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The effect of Heparin on Cerulein–Induced Pancreatitis in Albino Rats

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Keywords

Acute pancreatitis, Cerulein, Heparin, Interleukin-6, Activated partial thromboplastin time

Abstract

Aim: The present work aimed to investigate the effect of heparin on cerulein–induced acute pancreatitis model in albino rats. **Methods:** Thirty male albino rats were used in the study. They were divided into 3 groups: Control group, AP (Acute pancreatitis) group, and heparin–treated group. AP was induced by subcutaneous injection of cerulein (20µg/kg) four times at one hour intervals. At the end of experiment, the animals were sacrificed and blood samples were collected for determination of plasma amylase, lipase levels, tumor necrosis factor–alpha (TNF-α), interleukin-6 (IL-6), APTT (Activated partial thromboplastin time). Hematocrit levels were measured. Pancreatic tissue was evaluated histopathologically. **Results:** Compared with control group, plasma amylase, lipase, TNF-α, IL-6 and hematocrit levels in AP group were significantly increased ($P<0.05$). After heparin treatment, plasma amylase, lipase, TNF-α, IL-6 and hematocrit levels were significantly decreased ($P<0.05$). APTT was significantly prolonged in AP group as compared to control group, but was significantly decreased after heparin treatment. **Conclusions:** Treatment with heparin improved the biochemical and histopathological findings in a rat model of experimental pancreatitis. Although, our findings suggest that heparin might be considered an effective agent for the treatment of acute pancreatitis, this notion should be supported with further clinical investigations.

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INTRODUCTION

Acute pancreatitis (AP) is a severe and frequently lethal disorder which occurs suddenly and develops rapidly [1]. Coagulative disorders are known to occur in AP and related to the severity of this disease[2]. AP activates the haemostatic system with formation of thrombi within blood vessels and coagulative disorders may range from scattered intravascular thrombosis to severe disseminated intravascular coagulation (DIC) [3]. Heparin prevents coagulation after binding with a plasma α_2-globulin and anti-thrombin III [4]. Anti-thrombin III is a protease inhibitor and complex heparin–anti-thrombin III inhibits activity of thombin, as well as neutralizes active forms of factors IX, X, XI and XII [5]. However, the most important action of heparin is not inhibition of thrombin activity, but inhibition of thrombin creation, especially through accelerating the neutralization of factor Xa [6]. In large concentration, heparin combined with antithrombin III also inhibits platelet aggregation[7]. In various experimental and clinical studies, heparin has been found to exhibit the anti–inflammatory activity[8].

Heparin has shown protective and therapeutic effect in patients suffering from a range of inflammatory diseases, including rheumatoid arthritis [9], allergy [10] and ulcerative colitis [11.]

There are several models of experimental pancreatitis, including the cerulein–induced and sodium–taurocholate models. Pancreatic injury was evenly distributed throughout the pancreas in the cerulein–induced model. The reason we preferred the cerulein–induced AP model were that the characteristics of AP in this model are very similar to those of human pancreatitis and because the inflammation develops rapidly [12, 13].

The reports of prophylactic administration of low dose unfractionated heparin or LMWH on the development of acute post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis are not conclusive [14]. Some have indicated that pretreatment with heparin reduces the frequency of ERCP–pancratitis [15], whereas others have not shown a protective effect of unfractionated heparin [16] or LMWH [17].

In the present study, we try to investigate the effect of heparin on cerulein–induced acute pancreatitis model in albino rats.

MATERIALS AND METHODS

Animals:

The study was carried on eight to ten weeks old thirty male albino rats weighing from 180-200g. They were housed in standard cages. Rats were kept at a room temperature (22±3°C). Food and water were available.

Experimental design:

Rats were divided into 3 groups, each consisting of 10 animals. Group I: control group received saline (1ml/kg) subcutaneously four times at 1-h intervals. Group II: AP group was injected subcutaneously with cerulein (Sigma Chemical Co.) (20µg/kg in saline) four times at 1-h intervals[18]. Group III: cerulein–induced AP treated with heparin subcutaneously at a dose of 150U/kg [4] was administered after 3 to 4 hours after the first cerulein injection.

Biochemical assay:

At the end of the treatment period, the animals were sacrificed; the blood samples were collected with 3.8% sodium citrate as anticoagulant. Blood samples were centrifuged at 3000 rpm for 10 min. plasma amylase and lipase levels were assessed by enzymatic photometric method [19]. Plasma TNF-α and IL-6 levels were assessed by immunoassay kit [20]. Hematocrit value was measured using a microcapillary reader (International Micro capillary Reader; following 3 min of centrifugation)[21]. Also the whole pancreas was extracted for Histopathological evaluation of the pancreatic tissue.

Histopathological evaluation of the pancreatic tissue:

Pancreatic tissue was fixed in formaldehyde solution and embedded in paraffin. Sections were stained with hematoxylin and eosin and evaluated under light microscope by experienced pathologist. The histological grading of edema and leukocytic inflammatory infiltration was made using a scale ranging from 0 (absent) to 3 for maximal alteration as described by Tomaszewska et al., [22]. Results of histological examination have been expressed as a predominant histological grading in each experimental group of animals.

Statistical analysis:

Results, except histopathological data, are presented as the mean ± standard deviation. Data were analyzed using the unpaired student's t-test and ANOVA. Probability values less than 0.05 were considered significant. All the analyses were performed using SPSS for windows (Version 10.0).

RESULTS

Histopathological evaluation:

As shown in table1 & figure 1, in the AP group, the histopathological evaluation showed massive edema and leukocytic infiltration (grade 3) as compared to the control (grade 0). But, in the heparin-treated group, the inflammation was resolved (grade 0).

Table (1): Effect of heparin administration after induction of acute pancreatitis on the histopathological signs of pancreatitis.

Groups	Edema (0-3)	Inflammatory infiltration (0-3)
Control	0	0
AP	3	3
heparin treated	0	0

Numbers represent the predominant grading in each group.

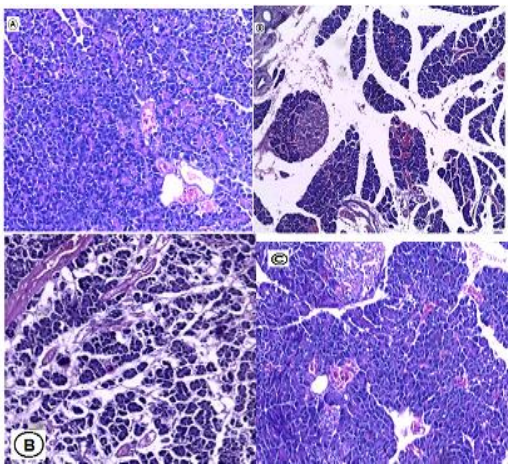

Fig. (1): (A) Normal pancreatic tissue in control group (grade 0); (B and C) Interstitial edema and inflammatory cell infiltration in pancreatic tissue in the AP group (grade 3) (D) Reduction of interstitial edema and inflammatory cell infiltration in the pancreatic tissue after heparin treatment (grade 0).

Effect of heparin on the plasma levels of amylase and lipase:

As shown in table 2 & figure 2, the levels of plasma amylase and lipase were significantly higher in AP group as compared to control group (P<0.05). On the other hand, levels of plasma amylase and lipase were significantly decreased in heparin-treated group (P < 0.05) as compared with AP group, but the levels were still significantly higher than those of the control.

Effect of heparin on the plasma levels of TNF-α and IL-6:

The levels of plasma TNF-α and IL-6 were significantly increased in AP group as compared to those in control. But, these levels were significantly decreased after heparin treatment as compared to AP group. The levels of IL-6 were still significantly higher than those of the control group. However, TNF-α levels showed insignificant difference between control and heparin treated groups (P > 0.05) table (2) & figure (3).

Table (2): Effect of heparin administration after induction of acute pancreatitis on the studied biochemical parameters.

Parameters	Group I (Control)	Group II (AP)	Group III (heparin treated)
Plasma amylase (U/L)	564.54± 33.26	2124.43 ±55.37[a]	1165.71 ±68.55[a,b]
Plasma lipase (U/L)	14.62± 1.17	123.02 ±31.84[a]	26.02±5. 03[a,b]
TNF-α (pg/ml)	21.63± 0.86	60.67± 4.73[a]	25.59± 4.2[b]
IL-6 (U/ml)	43.53± 7.47	352.87 ±21.78[a]	286.41± 16.32[a,b]
APTT (sec)	35.7±2.32	60.6± 1.23[a]	46.4±1.6 4[a,b]
Hematocrit value %	41±1.83	51.9± 2.77[a]	43.2± 2.39[b]

Data are given as mean ± SD. [a]P < 0.05 AP vs control, [b]P <0.05 Heparin treated vs AP.

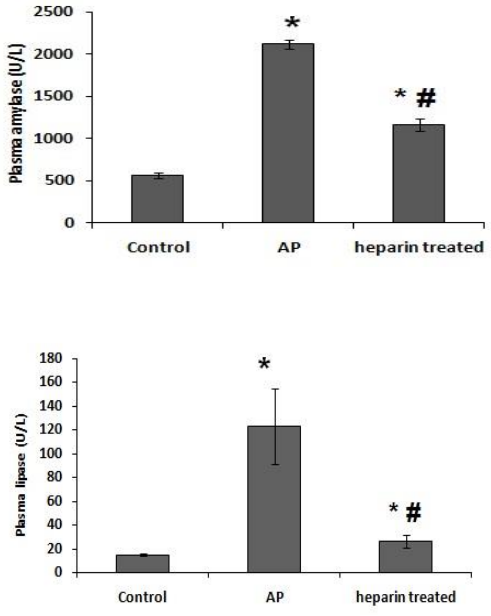

Fig. (2): Effect of heparin administration after induction of acute pancreatitis on plasma amylase and lipase levels. [*]P < 0.05 AP vs control, [#]P <0.05 Heparin treated vs AP

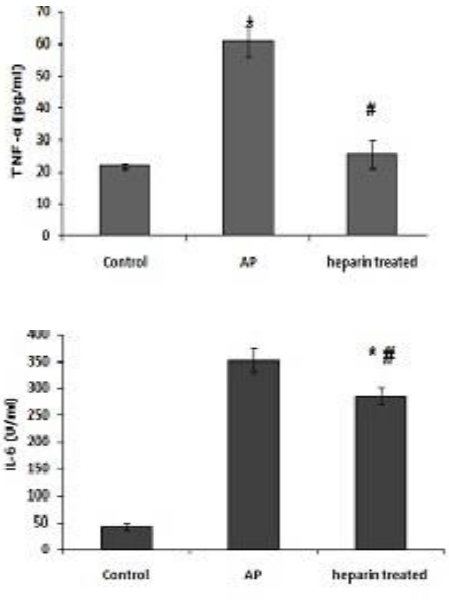

Fig. (3): Effect of heparin administration after induction of acute pancreatitis on plasma TNF-α and IL-6 levels. *P < 0.05 AP vs control, #P <0.05 Heparin treated vs AP.

Effect of heparin on APTT:

As shown in table 2 & figure 4, in AP group, APTT levels were significantly prolonged compared to control group (P< 0.05). On the other hand, APTT levels were significantly decreased in heparin-treated group as compared to AP group, but its levels were still significantly higher than those of the control group.

Effect of heparin on hematocrit value:

In AP group, hematocrit value was significantly increased compared to control group (P< 0.05). However, hematocrit value was significantly decreased in heparin-treated group as compared to AP group. But, these levels showed insignificant difference between control and heparin treated groups (P > 0.05) (table2 & figure 4).

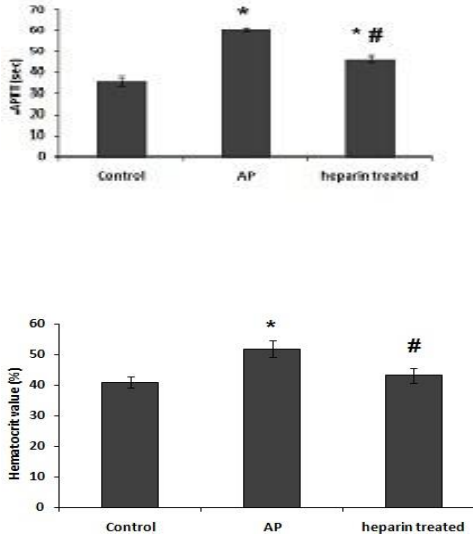

Fig. (4): Effect of heparin administration after induction of acute pancreatitis on Hematocrit value and APTT levels. *P < 0.05 AP vs control, #P <0.05 Heparin treated vs AP.

DISCUSSION

Acute pancreatitis is a disease which has many etiologies. Each etiology seems to affect the pancreatic acinar cells in some way that results in premature activation and retention of proteolytic enzymes [1].

The results of the present work showed that subcutaneous injection of heparin caused significant protective effect against cerulein-induced AP compared to the control group. This manifested by normalization of pancreatic histology, as well as a reduction in biochemical markers of acute pancreatitis. Morphological examination has shown that treatment with heparin reduces pancreatic edema and inflammatory leukocytic infiltration of pancreatic tissue. Reduction of inflammatory infiltration was associated

with significant reduction in plasma levels of pro-inflammatory TNF-α and IL-6 and plasma levels of pancreatic enzymes amylase and lipase. This anti-inflammatory effect of heparin is in accordance with the previous observations [23, 24]. Hecht et al., [25] found that heparin treatment significantly attenuates lipopolysaccharide–induced production of pro-inflammatory TNF-α, and IL-6.

There are several theories for explanation of the mechanism of the inflammatory process occurring in cerulein-induced AP, but the exact mechanisms are still not completely understood. Cerulein, as an analog of cholecystokinin (CCK) acts as an agonist for CCK1 and CCK2 receptors which in turn activates JAK/Stat pathway and activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$_k$B), and hence increases cytokine expression as TNF-α and IL-6 [26].

Beside its anti-coagulant properties, heparin may play a positive role in AP due to its anti-inflammatory effects. The mechanism by which heparin induces its anti-inflammatory effects is yet to be elucidated, but it is suggested to be due to: TNF-α inhibition[27], protection from oxygen free radicals [28], the blockade of complement activity[29], blockade of histamine release [27] and inhibition of NF-$_k$B activation[30]. The inhibition of the pro-inflammatory NF-$_k$B activation probably represents one of the most important mechanisms by which heparin exerts its anti-inflammatory effects. Also, products of enzymatic degradation of heparin exhibit this anti-inflammatory effect.

NF-$_k$B activation is considered to be an amplifying and perpetuating mechanism of the inflammatory process, and is implicated in a wide range of inflammatory diseases [31]. NF-$_k$B regulates the expression of many genes whose products are chemokines, immune receptors and adhesion molecules [30]. Its activation is a vital for pro-inflammatory cytokines regulation [32]. It promotes the transcription of the TNF-α gene [33]. The inhibition of NF-$_k$B would interrupt the positive inflammatory feedback loop generated by TNF-α and IL-6 and globally down-regulate the production of a wide range of pro-inflammatory molecules [34]. Previous studies have reported an inhibitory effect of heparin on endothelial NF-$_k$B activation[30]. Hochart et al., [35] showed that heparin down-regulated NF-$_k$B mediated activation of TNF-α stimulated human umbilical vascular endothelial cells. Similarly, a study by Young[36] demonstrated a significant inhibition of NF-$_k$B expression by heparin in high glucose stimulated human endothelial cells. Also, Wang et al., [37] found that heparin given after lipopolysaccharide injection attenuated inflammatory response, TNF-α and NF-$_k$B activation.

The increase in plasma levels of amylase and lipase is a well established index of acute pancreatitis [38]. In our

present work, heparin treatment has significantly reduced the pancreatitis evoked increase in plasma levels of pancreatic enzymes amylase and lipase. This finding is an evidence of protective effect of heparin on the pancreas. Heparin reduces activity of trypsin[39] and chemotrypsin [4] and inhibits conversion of trypsinogen to trypsin [40]. For this reason, the heparin evoked reduction in plasma levels of pancreatic enzymes in AP can be a result or/ and cause of its protective effect on pancreas.

The results of the present work showed that induction of AP by cerulein led to significant prolongation of APTT. These data indicate that development of AP is associated with formation of thrombi within pancreatic and systemic circulation. In short, AP promotes coagulation via a large number of molecular and cellular mechanisms. The primary mechanism responsible for this pro-coagulant activity may be the generation of pro-inflammatory cytokines especially TNF-α and IL-6[30]. These cytokines, in turn, induce tissue factor (TF) expression in endothelial cells, whereby extrinsic coagulation cascade is initiated [41]. At the same time, many clotting system components, such as thrombin, Factor Xa and the TF-factor VIIa complex, working in conjunction with the inhibition of endogenous anticoagulants as anti-thrombin and activated protein C [30]. So, the prolongation in APTT seems to be a result of consumption of factors involved in coagulation.

The results of the present work showed that treatment with heparin significantly reduced pancreatitis–induced increase in APTT. This observation indicates that treatment with heparin prevents activation of coagulation and for this reason, reduces consumption of coagulation factors and creation of products of fibinolysis [42].

In our present study, heparin administration significantly reduced hematocrit level which may suggest that heparin reduces capillary permeability. Therefore, heparin therapy may reduce the need for vigorous fluid resuscitation as applied in patients with AP [43].

CONCLUSION:

We conclude that heparin exhibits therapeutic effect in cerulein–induced experimental acute pancreatitis in rats and this effect is related to improvement of the biochemical and histopathological parameters. The findings of this study might provide a basis for new clinical studies investigating the therapeutic role of heparin in acute pancreatitis.

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الملخص العربي

هدف البحث:

يهدف هذا البحث إلى دراسة تأثير الهيبارين على التهاب البنكرياس الحاد المستحدث بالسيروليين في الفئران البيضاء.

طرق البحث :- تم إجراء البحث على ٣٠ فأر يتراوح وزنهم بين١٨٠-٢٠٠ جم. وتم تقسيمهم إلى ٣ مجموعات:

١- المجموعة الضابطة: تم إعطاءها المحلول الملحى بجرعة ١ مل لكل كيلو جرام من وزن الجسم تحت الجلد أربع مرات.

٢- المجموعة المصابه بإلتهاب البنكرياس الحاد: تم ذلك عن طريق حقن السيروليين تحت الجلد بجرعة ٢٠ميكروجرام لكل كيلو جرام من وزن الجسم أربع مرات

٣- المجموعة التي تم علاجها بالهيبارين: تم إعطاءها الهيبارين بجرعة ١٥٠ وحده لكل كيلو جرام من وزن الجسم وذلك بعد من ٣-٤ ساعات من الحقن الاول للسيروليين

وقد تم أخذ عينات الدم التي جمعت من أجل قياس مستوى الأميليز،الليباز، عامل نخر الورم ألفا، انترلوكين ٦، زمن التنشيط الجزئي لتجلط الدم ومستويات الهيماتوكريت.وقد أجرى بحث مجهرى لنسيج البنكرياس.

النتائج: بمقارنة المجموعة المصابه بالتهاب البنكرياس الحاد بالمجموعة الضابطة وجد انه قد زادت مستويات الأميليز، والليباز، عامل نخر الورم ألفا ، انترلوكين ٦، مستويات الهيماتوكريت وزمن التنشيط الجزئي لتجلط الدم زيادة ذات دلالة إحصائية. أما بعد العلاج بالهيبارين انخفضت مستويات الأميليز،والليباز، عامل نخر الورم ألفا ،انترلوكين ٦، مستويات الهيماتوكريت وزمن التنشيط الجزئي لتجلط الدم انخفاضا ذو دلالة إحصائية بالمقارنة بالمجموعة المصابه بالتهاب البنكرياس الحاد. كما وجد ان التغيرات المرضيه لنسيج البنكرياس قد تحسنت.

الاستنتاجات: من النتائج السابقه يتضح أن العلاج بالهيبارين ادى الى تحسين النتائج البيوكيميائية والتغيرات المرضية لنسيج البنكرياس في النموذج التجريبي للفئران المصابة بإلتهاب البنكرياس الحاد. ولذلك فإن الهيبارين قد يعتبر علاجا فعالا لالتهاب البنكرياس الحاد.