Acute pancreatitis caused by hypertriglyceridemia : Role of heparin and insulin in treatment.

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Abstract

Acute pancreatitis is an inflammatory condition of the pancreas that is painful and at times deadly. Despite the great advances in critical care medicine over the past 20 years, the mortality rate of acute pancreatitis has remained at about 10%. The most common causes of acute pancreatitis are stones in the gallbladder and heavy alcohol consumption. There are several other causes of acute pancreatitis including, ingested medicines high triglyceride levels in the blood, infective causes, infiltrative, and neoplastic causes. Acute pancreatitis is confirmed by medical history, physical examination, and typically a blood test (amylase or lipase) for digestive enzymes of the pancreas. Blood amylase or lipase levels are typically elevated 3 times the normal level during acute pancreatitis. In some cases when the blood tests are not elevated and the diagnosis is still in question, abdominal imaging, such as a Computed Tomography (CT) scan, Magnetic Resonance Cholangiopancreatography (MRCP) might be performed. In most cases, acute pancreatitis resolves with therapy, but approximately 15% of patients develop severe disease. Severe acute pancreatitis can lead to life-threatening failure of multiple organs and to infection. Therefore, it is extremely important to seek medical attention if experiencing signs or symptoms of acute pancreatitis. Several clinical risk-scoring systems are available to help physicians predict who is most likely to develop severe acute pancreatitis. One of the primary therapies for acute pancreatitis is adequate early fluid resuscitation, especially within the first 24 hours of onset. Intravenous medications, typically potent narcotic pain medications, are effective in controlling pain associated with acute pancreatitis.

Nutrition should be implemented because acute pancreatitis is a highly active state of inflammation and injury that requires a lot of calories to support the healing process. In most cases, patients can start to take in food on their own by 48 hours. In addition to providing supportive care, underlying causes need to be promptly evaluated. If the acute pancreatitis is thought to be due togallstones, medication, high triglycerides, or high calcium levels within the patient's body (or other external causes), directed therapy can be implemented. In this case, patient had severe acute pancreatitis induced by high triglyceride levels, resultant initial respiratory depression and acute kidney insult. With establishment of supportive care in critical care setup, he was managed with specific treatment regime (heparin and insulin) as it was triglyceride induced acute pancreatitis.

Introduction

Clinical problem

A 29 years old morbidly obese (BMI 45), non smoker and teetotaller with newly diagnosed type 2 diabetes mellitus presented with generalised unwell, central abdominal pain for 3 days and short history of acute breathlessness. Clinically it was queried as acute pancreatitis and was proven by elevated amylase levels. Simultaneously his WBC was high with risen C-reactive protein count as well. Therefore, treated in ward setup as acute pancreatitis with SIRS [1].

During his ward stay he was deteriorated suddenly as he become hypoxic and tachypnoeic with arterial blood gases were showing worsening type 2 respiratory failure. He was followed by critical care outreach team with frequent seeking advices from critical care team. However, as his respiration was not improved, as well as he was in critical stage and required NIV, made him transfer to HDU. Initially he was given nasal high flow oxygen (optiflow) therapy. But, as his repiratory parameters were not improved to optiflow and anticipated possible mechanical ventilation as well as evidence of associated acute kidney injury with sepsis patient was transfer to ICU following day.

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Management

He was managed conservatively as severe acute pancreatitis, supported by multi disciplinary teams. Respiratory system support was given with BiPAP ventilation to overcome worsening type 2 respiratory failure and severe acidosis. Frequent physiotherapy, nebulisations, improved his respiratory compromise. There was a mild pleural effusion noted in radiological and was managed conservatively without any interventions.

Fluid resuscitation was carried out in targeting Mean Arterial Pressure (MAP) of more than 70 mmHg in invasive blood pressure monitoring and maintaining adequate urine output. Even he had marginal blood pressures on admission to level 3 care, without initiating any ionotropes maintained satisfactory MAP. Both kidneys were at risk on admission to HDU. He was quite dehydrated and marginal blood pressures with ongoing sepsis had drawn him on insult stage according to RIFLE criteria. However, good renal perfusion improved his kidney functions as well as urine output without going for any renal replacement treatments. His condition was frequently assessed according to Glasgow risk stratification. Nutrition was able to start with oral with 48 hrs of initial bowel resting and the dietician had a daily review on him for calorie adjustments accordingly. He was in severe abdominal pain on admission to HDU where Patient Controlled Analgesia (PCA) with morphine initiated as main analgesic modality.

DVT prophylaxis was with TEDs stockings and flowtrons (pneumatic calf compression device). Enoxaparin was not given on him as heparin infusion was initiated for definitive treatment of triglyceridemic induced pancreatitis.(discussed below) Intravenous Variable Rate of Soluble Insulin Infusion (VRII) started as he was known diabetic and high blood glucose levels. As initial CT didn't have any evidence of intra-abdominal or chest sepsis, antibiotics were not commenced. To rule out cause of acute pancreatitis USS abdomen was done to see Gall stones which was found no stones,and was proven by the initial CT scan as well.

His blood results had elevated triglyceride levels as high as 38.1 mmol/L on day of admission and repeat values. (Normal <1.7 mmol/L). Heparin bolus treatment of 18u/kg for 24 hours was given as 6 hourly with insulin VRII. Two days after initiating of heparin and insulin his triglyceride levels reduced markedly and it was around 5mmol/L after ten days of treatment. APTT and APTT ratio was monitored 4 hourly initially and then 8 hourly. To rule out any local complications second CT was done on fifth day of ICU stay, found as no evidence of pancreatic cysts, necrosis etc [2].

Discussion

Acute pancreatitis is characterized by upper abdominal pain and elevated levels of pancreatic enzymes in the blood. This is associated with varying degrees of endocrine and exocrine dysfunction.

The disease may be mild and self-limiting or may rapidly progress to multi-organ dysfunction (MODS) with or without sepsis, and ultimately to death. It is usually possible to establish a cause that is treatable.

Causes and pathogenesis

The pathogenesis of pancreatitis is not fully understood. There are numerous conditions known to cause pancreatitis. Gallstones and chronic alcohol abuse account for majority of cases. The mortality in the first two-week period is usually due to Systemic Inflammatory Response Syndrome (SIRS) and organ failure; thereafter it is usually due to sepsis and its complications. Advances in diagnostic and therapeutic interventions have lead to a decrease in mortality from acute pancreatitis, especially in those with severe, often necrotizing, pancreatitis.

Approximately 10 percent of chronic alcoholics develop attacks of clinically acute pancreatitis that are indistinguishable from other forms of acute pancreatitis. Alcohol may act by increasing the synthesis of enzymes by pancreatic acinar cells to synthesize the digestive and lysosomal enzymes that are thought to be responsible for acute pancreatitis. Causes such as hyperlipidaemia (often co-existing with alcoholism) and drug induced pancreatitis can usually be identified from the history, but the diagnosis should only made having carefully excluded biliary disease. Acute pancreatitis is an important cause of acute upper abdominal pain. Because its clinical features are similar to a number of other acute illnesses, it is difficult to base a diagnosis only on symptoms and signs. The disease varies in severity and the diagnosis is often missed [3].

Investigations and severity scoring systems

Acute pancreatitis can be suspected clinically, but requires biochemical and radiology tests to confirm the diagnosis. Clinical, biochemical and radiological features need to be considered together since none of them alone is diagnostic of acute pancreatitis. Most attacks of acute pancreatitis are mild, with recovery occurring within five to seven days. Death is unusual in such patients. In contrast, severe necrotizing pancreatitis is associated with a high rate of complications and significant mortality. Early detection of this high-risk group has led to the development of scoring systems to help identify those who will require a higher degree of intervention [4].

Biochemical tests

Pancreatic enzymes

Early in the acute phase of an attack, there is continued synthesis of pancreatic enzymes, but their exocrine secretion is obstructed. As a result these enzymes are released into the systemic circulation. Serum amylase rises within 6 –12 hours of an acute attack; and is rapidly cleared from the circulation. It is usually elevated for 3-5 days during an acute attack. It is also elevated in other conditions such as visceral perforation, so cannot be used alone in the diagnosis. Other enzymes are elevated but have no real advantage over amylase. They include serum lipase, urinary amylase.

CT Scan

Most important test for establishing diagnosis of pancreatitis, establishing severity and detecting complications. Patients should be scanned after 48 hrs, with oral and intravenous contrast. This enables an estimation of degree of unenhanced pancreatic necrosis.

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Severity Scoring Systems

A number of disease-specific scoring systems have been developed, but none are ideal. Examples of such systems are Ranson criteria, Glasgow system to predict severity of acute pancreatitis, CT Scan assessment of severity, Atlanta classification [5].

Clinical Management

The clinical management of Severe Acute Pancreatitis (SAP) relies on a number of key points:

- Early recognition of severe disease, which has a higher mortality.
- Fluid resuscitation and organ support with appropriate monitoring.
- Pain management.
- Removal of underlying predisposing cause
- Prevention and early recognition of complications.
- Nutrition.
- Novel Therapies.
- Surgical intervention where indicated.

Early recognition

In Early recognition, Gold standard first line investigation is USS abdomen, followed by CT

at least 72-96 hours after onset of symptoms. MRCP is only indicated in patients with abnormal LFTs and common bile duct dilatation that either progressively worsen or fail to settle, where a common bile duct stone is suspected. In our patient we did those investigations to find out the probable cause.

Fluid resuscitation and organ support with appropriate monitoring

In the absence of adequate fluid resuscitation and cardiovascular optimisation will result in tissue ischaemia and regional hypo-perfusion and end-organ damage. Invasive monitoring of the arterial and central venous pressures to guide fluid resuscitation is considered mandatory, if available. Fluid resuscitation is particularly important because it accumulate vast amounts of fluid in the injured pancreatic bed.

Respiratory

Regular measurement of oxygen saturations may enable early detection of pulmonary dysfunction.

Fluid accumulation within the pleural space with resultant lung compression, and respiratory distress syndrome are serious complications of pancreatitis. Acute pleural fluid collection, pancreatic-pleural fistula , and effusions may result from acute inflammation of the pancreas. Most often, pleural effusions spontaneously resolve.

In our patient also had respiratory compromise with evidence of hypoxia (low PaO2 in arterial blood gases) and hypercapnea. Initiating of BiPAP improved the oxygenation remarkably and settled the CO2 retention issue as well. His right sided pleural effusion was mild and it was settled spontaneously with improvement of clinical state.

Renal

Renal hypo perfusion and significant hypotension causes acute renal insult. Adequate fluid resuscitation, maintenance of renal perfusion and blood pressures, avoidance of nephrotoxix medication are the key points in protecting kidneys in such vulnerable patients.

In this patient also had acute kidney insult and supportive care as mentioned helped to recover kidneys without any further damage.

Pain management

Severe abdominal pain is the main symptom and adequate analgesia is essential. This can be provided by systemic opioids ,usually using Patient Controlled Analgesia – PCA, as we had in our patient.

Prevention and early recognition of complications

Complications of acute pancreatitis may result in local or systemic problems. The systemic problems are usually seen in acute, severe pancreatitis. These include pulmonary complications, such as pulmonary oedema and adult respiratory distress syndrome. Inflammatory changes from the pancreas may extend to the kidneys, stomach, colon and splenic vein. This may result in renal dysfunction, gastrointestinal bleeding, colitis and splenic vein thrombosis etc. The management of these complications is supportive.

Local complications include fluid collection, ascites , pancreatic pseudocyst, pancreatic necrosis, and infective pancreatic necrosis. These complications are twice as frequent in patients with alcoholic and biliary pancreatitis.

The most serious local complication is pancreatic infection, occurring in approximately 30% of patients with SAP. The role of systemic antibiotics remains controversial despite a large number of studies. Current practice is to give intravenous antibiotics with good pancreatic penetration [6]

Nutrition

Adequate nutrition is vital in the critically patient with severe disease. In SAP most patients have abdominal pain and ileus is common. There is a concern that enteral feeding may stimulate pancreatic secretion, therefore worsening auto-digestion. But current evidence and studies are revealing that enteral feeding is safe and may reduce complications. Initially, no nutrition is given to rest the pancreas and bowels during the first 24 to 48 hours. After 48 hours, a plan to provide nutrition should be implemented because acute pancreatitis is a highly active state of inflammation and injury that requires a lot of calories to support the healing process. In most cases, patients can start to take in food on their own by 48 hours. If this is not possible, then a feeding tube that is passed through the nose into the intestines can be used to provide nutrition. This method is safer than providing nutrition intravenously. There is no benefit to using probiotics for acute pancreatitis.

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Removal of underlying predisposing cause

With establishing all supportive therapy, we managed our patient in critical care setup. As causative factor for the acute pancreatitis in our patient was high Triglyceride related, have to initiate particular treatment with heparin and insulin.

Role of Heparin and insulin in Triglyceride related acute pancreatitis

Hypertri Glyceridemia (HTG) is not a common cause of Acute Pancreatitis (AP). Alcohol and gallstones are known common reasons for acute pancreatitis throughout the worldwide so far reported. Statistically incidents are as 1 – 4% of all cases of acute pancreatitis [7].

Hypertriglyceridemia is defined by fasting level of serum triglyceride as high as >150 mg/dL (1.7 mmol/L). Hypertriglyceridemia is classified as mild, moderate and severe depends on plasma levels. Levels range between 150 to 199 mg/dL (1.7 to 2.2 mmol/L) are indicated as mild, and 200 to 999 mg/dL, (2.3 to 11.2 mmol/L) as moderate, and severe when the levels are as 1000 to 1999 mg/dL, (11.2 to 22.4 mmol/L), and very severe Hypertriglyceridemia once levels exceeds >2000 mg/dL, (>22.4 mmol/L).

When the levels are as high as >1000 mg/dL (11.2 mmol/L) is considered as a risk for occurrence of pancreatitis [4]. Therefore, it is extremely important to have early diagnosis of Hypertri Glyceridemia-Associated Pancreatitis (HTGP) to provide and initiate the appropriate therapy and to prevent further episodes as well as known complications of acute pancreatitis.

Aetiology of Hypertriglyceridemia can be classified as follows:

- Primary causes are the Genetic causes
- Secondary causes known to be commoner than primary causes. Excessive weight gain associated with unhealthy diet habits is more common than other.

Presence of drugs such as exogenous estrogens, thiazides, beta blockers, propofol are the other common contributors. Use of parenteral lipid infusions commonly in ICU set up has higher tendency as well.

Diabetes, pregnancy, chronic renal failure, hypothyroidism known to be the medically related disease conditions causing it.

Hypertriglyceridemic pancreatitis : Pathophysiology

The actual mechanism lead to the development of Acute Pancreatitis (AP) due to elevated Tri Glycerides (TG) levels is not fully understood. But there are several theories to explain it. To precipitate an episode of pancreatitis it is thought to need a level greater than 1000 mg/dl. The exocrine pancreas participates in TG degradation. Pancreatic lipase, a digestive enzyme that secreted from pancreas, liberated in acute pancreatitis and in unregulated fashion cause the tissue breakdown. Free fatty acids begin to accumulate if the plasma TG level increases beyond the enzymatic capacity of the pancreas causing injury to acinar cells as well as the surrounding pancreatic tissues. Hyperviscosity due to chylomicronemia leads to alteration in pancreatic blood flow, creating a more acidic hence, creating more toxic environment to the surrounding tissue. With such tissue injury cause pancreatic inflammation further, and destruction of the whole pancreas at the end. Treating the precipitating cause is equally important along with the supportive treatment of acute pancreatitis, as well. Although there are no established guidelines for efficacy of heparin and insulin been used for acute reduction of triglyceride levels, there have been several case reports published to support as evidence.

On the contrary, it is beneficial to have a rapid decrease in triglyceride levels. Plasmapheresis has been performed in some patients to remove chylomicrons from the circulation, hence reduction of triglyceride levels. Disturbances in pancreatic microcirculation is associated with initiation of pancreatitis as well as progression of the condition. Multi organ dysfunction can be seen in acute setting which is mainly due to microcirculatory changes.

Heparin

In the management of elevated levels of triglycerides with the presence of hypertriglyceridemia - associated pancreatitis Heparin is an effective treatment option available. The enzyme which responsible to hydrolyze TG rich lipoproteins is known as, Lipoprotein Lipase (LPL), It is normally bound to capillary endothelium with a heparan sulfate proteoglycan chain. When heparin is administered as a bolus dose, LPL dissociate from the endothelium tissue binding sites, into the plasma as a heparan-LPL complex. This sudden rise of “free” LPL is then accelerating the rate of binding and metabolizing of lipoproteins, thus it cause lowering of the serum TG levels.

Initial rise in LPL levels normally happens, but peaking of activity is followed, after then, as the enzyme is transported and degraded in the liver LPL activity begins to wane. This heparin stimulated increase and then reduction in LPL activity can be minimized by the use of intermittent heparin dosing and results in an initial drop in serum TGs, but then followed by a gradual increase. This is seen more pronounced with the use of LMW heparin, than the un- fractionated heparin, but, studies have shown lowering severely risen TG in the scenario of a Hypertriglyceridemia, both preparations are equally capable.

Insulin

By enhancing lipoprotein lipase activity, serum triglyceride levels are lessens by insulin. Chylomicron and VLDL metabolism is enhanced by the presence of the enzyme Lipoprotein lipase to its immediate metabolites such as fatty free acids and glycerol. In adipocytes hormone- sensitive lipase is inhibited by the presence of insulin . this lipase is the main enzyme responsible for breaking down of triglycerides in adipocytes and releasing free fatty acids into the circulation [8].

Lessons learnt

With reviewing the literature and treating the patient with heparin and insulin remarkably lowed the triglyceride levels . Furthermore it is necessary to diagnose the cause for acute pancreatitis early as well.

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Conclusion

Acute pancreatitis remains a significant cause of morbidity and mortality. Most patients with mild acute pancreatitis will recover with conservative measures, although patients who develop more severe pancreatitis, especially those with pancreatic necrosis, require aggressive management and can still have a poor outcome. A multidisciplinary approach is warranted in patients with severe pancreatitis as input from intensivists, gastroenterologists, surgeons, radiologists and other specialists is usually required. Treatable causes of pancreatitis should be identified and managed appropriately**.**

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