A RANDOMISED CONTROL STUDY ON EFFECT OF OCTREOTIDE IN MANAGEMENT OF ACUTE PANCREATITIS WITH VARYING SEVERITIES

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ABSTRACTS

Background: Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or organ systems. Theories on pathogenesis of acute pancreatitis suggest that autodigestion of the gland and peripancreatic tissues by activated digestive enzymes is a key component. Octreotide is a potent inhibitor of pancreatic secretion, but the benefits of octreotide in acute pancreatitis in humans is still inconclusive.

Aim: To study the effect of octreotide in acute pancreatitis with different severities.

Method: 284 patients were assigned into two groups randomly, the study group comprising of 138 patients received inj octreotide 100 μg S.C. 8 hrly. The other aspects of the treatment protocol were similar in both groups. Severity of the disease was evaluated initially according to Ranson criteria, APACHE II SCORING, CRP values & Balthazar grading. Both the groups were observed prospectively and outcome of treatment was evaluated.

Results: The results were analysed after dividing both the study and control group into 5 groups each according-to increased severities. The complication rate was 10% in group 1 and 28% in group 2 according to APACHE II among the study group, whereas it was 23% and 46% in the control group respectively. The results in patients stratified according to other criterias were also comparable. The results in cases of severe pancreatitis were poor, complication rates varying from 56% to 100% in the 3’rd and 5’th group according to Ranson criteria among the study group and 62% to 100% respectively among the control group. Mortality of the study and control group also did not show any significant changes.

Conclusion: Inhibition of secretory function in the early course of the disease especially in mild and moderate cases of pancreatitis has been shown to improve final outcome. As in case of acute pancreatitis it is very difficult to estimate the severity and disease progress at the very onset, and as the majority of cases are mild to moderate in severity, it will be beneficial to start with octreotide in any treatment protocol along with supportive resuscitative measures.

KEYWORDS: Acute Pancreatitis, Management, Octreotide

INTRODUCTION

Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or other organ systems. It is clinically classified into mild and severe forms. Mild or edematous acute pancreatitis is a self-limiting disease with a low complication and mortality rate. However severe
necrotising pancreatitis has an unacceptable high morbidity and mortality rate. Multiple therapeutic modalities have been suggested for acute pancreatitis but none has been unambiguously proven to be effective yet. The major problem is that the pathophysiology of the disease is not fully understood and hence, there is no specific causal treatment. The treatment of acute pancreatitis to date is essentially supportive [1],[2],[3]

Theories on pathogenesis of acute pancreatitis suggest that autodigestion of the 'gland and peri-pancreatic tissues by activated digestive enzymes is a key component [4],[5]. 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[6],[7]. The efficacy of somatostatin and octreotide in the management of acute pancreatitis has been studied for decades, yet the data still remains inconclusive [8]. Some experimental and clinical studies have shown beneficial results, but others demonstrated no benefit [9],[10]. In this study we evaluated the effect of octreotide in the management of pancreatitis with varying severities

METHODS

A total of 284 patients of acute pancreatitis of different severity who were admitted at department of general surgery, IPGME&R, Kolkata between 2009 to 2012 are evaluated. Patients were diagnosed based on clinical, laboratory and imaging findings. The patients were initially resuscitated and were managed with conservative supportive care. Patients were randomly assigned into 2 groups. One group (n=138) received inj. Octreotide 100 μg S.C. 8 hrly. The other group (n=146) was managed conservatively without giving octreotide. The other aspects of the treatment protocol were similar in both groups. Severity of the disease was evaluated initially according to Ranson criteria, APACHE II SCORING, CRP values & Balthazar grading. Both the groups were followed up prospectively and outcome of treatment was evaluated based on complication rate, hospital stay, requirement of surgical intervention and mortality.

RESULTS

284 patients diagnosed as acute pancreatitis were evaluated under this study. The mean age of presentation was 34 years ranging from 26 to 53 years, male to female ratio was 3:1. The aetiology spectrum included 128 (45%) cases of gallstone pancreatitis, 80 (28%) cases of alcoholic pancreatitis, 19 (6.7%) cases following ERCP , 5 (1.7%) cases following trauma and 42(14.8%) cases were idiopathic. Out of these 284 patients, all patients (100%) had pain abdomen ranging from mild epigastric pain to severe diffuse abdominal pain radiating to flanks and back, 217 patients (76.4%) had vomiting, 192 patients (67.6%) had serum amylase level > 3times the normal value and 267 patients (94%) had raised serum lipase level. 279 patients (98%) had features suggestive of acute pancreatitis on CT Scan and 258 patients (91%) on USG.

All the patients from study (n = 138) and control (n=146) were assessed initially, using Ranson criteria, APACHE II SCORING, CRP values and subsequently they underwent ultrasonographic and CT scan evaluation.

Table 1: Follow up data of patients stratified according to Ranson criteria

<table>
<thead>
<tr>
<th>Groups according to Ranson criteria positive</th>
<th>Patients (no.)</th>
<th>Complication rate (no.) (%)</th>
<th>Average hospital stay( days)</th>
<th>Requirement of surgery(no.)</th>
<th>Mortality (no.)</th>
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<tbody>
<tr>
<td></td>
<td>Cas</td>
<td>Con</td>
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</tr>
<tr>
<td>a.0-1</td>
<td>9</td>
<td>11</td>
<td>1(11%)</td>
<td>3(27%)</td>
<td>10</td>
</tr>
<tr>
<td>b.2-3</td>
<td>54</td>
<td>61</td>
<td>15(28%)</td>
<td>28(46)</td>
<td>26</td>
</tr>
<tr>
<td>c.4-5</td>
<td>39</td>
<td>34</td>
<td>22(56%)</td>
<td>21(62)</td>
<td>26</td>
</tr>
<tr>
<td>d.6-7</td>
<td>31</td>
<td>36</td>
<td>27(87%)</td>
<td>31(86)</td>
<td>34</td>
</tr>
<tr>
<td>e.&gt;7</td>
<td>5</td>
<td>4</td>
<td>5(100%)</td>
<td>4(100)</td>
<td>45</td>
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Table 2: Follow up data of patients stratified according to APACHE II SCORE

<table>
<thead>
<tr>
<th>Groups according to APACHE II SCORE</th>
<th>Patients (no.)</th>
<th>Complication rate (no.) (%)</th>
<th>Average hospital stay (days)</th>
<th>Requirement of surgery (no.)</th>
<th>Mortality (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. &lt;15</td>
<td>20</td>
<td>2 (10%)</td>
<td>12</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>b. 15 - 24</td>
<td>39</td>
<td>11 (28%)</td>
<td>28</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>c. 25 - 34</td>
<td>42</td>
<td>23 (55%)</td>
<td>27</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>d. 35 - 44</td>
<td>33</td>
<td>27 (85%)</td>
<td>36</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>e. &gt;45</td>
<td>7</td>
<td>6 (86%)</td>
<td>42</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 3: Follow up data of patients stratified according to Balthazar grading

<table>
<thead>
<tr>
<th>Groups according to Balthazar grading</th>
<th>Patients (no.)</th>
<th>Complication rate (no.) (%)</th>
<th>Average hospital stay (days)</th>
<th>Requirement of surgery (no.)</th>
<th>Mortality (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1</td>
<td>2 (18%)</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
<td>12 (26%)</td>
<td>26</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>E</td>
<td>3</td>
<td>21 (55%)</td>
<td>28</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>F</td>
<td>3</td>
<td>25 (75%)</td>
<td>34</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>G</td>
<td>1</td>
<td>10 (83%)</td>
<td>41</td>
<td>5</td>
<td>7</td>
</tr>
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</table>

On follow up, 83 patients died during the course of treatment, 37 cases (27%) were from the patients receiving octreotide & 46 cases (31.5%) were from control group. The results of follow ups were analysed after dividing both study and control group into 5 groups each according to Ranson criteria, APACHE II and Balthazar grading. The disease process was mainly self-limiting in mild case with hospital stay ranging from 8 to 37 days, the average stay is being 10 – 12 days in first 2 groups according to Ranson criteria among the patients receiving octreotide (study group), whereas it was 12 and 33 days respectively among the patients not receiving octreotide (control group) [Table 1]. The values were in the similar range when the patients were stratified according to APACHE – II or Balthazar grading. [Table 2 & Table 3]. In analyzing the patient according to any of the three criteria, the hospital stay was found to be reduced in patients receiving octreotide. The complication rate was also lower in these 2 groups. The complication rate was 2 (10%) and 11 (28%) in the first 2 groups according to APACHE II among the study group, whereas the complication rate among the control group was a bit higher as it was 5 (23%) and 17 (46%) in the respective groups [Table 2]. The values in patients stratified according to other criteria were also comparable.[Table 1 & Table 3]

Graph 1: Comparison of complication rate(%) among study and control group (group a-e according to Ranson criteria, Table 1)
The course and outcome in cases of severe pancreatitis was poor, complication rate varying from 22 (56%) cases to 5 (100%) cases in the 3rd and 5th group according to Ranson criteria among the study group and 21 (62%) cases and 4 (100%) cases respectively among the control groups. The average hospital stay was 26 to 45 days among the study group and it was 36 to 44 days among control group. There was no significant improvement in outcome in patients receiving octreotide in those cases. Mortality of the study and control group also did not show significant changes [Table 1].

The analysis of the results was similar in patients stratified according to the other two criteria [Table 2 & Table 3].

Requirement of surgery were also higher in severe cases as compared to mild and moderate cases. 13 cases each from the study and control group required surgical intervention, almost all of them were among cases of severe pancreatitis. Patients receiving Octreotide was not shown to have any advantage in this aspect.

DISCUSSION

Acute pancreatitis is an important sometimes life threatening condition characterized by inflammation of glandular parenchyma. It differs well from chronic pancreatitis mainly based on morphologic patterns [11]. The inflammatory process of acinar damage in acute cases may resolve without significant effect or can lead to chronic inflammation, fibrosis and calcification resulting in chronic pancreatitis. The importance of proper evaluation, management and prevention of complications is thus emphasized to address this often fatal situation and its subsequent sequelae including chronicity. Increasing attention is being paid to the morphologic aspect of the disease in order to focus on the cause-and-effect relationship of duct obstruction and severity of disease.

Gall stone pancreatitis, being the most frequent type encountered in this part of India, along with alcoholic pancreatitis accounts for the majority of cases of acute pancreatitis [12]. The severity of the disease varies over a spectrum ranging from mild to acute severe pancreatitis associated with multi organ failure leading to catastrophic consequences. Serum amylase and lipase levels are still used to confirm the diagnosis of acute pancreatitis [13]. Although not routinely available, the serum trypsin level is the most accurate laboratory indicator for pancreatitis [14]. Ultrasonography, computed tomography and endoscopic retrograde cholangiopancreatography, are additional modalities that can help the physician choose the best treatment approach. The prognosis is mainly based on the severity at presentation along with adequacy of management initiatives. So different scoring systems have been introduced to adequately stratify the disease process. Ranson score, Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) , Glasgow grading system and Computed Tomography score including Balthazar grading are thus singly or in combination being increasingly utilised. Organ failure is an independent marker to define disease severity and to differentiate mild and moderate from acute severe pancreatitis which carries a high risk of major morbidity and mortality. C-reactive protein, among the different biochemical markers used, reflects the severity well with value greater than 150 mg/L usually being associated with severe disease.

The clinical course of acute pancreatitis is varied in its extent with some cases having a self-limiting course resulting in spontaneous recovery within a short duration being designated as mild pancreatitis. On the contrary severe pancreatitis cases are complicated with organ failure or local complications like necrosis, abscess formation or pseudocyst. There are different determinants, still not defined clearly, which may direct the course and severity of the condition. Several chemical mediators are involved in this varied manifestation of the process and it is there release, and interaction that contributes to the pathogenesis. It remains difficult to delineate at the very onset as to which course the disease process will take.

The management protocol in cases of acute pancreatitis is mainly supportive in the initial stages with frequent reassessment of severity and continuous monitoring [15]. The focus now is being shifted to treatment of specific complication in the later phase of the disease. 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. Therapies such as nasogastric suctioning, anticholinergics and histamine H2-receptor blockers have not been shown to decrease symptoms or hospital stays in patients with acute pancreatitis [16]. Somatostatin and its long-acting analogue, octreotide, are potent inhibitors of exocrine secretion of the pancreas, which plays an important role in the pathogenesis of acute pancreatitis. In addition, somatostatin and octreotide have direct anti-inflammatory and cytoprotective effects. It has therefore been suggested that somatostatin and octreotide be used in the treatment and prevention of acute pancreatitis, and this concept has been studied extensively over the past 2 decades. The results of these trials have been mixed. While some initial smaller-scale studies showed moderate benefits[17],[18],[19] a recent multicenter randomized study involving over 300 patients revealed no benefit of octreotide with regard to outcome or progression of pancreatitis(20). A prospective study on rats to find out the effects of the octreotide on the course of acute pancreatitis has revealed that if octreotide is given early in the course of the disease it may result in improved outcome[21], but it seems to be ineffective in severe pancreatitis in which acinar necrosis is already established. In our study there is clear evidence that overall mortality and morbidity along with hospital stay has been improved in patients receiving octreotide, the effect mainly contributed by significant improvement in early mild and moderate pancreatitis group (chart 1).

Conclusion

The role of octreotide in treatment of acute pancreatitis is somewhat inconclusive as a whole, but inhibition of secretory function in the early course of the disease especially in mild and moderate cases of pancreatitis has
been shown to improve final outcome. As in case of acute pancreatitis it is very difficult to estimate the severity and disease progress at the very onset, and as the majority of cases are mild to moderate in severity, it will be beneficial to start with octreotide in any treatment protocol along with supportive resuscitative measures.

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