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Efficacy of Granisetron on Recovery and Mortality and Morbidity Rate in Acute Pancreatitis

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ABSTRACT

Different treatments for control of symptoms, decrease hospitalization time and costs and reduction of complication and mortality rate of acute pancreatitis are designed and evaluated. Efficacy of serotonin antagonist confirmed in experimental studies. This study designed to evaluate the effect of Granisetron on morbidity and mortality rate of acute pancreatitis. In a single-blind clinical trial, 40 patients were divided randomly in two groups. Patients in control group received routine treatment for acute pancreatitis include food intake restriction, fluid and electrolyte management, prophylactic antibiotic and stomach decompression with gastric tube. In treatment group, Granisetron (1mg; 12h IV; 2 day) prescribed in addition to routine treatment. Ranson criteria at the time of admission and 48h after hospitalization, Apachi 2, severity of symptoms, severity of disease in CT-scan, hospitalization time and morbidity and mortality rate were compare in between groups. The results indicated that, prescription of Granisetron in addition to routine treatment was not affect significantly on morbidity and mortality rate and severity of pancreatitis and additional research must be designed.

Key words: Granisetron, mortality, morbidity, acute pancreatitis.

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INTRODUCTION

Acute pancreatitis is mild and self-limiting disease which can be acute in 15-20% and cause organs failure or local complications (i.e. necrosis, pseudocyst, abbesses) [1]. Most of patients with acute pancreatitis organs failure observed in first few days of disease which responsible for early death in these patients. Studies showed that local release of asinase, vasoactive mediators, vasoconstriction, increase vascular permeability, ischemia, intravascular coagulation and capillary stasis cause pancreatic edema, hemoconcentration, and impairment in vascular drainage and subsequently hemorrhagic pancreatic necrosis [2-6]. That is the opinion which activated pancreatic enzyme is a main role in beginning of pancreatic with digesting their own cell [7-8]. Normally, secretion of pancreatic enzyme are mediated by cholecystokinin hormone and vagovagal reflex which activated by cholinergic neurons [9-10]. Lominal factors like osmolality and disaccharides with activation of 5-hydroxy triptamin-3 (5HT3) and mechanical stimulations via activation of 5HT3 and 5HT2 receptors in vagus afferent nerve fibers in intestine cause stimulation of pancreatic enzyme secretion [11]. Studies in animals show that specific antagonist of 5HT3 and 5HT294 cause reduction in pancreas protein percentage [11]. Granisetron is specific antagonist of 5HT3 receptor with low affinity to dopamine, benzodiazepine, adrenergic and opioid receptors [12] and local and central effects which used for prevention of vomiting and nausea after chemotherapy (13, 14). Also in salivary glands, granisetron inhibit secretion of amylase [15]. Since the serotonin receptors, especially 5HT3 has main role in secretion of pancreatic enzyme and the main pathogenesis of pancreatitis is enzyme secretion and lysis of own cells, this is the hypothesis, with prevention of pancreatic enzyme secretion, progress of pancreatitis can be blocked. Therefore, the aim of this study was to evaluate the effect of granisetron plus routine treatment on

the improvement of symptoms of acute pancreatitis.

Acute pancreatitis

Several factors associated with acute pancreatitis include: congenital disorders, viral infection, abdominal trauma, cholelithiasis, hyperlipidaemia, some drugs and etc. The initial symptoms of acute pancreatitis are abdominal pain, nausea and vomiting. Every year 300,000 cases of pancreatitis diagnosed in US, which 10-20% of that is acute and cause 3000 death yearly. Financial burden of disease estimated around 2 billion dollars. However, the exact mechanism of disease not fully recognized. Based on epidemiologic properties different region, several factors can be included. In US and some European countries, most cases of acute pancreatitis are caused by alcohol abuse. In Iran, cholelithiasis is the main cause of acute pancreatitis (50%) which most observed in 41-50 age categories. Death from pancreatitis is around 10%. One of main causes of acute pancreatitis is cholelithiasis which can blocked pancreatic ducts (the pancreatic duct carries pancreatic enzymes from the pancreas to the intestines) and subsequently cause acute inflammation of pancreas. Also alcohol abuse can cause acute pancreatitis in some persons. Alcohol abuse in combination with smoking elevates risk of acute pancreatitis. Endoscopic retrograde cholangio-pancreatography (ERCP) which performed to diagnosis and treatment of stones and tumors of pancreas, liver and gallbladder can cause acute pancreatitis.

Other factors can cause acute pancreatitis include:

- Drugs: sulfonamide, diuretic drugs like hydrochlorothiazide, immunosuppressive drugs, drugs used in treatment of AIDS,
- Abdominal surgery,
- Abdominal injuries and trauma,
- Metabolic conditions like hypercalcemia or high levels of triglycerides in the bloodstream,
- Some infections like mumps or viral hepatitis,
- And unexplained conditions for acute pancreatitis.

Symptoms of acute pancreatitis

Acute abdominal pain, nausea, vomiting, sweating, myalgia, tympanites, lethargy, fever, hypotension and shock are main sings of acute pancreatitis. Pain mainly observed in middle part of the trunk and below the ribs but in some cases can be observed in left or right of abdomen. This pain is a permanent pain with a piercing or burning state. The pain can spread to the back, flanks, chest, or lower part of abdomen. In most of cases the pain reaches its maximum intensity during about thirty minutes. In acute pancreatitis caused by alcohol abuse, pain initiated 1-3 days after alcohol abuse. It may be difficult to find a situation in which a person is comfortable. Bending forward or lying down can reduce pain. Eating often worsens the pain. Other sings of acute pancreatitis include:

- Nausea and vomiting,
- Anorexia
- Tympanites
- In acute cases fever, dyspnea, weakness and shock.

Treatment of acute pancreatitis

Most of patients with acute pancreatitis hospitalized and received intravenous analgesia drugs and fluid and until the symptoms are improved, the patient is not allowed to eat or drink. In most of cases, there is no specific solution for shortening of duration of sings and pain and accelerate recovery. If the duration of sings is long and patient didn't eat more than one week, parenteral nutrition can be started. In some cases an antibiotic prescribed for prevention or improve the pancreas and surrounding tissue inflammation. Consumption of food is stopped and nasogastric tube used for aspiration of gastric secretion. Oral nutrition used when patient sings and appetite improved and serum amylase level back in normal range. Early food eating can worse the disease. In patient with acute pancreatitis, liquid is captured in the sub peritoneal region and for this reason, high volume of intravenous fluid administrated for maintenance of circulating blood volume and renal function. In these patients albumin must be administrated to avoid leakage from the capillary. The best way to control the amount of compensatory fluid, is monitoring of volume and specific gravity of urine. Since the possibility of infection in these patients is high, broad-spectrum antibiotic could be used. Diagnosis of hypocalcemia is important because this condition can lead cardiac dysrhythmia. Hypomagnesemia is common alcoholic patients which be monitored and keep in normal level. Acute hypoxia which need to treatment observed in 30% of patients with acute pancreatitis. Hypoxia is often gradual. There is no specific clinical or radiological indication, and it is not relevant to the severity of pancreatitis. Hypoxia often accompanied by hypocalcemia. Underlying problem is adult respiratory distress syndrome which is not fully understood. In the case of serve

a disease, for prevention of absorption in systemic blood stream, peritoneal lavage used for extracting poisons in peritoneal fluid. Peritoneal lavage is recommended in patients with acute pancreatitis, which they sign does not improve after 24-48h treatment. In acute pancreatitis caused by cholelithiasis, ERCP may be performed and in some cases surgeon may delicate cut in the bile duct enters for prevention of recurrence of obstruction. Cholecystectomy in some cases can be recommended which be done a days or week after relief of acute pancreatic signs. Emergency surgery, technically difficult and may worse pancreatitis conditions. In rare cases surgery is necessary:

- False cyst evacuation
- Treatment for abscesses
- Stop bleeding

Literature review

Li *et al.*, (2001) hypotheses that intestinal serotonin as a paracrine substance used for pancreas secretion which stimulated by luminal factors. They evaluated hypotheses in rat model and found that stimulation of lumen cause serotonin release induction and subsequently activation of 5HT3 receptors in afferent breaches of vague nerve. In this condition, serotonin act as a paracrine substance which stimulate secretion of pancreatic enzyme via cholinergic path of vague nerve [16].

Hamada *et al.,* (2007) evaluate the effect of endogen serotonin in exacerbation of Serolein induced pancreatitis in rat. The results, released endogen serotonin leading to activation of 5HT2A receptors which subsequently exacerbate Serolein induced pancreatitis. Also 5HT2A specific receptors can use as a new treatment plan for acute pancreatitis [17].

Sonda *et al*., (2013) in the study entitled "Serotonin regulates amylase secretion and acinar cell damage during murine pancreatitis" showed that serotonin can regulate zymogens secretion in pancreas acinar cells. Their results also indicated that serotonin is necessary for initiation of pancreas inflammation [18].

Vinokurova *et al*., (2008) designed study entitled "The role of neuromediators and cytokines in pathogenesis of chronic pancreatitis of alcohol etiology" evaluate 50 patients. According to the results, serotonin and acetylcholine has a main role in maintenance of pancreas function in acute alcoholic pancreatitis. In inflammation condition, the participation of nouromediators decreases which activate secretion activities in pancreas with weak prognosis [19].

Chemoiarova *et al.,* (1981) in the study entitled "Effect of serotonin on secretory and lysosomal enzyme activity in pancreatic tissue and the inhibitory properties of serum" shown that administration of serotonin in animals with legated pancreatic ducts lead to progression in pancreatitis with lipid necrosis in pancreas [20].

MATERIAL AND METHODS

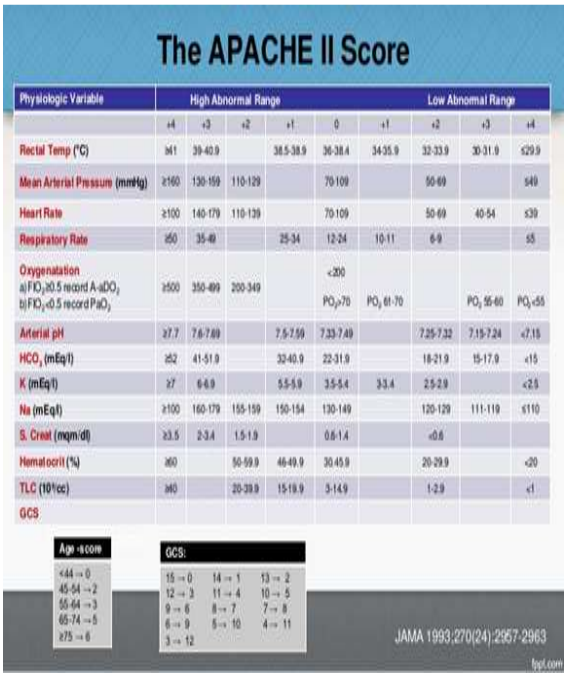
This study was double-blind clinical trial. Target population includes all patients with pancreatitis and study population was all patients with pancreatitis which referred Vali-Asr hospital emergency department.

This study was single-blind clinical trial. All patients with pain in epigaster region with high blood amylase which referred to Vali-asr hospital after abdominal and pelvic ultrasound and exclusion of other factors of abdominal pain like cholecystitis, cholangitis, colic bilirubin, peptic ulcer and after confirmation with spiral CT according to inclusion and exclusion criteria selected. Patients divided randomly in two groups: group 1 patients with standard treatment included: place NG tube, water and electrolytic resuscitation, prophylactic antibiotic therapy and group 2 administered by Granisetron (1mg/12h; 2days). Data analyzed by SPSS software were used. For descriptive analysis, central indicators and dispersion (frequency, mean and standard deviation) and for analytical analysis of variables, independent T-test or equivalent non-parametric test and for qualitative variable Chi^2 test were used. Ranson criteria calculated by follow chart:

TABELA 1 - Pancreatite aguda grave estabelecida pelos critérios de Ranson

Ranson (alcoholic etiology or other)	Ranson (biliar etiology)
At admission	**At admission**
Age > 55 years	Age > 70 years
Leukocytes > 16 000/mm3	Leukocytes > 18 000/mm3
LDH > 350 U/l	LDH > 250 U/l
AST > 250 U/l	AST > 250 U/l
Glicemia > 200 mg/dl	Glicemia > 220 mg/dl
After 48 hours	**After 48 hours**
Reduction in hematocrit > 10%	Reduction in hematocrit > 10%
Increase in BUN > 5 mg/dl	Increase in BUN > 2 mg/dl
Calcium < 8 mg/dl	Calcium < 8 mg/dl
PO2 < 60 mmHg	PO2 < 60 mmHg
Base excess> 4 mEq/l	Base excess > 5 mEq/l
Fluid leakage > 6L	Fluid leakage > 4L

Apachi criteria calculated according follow checklist:



Severity of complication index calculated by following table:

Table 5 Complication score as primary outcome variable

Organ complication	*Points*	*Metabolic complication*	*Points*
Shock	4	Hypocalcaemia	2
Sepsis	4	Coagulopathy	2
Pulmonary insufficiency	3	Hyperglycaemia	2
Renal insufficiency	3	Metabolic acidosis	2
Peritonitis	3	Jaundice	1
Haemorrhage	3	Encephalopathy	1
Abscess	3		
Pseudocyst	3		
Ileus/subileus	1		
Death	38		

TABLE 1 CT Severity Index [9]

Prognostic Indicator	Points
Pancreatic inflammation	
Normal pancreas	0
Focal or diffuse enlargement of the pancreas	1
Intrinsic pancreatic abnormalities with inflammatory changes in peripancreatic fat	2
Single, ill-defined fluid collection or phlegmon	3
Two or more poorly defined collections or presence of gas in or adjacent to the pancreas	4
Pancreatic necrosis	
None	0
≤ 30%	2
> 30–50%	4
> 50%	6

RESULTS

Analysis of data

Mean (standard deviation) of participants were 60.4 (11.12) years and the two groups were identical in terms of age. (P>0.05). 65% of patients were men and both groups were identical in terms of age. In 87% cholelithiasis was main cause of pancreatitis and there is no significant difference observed between two groups in terms of the cause of pancreatitis.

All patients complained form anorexia and abdominal pain. Nausea and vomiting observed in 96% and 85% respectively. Pain in 62% distributed to back, abdominal tenderness and dehydration were reported in in 95% and 90% respectively. Rebound tenderness in 40% positive and Reduce abdominal sounds observed in 78%. CT findings reported in table 2.

Mean (standard division) of Ranson score in the beginning of study was 1.85 (0.82%) and 48h after hospitalization were 2.95 (0.83%) and 4.45 (1.46%). These scores for Apachi criteria and severity of disease in CT-Scan were 8.66 (6.15%) and 2.71 (2.53%) respectively. Mean (standard division) disease complication criteria and duration of hospitalization were 6.63 (7.95%) and 11.94 (4.6%) respectively.

Table 1: Compression of underlying cause of pancreatitis in studied groups

Groups	Cholelithiasis	Alcohol	Cholelithiasis + Alcohol	Other factors	p value
Control	34 (89.5%)	2 (5.3%)	1 (2.6%)	1 (2.6%)	0.88
Intervention	33 (84.6%)	2 (5.1%)	2 (5.1%)	2 (5.1%)	

Table 2: Compression of frequency of CT findings in studied groups

Groups	Control	Intervention	p value
Normal	7 (18.4%)	5 (12.8%)	0.63
edema	5 (13.2%)	9 (23.1%	
edema &exudate	17 (44.7%)	14 (35.9%)	
Necrosis under 30	4 (10.5%)	5 (12.8%)	
Necrosis 30-50%	4 (10.5%)	2 (5.1%)	
Necrosis above 50%	1 (2.6%)	4 (10.25%)	

Table 3: Comparison of severity of pancreatitis and complication and duration of hospitalization

variable	Group	Frequency	Mean	SD	p value
Ranson criteria	Control	38	1.89	0.89	0.85
	Intervention	39	1.82	0.75	
48h Ranson criteria	Control	38	2.63	0.78	0.72
	Intervention	39	2.56	0.88	
Total Ranson criteria	Control	38	4.52	1.53	0.83
	Intervention	39	4.38	1.4	
Apachi 2 criteria	Control	38	9.28	6.25	0.29
	Intervention	39	8.05	6.8	
Complication index	Control	38	6.84	8.1	0.61
	Intervention	39	6.43	7.9	
Severity on CT	Control	38	2.52	2.28	0.72
	Intervention	39	2.89	2.77	
Hospitalization	Control	38	12.31	4.46	0.33
	Intervention	39	11.58	4.76	

Table 4: Comparison of complication frequency in studied groups

Variable	Control	Intervention	p value
Need for surgery	8 (21.1%)	10 (25.6%)	0.63
Reoccurrence	3 (7.9%)	2(5.1%)	0.62%
Infection	6 (15.8%)	3 (7.7%)	0.26%
pseudocyst	3 (7.9%)	2 (5.1%)	0.62
Death	2 (5.1%)	2 (5.1%)	0.97

Comparison of disease severity according to initial, 48h after and total Ranson criteria and Apachi 2 criteria were presented in table 2. Both groups are same in initial Ranson criteria, and no significant difference between 24h Apachi and 48h Ranson criteria were observed. However mean of variables are lower in patients received Granisetron. Difference between two groups according to complication and severity score of CT-Scan and duration of hospitalization were not significant (P>0.05). However duration of hospitalization in groups received Granisetron was lower than control group (P=0.33).

According to results, mortality risk were 15-40%. Comparison of patients in acute pancreatitis complication like reoccurrence, sepsis, pseudocyst, need for surgery and death were summarized in table 4. The results were not significantly different and morbidity and mortality rate were same in both groups (P>0.05). Rate of infection in Granisetron was half of control group which not significant (P=0.26).

DISCUSSION

The present study was single-blind clinical trial which designed to evaluate effect of Granisetron in addition to routine treatment and compression with routine treatment on morbidity and mortality rates. In Granisetron groups, patients received 1mg Granisetron every 12h and severity of pancreatitis, initial Ranson index and 48h after hospitalization, Apachi 2 index in first 24h of hospitalization, severity of pancreatitis index in CT-Scan, complication score and frequency of each complication and duration of hospitalization were compared between two groups. Mean (standard deviation) of participate was 60.4 [11.12] and 65% of patients were men. In the study conducted by Uhl et al. mean age was 53 and 60% of patients was men [22] which in consistent with our results. In the study of Talaeizade et al, mean age was 40 years and 60% of patients were women [23].

In our study main cause of pancreatitis (87%) was cholelithiasis which in consistent with Talaeizade et al study but in Uhl study the main cause was alcohol abuse (42%) which can be explained by

low amount of alcohol use in Iran. In our study all patients complained from anorexia and abdominal pain. Nausea and vomiting observed in 96% and 85% respectively. Pain in 62% distributed to back, abdominal tenderness and dehydration were reported in in 95% and 90% respectively. Rebound tenderness in 40% positive and Reduce abdominal sounds observed in 78%. In study conducted by Talaeizadeh et al., all patients suffered from anorexia and epiagaster pain and nausea observed in 96% and vomiting in 60% of patients. Pain distribution diagnosed in 60% and abdominal tenderness observed in 100% of patients. Dehydration and rebound tenderness observed in 80% and 44% respectively [23].

Mean (standard division) of Ranson score in the beginning of study was 1.85 (0.82%) and 48h after hospitalization were 2.95 (0.83%) and 4.45 (1.46%). These scores for Apachi criteria and severity of disease in CT-Scan were 8.66 (6.15%) and 2.71 (2.53%) respectively. Mean (standard division) disease complication criteria and duration of hospitalization were 6.63 (7.95%) and 11.94 (4.6%) respectively. In Uhl study mean of Ranson index and Apachi 2 index were 3 and 7 respectively and the severity index of complication was 6 [22].

Both groups are same in initial Ranson criteria, and no significant difference between 24h Apachi and 48h Ranson criteria were observed. Difference between two groups according to complication and severity score of CT-Scan and duration of hospitalization were not significant. However duration of hospitalization in groups received Granisetron was lower than control group but the morbidity and mortality rate in both groups were same. In literature review, there is no same study about effects of granisetron on pancreatitis was found and most of studies are theatrical or experimental. Li et al. found that serotonin act as a paracrine substance which stimulate pancreas enzyme secretion via cholinergic path of vague nerve [16]. Hamada et al found that released endogen serotonin leading to activation of 5HT2A receptors. Also 5HT2A specific receptors can use as a new treatment plan for acute pancreatitis [17]. These studies in consistent with Sonda *et al.*, which showed that serotonin can regulate zymogens secretion in pancreas acinar cells. Their results also indicated that serotonin is necessary for initiation of pancreas inflammation [18]. In animal model, administration of serotonin with legated pancreatic ducts leads to progression in pancreatitis with lipid necrosis in pancreas [20].

Despite strong evidence of efficacy of serotonin antagonist on reduction of severity of pancreatitis in experimental and animal studies, there is no clinical evidence on these effects were found. According to our results administration of granisetron in addition to routine treatment in compression to routine treatment not differ in severity of pancreatitis and morbidity and mortality in patients and further studies are recommended.

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