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Ameliorating Effect of Standard Treatment on Cerulein-Induced Acute Pancreatitis in Rat Model

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ABSTRACT

An experiment was designed on diagnostic biomarkers and effect of standard therapy followed during acute pancreatitis in rat model. Rats were divided in three groups, A (Control), B (acute pancreatitis) and C (treatment) groups, 12 rats in each. Supra-maximal dose of cerulein (50 µg/kg b wt) was given i.p. at hourly interval for 7 h in groups B and C. Group A was treated with 0.25 ml of NSS at same interval. Treatment and sampling started after 12 h of last injection of cerulein. Group C rats were treated by antibiotic, anti-inflammatory and vit-E. Hematological and biochemical estimations were carried out at 12, 24, 60 and 156 h of last dose of cerulein. Hematological parameters found to increase significantly in group B and C than A and significant reduction noted in group C after treatment. Serum lipase and amylase were considered as accurate biomarkers and their values were found to increase several times in induction groups and became almost normal at 156 h of sampling in C group. Significant reduction in AST and ALT values noticed in treatment group. BUN and creatinine became normal in Group C at 156 and 60 h, respectively. Serum calcium became normal at 60 h. It was concluded that significant increase in serum lipase, amylase, AST, ALT, BUN, creatinine and CK-MB had diagnostic significance of acute pancreatitis and their values became normal in treatment group earlier and faster than group AP showing that standard treatment had significant role in acute pancreatitis.

Keywords: Acute pancreatitis, Cerulein, Rat model, Hemato-biochemical, Treatment

For the diagnosis of pancreatitis, clinicians have to explore the risk factors, symptoms, history, laboratory investigation especially pancreatic enzymes, biochemical and hematological examinations (Lippi *et al*., 2012). Its pathogenesis is not fully known but premature activation of exocrine enzymes resulting in autodigetion is supposed to be the basic cause (Yu *et al*., 2002). Biopsy and exploration as done in gastric or colon are not possible due to its anatomical positions, so use of animal models are preferred for detailed study of acute pancreatitis.

Rodent models are more common due to structural similarity to human. Cerulein is one of the most common agents used in the induction of acute pancreatitis in animals (Arafa, *et al*., 2009). Experimentally induced pancreatitis by cerulein causes inhibition of exocytosis (Saluja, *et al*., 1985) resulting in lysosomal degradation of intracellular organelles and marked interstitial edema (Gorelick *et al*., 1993). These features resemble the early phase of acute pancreatitis in human beings (Adler and Kern, 1984). To predict the changes at cellular levels various biomarkers are in the use but serum amylase and lipase are most important. It can also be associated with liver and kidney.

Kalli *et al*. (2009) suggested 5 steps in the treatment of acute pancreatitis including as removal of the inciting cause, maintenance of fluid and electrolyte balance, relief of pain, management of complications and constant monitoring of case for any deviation in clinical pathology.

Keeping all the above facts, an experiment was planned to explore the effect of standard treatment on the acute pancreatitis in rat's model and evaluate hematological and biochemical changes during acute pancreatitis in rat model by using supra-maximal dose of cerulein.

MATERIALS AND METHODS

Experimental animals

The experiment was carried out on SD male rats of 6-8 weeks age with 225-250 g body weight purchased from CDRI, Lucknow. They were kept with ambient temperature of 23ºC± 2ºC and 12 hour light-dark cycle and acclimatized for 10 days before start of the actual test procedure. Animals were maintained on free access of feed and fresh drinking water during the entire study period of the experiment. The experiment was carried out as per the guidelines of Institutional Animal Ethics Committee (IAEC), Pantnagar accredited by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi vide approval number IAEC/VMD/CVASc/246 dated 08/12/2016 (CPCSEA Reg. No. 33/GO/ERe/SL/01/CPCSEA 03.01.2001).

Grouping of rats

The rats were divided in three groups of 12 each, group A (Control group), group B (Acute pancreatitis group) and Group C (Treatment group). Acute pancreatitis was induced in group B and group C, by intraperitoneal injections of supra-maximal concentration of cerulein (50 µg/kg) (Sigmai-Aldrich Chemical, Germany) by diluting in saline solution at every hour for total 7 h. The rats of group A were given intraperitoneal injections of 0.25 ml of 0.9% normal saline solution on hourly basis for 7 times as cerulein was given in induction group. Rats were fasted for 18 h before start of intraperitoneal injections of cerulein. Rats of group B were given only feed and water as in group A after induction of pancreatitis without any treatment while in group C standard treatment was carried out after induction of pancreatitis.

Treatment protocol

In group C treatment started after 12 h of the last injection of the cerulein with antibiotics (Supracif, Ciprofloxacin, @ 20 mg/kg body weight in aqueous medium), anti-inflammatory (Ibuprofen, @ 100 mg/kg body weight in aqueous) and Vit-E @ 100 mg/kg body weight (Evion 200 mg in groundnut oil) daily for continuous upto 7 days with ad-lib fresh water and standard feed. In Group A and group C no treatment were given and availability of ad-lib fresh water and standard feed were insured throughout the experiment.

Sampling and examinations

Faecal, blood and pancreas tissue sample were collected after 12 h of last injection of cerulein at 12, 24, 60 and 156 h. Blood samples were collected in two vials one with anticoagulant and another without anticoagulant. Blood with anticoagulant was used for haematological examination and blood without anticoagulant was used for serum separation for various biochemical examinations. Tissue samples of pancreas were fixed in 10% normal buffered formalin for further histological examinations. The blood samples were analyesed for Hb, PCV, TEC and TLC within 2 h of blood collection as per standard method described by Jain (1986).

Serum pancreatic amylase and lipase were estimated by using ELISA kit, (Chongqing Biospes (Catalog No. BYEK 2665 and BYEK2664) supplied by Infobio, Co., Ltd, New Delhi. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were estimated using commercially available kits as per standard method of Reitman Frankels (1957) and Reitman Frankels (1957).

Serum creatine kinase -MB was analysed by method described by Bremmer (1987) using Erba diagnostic kit. Blood urea nitrogen level was estimated by enzymatic method using Autospan diagnostic kit at 340 nm wavelength (Newman, 1999). Serum calcium and creatinine were also estimated by standard methods using Erba diagnostic kits.

Statistical analysis

The results were analysed by using two way ANOVA test according to the method described by Snedecor and Cochran (2004) and probability values less than 0.05 were considered significant.

RESULTS AND DISCUSSION

Haematological changes

There was significant increase in Hb, PCV, TEC and TLC values at 12 and 24 h of sampling in B (AP) and C (treatment) groups than A (control), but at 60 h and 156 h no significant variation was recorded. In AP and treatment

groups Hb, PCV and TEC values became almost normal at 60 h of sampling. At 60 h sampling, only AP group had significant higher TLC levels than control but treatment groups became non-significant. AP group showed non-significant decrease in TLC values at every interval of sampling while treatment groups had significant decrease at 60 h of sampling (Table 1).

Hematological values were noticed higher in both AP and treatment groups and it is due to the inflammatory changes in pancreas. Hb, PCV and TEC were noted higher at initial samplings due to dehydration in animals (Levitt and Eckfeldt, 1993). Ozkardes *et al*. (2015) also noticed increase in the Hb, PCV and TEC values in acute pancreatitis in rats. Significant higher level of TLC in induction groups was due to inflammatory changes in the pancreas but inflammation is sterile so, levels become normal after few days. Higher levels of TLC were also noticed by Strauss (1993), Levitt and Eckfeldt (1993) and Angi *et al*. (2016).

Pancreatic enzymes

Serum lipase and amylase both were found significantly higher in B (AP) and C (treatment groups) at 12 and 24 h of sampling, Angi *et al*. (2016) and Yin *et al*. (2017) were also reported increase in the levels of serum lipase and amylase values during induced acute pancreatitis in rat models. Our finding showed similarities with them. At 60 and 156 h of sampling, significant higher levels noted in B groups than A and C group and in C group the lipase and amylase reached to almost normal range. B and C groups showed significant reduction in the levels of lipase and amylase at all intervals of sampling except in treatment group, lipase which showed significant fall only at 24 and 60 h and non-significant reduction at 156 h and values became almost normal.

It is believed that activation of premature typsin in side pancreatic parenchyma starts the cascade of pancreatitis and autodigetion of self-tissues, mainly due to proelatase

Table 1: Hemato-biochemical alterations in the cerulein-induced acute pancreatitis in rats model

Parameter	Group A (Control)				Group B (Acute Pancreatitis)				Group C (Treatment)			
	12 h	24 h	60 h	156 h	12 h	24 h	60 h	156 h	12 h	24 h	60 h	156 h
Hb (g/dl)	12.74 ± 0.06^{bA}	12.60 ± 0.14^{bA}	12.87 ± 0.13^{aA}	12.40 ± 0.16^{aA}	13.66 ± 0.16^{aA}	13.76 ± 0.15^{aA}	12.89 ± 0.14^{aB}	12.79 ± 0.19^{aB}	13.78 ± 0.12^{aA}	13.61 ± 0.12^{aA}	12.81 ± 0.22^{aB}	12.63 ± 0.21^{aB}
PCV (%)	39.43 ± 0.31^{dB}	40.23 ± 0.17^{cA}	39.88 ± 0.13^{cAB}	39.76 ± 0.28^{abAB}	42.23 ± 0.20^{cA}	42.46 ± 0.17^{bA}	40.16 ± 0.22^{cB}	39.47 ± 0.17^{bC}	42.57 ± 0.14^{cA}	42.13 ± 0.23^{bA}	39.78 ± 0.23^{cB}	39.56 ± 0.19^{abB}
TEC (× 10^6/ cu mm)	7.67 ± 0.18^{cA}	7.89 ± 0.24^{cA}	7.75 ± 0.23^{bA}	7.82 ± 0.13^{aA}	8.69 ± 0.16^{bA}	8.98 ± 0.29^{bA}	8.13 ± 0.18^{bAB}	7.71 ± 0.10^{aB}	9.14 ± 0.27^{bA}	8.11 ± 0.26^{cB}	7.71 ± 0.13^{bB}	7.69 ± 0.20^{aB}
TLC (× 10^3/ cu mm)	11.13 ± 0.11^{bA}	11.03 ± 0.14^{bA}	10.85 ± 0.14^{bA}	10.68 ± 0.15^{aA}	12.23 ± 0.03^{aA}	12.10 ± 0.16^{aA}	11.87 ± 0.12^{aAB}	11.39 ± 0.20^{aB}	12.37 ± 0.08^{aA}	11.79 ± 0.03^{aA}	11.16 ± 0.16^{bB}	10.89 ± 0.21^{aB}
ALT (U/L)	23.51 ± 1.07^{cA}	25.32 ± 1.40^{bA}	24.87 ± 1.26^{dA}	23.19 ± 1.03^{dA}	70.10 ± 1.03^{aA}	61.95 ± 1.36a^{BC}	60.84 ± 1.35^{aC}	65.67 ± 1.03^{aB}	68.74 ± 1.06^{aA}	60.37 ± 0.84^{aB}	42.47 ± 1.29^{cC}	37.59 ± 1.11^{cD}
AST (U/L	47.38 ± 1.03^{eA}	49.74 ± 0.85^{dA}	48.23 ± 1.12^{dA}	46.87 ± 0.65^{dA}	228.47 ± 1.00^{dA}	210.84 ± 2.51^{cB}	139.73 ± 1.82^{aaC}	102.25 ± 2.48^{aD}	243.57 ± 1.96^{cA}	223.13 ± 3.31^{bB}	123.18 ± 1.35^{cC}	77.53 ± 1.26^{bD}
BUN (mg/dl)	8.04 ± 0.13^{bA}	7.78 ± 0.34^{bA}	7.35 ± 0.33^{cA}	7.73 ± 0.32^{bA}	15.76 ± 0.82^{aA}	14.19 ± 0.60^{aA}	11.78 ± 0.34^{aB}	9.93 ± 0.26^{aC}	14.69 ± 0.72^{aA}	13.47 ± 0.68^{aA}	9.73 ± 0.11^{bB}	8.21 ± 0.38a^{bB}
Creatinine (mg/dl)	0.29 ± 0.05^{bA}	0.30 ± 0.05^{bA}	0.31 ± 0.03^{bA}	0.32 ± 0.04^{aA}	1.02 ± 0.10^{aA}	0.91 ± 0.06^{aA}	0.64 ± 0.11^{aB}	0.48 ± 0.08^{aB}	0.98 ± 0.10^{aA}	0.88 ± 0.05^{aA}	0.42 ± 0.02^{bB}	0.32 ± 0.04^{aB}
Serum CK – MB (IU/L)	431.52 ± 6.21^{bA}	428.42 ± 6.53^{cA}	432.84 ± 10.78^{dA}	429.59 ± 5.39^{cA}	1324.23 ± 9.95^{aA}	1298.42 ± 11.12^{aA}	987.45 ± 6.50^{aB}	677.57 ± 7.08^{aC}	1341.91 ± 19.88^{aA}	1261.97 ± 12.25^{bB}	580.74 ± 9.96^{bC}	480.19 ± 13.55^{bD}
Calcium (mg/ dl)	8.83 ± 0.51^{aA}	8.97 ± 0.36^{aA}	9.11 ± 0.43^{aA}	8.86 ± 0.14^{bA}	7.13 ± 0.13^{bC}	7.31 ± 0.33^{bC}	8.12 ± 0.33^{bB}	9.09 ± 0.17^{bA}	7.18 ± 0.42^{bB}	7.40 ± 0.18^{bB}	9.13 ± 0.14^{aA}	9.18 ± 0.03^{bA}
Serum lipase (U/L)	98.35 ± 3.82^{bA}	95.59 ± 6.13^{bA}	93.74 ± 2.75^{cA}	94.18 ± 5.49^{bA}	418.87 ± 4.98^{aA}	239.59 ± 10.29^{aB}	163.18 ± 8.92^{aC}	119.79 ± 3.86^{aD}	421.63 ± 11.64^{aA}	210.39 ± 7.38^{aB}	110.78 ± 6.17^{bC}	98.53 ± 5.22^{abC}
Serum amylase (U/L)	328.42 ± 4.88^{cA}	328.42 ± 4.88^{cA}	328.42 ± 4.88^{cA}	328.42 ± 4.88^{cA}	2318.49 ± 23.92^{bA}	1749.59 ± 20.24^{bB}	931.96 ± 20.45^{aC}	473.72 ± 8.67^{aD}	2378.72 ± 64.01^{abA}	1692.83 ± 27.92^{abB}	639.39 ± 7.14^{bC}	321.71 ± 12.09^{bD}

Values are Mean ± SE .Mean values bearing different superscripts differed significantly.

and prophospholipase (Bunch, 2003 and Watson, 2004). These activated enzymes cause inflammatory changes in the pancreatic tissues along with necrosis of acinar as well as peri-pancreatic fats. They also damage the vasculature, causes coagulation, fibrinolytic and activated vasoactive amines and complementary systems (Van den Bossche *et al*., 2010). Autodigetion of pancreatic tissues results in the higher levels of the serum lipase and amylase and have diagnostic significance of acute pancreatitis.

Liver enzymes

Significant increased activity of ALT and AST enzymes was noted in B (AP) and C (treatment) group at 12 h and 24 h of sampling but at 60 h and 156 h of sampling significant reduction in C group was noted than B group. Emam and Abo El gheit, (2016) and Zeren *et al*. (2017) also reported increase in ALT and AST levels during induced acute pancreatitis. Significant reduction was noticed in AST and ALT at 24 h, 60 h and 156 h of sampling group B and C but ALT in Group B was found to reduce non-significantly at 60 h and increased significantly at 156 h.

Marked hepatic damage resulting in the increased levels of AST and ALT were described by several workers. It is considered that the systemic inflammatory response in acute pancreatitis causes abnormal hepatic microcirculation, tissue hypoxia and released cytokines in pancreatitis causes damage to liver parenchyma resulting in increased ALT and AST values (Emam and Abo El gheit, 2016). Carroll *et al*. (2007) reported three fold or greater elevation in AST levels during acute pancreatitis is 95% predictive indication of presence of gallstone acute pancreatitis.

Other biochemical

BUN was found to increase in B (AP) and C (treatment) groups at 12, 24, and 60 h of sampling but at 156 h only B group had significant higher value than control group. Zhu *et al*. (2017) and Liu *et al*. (2017) reported significant increase in BUN and creatinine levels in acute pancreatitis having agreement with our finding. B group had significant reduction at 60 and 156 h of sampling while in C group significant reduction was noted only at 60 h of sampling and values became normal. Creatinine was found significant higher at 12 and 24 h but at 60 h only B group had significant higher levels but C group had non-significant higher value. At 156 h of sampling, C group had same value as in control but B group had non-significantly higher value. B and C both groups showed significant fall at 60 h of sampling (Table 1).

Release of inflammatory substances and cytokines from the pancreatic tissues results in the systemic inflammatory response syndrome (SIRS). SIRS may also cause release of more inflammatory mediators from the tissues and amplification in pancreatitis with multiple organs/ system failure within 24-72 hours (Akyuz *et al*., 2009). The systemic lesions can result in respiratory, cardiovascular, renal and immunological disorders. These changes tend to increase the BUN and creatinine levels in the patients suffering from the acute pancreatitis.

CK-MB values was significantly higher at 12, 24, 60 and 156 h than control in B and C groups but it was significantly reduced in C group than B group at 60 and 156 h. Wang and Chen (2017) and Xie *et al*. (2017) reported increased levels of CK-MB in induced acute pancreatitis in rats as in our case. Significant reduction in B group was noted at 60 and 156 h while in C group significant reduction noted at 24, 60 and 156 h (Table 1).

Increased CK-MB levels may be due to damage to cardiac cells due to pancreatitis. In pancreatitis, systemic lesions can results in respiratory, cardiovascular, renal and immunological disorders. Cardiovascular system showed effects on cardiac rhythm and contractility and vasomotor tone of peripheral vessels. Cardiac changes could be seen as vasoactive peptides modulation and myocardial depressant factor (Meyer *et al*., 2014).

Serum calcium was found significantly low at 12 and 24 h of sampling in both B (AP) and C (treatment) groups. Zhou *et al*. (1996) reported fall in calcium level during acute pancreatitis in experimental model in rats as in our findings, so our result had agreement with them. At 60 h, it became normal in C group but in B group it was still significantly low. At 156 h its levels became normal in B group also. In B group, significant increase was noticed at 60 and 156 h while in C group, only at 60 h of sampling (Table 1).

Higher levels of serum lipase would resulted in the degradation of triglycerides and increase in the higher levels free fatty acid which binds to blood calcium and resulted in the hypocalcemia (Arafa *et al*., 2009)

CONCLUSION

In our present study all the parameters studied was found to be increased significantly in acute pancreatitis except serum calcium, with diagnostic significance. Increased values were found to reduce significantly in C (treatment) groups than B (AP) groups with reaching to basal levels in group C faster and earlier than the B group. Our treatment started after 12 h of the last injection of the cerulein, as per protocol, that's why some parameters took more time than usual but overall the therapeutic effect was found significant over control and AP groups.

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