Original Research Article

Outcome following necrotizing pancreatitis

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ABSTRACT

Objective: To study the long-term outcome following recovery from acute necrotizing pancreatitis in terms of structural and functional status of pancreas (both exocrine and endocrine) and to study the correlation, if any, of the long-term consequences with respect to the severity of necrotizing pancreatitis and between the groups of patients managed conservatively and operatively.

Materials and Methods: All patients with a diagnosis of acute necrotizing pancreatitis based on Balthazar CT severity index (CTSI) in AIIMS, New Delhi following recovery of the illness were included in the study between the period from March, 2011 to June, 2012. Patients managed both operatively and non-operatively were followed up at six months and at one year. Structural changes were assessed by ultrasound at 6 months and 1 year. CECT scan/ MRI with MRCP/ ERCP/ EUS were done if ultrasound revealed any abnormality. Exocrine function of pancreas was assessed by fecal fat and stool elastase and endocrine function by fasting blood sugar, fasting serum c-peptide and HbA1c levels.

Results: Pancreatic atrophy was more in the operated patients compared to non-operated patients at discharge and at 6 months of follow up. Pancreatic exocrine and endocrine insufficiency, were similar in both groups.

Conclusion: There was a high correlation between extent of necrosis and subsequent development of pancreatic atrophy and diabetes in both groups of patients. Exocrine and endocrine functions deteriorated after necrotizing pancreatitis irrespective of conservative or operative treatment and there was no statistically significant difference between the two modes of treatment.

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1. Introduction

Acute pancreatitis can be non-necrotizing with an acute inflammatory process of the gland with interstitial edema (interstitial edematous pancreatitis), or it can be necrotizing. Pancreatic necrosis occurs in approximately 20% of patients with acute pancreatitis.1 Necrotizing variety can take 2 forms - 1. peripancreatic necrosis alone and 2. pancreatic necrosis with or without peripancreatic necrosis, which constitutes 80% of patients with necrotizing pancreatitis. Necrotizing pancreatitis can have diffuse or focal area(s) of non-viable pancreatic parenchyma; it can be sterile or infected and is always associated with a possible damage to the pancreas. The initial (< 1 week) solid necrosis liquefies by a process of liquefaction necrosis and later (>4 weeks) a more semi-solid, non- homogenous appearance is common. So, in the later stages of necrosis, the content may be predominantly pus in addition to some solid components, as the process of liquefaction necrosis matures.

In pancreatic necrosis when the non-enhanced pancreatic parenchyma is >3 cm or involves > 30% of the area of the
pancreas, exocrine and endocrine functions are impaired to a variable degree and for a variable duration. If necrosis involves a segment of the main pancreatic duct, stenosis may result, leading to obstructive chronic pancreatitis distal to the site of necrosis - 'disconnected-duct syndrome'. It is not clear when functional changes resolve and to what extent.²

2. Objective
To study the long-term functional outcome following recovery from acute necrotizing pancreatitis in terms of:

1. Structural change.
2. Exocrine function status.
3. Endocrine function status and to study the correlation, if any, of the long-term consequences with respect to the severity of necrotizing pancreatitis and between the groups of patients managed conservatively and operatively.

3. Materials and Methods
After approval from ethical committee of AIIMS, New Delhi, patients were recruited in the study. All patients with a diagnosis of acute necrotizing pancreatitis following recovery of the illness were included in the study between the period from March 2011 to June, 2012.

Detailed history was taken from the patients. Demographic details (age, sex, weight, body mass index) were noted, etiology was assessed and clinical examination was done. Patients were evaluated with standard laboratory investigations (hemogram, renal function test, and liver function test) and specific laboratory investigations (lipase/amylase in case of abdominal pain and triglycerides in case of recurrent episodes of pain). Patients managed both operatively and non-operatively were followed up at six months and at one year to look into the structural and functional aspects of pancreas.

3.1. Inclusion criteria
All patients with diagnosis of acute necrotizing pancreatitis based on Balthazar CT severity index (CTSI) who were managed by conservative or surgical means, following recovery of their illness, were included.³ The date of recovery was taken as the date of discharge from the Department of Gastroenterology following index admission for acute necrotizing pancreatitis in case of conservative management and date of necrosectomy in case of patients who underwent surgical treatment.

3.2. Exclusion criteria
1. Patients who refused to give consent.
2. Patients with documented or suspected chronic pancreatitis based on history of chronic alcohol intake, profound loss of weight or other symptoms suggestive of chronic pancreatitis, like steatorrhea.
3. Pancreatic head cancer leading to pancreatitis.
4. Surgery other than pancreatic necrosectomy following acute necrotising pancreatitis.
5. Patients with severe systemic disease (cardiovascular or respiratory).
6. History of diabetes mellitus prior to acute necrotizing pancreatitis.
7. Patients who did not come for follow up.

3.3. Outcome
3.4. Structural changes
The structural changes were assessed by doing an ultrasound at 6 months and 1 year. In case any abnormality was detected on ultrasound, appropriate further investigations such as contrast-enhanced computed tomography (CECT scan)/magnetic resonance imaging with magnetic resonance cholangiopancreatography (MRI with MRCP)/endoscopic retrograde cholangiopancreatography (ERCP)/endoscopic ultrasound (EUS) were done.

3.5. Functional changes
Functional outcome was assessed by evaluating the exocrine and endocrine functions of pancreas in these participants. Fecal fat and stool elastase estimation were done for exocrine function. Fasting blood sugar, fasting serum c-peptide and HbA1c levels were measured for evaluating endocrine function. Weight and nutritional parameters such as serum albumin were measured. Need for pancreatic enzyme supplementation and oral hypoglycemics or insulin was noted. Height and BMI were also recorded. Data of patients managed conservatively and those managed surgically were compared.

3.6. Statistical methods
Data was entered in a Microsoft Excel worksheet and statistical analysis was done using SPSS-15 software (ILLINOIS Chicago, USA). Data was expressed as mean ± Standard Deviation. Chi-square test / Fisher’s exact test was used for comparing dichotomous data. Paired-t test / Wilcoxon signed rank test was used to compare measured data of paired samples. Independent variable t-test / Mann Whitney U test was used for comparing measured data of unrelated samples. A p value of 0.05 or less was taken as significant.

4. Results and Discussion
One hundred seventy-four patients with acute pancreatitis were studied during the period from March 2011 to June 2012. Out of the 129 patients with necrotizing
pancreatitis, 91 patients were followed up: 56 patients were managed conservatively and 35 patients underwent surgery. Following tables reveal the data of these 91 patients, who have been followed up.

4.1. Demography and etiology

Patient subgroup managed conservatively in this study were significantly older than those who underwent surgery (mean age 40.9 ± 13.8 years versus 33 ± 12.4 years), which is statistically significant. Male gender was affected commonly (72.6%) in both operated and non-operated patients which is supported by other studies as well. Biliary etiology was found to be the commonest in both non-operated (46.4%) and operated groups (57.1%) followed by alcohol in operated (20%) and idiopathic in non-operated groups (26.7%). Overall biliary etiology was most common (50.5%) followed by alcohol (23%) and idiopathic cause (21.9%). Literature review reveals similar findings. Fernandez-Cruz et al., reviewed 233 patients with acute necrotizing pancreatitis and found 45.5% of their patients were of biliary etiology. Similarly bile duct stones and alcohol abuse together accounted for about 80% of acute pancreatitis in the study by Sakorafaset al.

4.2. Nutritional, exocrine and endocrine parameters

Mean weight of the patients at 6 months (59.5 ± 8.9 kg) and one year (64.7 ± 11.6 kg) following discharge were significantly higher (p value 0.003) compared to the weight at discharge (52.3 ± 10.1 kg) in both groups of patients. All patients in the operated group and all but two patients in the non-operated group had gained weight at one year compared to weight at 6 months. Weight of the patients at discharge showed a statistical difference (p value 0.018) according to the extent of pancreatic necrosis. Mean weight of patients at discharge was 47.0 kg in the group of patients with <30% pancreatic necrosis versus 55.9 kg in patients with extent of pancreatic necrosis > 50%. Johnson et al., also observed a more severe disease in overweight patients.

There was an increase in serum albumin level at 6 months (4.3 ± 0.78 mg/dl) and one year (4.8 ± 0.48 mg/dl) following recovery of the illness in both groups of patients, and increase was highly significant. The difference of serum albumin at 6 months following recovery between the two groups was significant statistically, and rise in serum albumin was more in the operated group. Table 1

Diabetes was present in four patients each in either group, constituting 14.03% (8/57) of total patients studied. At follow up at 6 months and one year, 7.8% (4/51) and 11.1% (4/36) patients had diabetes respectively. Pancreatic exocrine deficiency manifesting as diarrhea is not an unusual outcome following acute necrotizing pancreatitis. Our experience from this study reveals diarrhea rate of 14.03%, 7.8% and 11.1% of patients at the time of discharge, at 6 months and at one year respectively. Literature review suggests diarrhea in one-fourth to more than half of patients.

4.3. Fecal fat and elastase

Fecal fat test is a diagnostic test for fat malabsorption, due to deficiency of pancreatic lipase which leads to excess fat in the feces (steatorrhea). The normal value of fecal fat is < 7g/24 hours stool. In the non-operated group, 7 to 28% of patients had excessive fecal fat level at different times of follow up and in the operated group this was between 7 to 18%. There was no statistically significant difference between the two groups. Table 2

Severe exocrine pancreatic insufficiency was considered when the elastase level was <100 µg/g stool and moderate when it was 100-200 µg/g stool. Fecal elastase was severely reduced in both groups of patients. There was slight increase in elastase level at 6 months, and the increase between the two groups was statistically significant; the increase being more in favor of operated group. At one year of follow up there was no difference in the increase in level between the two groups.

4.4. Enzyme supplementation and development of diabetes

Enzyme supplementation was needed in only 12.2, 7.8 and 11.1% of patients at discharge, 6 months and 1 year respectively. The difference in use of the pancreatic enzymes in both groups was not statistically significant. Bavare et al., found 11% of their post necrosectomy patients requiring enzyme supplementation after 18 months follow up.
Table 1: Nutritional, exocrine and endocrine parameters

| Parameters                | Operated | Non-op. | Operated | Non-op. | Operated | Non-op. |
|---------------------------|----------|---------|----------|---------|----------|---------|
| FBS (mg/dl)               | 105.1±16.8 | 117±49.8 | 111.2±38.2 | 147.0±100.4 | 156.7±97.8 | 151.1±122.5 |
| C-peptide (ng/ml)         | 3.8±2.9 | 3.3±1.2 | 2.5±1.3 | 2.8±1.3 | 5.1±0.9 | 3.0±1.2 |
| HbA1c (%)                 | 5.1±0.9 | 5.4±1.6 | 5.6±1.6 | 6.6±2.8 | 6.6±2.8 | 6.7±2.9 |
| Diabetes                  | 26%      | 26.40%  | 30%      | 35.40%  | 33.30%  | 45.40%  |
| Elastase (µg/g of stool)  | 41.5±32.5 | 96±83.4 | 74.2±50.4 | 36.7±35 | 94.8±67.0 | 69.4±55.3 |
| Fecal fat (g/24 hrs.)     | 5.23±5.8 | 5.2±3.3 | 3.7±3.4 | 4±2.5 | 10.1±19.5 | 21±85.5 |
| Albumin (mg/dl)*          | 3.3±0.6 | 3.3±0.63 | 4.6±0.5 | 4.0±0.8 | 4.9±0.4 | 4.7±0.4 |
| BMI                       | 17.8±3.1 | 19.6±4.0 | 21.1±2.8 | 21.9±3.5 | 22.7±3.3 | 23.9±5.5 |

FBS- Fasting blood sugar; HbA1c- Glycosylated hemoglobin; BMI- Body Mass Index; * P< 0.05

Table 2: Fecal fat and elastase value

| Both op. and non-op. patients | Fecal fat (g/24 hrs.) | P value | Fecal elastase (µg/g stool) | P value |
|--------------------------------|-----------------------|---------|-----------------------------|---------|
| At discharge                   | 5.64±5.6              | 0.745   | 31.7±26.7                   | 0.028   |
| At 6 months                    | 3.83±3.0              | 0.529   | 100±54.8                    | 1       |
| At 1 year                      | 7.5±16.2              | 0.49    | 169±41.0                    | 0.18    |

Table 3: Enzyme supplementation

| Enzyme supplementation | Non-op. patients | Operated patients | Total | P value |
|------------------------|------------------|-------------------|-------|---------|
| At discharge           | 3/34 (8.8%)      | 4/23 (17.3%)      | 7/57 (12.2%) | 0.432   |
| At 6 months            | 3/31 (9.6%)      | 1/20 (5%)         | 4/51 (7.8%) | 1       |
| At 1 year              | 3/24 (12.5%)     | 1/12 (8.3%)       | 4/36 (11.1%) | 1.03    |

Table 4: Development of diabetes

| Development of diabetes | Non-op. patients | Operated patients | Total | P value |
|------------------------|------------------|-------------------|-------|---------|
| During illness          | 18/56 (32.1%)    | 8/35 (22.8%)      | 26/91 (28.5%) | 0.475   |
| At discharge            | 9/34 (26.4%)     | 6/23 (26%)        | 15/57 (26.3%) | 0.497   |
| At 6 months             | 11/31 (35.4%)    | 6/20 (30%)        | 17/51 (33.3%) | 0.463   |
| At 1 year               | 10/22 (45.4%)    | 4/12 (33.3%)      | 14/34 (41.1%) | 0.377   |

Table 5: Extent of necrosis and laboratory parameters

| Necrosis (%) | <30% | 30-50% | >50% | Total | <30% | 30-50% | >50% | Total | <30% | 30-50% | >50% | Total |
|--------------|------|--------|------|-------|------|--------|------|-------|------|--------|------|-------|
| Diabetes     | 4    | 2      | 9    | 15    | 5    | 3      | 9    | 17    | 6    | 3      | 5    | 14    |
| Fecal Elastase<100 µg/g stool | 2    | 1      | 7    | 10    | 5    | 3      | 6    | 14    | 5    | 3      | 6    | 14    |
| Albumin (mg/dl) | 3.1±0.5 | 3.5±0.4 | 3.3±0.7 | 4±0.6 | 4.1±0.8 | 4.6±0.7 | 4.8±0.44.6±0.60.±0.3 |

It has long been known that endocrine pancreatic function is impaired during and after an attack of acute necrotizing pancreatitis. Some 25-40% of our patients developed diabetes mellitus in the follow up period and there was no statistical difference between the two groups of patients. Other studies also reveal similar results. We also observed that 60% (9/15) of the patients developing diabetes mellitus at discharge and 52% (9/17) at 6 months had more than 50% of pancreatic necrosis.

4.5. HbA1c

HbA1c levels were found to be elevated in increasing number of patients at the time of discharge, at 6 months and at 1 year respectively in both groups of patients, implying that the number of patients developing diabetes increase over time (the normal value of HbA1c in our laboratory is 4.27-6.07%). There was no statistically significant difference in elevated HbA1c levels between the two groups of patients.

Uomo et al., also found that with increased duration of follow up, the prevalence of diabetes in the postacu
necrotizing pancreatitis patient population increases. Wu et al., observed only 8% of his 59 patients with abnormal glycosylated hemoglobin level after an attack of pancreatitis, although 32% were found to have elevated fasting blood glucose. This means that the onset of diabetes was new in these patients and they are prone to have increased levels of glycosylated hemoglobin at a later follow up.

4.6. C-peptide

Most of the patients got their c-peptide done in our series and the values were largely within normal range (1.1 to 4.4 ng/ml) at discharge and follow ups in both groups. Increased levels of c-peptide in non-operated and operated groups at one year follow up in our series was 21.7% and 8.3% respectively and decreased levels of c-peptide was found in 17.3% and 8.3% of patients respectively. Buscher et al., found increased basal level of c-peptide in patients undergoing conservative management of acute necrotizing pancreatitis. Similar findings were also obtained by Tsiotos et al., after acute pancreatitis. The difference in findings might well be attributable to the complex equilibrium between the amount of beta cell loss leading to decrease in serum c-peptide level versus the development of secondary diabetes due to peripheral insulin resistance and consequent increase in serum c-peptide level.

4.7. Oral hypoglycemic agent (OHA and insulin use

One patient from each group required OHA at the time of discharge, at 6 months and at 1 year.

Percentage of non-operated patients dependent on insulin at the time of discharge, at 6 months and at 1 year were 14.7%, 22.5%, 20.8% respectively. The same figures in case of operated patients were 11.1%, 15% and 25% respectively. There was no statistical difference between two patient groups in terms of insulin requirement.

4.8. Structural abnormalities

The number of patients with collection or pseudocyst was markedly less in operated patients compared to non-operated patients at all stages of follow up and the difference between them was statistically significant.

Pancreatic atrophy was statistically significant in operated patients compared to non-operated patients at discharge and at 6 months, though there was no difference at 1 year of follow up.

We found a high correlation between extent of necrosis and subsequent development of pancreatic atrophy in both group of patients at all stages of follow up, but the difference between them was not statistically significant.

Locoregional complications occurred in a fewer number of patients and there was no statistical difference between two groups of patients. The range of locoregional complications varied from dilated main pancreatic duct, splenic vein thrombosis, splenomegaly, splenic hilar collaterals, pleural effusion (unilateral/ bilateral), ascites etc. Most of them were kept on follow up except for tapping pleural effusion and ascites.

4.9. Imaging

Only few patients required cross-sectional imaging at follow up, barring ultrasound of the abdomen and there was no statistical difference between the two groups. The numbers were 7/57 (12.2%) at discharge, 3/51 (5.8%) at 6 months and 3/36 (5.3%) at 1 year. These included CT scan and MRI with MRCP. One patient required ERCP and stenting of the pancreatic duct and one patient underwent endoscopic ultrasound.

4.10. Mortality

Mortality rate was 39.2% (22/56) in non-operated group and 34.2% (12/35) in operated group and there was no statistically significant difference between the two groups. Although newer modalities of management of acute necrotizing pancreatitis are in vogue, reduction in mortality by any particular management option is not yet answered.

5. Conclusion

This clinical paradigm ‘functional outcome following necrotizing pancreatitis’ is not adequately addressed in literature. We studied two groups of patients, i.e., patients managed by conservative means and managed by surgery, and compared the outcomes of both. Non-operated patients were older than the operated group (mean age 40.9 years versus 30 years). Male population constituted 67.8% of non-operated patients and 80% of operated patients. Etiology was predominantly biliary (50.5%) followed by alcohol (23%) and idiopathic cause (21.9%). Mortality was high, but comparable in both groups (39.2% versus 36.3%). Difference in the outcome among these groups was noted in the following parameters. Peripancreatic collections and/or development of pseudocysts remained higher in the non-

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**Table 6: Hb1Ac**

| Both op. and non-op. patients | HbA1c (%) | P value |
|------------------------------|-----------|---------|
| At discharge                 | 5.5±1.22  | 0.030 (HbA1c at discharge vs at 6 months) |
| At 6 months                  | 6.24±2.4  | 0.000 (HbA1c at discharge vs at 1 year) |
| At 1 year                    | 6.97±3.12 |         |
operated group in the follow up period (72%, 45%, and 48% at discharge, 6 months, and 1 year versus 22%, 10%, and 0% at 1 year). Pancreatic atrophy was more in the operated patients compared to non-operated patients at discharge and at 6 months, though there was no difference at 1 year of follow up. Performance status at discharge was better in the non-operated group.

Other outcomes were similar in both groups. Nutritional parameters like weight and albumin improved at follow up visits. Pancreatic exocrine insufficiency manifesting as diarrhea was noted in 10-15% of patients. Fecal fat level was increased in 10-25% of patients. All patients had low levels of fecal elastase. Severe exocrine pancreatic insufficiency was found in 80% of patients and moderate insufficiency in 20%. Pancreatic enzyme supplementation was needed in 80% of patients. Pancreatic atrophy was statistically significant in operated patients compared to non-operated patients at discharge and at 6 months, though there was no difference at 1 year of follow up.

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7. Conflicts of Interest

No conflicts of interest.

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