REVIEW ARTICLE

Lessons Learnt in Management of Acute Pancreatitis

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ABSTRACT

Objective Acute Pancreatitis continues to be a confounding clinical problem and can pose a formidable challenge in its management. This invited review discusses the various clinical studies done while managing cases of acute pancreatitis and the possible avenues for further studies. **Method** Clinical studies done on various aspects of pancreatitis viz. severity prediction using bedside index of severity in acute pancreatitis score and its validation in Indian patients, current status of interventions in pancreatitis, timing of enteral nutrition in acute pancreatitis, vasospasm in early phase of acute pancreatitis and ductal involvement in acute pancreatitis were reviewed. Results of each study are discussed briefly. The shortcomings of each study were analysed. A review of current literature pertaining to each of these aspects was carried out. **Results** In all, 5 clinical studies were reviewed. Validation of bedside index of severity in acute pancreatitis score, study of interventions in acute pancreatitis and timing of enteral feeding in acute pancreatitis were prospective observational studies. The results of the bedside index of severity in acute pancreatitis score validation and interventions in acute pancreatitis correlate well with the current literature. Existing literature on various modalities for intervention is discussed. There are not many studies addressing the issue of timing of institution of nasojejunal feeds. Study of vasospasm and ductal involvement in acute pancreatitis were both retrospective. Fluid management in early acute pancreatitis and ductal involvement with disconnected pancreatic duct syndrome are being studied extensively across many centres. **Conclusion** Clinical studies which address various issues in pancreatitis are building blocks for better understanding of the disease evolution. These lessons learnt also form the basis for further research.

INTRODUCTION

Acute Pancreatitis (AP) continues to be a confounding clinical problem and can pose a formidable challenge in its management. The reasons for this are manifold and have been discussed extensively. The challenge of severity stratification in acute pancreatitis has befuddled researchers for long and it continues to be an area of strong scientific research. In spite of this we have been unable to eliminate the incidence of mortality which can remain as high as 30% in high risk subgroups. The two primary reasons for mortality are organ failure in the early phase and infection in necrotic pancreas in the delayed phase. After applying certain principles in the management of AP learnt from clinical experience and from extensive research, we have been able to reduce the mortality; however the morbidity continues to stay high. This review talks about our clinical research in various aspects of the disease and the possible avenues for further studies.

Severity Scoring Systems in Acute Pancreatitis

Predicting severity of pancreatitis early in the course of disease is critical to maximize therapy and to prevent or minimize organ dysfunction and complications. Unfortunately the management of patients with acute pancreatitis is complicated by the inability to distinguish mild from severe disease during the early stages. Traditionally, Ranson's, Glasgow or APACHE –II scoring systems have been used for severity stratification. These scoring systems require multiple clinical parameters and set of laboratory investigations to be carried out which may or may not be possible at every institutional setup and require minimum 48 hours for calculation [1].

The bedside index of severity in acute pancreatitis (BISAP) score developed by Wu and Banks *et al*. after prospective evaluation of more than 17000 patients has made stratification of patients much simpler and quicker and hence more practical [2]. It uses the same parameters which most of us use to clinically stratify patients while on ward rounds. We attempted to validate the ability of BISAP Score to predict severity, organ failure, complications, interventions and mortality in acute Pancreatitis in Indian patients. After institutional review board (IRB) clearance, an Observational prospective study was performed over duration of 9 months in 2013 on 70 patients above the age of 12 years admitted in our hospital with diagnosis of acute pancreatitis. Patients who were diagnosed as acute on chronic pancreatitis or were transferred from other hospitals later in the course of illness with inadequate summary were excluded. The clinical, laboratory and radiological data was collected from the patients within 24 hours of presentation. BISAP score was calculated

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for each patient using the data obtained. The in hospital course of these patients was followed for development of local complications, organ failure and mortality. Patients with BISAP score between 3-5 had a statistically higher incidence of necrosis, organ failure and mortality. Organ failure influenced mortality more than pancreatic necrosis. BISAP score had 83% sensitivity and 85.9% specificity for predicting mortality and severity in acute pancreatitis. Area under curve (AUC) was 0.84. These findings are consistent with previous studies carried out on BISAP score. Thus, the scoring could be validated in Indian patients, albeit in a small number of cases. Recently two new severity classifications have been proposed; the revised Atlanta classification and the Determinants based Classification. Further research to validate them in Indian population and test ease of use can be performed to see whether there is further improvement in the predictive capacity [3].

Interventions in Pancreatitis

Management of acute pancreatitis has changed significantly over the past years [4]. Early management is non-surgical and solely supportive. Today, more patients survive the early phase of severe pancreatitis due to improvement in intensive-care-management. Advances in imaging, interventional radiology and minimal access interventions have revolutionized the management [5]. The focus of management in acute pancreatitis has shifted from interventional to aggressive conservative management with extensive use of minimal invasive means for intervention [6]. The concept of "later and lesser" has evolved in the last 7 – 8 years [7]. We studied the interventions needed in the management of acute pancreatitis in a cohort of 148 patients with diagnosed acute pancreatitis at our institute. The primary objective was to study the type and frequency of interventions performed in the management of acute pancreatitis. In necrotising pancreatitis, timing of intervention was also studied. As a post-hoc analysis we studied correlation between BISAP score and Computed Tomography severity Index (CTSI) with likelihood of interventions and outcome / mortality.

Of the 148 patients, 68% were of alcoholic pancreatitis, which is the usual pattern of distribution in our population. CT scans were performed in 110. Rest were mild pancreatitis, in whom no imaging was done. As per the APACHE II scores, 7% patients had severe pancreatitis and 16.07% (16/110) had CTSI between 7-10. Majority of the patients belonged to the category of moderately severe pancreatitis as described by Vege *et al*. [8]. The loco-regional complications seen were as follows: Acute fluid collection- 33, Pseudocyst– 18, Necrosis - 20, Portal vein / Splenic vein / Superior mesenteric vein thrombosis - 3, Splenic artery pseudoaneurysm – 2.

Despite the same initial conservative management, 31 patients [20.66%] required interventions. The first intervention was radiological or endoscopic in 2/3rd of the patients. Endoscopic Retrograde Cholangio-Pancreaticography (ERCP) with Common bile duct (CBD) stenting was done for 7 cases of gall stone induced pancreatitis. One patient required splenic artery embolization. Two patients underwent PD stenting.

Ultrasound or CT guided pig tailing of collections / liquefied necrosis / infected pseudo cysts were done in 11 patients. In case of necrotising pancreatitis (6/11), this was done at an average of 10 days from the onset of symptoms. The idea behind image guided drainage is to tide over the crisis by letting out the infected material and to buy time to let the necrosis get walled off or to improve the general condition of the patient. Five out of these 6 patients required necrosectomy as second intervention later on during their course of illness in view of infection, clinical deterioration or persistent unwellness. These surgical interventions were done on an average 23 days after the onset of symptoms. Thus radiological interventions early in the course of multimodality management helped to delay surgical interventions till the fourth week when they can be performed more safely.

Surgical necrosectomy was performed as the primary intervention in 4 patients. This was performed at an average of 15 days from onset of symptoms. These were the patients in whom surgery was performed in view of clinical deterioration when image guided interventions could not be done due to unavailability of window, diffuse necrosis without localization or, lack of resources.

Laparoscopic or open Cysto-gastrostomy or cysto-jejunostomy as the first intervention was performed in 6 patients. Four of these were for walled off necrosis (WON), who had withstood the initial acute inflammation phase without any interventions and were offered surgical internal drainage procedures for indications like pain or gastric compression. In this group of patients, the surgery was performed at an average of 70 days after the attack of acute pancreatitis.

Nine of the 31 patients (30%) required a second intervention. These were in the form of surgical necrosectomy (N=5), pigtailing of intra-abdominal collection (N=2), Splenic artery embolization for pseudo-aneurysm (N=1) and pancreatic ductal stenting (N=1)

Various minimal access techniques to deal with pancreatic necrosis are described. Some of these include percutaneous, large-bore catheters placed via image guidance [9], percutaneous laparoscopic necrosectomy [10], and small incision, focused operative necrosectomy [11]. These techniques are directed towards achieving limited access to the area of necrosis to allow drainage and debridement. Peroral, endoscopic, transmural access offers another minimal access approach for accessing the area of necrosis for drainage/debridement in selected patients. However, systematic review of publications reveals that the methodological quality of the available papers is limited and most of the patients subjected to this procedure are only moderately ill [12]. Also these procedures are recommended to be performed

at specialized centers [13]. At our center we have not used this approach. The step-up approach has been described by Santvoort *et al*. [14], which helps to access the necrotic cavity by minimally invasive means. The concept is to buy time by draining infected collection, to improve the general condition of the patient and allow the necrotic tissue to get "walled-off". The application of the step- up approach is limited because retroperitoneal access is not possible in all patients [15]. Though we prefer the retroperitoneal route to access the necrosis, in this series, we did not find any patient suitable for the same. However, using the same concept, percutaneous drainage of infected necrosis through available window on the anterior abdominal wall followed by a focused operative necrosectomy when necessary was done in 5 cases. Presence of the percutaneous catheter helps to have smaller incisions and allows easier access to the necrotic sac on opening the abdomen. Open Surgical Necrosectomy continues to be the gold standard in managing necrotizing pancreatitis requiring surgery [16]. Mean day of primary intervention in our patients of necrotizing pancreatitis was 21.23 days. It is recommended to delay the necrosectomy at least to the third week. However, infected necrosis is one indication where early laparotomy may be required [17]. It is a clinical challenge to balance the right time to intervene before the patient becomes too sick to undergo surgery.

Thus each patient warrants an individually tailored management strategy utilizing various radiological, endoscopic and surgical interventions [18]. The approach chosen also depends upon the general condition of the patient, the local morphological conditions in the individual patient and local expertise available. Outcomes have improved with multidisciplinary management and prudent use of minimal invasive techniques [19].

There was a statistically significant difference in the need for intervention between the patients with CTSI 0-6 compared to those with CTSI 7-10. (13.8% *vs.* 44.4%; P<0.0001). This was also true about need for a second intervention between these groups. There was no significant co-relation between BISAP score and need for intervention or re-intervention. Mortality rate was 6.67% (N=10). Patients with a BISAP score between 3-5 had a significantly higher mortality compared to those with a score of 0-2. (71.4% *vs.* 3.54%; P<0.0001) A similar correlation was not found between CTSI and mortality.

Eight out of the ten deaths occurred within the first 6 days after admission. They were due to irreversible organ failures in the early phase of pancreatitis. With the current treatment guidelines, these patients are not subjected to empirical surgery. Thus, by default, these patients fall in the "No intervention" group. This probably explains how BISAP had a significant impact on mortality but not on intervention or reintervention.

Enteral Feeding in Acute Pancreatitis

Several clinical studies and meta-analysis regarding the effectiveness of enteral nutrition concluded that enteral nutrition is safe and can preserve the integrity of intestinal mucosa to decrease the incidence of infectious complications and other severe complications [20-22]. Hence enteral feeding has been incorporated as an important component of treatment of SAP [23]. Enteral route is more convenient in clinical practice and can be applied early in the management of severe acute pancreatitis. An appreciable improvement in the morbidity and mortality in patients of acute pancreatitis was seen when nasojejunal feeding was incorporated into the standard treatment protocol. In 2011 we carried out a project to determine the average timing of institution of nasojejunal feeds in patients of AP in our setup which is a tertiary referral center. Study was conducted in compliance with the protocol and regulatory requirements. This was an open label, observational longitudinal study. Approval of Institutional review board was taken prior to initiation of study. The Study cohort included all patients admitted with a diagnosis of acute pancreatitis between Jan 2011 to May 2011 in the surgical unit. The primary objective was a: to determine the average time interval from hospitalization to recovery from ileus and b: Average time interval for actual implementation of nasojejunal feeds after hospitalization. The secondary objective was to find the rate of successful institution of enteral nutrition by nasojejunal route. Patients requiring ventilator support (N=5) and those who left the hospital against medical advice (N=4) were excluded. Of the 70 patients enrolled, data of 61 was included for analysis. Average APACHE score was 6.77 and average CTSI was 7.22. Morphologically severe cases were more as compared to the ones with physiologic severity. The average time for actual institution of feeds was 4.6days.Nasojejunal feeding could be successfully implemented in 87% (52/61) of patients. These findings were presented at the Annual Conference of American College of Clinical Pharmacalogy at Chicago in September 2011. The limitation was that patients with very high APACHE scores were excluded from analysis.

Various studies and meta-analysis now point towards benefits of instituting enteral feeds early within 48 hours as compared to the standard practice of starting at 72 hours [24, 25]. There are also studies promoting nasogastric feeding as well as early low fat oral feeding in these patients [26, 27]. These are areas of further investigation. Issues of pancreatic stimulation due to gastric feeds and possibility vomiting and aspiration need to be studied in a randomised fashion with large number of patients.

Vasospasm in Early Pancreatitis: A Reversible Phenomenon?

Necrotizing pancreatitis continues to remain a severe disease with reported mortality from 13-35% [28]. Various theories about its etiology have been proposed over the years. Presence of vasospasm has been documented in experimental and clinical studies [29, 30]. Perfusion computerised tomography (CT) has been used as late as in 2012 for stratification of patients at the time of admission [31].

It has been well established that this pancreatic hypoperfusion leads to inflammation and sets a vicious

cycle. However, degree of reversibility of this vasospasm, if any, and its clinical implications have not been tested. We carried out a small observational study in which all CT scans performed between January 2007 and June 2007 reporting a diagnosis of "acute necrotizing pancreatitis" were reviewed. Clinical charts of these patients were reviewed. 58 consecutive CT scans with a diagnosis of acute pancreatitis performed from January 2007 to June 2007 were studied and 28 out of these in whom the timing of the scan was within 48 hours of the onset of symptoms, were included for analysis. The CT severity index (CTSI) was more than 7 in 25 out of 28 patients. Twenty three patients had >50% necrosis of the gland and of these, in 20, the percentage necrosis was >80%. All patients had received standardized treatment protocol which consisted of oxygenation, fluid infusion, antibiotics in presence of SIRS, early enteral nutrition and other supportive treatment. Incidence of early organ failure was 2/28 (one renal and one respiratory failure). Surgical intervention was done in 1 patient. Average hospitalization was 12 days with a range of 6-31 days. Mortality in the early phase was 7% (2/28). One patient was readmitted after 3 weeks with local septic complications and died. The overall mortality was 11%, which was much less than the reported mortality in severe necrotising pancreatitis at that time.

In 7 patients, follow-up scans performed were available for review. In 6, there was partial or complete recovery of the enhancement pattern of the gland and also in the peripancreatic changes. However, this number was too small to apply any tests of significance. The limitations of the study were its retrospective nature and the small number. Based on these findings we postulated that the vasospasm responsible for early clinical and CT features in ANP may be reversible within a critical time frame. Treatment instituted in this "critical ischemia time" or the golden hours [32], might help to limit the ischemic insult to the pancreas thereby reducing the severity and limiting the course of illness. The findings were presented at the World Congress of International Hepato –Pancreatobiliary Association at Mumbai, February 2008. The importance of early management and fluid resuscitation is currently one of the thrust areas in pancreas related studies. This is likely to cause improvement of pancreatic perfusion [33].

Additional research could try to study in a prospective manner whether this vasospasm is reversible, to what extent, what are the cut offs of institution of treatment and whether the continued hypoperfusion is related to more incidence of infected necrosis [34].

Parenchymal Pancreatitis *vs.* Ductal Pancreatitis

While studying CT scans of patients under treatment for AP it appears that in the spectrum of severe acute pancreatitis, there are certain patients with limited parenchymal necrosis but more fluid collections and visible pancreatic duct in at least one of the segments of the pancreas. There is also an impression that these patients behaved in a different manner than those with significant parenchymal necrosis.In 2007, we reviewed retrospectively charts of 170 patients with moderate and severe acute pancreatitis for history, examination findings, clinical course in the ward, treatment given and outcome. Their CT scans were evaluated for various pancreatic parenchymal, ductal and peripancreatic changes. The clinical course of patients with visible pancreatic duct (Group B) was compared with those where pancreatic duct was not appreciated at all (Group A).

When the two groups were compared, we found that in the patient group with visible pancreatic duct (N=56), more patients were alcoholics (80% *vs.* 65%), rate of organ failure was less (5% *vs.* 8%), surgical intervention was required less frequently (12% *vs.* 18%) and was in the form of drainage of collections rather than necrosectomy or debridement (7/56 *vs.* 20/114). Pigtail drains were put in 15/56 patients as compared to 10/114 in the other group. Transpapillary pancreatic ductal stenting was offered to 9 patients in this group. Overall mortality was 10% *vs.* 16% and postsurgical mortality was 14% (1/7) as compared to 47% (9/20).

Thus, we found that in the study group, the percentage of gland involved in necrosis was less and there was more incidence of pigtail drains inserted as well as PD stenting for ductal disruptions. The surgical procedure was drainage of collections with few needing debridement of necrosis. The mortality in this group was also less. These findings were presented at the annual conference of the Maharashtra State Chapter of Association of Surgeons of India in January 2008 in the best paper session under the heading "Ductal fullness in acute pancreatitis: A pointer to better outcome?" It was summarily rejected by the local surgeons for 2 reasons: 1, it was a retrospective study with possibility of bias in data interpretation and 2, the speculation that the pancreatic duct can be damaged in acute pancreatitis and that it would mean a better outcome was too wild. The major limitation as we see now is that the study design and statistical analysis should have been more robust. We were dealing with the study of early pancreatic ductal involvement in AP but were unable to study the hypothesis in a more scientific manner. Also, the group with more glandular necrosis should be followed up over a longer term to find out how many of these patients eventually had ductal involvement or total disconnection syndrome.

The concept of ductal necrosis early in the course of pancreatitis with development of partial or complete ductal disruptions and intrapancreatic collections had been rarely discussed till then [35, 36]. Increasingly, more papers studying the problem of disconnected pancreatic duct syndrome (DPDS) are being published [37, 38].

Specific criteria have been proposed for diagnosing a DPDS [35]. It may be beneficial if patients with ductal involvement are identified early. Whether this will allow early endoscopic treatment and prevent the recurrent admissions as well as pancreatic atrophy will be area of further research. Multidisciplinary treatment is recommended for all such patients [39]. We are currently

prospectively testing the hypothesis that multiple fluid collections with ductal visualization are associated with higher incidence of ductal disruption. It would not be ethical to subject the patients to ERCP for diagnosing ductal involvement. Further questions that need to be answered are: 1. Incidence of ductal involvement in Severe AP. 2. How to identify these patients early? 3. In whom is the disruption likely to persist leading to stricture of PD or internal fistulae and 4. Frequency of complete disconnection requiring surgical intervention.

Studies to determine incidence of intraabdominal hypertension and abdominal compartment syndrome in acute pancreatitis could not be completed due to very small numbers and very low incidence of ACS in pancreatitis during the defined study period. Larger multicentre studies will be required to address this issue and also to understand whether prophylactic abdominal fasciotomy will prevent necrosis or infected necrosis in patients of ACS in AP.

Long-term consequences of walled off necrosis, sequelae of necrotising pancreatitis and quality of life studies in survivors of severe acute pancreatitis are other areas of interest for research.

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Conflict of interest

The authors have no conflict of interest to declare

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