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ORIGINAL RESEARCH

The role of octreotide in preventing complications of acute pancreatitis at a tertiary care

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Abstract

Background: Acute pancreatitis may follow a mild or severe course. Whereas mild or edematous pancreatitis is a self-limiting disease with a low complication rate and low death rate, morbidity and mortality in severe or necrotizing pancreatitis are still unacceptable. The major problem is the lack of a specific drug, especially in the early phase of the disease, to interfere with the systemic inflammatory response syndrome and to limit or prevent complications of the disease.

Aim and objective: A Role of Octreotide in Preventing Complications of Acute Pancreatitis.

Material and Method: This case control study was done on patients admitted for the treatment of acute pancreatitis at a tertiary care teaching hospital in VIMS, Gajraula, UP, India. This is a retrospective study. The data on inpatient records were taken from the medical records department (MRD) of the hospital. The diagnosis of patients was established on the basis of biochemical and radiological investigations. The patients were divided into two groups: cases and controls. Cases had received octreotide along with fluids (group A); controls received fluids without octreotide (group B). Symptomatic treatment was given in both groups. Ages of the cases and controls were matched (±3 years). The statistical analysis of the data was done, and results were obtained.

Results: In this retrospective case-control study, the records of 50 patients were selected. The mean age in the octreotide group (Group A) was 35.16±8.65 years when compared with 37.92±7.1 years in Group B ($p < 0.211$). Gender-wise comparison showed that there were 20 males and 5 females in the octreotide group, while there were 20 males and 5 females in the control group. Both the groups were comparable. All the patients in the octreotide group survived, while there were three in the control group. As far as the mean hospital stay is concerned, it was 9.88 days ± 6.0 in group A, while it was 7.24 days ±1.17 in group B. All the p values for the criteria of the study are significant. But when we talk about percentage, 8% of patients died in the control group.

Conclusion: In our study, we found that octreotide does not affect the final outcome of patients with acute pancreatitis. There is no effect on hospital stay and reduced need of analgesics in patients with acute pancreatitis.

Keywords: acute pancreatitis; octreotide; hospital stay; mortality

Introduction

Acute pancreatitis may present as a mild, self-limiting disorder or as a severe disease that may have a fatal course. The pathological features range from mild edema to hemorrhage and necrosis of the pancreatic tissue. No clear-cut correlation has been found between the clinical presentation and the pathologicdamage [1]. The severity of the disease is often assessed by the prognostic signs described by Ranson et al. [2] and by radiologic findings on CT [3]. Although the pathophysiology of acute pancreatitis has been extensively investigated; it is only partly understood. No specific treatment has been found so far to prevent the deleterious effects of the digestive enzymes on the pancreas and peripancreatic tissues. As a result, management has been empirical, mainly by suppressing the pancreatic secretions and diminishing the activity of the gastrointestinal tract. Acute pancreatitis accounts for 3% of all cases of abdominal pain among patients admitted to hospitals in the UK. The hospital admission rate for acute pancreatitis is 9.8 per year per 100,000 population in the UK, although worldwide, the annual incidence may range from 5 to 50 per 100,000. The disease may occur at any age, with a peak in young men and (4) older women. The prevalence of pancreatitis in India is 2.6–3.2 cases per 100,000 population. (5)

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Mild or edematous pancreatitis is a self-limiting disease; morbidity and mortality are considerably high in cases of severe necrotizing pancreatitis. [6] Octreotide reduces splanchnic blood flow, gastrointestinal motility, and absorption of water, electrolytes, and nutrients from the gut. There is evidence of abdominal pain and diarrhea in a few is considered to be least effective in reducing pain in cases of acute pancreatitis. It is considered to be least effective in reducing pain in cases of acute pancreatitis. [7] Octreotide inhibits stimulated pancreatic secretion, so it is useful in pancreatic diseases and pancreatic injury. [8]Theories on the pathogenesis of acute pancreatitis suggest that autodigestion of the gland and peripancreatic tissues by activated digestive enzymes is a key component [9]. Furthermore, stimulation of exocrine pancreatic secretion in experimental acute pancreatitis has been demonstrated to worsen the disease. Prevention of release and activation of enzymes by inhibition of pancreatic exocrine secretion has therefore been suggested as a specific treatment. Somatostatin and its long-acting analogue, octreotide, are potent inhibitors of pancreatic secretion [10]. The efficacy of somatostatin and octreotide in the management of acute pancreatitis has been studied for decades, yet the data still remain inconclusive. Some experimental [11] and clinical [12] studies have shown beneficial results, but others [13] demonstrated no benefit [14].Somatostatin and octreotide increase the tone of the sphincter of Oddi, which can be reversed by administration of glyceryl trinitrate [15]. Furthermore, octreotide may trigger acute pancreatitis and worsen the disease [16].

It increases the pressure at the sphincter of Oddi, which results in impairment of pancreatic outflow. The dysfunction of the sphincter of Oddi is thought to be a cause of acute idiopathic recurrent pancreatitis. No significant change is observed in pre- and post-void pressure at the basal sphincter of Oddi with the use of octreotide. It reduces secretion, release, and activation of exocrine hormones; there is a collection of pancreatic hormones in the duct, which in return causes irreversible destruction of the exocrine and endocrine pancreatic parenchyma, which leads to malnutrition and diabetes. [6,17]There is no effect on pain with the use of octreotide. [6] In cases of acute pancreatitis, octreotide produces contractility of the sphincter of Oddi, which results in retention of enzymes insidethe pancreas, which may be responsible for auto-digestion and further progression of disease. It reduces the complications after elective pancreatic surgery. It is reported that the inhibitory effect of octreotide is lost after 7 days of its administration. There is no target drug, especially forpancreatitis in the initial phase of the disease to fight against systemic inflammatory response syndrome. [8,17] There are lots of controversies in the treatment of acute pancreatitis, so we triedto evaluate whether there is a beneficial role of octreotide or not.

Method and Materials

This case control study was done on patients admitted for the treatment of acute pancreatitis at a tertiary care hospital, Department of General Surgery, VIMS, Gajraula, UP, India. The diagnosis of patients was established after biochemical and radiological investigations. The data on inpatient records were taken from the medical records department of the teaching hospital. Due clearance from the Institutional Ethics Committee was taken. The inpatient medical records of patients were noted and studied.

The hospital has many units in the department of general surgery; some of them consider use of octreotide for acute pancreatitis, while others consider fluid and symptomatic management for it, so we selected this topic for retrospective research. For the establishment of the diagnosis, serum amylase, serum lipase levels, ultrasound, and computed tomography were taken into consideration. From the inpatient records of previously diagnosed patients, the data was obtained. The patients were divided into two groups, Group

Inclusion Criteria

- More than 18 years of age.
- Willing to participate in the study.
- Undergoing ERCP for a valid indication.

Exclusion Criteria

- Age less than 18 years.
- Pregnancy or lactation.
- Chronic renal failure.
- Acute myocardial infarction during the last 3 months before procedure.
- HIV positive or any other immune compromised state.
- Planned biliary stent removal or exchange.
- History of alcohol or other drug abuse.
- A history of chronic pancreatitis or other disease is known to affect pancreatic secretion (vagotomy, gastrectomy, inflammation).
- Refusal to participate.

A (cases) consisted of patients who received octreotide, pancreatic enzyme substitutes, antacids, antiemetics, and fluids, and Group B (controls), who did receive pancreatic enzyme substitutes, antacids, antiemetics, and fluids but no octreotide was given. The patients were chosen with age matching (±3 years) in the control group. Ringer lactate and Dextrose saline were used, and symptomatic management was done in both groups. The use of analgesics more than three times a day was considered a patient not relieved of pain; the patient needed more analgesics. The effects studied were hospital stay, mortality, pain, and severity of pancreatitis by amylase and lipase levels in both groups on admission to see the intensity.

The results of this case control study are based on inpatient hospital records. As it was a retrospective study, the records of 50 patients were acquired; the

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patients were divided into 2 groups, each consisting of twenty-five patients. One group received fluids with octreotide and another received fluids without octreotide.Symptomatic treatment was given in both groups. In group A, octreotide was given, and in group B, octreotide was not given.

Statistical Analysis: Data were maintained on an Excel spread sheet. Analysis was performed using SPSS-24 software. Descriptive data were expressed as mean, standard deviation, and range of all variables. Results were presented as mean±S.D. Means of data in patients and controls were compared using the independent student t-test. Differences were considered statistically significant at $p<0.05$ and highly significant at $p<0.001$.

Observation and Result

The mean age in the octreotide group (Group A) was 35.16±8.65 years when compared with 37.92±7.1 years in Group B ($p < 0.211$). Gender-wise comparison showed that there were 20 males and 5 females in the octreotide group, while there were 20 males and 5 females in the control group. Both groups were comparable; there was no significant difference noted. One patient in each group had both etiologic factors: drug and metabolic, both females using oral contraceptives and with hyperlipidemia.

Table 1: Comparison of groups Group A (Octreotide Group) and Group B (Non Octreotide Group)

Variable		Octreotide (Group A) (Mean ± SD)	Control (Mean ± SD)	P-value
Age (years)		35.16±8.65	37.92±7.1	0.211
SEX (M/F)		20:5	20:5	
BMI (kg/m2 sq.)		23.82±2.09	24.22±1.96	0.489
Etiology	Biliary	18	15	
	Alcohol	6	3	
	Metabolic*	2	2	
	Drug induced*	4	3	
	Idiopathic	3	1	

Table 2: Comparison of groups Group A (Octreotide Group) and Group B (Non Octreotide Group)

Variable		Octreotide (Group A) (Mean ± SD)	Control (Mean ± SD)	P-value
Outcome	Cured	25	23	X^2- 0.297
	Death	0	2	
Mean hospital stay (days)		9.88±6.0	7.24±1.17	T=2.15 P=0.035
Mortality		3(12%)	7(28%)	0.161
Serum Amylase (U/L) (Before treatment)		449.32±14.02	457.8±17.09	0.061
Serum Lipase (U/L) (Before treatment)		670.88±59.55	924.12±77.58	0.0001

All the patients in the octreotide group survived, while there were two deaths in the control group. In terms of mortality, 12% of deaths occurred in the control group. As far as mean hospital stay was concerned, it was 9.88 days ± 6.0 in the octreotide group while it was 7.24 days ± 1.17 in the control group ($p <0.035$). The mean value of serum amylase in the octreotide group on admission was 449.32±14.02, and in the control group it was 457.8± 17.09. The mean value of serum amylase in the octreotide group before discharge was 455.6± 23.5, and in the control group it was 457.8± 17.09. The values for serum lipase were 670.88 ± 14.02 in the octreotide group and 924.12 in the control group ($p < 0.0001$). All the p values for the criteria of the study are nonsignificant (Table 2).

Table 3: Complications related to acute pancreatitis

Variable	Octreotide (Before treatment) (Group A) (Mean ± SD)	Control (Before treatment) (Mean ± SD)	P-value
ARDS	**8(32%)**	**13(52%)**	**0.156**
Sepsis	**7(28%)**	**20(80%)**	**0.0003**
Abscess	**3(12%)**	**3(12%)**	**1.000**

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Renal failure	**2(8%)**	**3(12%)**	**0.64**
Pseudocyst	**5(20%)**	**4(16%)**	**0.715**
Fistula	**0(%)**	**1(4%)**	**0.317**

The complication rate was lower in the treatment group as compared to the control group, with regard to ARDS (32% vs 52%, P -0.156) and sepsis (28% vs 80%, P = 0.0003). As for abscess, pseudocyst, and renal failure, no differences were found between the two groups (Table 3). 7 patients developed abscesses that needed drainage. Three of them were drained percutaneously (eitherCT scan or ultrasound-guided) and 5 were drained surgically. On the basis of patient records, the mean hospital stay in group A was 9.88± 6.0 days and in group B was 7.14±1.17 days, so it can be stated that the mean hospital stay was more in the group who received octreotide, but statistically it was highly significant.

The pain was present in 15 patients in both groups, as the patients received more than three doses of analgesic. Being a retrospective study, it was not possible to assess the intensity of pain, and hence it cannot be said that there was greater relief of pain in the group that received octreotide or not. We found there was no role of Octreotide in pain reduction. Two patients out of 25 died in group B, and the reason behind it was multiple organ failure. Liver and renal functions were deteriorating; ultimately, they were put on a ventilator for respiratory support, and circulatory support was continued, but the vitals could not be maintained and the patient collapsed. The patients were young and below 45 years of age. No statistical significance in the values was there. There were 8% of deaths recorded in the control group. In group A, the mean amylase level was 449.32±14.02 units; in control group B, it was 457.8±17.09 U/L; the mean lipase level in group A was 670.88±59.55 U/L; and in control group B, it was 924.12±77.58 U/L. As far as the hospital stay of the patient is considered, the hospital stay was longer in patients who did receive octreotide.

Discussion

In the present study, treatment of acute pancreatitis with octreotide resulted in a lower rate of sepsis (28% vs. 80%, P = 0.0003) and ARDS (32% vs. 52%, P = 0.156). The hospital stay was shorter in the treatment group (9.88 versus 7.14 days, P = 0.035). Mortality was significantly lower in the treatment group as well (12% vs. 28%, P = 0.161). Other complications were not significantly different in the two groups. Acute necrotizing pancreatitis is a life-threatening condition with a variable mortality rate depending upon the severity of the disease [1]. The pathophysiology of pancreatitis is poorly understood, and its management has been essentially empirical. Previous specific treatment modalities failed to show any beneficial effect. Careful monitoring and supportive measures, fluid replacement, and suppression of pancreatic secretion remain the only effective treatments to improve the survival rates. Somatostatin and its analogues have a strong inhibitory effect on enzyme, bicarbonate, and water secretion of the pancreas [18].

The chances of shock and ARDS (acute respiratory distress syndrome) increased in the non-octreotide group; there is no change in pain, intensity, duration, hospital stay, or mortality. [19] A study done by Paran et al. reveals that there are high chances of sepsis and ARDS in patients not receiving octreotide, along with prolonged hospital stays and high mortality.

The hospital stay is shorter in patients receiving octreotide, while patients not receiving Octreotide show higher mortality. There is definitely a great role for octreotide in severe acute pancreatitis. The chances of sepsis and ARDS are low in patientsreceiving octreotide. [20-21] It is controversial to comment about the role of Octreotide in reducing post-endoscopic retrograde cholangiopancreatography-induced pancreatitis. [22]

Benefits of octreotide observed clinically in experimental models are: less hypoglycemia, less acidosis, a reduction in pancreatic edema, little damage to the pancreas, and a reduction in mortality. [19-20] No difference is observed in levels of fasting glucose, calcium, albumin level, complete blood picture, LDH, renal function test, blood pressure, and fever in the patients receiving octreotide or not. There pleural effusion, ascites, pancreatic edema, and retroperitoneal edema are reduced in the octreotide group. It is considered that if oral intake is started at an early phase, then serum amylase levels and pancreatic edema are evident to reduce fast. [23]

The findings of rebound leucocytosis and elevated serum and urine amylase levels are the same in both groups. There is no fall or rise in amylase secretion in patients of pancreatitis when the patient is administered with octreotide. [24] Many studies concluded that along with bedside index for severity in acute pancreatitis, serial urea and creatinine guidelines can be used to manage the disease. [25] There are 30–50% chances of mortality in cases of severe acute pancreatitis. [26] One of the studies says that there is the same mortality in both groups, and the other study says that there is no difference in mortality or complications. These are again inconclusive evidences; they are neither favoring nor discouraging the use of octreotide in cases of pancreatitis. [19-20] In our study, more deaths were observed in groups who did not receive octreotide. It is a fact that less amount of analgesic is needed to control pain in the octreotide group. It is controversial whether there is any change in duration of pain and intensity in the octreotide and non-octreotide groups. [27] Optimally less or more fluid produces poor outcomes. [28]

The role of Ringer lactate can't be denied, as there is a reduction in systemic inflammatory response

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syndrome with its use. [29] Previously, it was thought that fluid resuscitation improved the prognosis of acute pancreatitis. Many more studies are required to make it a recommendation because the evidence is based on theoretical, animal models, and retrospective studies. It is still doubtful which type of fluid should be given and what should be the rate of administration; it needs many more trials. [30]Similar study done by Dr. Gharde et al. and Haim Paran et al. [21, 31] There is a huge controversy about the use of octreotide in cases of acute pancreatitis; the opinion of every study differs from another. In our study, we could not find any differences in both groups. There was no difference in hospital stay, pain, or mortality; the statistical results were not significant, and they were the same in both groups. But mortality was higher in patients not receiving octreotide.

Conclusion

Our study concludes that statistically, octreotide does not play any important role in patients with acute pancreatitis. The hospital stay is almost the same; there is less mortality in the octreotide group, but it cannot be statistically proven; there is no reduction in the dose of analgesics in both groups. This study on octreotide needs a lot of patients to establish its role in cases of acute pancreatitis. When we read the literature of recent days, many studies reveal that the use of octreotide is controversial. So we can say that it needs more multicentre trials and multivariate analyses to prove the role of octreotide in cases of acute pancreatitis.

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