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REVIEW: ENTERAL NUTRITION IN ACUTE PANCREATITIS

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ABSTRACT

The incidence of acute pancreatitis has been increasing in the world every year. Despite improvement in proper care and modern equipped technology, interventions & imaging there is still significant morbidity and mortality of it. Acute pancreatitis is related with systemic and metabolic disorders due to release of hydrolytic enzymes, toxins and cytokines and may result in multiple organ failure. Damage to gut barrier in early phase of acute pancreatitis leads to systemic inflammatory response syndrome (SIRS), sepsis and infected pancreatic necrosis. So, it is important to keep motility of intestine. Enteral nutrition has found to be better results in stimulation of intestinal motility and preserve gut mucosal integrity by reducing bacterial overgrowth. During early phase of acute pancreatitis surgery is usually not done unless if there is any complication like necrosis and abscess so almost all of the cases are under supportive care. Thus, nutrition support becomes an important part in patients care. We are reviewing some impressive effects of enteral feeding nutrition in recent studies.

KEYWORDS: Acute pancreatitis; nutrition; enteral; nasogastric feeding; pancreatitis.

INTRODUCTION

Acute pancreatitis is an inflammatory process of pancreas gland that can lead to fatal condition. It can ranges from mild to self limiting and severe form. Most of the cases are mild and self limiting who recovers without any complications. However about 25% of patient progress to develop severe acute pancreatitis that consequences as multi organ failure, local and systemic complications requiring high care and long hospital stay.[1] Severity of pancreatitis specially in SAP patients are related with systemic inflammatory response syndrome (SIRS) leading to multiple organ failure and finally to death. The vast majority of patients for acute pancreatitis are increasing day by day in hospitalizations. Gallstones and binge alcohol consumption still lies the most common cause for acute pancreatitis till date.[2] Acute pancreatitis is highly metabolic disease process that can lead to severe catabolic stress & immune compromise to malnourished.[3] It is believed that acute pancreatitis is caused due to trigger of inappropriate activation of pancreatic enzymes due to changes in intra acinar cells. This leads to auto digestion of cells and damage of cells following trypsin enzyme activation.[1] Small gallstone or sludge of bile can obstruct to ampulla of vater as a result there is a common channel between bile duct and pancreatic duct and bile reflux causes damage to the parenchyma of pancreas. Heavy alcohol intake can cause direct injury to the parenchyma of pancreas by reflux into the duct following vomiting. Nutritional support plays a vital role for patients with acute pancreatitis to counteract with this problem as soon as resuscitation is established. Early diagnosis, aggressive management and nutrition therapy is most essential to decrease morbidity and mortality of acute pancreatitis in hospital settings.

The incidence of AP has been increasing since last couple of decades. AP has been third most disease among gastrointestinal diseases that is responsible for admission in Unites States of America hospitals inpatient costing around 2.6 billion dollar annually.[4] The occurrence of AP has been increasing speedily in western countries which also increases the emergency department visits and inpatient rate simultaneously.[5] A lot of wealth and time is spend on the treatment of AP because as it require proper monitoring and may require intensive care according to severity of progression of the disease. The main burden for this stands are gallstone and alcohol abuse. It is said that gallstone is one of the most common risk factor for causing AP as obesity is also increasing. And obesity is regarded as one of the causative factor of gallstone. It is hypothesized that anatomic variations (Pancreas divisum and annular pancreas) leads to pressure in pancreatic duct and causes AP.[6] Endoscopic retrograde cholangiopancreatography (ERCP) procedure used during the intervention for common bile duct stone and exploration of pancreatic duct can cause mild AP due to multiple cannulation and stimulation of pancreatic duct.[7] About 2% of AP is also caused by effects of some drugs like sulfonamides, metronidazole, erythromycin, azathoprine etc.[8]

Diagnosis & classification of acute pancreatitis

The diagnosis of acute pancreatitis is done if criteria meet any two of the following. Firstly, sudden onset of severe epigastric pain often radiating towards back; secondly if serum lipase or serum amylase is three times higher than normal upper limit and lastly characteristic findings of computed tomography(CT) or magnetic resonance imaging(MRI).[1] Severe abdominal pain is the most prevalent symptom of acute pancreatitis that is seen with the AP and the pain may be associated with nausea and vomiting. The patient usually leans forward during the onset of the pain to get relief from it. Amylase and lipase are two laboratory tests generally used to detect AP. Amylase is very sensitive test in AP however, its half life is only 10 hours and it can also rise in other pathological conditions. So, it is necessary to do lipase test too and it is more specific test for AP. A threefold or higher level of normal value of both tests usually confirms the diagnosis. Contrast enhanced CT is usually done to evaluate the parenchyma of pancreas and collection of fluid near pancreas. It is also done to exclude other pathological diagnosis like perforation during the earlier stage of AP. MRI is only done after few days or weeks of onset of the disease in order to detect extent of necrosis, amount of free fluid collection in pancreas when complications arise. However, these imaging tests are expensive and only done in earlier stage incase if diagnosis is not satisfied with clinically and laboratory test.

Revised Atlanta Classification in the year 2012 classified acute pancreatitis on the presence of local complications and organ failure as mild, moderate and severe acute pancreatitis. Mild acute pancreatitis(MAP) is usually self limiting and not associated with distant organ failure and local complications.[9] MAP carries less than 1% mortality rate and majority of the patients about 80% to 85% patients belong to it. Moderately severe acute pancreatitis (MSAP) is associated with transient organ failure that resolves within 48 hours. While severe acute pancreatitis (SAP) is persistent organ failure lasting more than 48 hours and having high mortality rate 4% and even goes to higher 10% if patient develops pancreatic necrosis.

Here, local complications implies AP patients having any of the complications like acute necrotic collection, pancreatic pseudocyst, acute peripancreatic fluid collection and walled off necrosis.[10] Whereas, organ failure has been defined on the basis modified Marshall scoring system that consists of failure of at least two systems such as respiratory failure if $PaO_2/FiO_2 \leq 300$, cardiovascular systolic blood pressure falls below 90 mmHg and if serum creatinine ≥170mmol/L effecting renal system.[11]

Management of AP

Patients with mild AP are usually managed conservatively, can be admitted in ward providing adequate fluids and analgesics and invasive monitoring. Aggressive fluid management should be done according to age, associated co-morbidities and urine output. Patients having comorbidities of cardiac, renal and pleural need close monitoring and foley's catheterization. Patients suffering from SAP must be admitted in intensive care with proper monitoring of vitals, input of fluids and output charting of urine. Hypoxemia may be seen in AP patients due to circulating mediators effecting in pulmonary changes. Patient can require supplementary oxygen and saturation of oxygen monitoring to maintain more than 95% of oxygen saturation. Antibiotics can be administrated if there is source of infection like necrosis and abscess. As progression of disease and development of its complications, surgical intervention like necrosectomy, peripancreatic fluid drain and drainage of abscess can be required.[12] Nutrition is very important for AP patients as the metabolism is very high and the requirement of calorie is high. Patient can be kept in rest by not feeding the patient for some brief period in onset of mild AP as it is self limiting and can be resolve early. But in case of SAP patients there are complications associated like pancreatic necrosis, abscess formation which can deteriorate the patient and makes patient weaker. Nutrition plays vital role in prevention from secondary infections of necrosis and helps to improve the prognosis of the patient by providing immunity. There are many ways of providing nutrition like oral feeding, nasogastric feeding, nasojejunal feeding, total parenteral feeding. There should be proper timing and route to provide nutrition in AP so that it will not hamper the patient in terms of pain, infection and outcome. Oral feeding is not possible as pain is aroused after intake of food. In such condition enteral nutrition or total parenteral nutrition is required. Enteral nutrition has shown its better effect in reducing the complications.

Enteral nutrition

Traditionally, it was found that nutritional support was not applied for the management of acute pancreatitis instead patients were kept in nil per os (NPO) in intention to keep bowl and pancreas both in rest. Also, enteral nutrition(EN) was not practiced usually due to thinking that it would lead to bad prognosis by stimulating exocrine pancreatic secretion developing an autolytic processes of the pancreas and surrounding soft tissues.[13] The concept of keeping pancreas has been now out dated. Bowel at rest is more prone for intestinal mucosal atrophy that results in infection from translocation of bacteria in gut. With the early progression of SAP, the intestinal barrier is damaged and permeability is increased which helps in transportation of inflammatory mediators and cytokines. Recently, there is substantial experimental evidence proving that nutrition therapy helps to reduce metabolic response to stress, prevent oxidative cellular injury and helps in modulating immune responses.[14] One of the reason for development of sepsis in SAP may be the result of bacterial translocation from the gastrointestinal tract through increased intestinal permeability.[15] The gut bacteria can pass to the systemic circulation that may result in sepsis

and transmit to the necroses tissues of pancreas to form pancreatic abscess. It is also said that pancreatic necrosis infection is initiated by bacterial translocation from the gut, altered intestinal motility and increased mucosal permeability.[16] To maintain gut bacteria, natural environment is very essential to prevent patient from undergoing sepsis and poor outcomes. Bacterial translocation increase can progress to the systemic inflammatory response and may develop further infection such as pancreatic necrosis.[17] In pancreatic necrosis conditions protein loss is also present so, requirement of calorie is very high in patient. If nutrition supply is insufficient then the patient become more cachectic, lacks in immunity and prone for more bacterial infections. One of the five systemic review and meta-analysis compared with EN and PN in SAP patients demonstrated that EN is beneficial in reducing infection and decrease in mortality.[18] The mortality of patients suffered with pancreatic necrosis is >30% and it may rise to 100% if it is associated with multiple organ failure in non operative management cases. Patient suffered with pancreatic necrosis with complication must need to undergo surgical intervention for better outcome. The management of pancreatic necrosis has seen better effect by doing surgery and the mortality falls below 30% whereas keeping the patient conservatively has high mortality.[19] Enteral nutrition plays great role in postoperative patients. Enteral nutrition helps to maintain IEC(intestinal epithelial cells) derived cytokine secretion that preserves intestinal mucosal functions as well as functions of lymphocytes and potentially alleviating subsequent bacterial translocation.[20] Thus, EN has good effect of immunity in intestinal mucosa that overcomes with the starving patients. Whereas, parenteral nutrition(PN) lacks motility of the gut that results in stagnant bowel contents which may cause atrophy and increased permeability of the gut mucosa and changes in intestinal microflora.[21] A metaanalysis done by Fengming Yi et al involving eight RCTs have showed that EN plays an important part in less infection complications(p= 0.004), lower mortality (p = 0.001) and reduction in multi organ failure (p = 0.02) in acute pancreatitis.[22] EN has been found to be superior while comparing with PN. Recent meta-analysis done by Yao and et al consist of five studies including 348 patients demonstrated that EN has been more effective in critically ill patients with SAP in decreasing overall mortality(p=0.001) and reducing in multi organ failure(p=0.003) compared with PN.[23] As SAP is responsible for high morbidity and mortality, EN has better effect on SAP patients to attain immunity and to minimize mortality. So, EN has been preferred and recommended route of nutrition for SAP. However, If patient is not tolerable and not meeting adequate nutritional goals by enteral feed then it is advised to start parental nutrition, while slow rate of enteral feeds can also be supplied side by as well.[24] Furthermore, Patients with AP who were under PN were more prone for developing prediabetes or diabetes mellitus after discharge from hospital but early enteral nutrition(EEN) compared with parenteral nutrition showed significantly reduced incidence in hyperglycemia and improvement in blood glucose control.[25]

Route of enteral feeding

As we have seen EN was found to be more superior to PN. There are different route of supplying EN. Nasojejunal enteral nutrition and nasogastric enteral nutrition is common route of supplying nutrition for EN. In past couple of decades nasojejunal enteral nutrition (NJ EN) was more preferred rather than nasogastric enteral nutrition (NG EN) due to concept that proximal feeding would result in secretion of more pancreatic enzymes and leads to severe pancreatitis. However, recent multiple randomized controlled trials have been predicted that nasogastric(NG) feeding has been safe, well tolerated and a better alternative to nasoduodenal or nasojejunal(NJ) routes for AP patients.[26] Previously, it was found that nasogastric or nasoduodenal can leads to aspiration pneumonitis as well as increase in pain but nasojejunal don't used to have such complications. But a review article had also shown that NG route had been as effective as NJ route feeding and no significant difference in aspects of mortality, tracheal aspiration, and exacerbation of pain.[27] In one of the study done by Singh and et al comparing NG with NJ in randomized seventy eight patients admitted in hospital for infectious complications evaluations were found that 23.1% patients got various infections by NG whereas 35.9% patients were infected by NJ. Similary in another study three RCTs comparing with NJ feeding, NG feeding was found to be non inferior to NJ feeding and also both routes were regarded for their feasibility and safety.[28, 29] Although NG feeding has been found to be more efficacious in severe acute pancreatitis but vomiting and diarrhea has been seen most of its side effects associated with it.[30] There is also some findings had shown that early enteral nutrition has also shown paralytic ileus in some SAP patients.[31] To verify it, there should be trials studied in large sample of population. It was also found that if NJ tube placed further into the loop of jejunum showed recovery of acute necrotic fluid collection and improvement in further progression of jaundice with gastric outlet obstructions.[32] But one study demonstrated that only 15% of NJ feeding tubes pass spontaneously through pylorus that's why NJ tube insertion are more difficult to insert and usually done by expert in endoscopic or under radiographic screening.[33] Additionally,it may be difficult for critically ill patients to transfer from one place to another for intervention. In such conditions in chronic patients nasogastric tube insertion is feasible and beneficial to perform bedside. Furthermore, nasojejunal costs more expensive to perform radiological intervention, endoscopy and also time consumptive. Many published guidelines suggested that EN should be primary therapy for patients suffering from SAP. However, one meta-analysis study demonstrated that EN is not only efficient in SAP but also in mild and moderate acute pancreatitis compared with NPO.[34] Nasogastric feeding was also seen to be

benefited compared with NPO regime in case of length of hospital stay, days with pain, need of opiates and risk for oral food intolerance.[35] As the period of hospitalization is reduced and medicine like opiates is decreased in amount then there will be fewer expenses to bear from patient which is economically beneficial for family members too. It was found that NJ feeding still stimulates the pancreas by hormonal pathways through blood and cholinergic enteropancreatic refluxes even if it is supplied with elemental nutrition.[36] NG feeding has been beneficial and well tolerated in majority of patients with SAP and advised as first line of management but if failed then rapid change to NJ route can be replaced.[37] American College of Gastroenterology Guideline recommended that oral feeding including low fat solid diet is safe and should be started as soon as possible if patient tolerable in case of mild AP whereas, in SAP patients its is recommended that nutrition provided should be EN through nasogastric feeding and PN should be avoided as it is associated with various infectious complications.[38]

Timing of enteral feeding

Compared with PN, Enteral nutrition either early or delayed were shown to be reduced risk of pancreatic infection, mortality, organ failure, hyperglycemia and catheter related infection according to the recent pooled analysis of twelve RCTs in a meta-analysis.[39] As EN has been found superior to parenteral nutrition as from above, but there is still controversy in appropriate timing to feed. Various authors have demonstrated their views regarding early enteral nutrition(EEN) that is feeding given within 48 hours and delayed enteral nutrition feeding after 48 hours. Some non randomized studies done in acute pancreatitis had shown that enteric feeding within 48 hours after admission were found to be decreased rate of major infections and even mortality.[16] Early EN in SAP patients helps in modulating excessive immunity that is needed in early phase of SAP which decreases pancreatic infection, ICU stay duration in hospitals, and maintains SIRS. The patients receiving delayed EN after 48 hours or more after 7 days of admission has found they had difference in immune function like CD4 cells, T lymphocytes percentage and CRP values than the patients who receive early EN in SAP patients.[20] Furthermore, recent meta-analysis done in 12 randomized controlled trials have patients receiving early EN within 24 hours revealed significant decreased in mortality and reduced in intensity and duration of abdominal pain, hyperglycemia and catheter related infections compared to delayed EN and PN.[39] Additionally, a meta-analysis study done in eight randomized controlled trials in patients having early nutrition within 24 hours feeding of EN found to have decreased odds ratio of developing organ failure.[40] Patients of SAP are critically ill patients lacking immunity in such patients it would be better to provide nutrition management as soon as possible after the onset of the symptoms. Early enteral feeding had also shown that deduction of costs and shorter length during hospital stay.[41] American gastroenterological association(AGA) highly recommended that it's better to start early enteral feeding usually within 24 hours if tolerated rather than keeping the patient in NPO.[42] In studies including 11 RCTs analysis where early feeding done <48 hours and delayed feeding >48 hours results were found that length of stay in adults hospitalization in mild or moderate acute pancreatitis were remarkably reduced in early feeding compared with delayed feeding.[43] Additionally, limited studies suggested length of hospital stay were reduced in mild and moderate acute pancreatitis among early feeding patients.[44] In another prospective randomized control trial done among visceral fat obesity and non visceral fat obesity providing early enteral nutrition and delayed enteral nutrition(>48 hours of admission) in MSAP and SAP patients. They have shown that early EN prevented visceral fat obesity patients from further developing pancreatic necrotic infection and deteriorating patients.[45] As the Japanese guidelines recommended early enteral nutrition for SAP within 2 days of admission, however in multivariate analysis done in high age >70 years old with pancreatic localized infection had significantly improved mortality if EN given within 4 days.[46] In one of the metanalysis done by song and et al including ten RCTs containing 1051 patients comparing early EN(<48 hours after admission) to late EN or total PN in SAP or predicted SAP have demonstrated that early EN is significantly reduced the mortality, multiple organ failure, operative intervention, local septic complication, systemic infection compared with late EN or PN.[47] One of the prospective cohort study of 104 eligible acute pancreatitis has shown that EN feeding started within 3 days resulted in significantly reduction in secondary risk infection including infected pancreatic necrosis, extrapancreatic infection and also better progress in acute gastrointestinal injury(AGI) rating and serum albumin level than those who receiving late EN.[48] Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) suggested that to provide oral diet as tolerated to mild acute pancreatitis rather than providing any specialized nutrition therapy but if failure of oral diet within 7 days of admission seen or any unexpected complication develops then better to consider any specialized nutrition.[14] So, it is preferred to initiate early enteral nutrition as soon as possible preferably in the first 24 to 48 hours after the onset of pancreatitis.[18, 49] Additionally, in EEN(<48 hrs) was related with reduced risk of multiple organ failure and found preventive to intra-abdominal hypertension in SAP patients.[50, 51] It has been said that the first 48 to 72 hours period so called therapeutic window period that is after the onset of acute pancreatitis is the favorable period of prevention & attenuation of the inflammatory response and applying treatment modalities.[52]

Enteral feeding supplements

As enteral nutrition has been superior to parenteral nutrition, immune enhanced enteral formulations may influence for further better effect of intraluminal therapy

in acute pancreatitis.[53] There are various enteral nutrition formulations available for acute pancreatitis. Some formulations are categorized as polymeric formulations that contain intact proteins, complex carbohydrates and long chain triglycerides of fats. Another one is elemental formulations that constituents free fatty acids, aminoacids and chains of carbohydrates. Elemental diet formulas are available in liquid form nutrients that are easily dissolvable. These diets provide protein in form of amino acids and tryglycerides as fatty acids form. Such formulations are helpful for digestion, absorption and motility in intestine. There is also semi-elemental formulations which contain medium chain triglycerides of fat and peptides of varying chain length. It is said that semi-elemental diet are more used as it is better absorbed and palatable than other formulations but it is cost effective than others. Despite of expensive price, many clinicians still use elemental and semi-elemental formulations in AP in belief that stimulation of pancreas is minimal. In one of the randomized prospective study done by Tiengou et al by comparing with semi elemental formula with polymeric formula in 15 patients with SAP. Both formulations were provided for seven days and the progress were seen that semi elemental had better effect in significantly shorter hospitalization duration (p=0.006), significant less weight loss in patients (p=0.001) and reduced risk of infection.[54] Though both formulations were tolerable in SAP patients however large number of clinical trials need for more specific. There are some other micronutrients which effects in inflammation, immune response and white blood cell recruitment of acute pancreatitis those immunonutritions are omega 3 fatty acids, glutamine and arginine, probiotics and so on.[55] In recent meta analysis shown that immune nutrients like glutamine and omega 3 had better results by reducing risk of infectious complications and mortality if used in parenteral nutrients.[56] Semi elemental diets are widely used because they are better absorbed and tolerated in patients with malabsorptive conditions and palatable than conventional elemental formulations.[57] Study done in twenty six RCTs showed that semi elemental EN had significant effect in reduction of motality(P=0.002), few in organ failure(p<0.00001) and decrease in local septic complications(p<0.00001) but polymeric and fibre enriched formulas showed no any significant effect.[58] However, a recent study demonstrated that a higher incidence of Chylous ascites shown in those patients who were started on polymeric feeds.[59] The intestinal micro biota plays a vital role in circulation of infections in SAP condition. So, to make intestinal microbes powerful and stop transmitting infections, probiotics and prebiotics can be helpful. Probiotics are exogenous microbes which favors for host digestion physiology and metabolism while prebiotics are non digestable carbohydrates which are fermented by gut bacteria for their metabolism. It is hypothesized that both nutritions contribute to protect against pathogens in gut and maintain immune and metabolic homeostasis.[20] However, another recent study has suggested that use of multispecies probiotic with bifidobacterium therapy could be lethal if it is combined with proteolytics enzymes and may result in high risk of increased rate of fatal bowel ischemia and multi organ failure.[60] A recent systematic review and meta-analysis of six randomized controlled trials comprising 536 patients done by Gou and et al had demonstrated that probiotics had non beneficial effects on clinical outcomes in severe acute pancreatitis. The analysis for probiotic was not significantly effect in pancreatic infection rate(p=0.47) neither in hospital stay(p=0.35) nor in mortality(p=0.25).[61] A new study has recommended that enteral feeding through nasogastric tube using polymeric formula in SAP patients however; it has shown no beneficial in survival comparing with parenteral nutrition.[62] Additionally, they have also said that probiotic could be beneficial. Due to controversial findings furthermore qualitative study in large number of clinical trials are needed for better recommendation for nutrition supplements in enteral nutrition.

CONCLUSION

Considering above all, enteral nutrition is superior to parenteral nutrition. NG feeding is safe and clinically applicable in bedside. We commence NG feeding with semi elemental preparation but immuno nutrition is not recommended as supplement to enteral nutrition. NG feeding is also economically affordable and cheaper than PN feeding. We also recommended that oral diet should be given if patient can tolerate, if not then NG tube feeding should be started within 48 hours of admission. Enteral nutrition has better effect in maintaining gut barrier function so the purpose of commencement of feeding shouldn't be delayed specially in SAP patients. Lastly, enteral nutrition is feasible and generally well tolerated and has been shown more effective than parenteral nutrition.

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