylase PO day 0 (IU/L)	22.25 ± 7.74	779 ± 512.80	0.000
Amylase PO day 1 (IU/L)	30 ± 37.09	1522.77 ± 451.18	0.000
Amylase PO day 2 (IU/L)	16.62 ± 13.42	1811.44 ± 1046.64	0.000
Amylase PO day 3 (IU/L)	39.37 ± 16.95	2140.88 ± 1020.74	0.000
Amylase PO day 4 (IU/L)	43 ± 26.15	5600.66 ± 2546.36	0.000

PO: Postoperative; *P* values calculated with the Mann-Whitney *U* test. p<0.05 is statistically significantly.

of drain amylase levels at postoperative day 0 and 1 in GroupB can be explained by the surgical technique of direct suture closure of sleeved stomach, which probably has allowed perioperative leak of gastric fluid/saliva. However, this would not be expected in the wholly closed stapled technique that is used in humans and may wait a lower cut off value of amylase. On postoperative day 1 drain amylase levels started to rise in GroupC and started to decrease in GroupB; these levels continued to change in the same direction up to postoperative day 4. Amylase is derived from two sources; salivary glands and pancreas [27,28]. We think, that increasing drain amylase levels on postoperative day 0 were caused by a mixture of pancreatic and salivary amylase and were the reason for the increase in amylase levels both in GroupB and GroupC. But at postoperative day 1 and the other days, source of drain amylase was just salivary amylase. We made a ROC curve analysis to find a cut-off level for drain amylase in the early diagnosis of gastric leaks and found that levels over 1514 IU were statistically meaningful for postoperative day 1.

In this study we aimed to find an easy and cost-effective method to diagnose staple-line leakage. In previous studies drain amylase monitoring was useful in oesophagectomy and pancreaticoduodenectomy but we have no data on SG [25, 29].

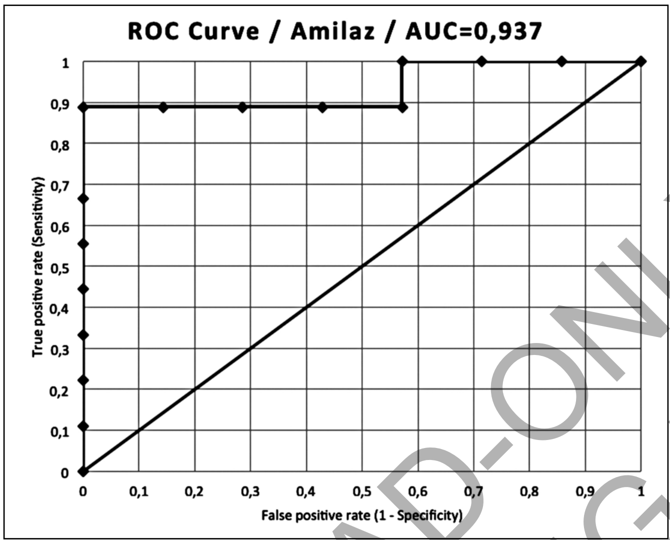
According to enhanced recovery after surgery (ERAS) principles for laparoscopic operations drain placement is

TABLE V - *Comparison of Group B (laparotomy, sleeve gastrectomy and drain fixation) with Group C (laparotomy, sleeve gastrectomy, drain fixation and 3 mm fistula).*

	Group B	Group C	*P* value
Body weight (gram)	420.14 ± 9.31	419.22 ± 10.04	0.918
Amylase PO day 0 (IU/L)	501.28 ± 352.54	779 ± 512.80	0.299
Amylase PO day 1 (IU/L)	454.85 ± 310.26	1522.77 ± 451.18	0.002
Amylase PO day 2 (IU/L)	24.71 ± 11.26	1811.44 ± 1046.64	0.000
Amylase PO day 3 (IU/L)	32.85 ± 3.28	2140.88 ± 1020.74	0.000
Amylase PO day 4 (IU/L)	61.57 ± 25.19	5600.66 ± 2546.36	0.000

PO: Postoperative; *P* values calculated with the Mann–Whitney *U* test. $p<0.05$ is statistically significantly.

TABLE VI - *ROC curve for postoperative day 1.*



ROC: Receiver Operating Characteristic; AUC: Area under the curve

dropping these days and patients are discharging on postoperative day 0 or 1. In previous studies the implementation of ERAS principles after bariatric surgery was feasible, well tolerated, significantly reduced the length of hospital stay and increase the patient satisfactory [30, 31]. On the other hand, we suggest, that drain amylase level monitoring is relevant for high risk patients (BMI>50kg/m^2), because standard CTs cannot be used in this patient group and methylene blue dye drinking test has more than 50% false negative prediction in all patients and using suction drains may reduce intra-abdominal collections and infections [32,33].

This study has several limitations. This is an animal study with a small number of samples, which lowers our test's sensitivity. A second limitation is that amylase levels are different in humans and Wistar rats and therefore our cut-off value is not valid for human patients. And last limitation is that our amylase assay kit has no ability to distinguish amylase source whether salivary or pancreatic.

Conclusion

In conclusion, we believe our results show that monitoring drain amylase levels might be a good option for early diagnosis of staple-line leakage for high risk patients (BMI>50kg/m^2) that we can not use radiological imaging.. Further prospective clinical research is necessary to verify this hypothesis. Moreover, we believe that this study demonstrates that monitoring drain amylase levels may become a standard postoperative leak detection method for high risk patients. It is cheap, easy, and harmless to the patient.

Riassunto

La sleeve gastrectomy (SG) è una procedura di chirurgia bariatrica molto diffusa, gravata con rare ma pericolore complicazioni. Sebbene i livelli di amilasi dal drenaggio rappresentano un affidabile undicatore precoce di deiscenza dell'anastomosi nell'esofagectomia e nella pancreaticoduodenectomia, ciò non è stato studiato nella SG. Ci siamo proposti di monitorare sperimentalmente il livello dell'amilasi dal drenaggio per accertare l'utilizzazione nella diagnosi precoce di deiscenza nella SG.

24 ratti sono stati divisi a random in tre gruppi. GruppoA: ratti sottoposti a semplice laparotomia e drenaggio. Gruppo B: laparotomia, SG e drenaggio. Gruppo C: laparotomia, SG con fistola e drenaggio.

Nei giorni postintervento 0, 1, 2, 3 e 4 sono stati effettuati con lavaggio prelievi dai drenaggio per la misurazione dell'amilasi.

I gruppi sono stati paragonati a coppia. Il peso preoperatorio dei ratti non ha presentato differenzxe significative in tutti i confronti. I livelli di amilasi dai drenaggio nei giorni postopeatori 0, 1,2,3,4 sono risultati significativamente inferiori nel Gruppo A rispetto al Gruppo B, ad analogamente nel Gruppo A rispetto al Gruppo C, ma sono risultati più elevati nel Gruppo C rispetto al Gruppo B.

Nel primo giorno postoperatorio è stata eseguita una curva di caratteristica operativa (ROC). I livelli di amilasi superiori alle 1514 IU sono stati statisticamente indicatori significativi della deiscenza.

In conclusionne i livelli di amilasi dai drenaggi risultano più elevati nella SG con fistola, indicando che il loro monitoraggio può rappresentare una facile ed economica alternativa per individuare una deiscenza della linea anastomotica in pazienti ad alto rischio, con BMI > 50 kg m^2 in cui non è realizzabile l'imaging radiologica.

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