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(71) Demandeur/Applicant:
SHENZHEN HIGHTIDE BIOPHARMACEUTICAL, LTD.,
CN
(72) Inventeurs/Inventors:
LIU, LIPING, CN;
BAI, RU, CN
(74) Agent: GOWLING WLG (CANADA) LLP

(54) Titre : UTILISATION D'UN COMPOSE POLYPEPTIDIQUE DANS LE TRAITEMENT DE LA PANCREATITE AIGUE
(54) Title: USE OF PEPTIDE COMPOUNDS IN TREATING ACUTE PANCREATITIS

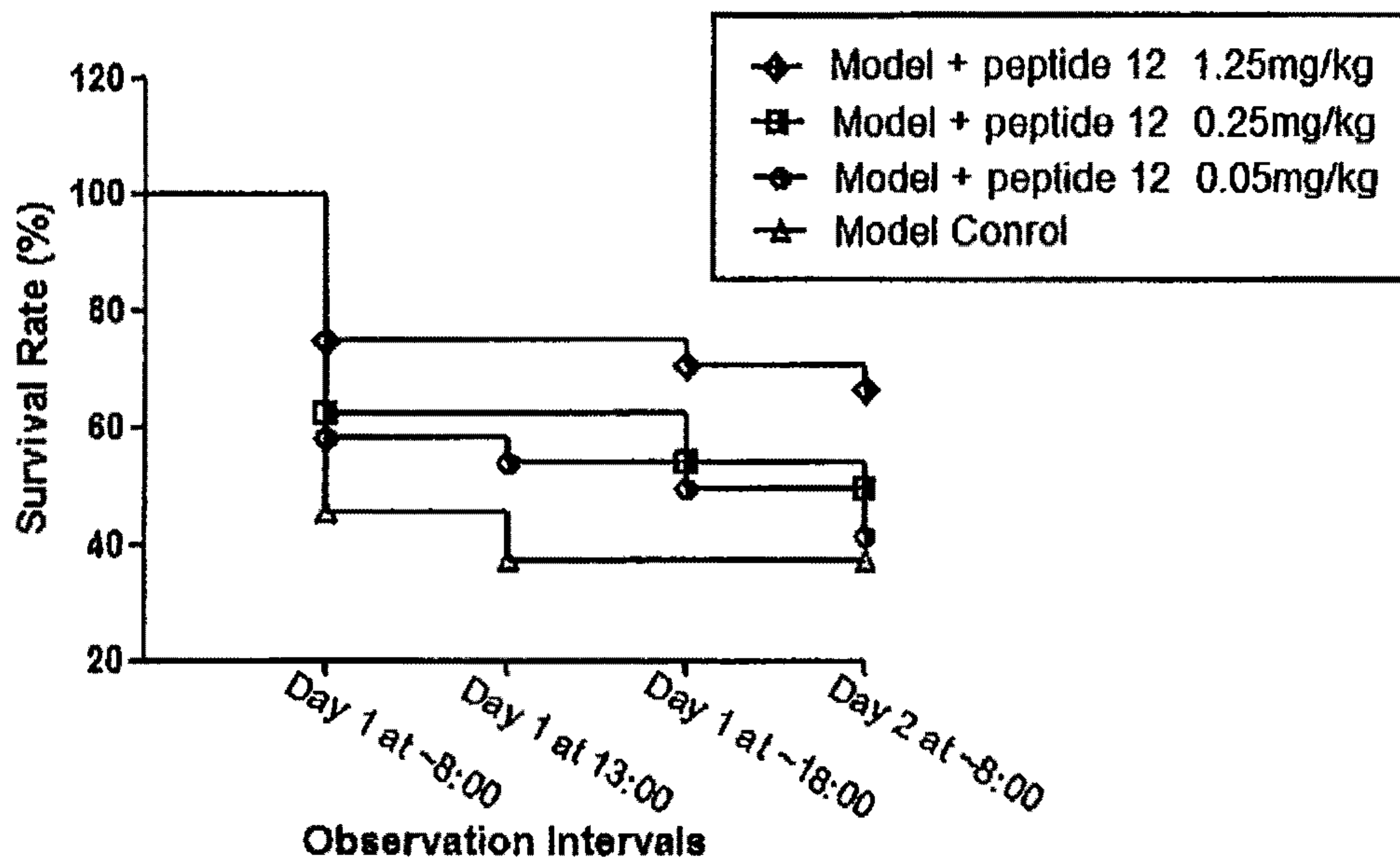


Figure 1. Beneficial effects of peptide No. 12 on the survival outcome in sodium taurocholate induced pancreatitis model

(57) **Abrégé/Abstract:**

Disclosed is the use of an INGAP-PP peptide, an HIP peptide or an analogue thereof in the preparation of a drug for treating acute pancreatitis. The polypeptide compound can significantly reduce the increase in the levels of amylase and lipase in the blood caused by acute pancreatitis, reduce the degree of pancreatic pathological damage caused by pancreatitis, and significantly decrease death caused by acute pancreatitis.

ABSTRACT

5 This invention discloses certain method of use of peptides and their analogs in the treatment of acute pancreatitis. The disclosed peptides and analogs can significantly lower the elevated blood amylase and lipase levels caused by acute pancreatitis, reduce the degree of injury observed in pancreatic histopathology caused by pancreatitis, and significantly lower the mortality rate of acute pancreatitis.

USE OF PEPTIDE COMPOUNDS IN TREATING ACUTE PANCREATITIS

Description of the Invention

Technical field

5 The invention generally relates to the field of peptide compounds for treating acute pancreatitis, and more specifically to the use of INGAP-PP peptide, HIP peptide, or analogs thereof in treating acute pancreatitis.

Background of the invention

10 Pancreatitis is generally considered as a disease of the pancreas caused by the digestion of trypsin itself. Based on the course of the disease, pancreatitis can be divided into acute pancreatitis (AP) and chronic pancreatitis (CP). The annual occurrence of pancreatitis is reported to be 13-45/100,000, and the occurrence of acute pancreatitis has been increasing over the past 30 years.

15 Acute pancreatitis is a disease of multiple organ dysfunction involving a variety of factors. Its typical symptoms include severe and persistent upper abdominal pain, which usually radiates to the back and ribs, and is often accompanied by vomiting, abdominal distention, fever, increased heart rate, increased white blood cell count, elevated blood or urinary amylase levels. Interstitial edema and fat necrosis to macroscopic pancreatic parenchyma or peripancreatic necrosis and hemorrhage can be seen from microscopic observation. The causes and pathogenesis of acute pancreatitis vary, and various etiologies and mechanisms may interact, leading to poor clinical prognosis.

20 At present, the existing treatment methods are limited to supportive and conservative treatments including pain relief, fluid replacement to maintain water and electrolyte balance, nutritional support, infection prevention and prevention of complications. There is no drug proven to have significant efficacy in curing acute pancreatitis.

Therefore, it is still necessary to develop new drugs and methods that can effectively treat acute pancreatitis.

Summary of invention

30 The diagnostic criteria of acute pancreatitis are basically the same as an international consensus. It is considered that the diagnosis of acute pancreatitis should meet at least

two of the following three criteria: (1) abdominal pain symptoms consistent with acute pancreatitis; (2) serum amylase and/or lipase ≥ 3 times the upper limit of their normal values; and (3) imaging characteristics of acute pancreatitis.

5 The applicant unexpectedly found that INGAP-PP peptide, HIP peptide, or their analogs may significantly reduce the elevation of blood amylase and lipase levels caused by pancreatitis, lower the degree of pancreatic pathological damage caused by pancreatitis, and significantly improve the survival rate of animal models of acute pancreatitis induced by sodium taurocholate.

10 Therefore, in some respects, this invention provides the use of INGAP-PP peptide, HIP peptide, or analogs thereof in the treatment of acute pancreatitis.

In other respects, the invention provides a method of treating acute pancreatitis, including administering a patient a composition comprising an INGAP-PP peptide, HIP peptide, or analogs thereof.

15 These and other aspects, features and advantages of the disclosure will become apparent in accordance with the following description of the disclosure and in conjunction with the drawings.

Brief Description of the Drawings

20 In conjunction with the drawings, the above and other features, aspects and advantages of the disclosure herein will be readily understood from the following description:

Figure 1 shows the comparison of the survival rate between the peptide treatment groups and the model control group in sodium taurocholate-induced severe acute pancreatitis (SAP) model.

25 Figure 2 shows the comparison of the serum amylase levels between the peptide treatment groups and the model control group in sodium taurocholate-induced severe acute pancreatitis (SAP) model.

Figure 3 shows the comparison of the serum lipase levels between the peptide treatment groups and the model control group in sodium taurocholate-induced severe acute pancreatitis (SAP) model.

30 Figure 4 shows the comparison of pathological changes of edema between the peptide

treatment groups and the model control group in sodium taurocholate-induced severe acute pancreatitis (SAP) model.

5 Figure 5 shows the comparison of pathological changes of inflammation between the peptide treatment groups and the model control group in sodium taurocholate-induced severe acute pancreatitis (SAP) model.

Figure 6 shows the comparison of pathological changes of hemorrhage between the peptide treatment groups and the model control group in sodium taurocholate-induced severe acute pancreatitis (SAP) model.

10 Figure 7 shows the comparison of pathological changes of necrosis between the peptide treatment groups and the model control group in sodium taurocholate-induced severe acute pancreatitis (SAP) model.

Figure 8 shows the comparison of pathological changes of total damage between the peptide treatment groups and the model control group in sodium taurocholate-induced severe acute pancreatitis (SAP) model.

15 Figure 9 shows the comparison of pancreatic index between the peptide treatment groups and the model control group in caerulein-induced acute pancreatitis (AP) model.

20 Figure 10 shows the comparison of amylase levels between the peptide treatment groups and the model control group in caerulein-induced acute pancreatitis (AP) model.

Figure 11 shows the comparison of lipase levels between the peptide treatment groups and the model control group in caerulein-induced acute pancreatitis (AP) model.

25 Figure 12 shows the comparison of pathological changes of edema between the peptide treatment groups and the model control group in caerulein-induced acute pancreatitis (AP) model.

Figure 13 shows the comparison of pathological changes of inflammation between the peptide treatment groups and the model control group in caerulein-induced acute pancreatitis (AP) model.

Detailed Description of the Invention

30 Each of the embodiments provided below contributes to the interpretation of certain

aspects of the disclosure herein, but should not be construed as limiting the scope of the invention. In addition, throughout the Description of the Invention and Claims, as used herein, similar language may be applied to modify any quantitative representation that allows for changes, but will not lead to changes in the related basic functions. Thus, the value modified by one or more terms such as "approximate" is not limited to the specified exact value. In some cases, the similar language may correspond to the precision of the instrument used to measure the value.

The phrases "parenteral administration" and "non-gastrointestinal administration" are well-known terms in the field, including modes of administration other than intestinal and local administration, such as injections, but not limited to injection and infusion via intravenous, intramuscular, intrapleural, intravascular, intrapericardial, arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, tracheal, subcutaneous, subepidermal, intraarticular, subcapsular, subarachnoid, spinal, and sternum.

The term "treatment" includes preventing the occurrence of disease, disorder or symptom in an animal that may be susceptible to disease, disorder and/or condition but has not yet been diagnosed; inhibiting disease, disorder or symptom, such as impeding its development; and alleviating disease, disorder or symptom, such as subsiding the disease, disorder, and/or symptom of the disease. Treatment of diseases or symptom includes the improvement of specific disease or at least one specific symptom of the disease.

The phrase "pharmaceutically acceptable" refers to compositions, polymers, and other materials and/or dosage forms that are within reasonable medical judgment applicable to contact with human and animal tissues without excessive toxicity, irritation, allergy or other problems or complications.

The phrase "pharmaceutically acceptable carrier" refers to a pharmaceutically acceptable material, composition or medium, such as a liquid or solid filler, diluent, solvent, or encapsulation material, involved in carrying or transporting any test composition from one organ or part of the body to another. It must be "acceptable" in the sense that it is compatible with other components of the test composition and does not harm the patient.

As used herein, the term "patient" refers to a mammal, such as a mouse, guinea pig, rat, dog or human. A preferred patient is a human.

The preparations of certain INGAP-PP peptide, HIP peptide and their analogs were

disclosed in PCT/CN2014/073483 and PCT/CN2013/072771, previously submitted by this applicant, indicating that certain INGAP-PP peptide, HIP peptide, and their analogs have multiple pharmacological activities, but anti-acute pancreatitis activities were not disclosed. PCT/CN2014/073483 and PCT/CN2013/072771 are both integrated herein in their entireties by reference.

The applicant unexpectedly discovered that certain INGAP-PP peptide, HIP peptide, and their analog (as exemplified by Ac-IGLHD PSHGT LPAGS-OH, SEQ ID NO. 12 in Table 2 below), significantly reduced the pathological changes of pancreatic edema and inflammation, and significantly reduced the levels of blood amylase and lipase (see Figure 10 and Figure 11) in a mouse model of acute pancreatitis induced by caerulein. Administered with certain INGAP-PP peptide, HIP peptide, and their analog (as exemplified by Ac-IGLHD PSHGT LPAGS-OH, SEQ ID NO. 12 in Table 2 below) can significantly increase the survival rate of rats with acute pancreatitis induced by sodium taurocholate. In Example 1, three doses (low dose of 0.05 mg/kg, medium dose of 0.25 mg/kg and high dose of 1.25 mg/kg) were tested. All the surviving animals in the treatment groups maintained good mental status and activity status, which were significantly better than those in the model control group.

Therefore, in one aspect, the application provides the use of INGAP-PP peptide, HIP peptide or their analogs in the treatment of patients with acute pancreatitis. The application also provides the use of INGAP-PP peptide, HIP peptide or their analogs in the preparation of medicament for the treatment of acute pancreatitis. In one embodiment, the INGAP-PP peptide analog is Ac-IGLHD PSHGT LPAGS-OH.

INGAP-PP peptide, HIP peptide and their analogs are provided in Table 1 to Table 3 below.

25

Table 1. INGAP-PP and HIP Peptides

Peptide ID / SEQ ID NO.	Sequence
1(INGAP-PP)	H-IGLHDPSHGTLPNGS-OH
2(HIP)	H-IGLHDPTQGTEPNGE-OH

Table 2. Exemplary INGAP-PP Analogs

Peptide ID /	Sequence

SEQ ID NO.	
1	H-IGLHDPSHGTLPNGS-OH
6	H-IGLHAPSHGTLPNGS-OH
7	H-IGLHDPSHGTLPAGS-OH
8	H-IGLHAPSHGTLPAGS-OH
9	H-IGLHDPSHGTLPAGSK-OH
10	H-IGLHDPSHGTLP(Aib)GS-OH
11	H-IGLHDPSHGTLP(N-methyl-L-Alanine)GS-OH
12	Ac-IGLHDPSHGTLPAGS-OH
13	H-(D-Isoleucine)GLHDPSHGTLPAGS-OH
14	H-(L-NorValine)GLHDPSHGTLPAGS-OH
15	H-(L-NorLeucine)GLHDPSHGTLPAGS-OH
16	Ac-IGLHDPSHGTLPNGS-OH
17	H-(D-Isoleucine)GLHDPSHGTLPNGS-OH
18	H-IGLHDPSHGTEPNGS-OH
19	H-IGLHDPSQGTLPNGS-OH
20	H-IGLHDPTHGTLPNGS-OH
21	H-IGLHDPSHGTLPNGE-OH
22	H-IGLHDPSHGTLPNGK-OH
23	H-IGLHDPSHGTLPAGK-OH
24	H-IGLHDPSHGTEPAGS-OH
25	H-IGLHDPSQGTLPAGS-OH
26	H-IGLHDPTHGTLPAGS-OH
27	H-IGLHDPSHGTLPAGE-OH
28	H-IGLHDPSHGTLPAG-NH2
29	Ac-IGLHDPSHGTLPAGS-NH2
30	Ac-IGLHDPSHGTLPAG-NH2
31	Ac-IGLHDPSHGTLPNGS-NH2
32	H-IGLHDPSHGTLPNGS-NH2
33	H-IGLHDPSHGTLPNGSC-OH
34	Ac-IGLHDPSHGTLPNGSC-OH
35	H-IGLHDPSHGTLPNGSC-NH2
36	Ac-IGLHDPSHGTLPNGSC-NH2
37	H-IGLHDPSHGTLPNGC-OH
38	Ac-IGLHDPSHGTLPNGC-OH
39	H-IGLHDPSHGTLPNGC-NH2

40	Ac-IGLHDP SHGTL PNGC-NH2
41	H-IGLHDP SHGTL P AGS-NH2
42	H-IGLHDP SHGTL P AGSC-OH
43	Ac-IGLHDP SHGTL P AGSC-OH
44	H-IGLHDP SHGTL P AGSC-NH2
45	Ac-IGLHDP SHGTL P AGSC-NH2
46	H-IGLHDP SHGTL P AGC-OH
47	Ac-IGLHDP SHGTL P AGC-OH
48	H-IGLHDP SHGTL P AGC-NH2
49	Ac-IGLHDP SHGTL P AGC-NH2
73	IGLHDP SHGTL P AG
74	IGLHDP SHGTL PNG
75	Ac-IGLHDP SHGTL PNG
76	IGLHDP SHGTL PNG-NH2
77	Ac-IGLHDP SHGTL PNG-NH2
78	H-IGLHDP SHGTL P QGS-OH
79	H-IGLHDP SHGTL P DGS-OH
80	H-IGLHDP SHGTL P EGS-OH
81	H-IGLHEP SHGTL P NGS-OH
82	H-IGLHQP SHGTL P NGS-OH
83	H-IGLHNPSHGTL P NGS-OH
84	H-IGLHEP SHGTL P AGS-OH
85	H-IGLHQP SHGTL P AGS-OH
86	H-IGLHNPSHGTL P AGS-OH
87	H-IGLHDP SHGTL P QGSC-OH
88	H-IGLHDP SHGTL P DGSC-OH
89	H-IGLHDP SHGTL P EGSC-OH
90	H-IGLHEP SHGTL P NGSC-OH
91	H-IGLHQP SHGTL P NGSC-OH
92	H-IGLHNPSHGTL P NGSC-OH
93	H-IGLHDP SHGTL P QG-OH
94	H-IGLHDP SHGTL P DG-OH
95	H-IGLHDP SHGTL P EG-OH
96	H-IGLHEP SHGTL P NG-OH
97	H-IGLHQP SHGTL P NG-OH
98	H-IGLHNPSHGTL P NG-OH
99	H-IGLHEP SHGTL P AG-OH

100	H-IGLHQPSHGTLPAG-OH
101	H-IGLHNPSHGTLPAG-OH
102	H-IGLHDPSHGTLPQGE-OH
103	H-IGLHDPSHGTLPDGE-OH
104	H-IGLHDPSHGTLPEGE-OH
105	H-IGLHEPSHGTLPNGE-OH
106	H-IGLHQPSHGTLPNGE-OH
107	H-IGLHNPSHGTLPNGE-OH
108	H-IGLHEPSHGTLPAGE-OH
109	H-IGLHQPSHGTLPAGE-OH
110	H-IGLHNPSHGTLPAGE-OH

Table 3. Exemplary HIP Analogs

Peptide ID / SEQ ID NO.	Sequence
2	H-IGLHDPTQGTEPNGE-OH
50	H-IGLHDPTQGTEPAGE-OH
51	H-IGLHDPTQGTEP(Aib)GE-OH
52	Ac-IGLHDPTQGTEPAGE-OH
53	H-(D-Isoleucine)GLHDPTQGTEPAGE-OH
54	Ac-IGLHDPTQGTEPNGE-OH
55	H-(D-Isoleucine)GLHDPTQGTEPNGE-OH
56	H-IGLHDPTQGTEPNGS-OH
57	H-IGLHDPTQGTEPAGS-OH
58	H-IGLHDPTQGTLPNGE-OH
59	H-IGLHDPTQGTLPAGE-OH
60	Ac-IGLHDPTQGTEPAG-NH ₂
61	Ac-IGLHDPTQGTEPNGE-NH ₂
62	Ac-IGLHDPTQGTEPAGE-NH ₂
63	H-IGLHDPTQGTEPNGE-NH ₂
64	H-IGLHDPTQGTEPNGC-OH
65	Ac-IGLHDPTQGTEPNGC-OH
66	H-IGLHDPTQGTEPNGC-NH ₂
67	Ac-IGLHDPTQGTEPNGC-NH ₂
68	H-IGLHDPTQGTEPAGE-NH ₂

69	H-IGLHDPTQGTEPAGC-OH
70	Ac-IGLHDPTQGTEPAGC-OH
71	H-IGLHDPTQGTEPAGC-NH ₂
72	Ac-IGLHDPTQGTEPAGC-NH ₂

As is well known to those skilled in the art, in the peptide sequence, the symbols and the amino acids they represent are shown in Table 4 below.

Table 4

Chinese Name	English Name	Symbols or Abbreviations
丙氨酸	Alanine	A or Ala
精氨酸	Arginine	R or Arg
天冬酰胺	Asparagine	N or Asn
天冬氨酸	Aspartic acid	D or Asp
半胱氨酸	Cysteine	C or Cys
谷氨酰胺	Glutamine	Q or Gln
谷氨酸	Glutamic acid	E or Glu
甘氨酸	Glycine	G or Gly
组氨酸	Histidine	H or His
异亮氨酸	Isoleucine	I or Ile
亮氨酸	Leucine	L or Leu
赖氨酸	Lysine	K or Lys
蛋氨酸	Methionine	M or Met
苯丙氨酸	Phenylalanine	F or Phe
脯氨酸	Proline	P or Pro
丝氨酸	Serine	S or Ser
苏氨酸	Threonine	T or Thr
色氨酸	Tryptophan	W or Trp
酪氨酸	Tyrosine	Y or Tyr
缬氨酸	Valine	V or Val

5

In one embodiment, the INGAP-PP peptide analogs comprise the following general

formula.



wherein, X¹ is selected from Isoleucine (I), D-Isoleucine, L-NorValine or L-NorLeucine; X² is selected from Alanine (A) or Aspartic Acid (D); X³ is selected from Serine (S) or Threonine (T); X⁴ is selected from Histidine (H) or Glutamine (Q); X⁵ is selected from Leucine (L) or Glutamic acid (E); and

when it is established that X¹ is Isoleucine (I), X² is Aspartic Acid (D), X³ is Serine (S), X⁴ is Histidine (H), and X⁵ is Leucine (L), then X⁶ is selected from either Alanine (A), α -Amino-isobutyric acid or N-methyl-L-Alanine; and

when it is not established that X¹ is Isoleucine (I), X² is Aspartic Acid (D), X³ is Serine (S), X⁴ is Histidine (H) and X⁵ is Leucine (L), then X⁶ is selected from Alanine (A), Asparagine (N), α -Amino-isobutyric acid or N-methyl-L-Alanine.

In one embodiment, the INGAP-PP peptide analogs of formula (1) can be selected from the following peptides.

- H-IGLHAPSHGTLPNGS-OH (SEQ ID NO:6);
- H-IGLHDPSHGTLP(Aib)GS-OH (SEQ ID NO:10);
- H-IGLHDPSHGTLP(N-methyl-L-Alanine)GS-OH (SEQ ID NO:11);
- H-(D-Isoleucine)GLHDPSHGTLPNGS-OH (SEQ ID NO:17);
- H-IGLHDPSHGTEPNGS-OH (SEQ ID NO:18);
- H-IGLHDPSQGTLPNGS-OH (SEQ ID NO:19); and
- H-IGLHDPTHGTLPNGS-OH (SEQ ID NO:20).

In another embodiment, the INGAP-PP peptide analogs of formula (1) can be selected from the following peptides.

- H-IGLHDPSHGTLPAGS-OH (SEQ ID NO:7);
- H-IGLHAPSHGTLPAGS-OH (SEQ ID NO:8);
- H-(D-Isoleucine)GLHDPSHGTLPAGS-OH (SEQ ID NO:13);

H-(L-NorValine)GLHDPSHGTLPAGS-OH (SEQ ID NO:14);

H-(L-NorLeucine)GLHDPSHGTLPAGS-OH (SEQ ID NO:15);

H-IGLHDPSHGTEPAGS-OH (SEQ ID NO:24);

H-IGLHDPSQGTLPAGS-OH (SEQ ID NO:25); and

5 H-IGLHDPTHGTLPAGS-OH (SEQ ID NO:26).

In another embodiment, the INGAP-PP peptide analogs comprise the following general formula.



10 wherein, m is 0 or 1; R¹ is selected from -H or -Ac; R² is selected from -OH or -NH₂; and

when it is established that R¹ is -H, R² is -OH and m is 0, then X¹ is selected from Glutamic acid (E), Cysteine (C) or Lysine (K); and

when it is not established that R¹ is -H, R² is -OH and m is 0, then X¹ is selected from Serine (S), Glutamic acid (E), Cysteine (C) or Lysine (K).

15 In one embodiment, the INGAP-PP peptide analogs in formula (2) can be selected from H-IGLHDPSHGTLPNGE-OH (SEQ ID NO :21) and H-IGLHDPSHGTLPNGK-OH (SEQ ID NO: 22).

In one embodiment, the INGAP-PP peptide analogs in formula (2) can be selected from the following peptides.

20 Ac-IGLHDPSHGTLPNGS-NH₂ (SEQ ID NO: 31);

H-IGLHDPSHGTLPNGS-NH₂ (SEQ ID NO: 32); and

Ac-IGLHDPSHGTLPNGS-OH (SEQ ID NO: 16).

In one embodiment, the INGAP-PP peptide analogs in formula (2) can be selected from the following peptides.

25 H-IGLHDPSHGTLPNGC-OH (SEQ ID NO: 37);

Ac-IGLHDPSHGTLPNGC-OH (SEQ ID NO: 38);

H-IGLHDPSHGTLPNGC-NH₂ (SEQ ID NO: 39); and

Ac-IGLHDPSHGTLPNGC-NH₂ (SEQ ID NO: 40).

In one embodiment, the INGAP-PP peptide analogs in formula (2) can be selected from the following peptides.

5 H-IGLHDPSHGTLPNGSC-OH (SEQ ID NO: 33);

Ac-IGLHDPSHGTLPNGSC-OH (SEQ ID NO: 34);

H-IGLHDPSHGTLPNGSC-NH₂ (SEQ ID NO: 35); and

Ac-IGLHDPSHGTLPNGSC-NH₂ (SEQ ID NO: 36).

10 In one embodiment, the INGAP-PP peptide analogs in formula (2) can be selected from the following peptides.

H- IGLHDPSHGTLPNG -OH (SEQ ID NO: 74);

Ac-IGLHDPSHGTLPNG -OH (SEQ ID NO: 75);

H- IGLHDPSHGTLPNG-NH₂ (SEQ ID NO: 76); and

Ac-IGLHDPSHGTLPNG-NH₂ (SEQ ID NO: 77).

15 In another embodiment, the INGAP-PP peptide analogs comprise the following general formula.



wherein, m is 0 or 1; R¹ is selected from -H or -Ac; R² is selected from -OH or -NH₂; and

20 when it is established that R¹ is -H, R² is -OH and m is 1, then X¹ is selected from Glutamic acid (E), Cysteine (C) or Lysine (K); and

when it is not established that R¹ is -H, R² is -OH and m is 1, then X¹ is selected from Serine (S), Glutamic acid (E), Cysteine (C) or Lysine (K).

25 In one embodiment, the INGAP-PP peptide analogs of formula (3) can be selected from H-IGLHDPSHGTLPAGE-OH (SEQ ID NO : 27) and H-IGLHDPSHGTLPAGK-OH (SEQ ID NO: 23).

In one embodiment, the INGAP-PP peptide analogs of formula (3) can be selected from the following peptides.

Ac-IGLHDPSHGTLPAGS-NH₂ (SEQ ID NO: 29);

H-IGLHDPSHGTLPAGS-NH₂ (SEQ ID NO: 41); and

5 Ac-IGLHDPSHGTLPAGS-OH (SEQ ID NO: 12).

In one embodiment, the INGAP-PP peptide analogs of formula (3) can be selected from the following peptides.

H-IGLHDPSHGTLPAGC-OH (SEQ ID NO: 46);

Ac-IGLHDPSHGTLPAGC-OH (SEQ ID NO: 47);

10 H-IGLHDPSHGTLPAGC-NH₂ (SEQ ID NO: 48); and

Ac-IGLHDPSHGTLPAGC-NH₂ (SEQ ID NO: 49).

In one embodiment, the INGAP-PP peptide analogs of formula (3) can be selected from the following peptides.

H-IGLHDPSHGTLPAG-OH (SEQ ID NO: 73);

15 H-IGLHDPSHGTLPAG-NH₂ (SEQ ID NO: 28); and

Ac-IGLHDPSHGTLPAG-NH₂ (SEQ ID NO: 30).

In one embodiment, the INGAP-PP peptide analogs comprise the following general formula.

R^1 -IGLHDPSHGTLPAGSX²-R² (4);

20 wherein, X² is selected from Lysine (K) or Cysteine (C); R¹ is selected from -H or -Ac, R² is selected from -OH or -NH₂.

In one embodiment, the INGAP-PP peptide analogs of formula (4) can be selected from the following peptides.

H-IGLHDPSHGTLPAGSK-OH (SEQ ID NO: 9);

25 H-IGLHDPSHGTLPAGSC-OH (SEQ ID NO: 42);

or Cysteine (C); and

when it is not established that R¹ is -H and R² is -OH, then X¹ is selected from Serine (S), Glutamic acid (E) or Cysteine (C).

5 In one embodiment, the HIP peptide analogs of formula (6) can be selected from the following peptides.

Ac-IGLHDPTQGTEPNGE-OH (SEQ ID NO: 54);

Ac-IGLHDPTQGTEPNGE-NH₂ (SEQ ID NO: 61); and

H-IGLHDPTQGTEPNGE-NH₂ (SEQ ID NO: 63).

10 In one embodiment, the HIP peptide analogs of formula (6) can be selected from the following peptides.

H-IGLHDPTQGTEPNGS-OH (SEQ ID NO: 56);

H-IGLHDPTQGTEPNGC-OH (SEQ ID NO: 64);

Ac-IGLHDPTQGTEPNGC-OH (SEQ ID NO: 65);

H-IGLHDPTQGTEPNGC-NH₂ (SEQ ID NO: 66); and

15 Ac-IGLHDPTQGTEPNGC-NH₂ (SEQ ID NO: 67).

In one embodiment, the HIP peptide analogs comprise the following general formula.

$$R^1\text{-IGLHDPTQGTEPAG}(X^1)_n\text{-R}^2 \quad (7);$$

wherein, R¹ is selected from -H or -Ac; R² is selected from -OH or -NH₂; n is 0 or 1; X¹ is selected from Serine (S) or Cysteine (C).

20 In one embodiment, the HIP peptide analogs of formula (7) can be selected from the following peptides.

H-IGLHDPTQGTEPAGS-OH (SEQ ID NO: 57);

Ac-IGLHDPTQGTEPAG-NH₂ (SEQ ID NO: 60);

H-IGLHDPTQGTEPAGC-OH (SEQ ID NO: 69);

25 Ac-IGLHDPTQGTEPAGC-OH (SEQ ID NO: 70);

H-IGLHDPTQGTEPAGC-NH₂ (SEQ ID NO: 71); and

Ac-IGLHDPTQGTEPAGC-NH₂ (SEQ ID NO: 72).

In one embodiment, the HIP peptide analogs of formula (7) can be selected from the following peptides.

5 Ac-IGLHDPTQGTEPAGE-OH (SEQ ID NO: 52);

Ac-IGLHDPTQGTEPAGE-NH₂ (SEQ ID NO: 62); and

H-IGLHDPTQGTEPAGE-NH₂ (SEQ ID NO: 68).

10 The INGAP-PP peptide, HIP peptide, or analogs thereof for the invention can exist in any pharmaceutically acceptable salt form. Especially useful salt forms are acetate and hydrochloride. When the INGAP-PP peptide, HIP peptide, or their analogs of the invention have acid or alkaline group, they can be provided in pharmaceutically acceptable salt form (see, for example, Berge *et al.*, *J. Pharm. Sci.* 1977, 66, 1-19; and *Handbook of Pharmaceutical Salts, Properties, and Use*; Stahl and Wermuth, Ed.; Wiley-VCH and VHCA: Zurich, Switzerland, 2002).

15 Suitable acids for the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetylamino benzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, decanoic acid, hexanoic acid, octanoic acid, 20 cinnamic acid, citric acid, cyclic acid, cyclohexyl aminosulfonic acid, dodecyl sulfuric acid, 1,2-ethanedithionyl acid, ethyl sulfuric acid, 2-hydroxyethyl sulfuric acid, formic acid, fumaric acid, galactose diacid, gentioic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α -oxoglutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+) – L-lactic acid, 25 (\pm) – DL-lactic acid, lactose acid, lauric acid, maleic acid, (-) – L-malic acid, malonic acid, (\pm) – DL-mandelic acid, methanesulfonic acid, 2-naphthalene sulfuric acid, 1,5-naphthalene disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pantoic acid, perchloric acid, phosphoric acid, L- pyroglutamic acid, glucaric acid, salicylic acid, 4-aminosalicylic acid, 30 sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, L-tartaric acid, thiocyanic acid, p-toluene sulfuric acid, undecylenic acid and valeric acid.

Suitable bases for the preparation of pharmaceutically acceptable salts include, but are not limited to, inorganic bases such as magnesium hydroxide, calcium hydroxide,

potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, morphine, 4-(2-hydroxyethyl) morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl) pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amine, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucosamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

The INGAP-PP peptide, HIP peptide, or their analogs of the invention may be combined with pharmaceutically acceptable carriers to prepare compositions for the treatment of acute pancreatitis in patients. Pharmaceutically acceptable carriers may be, for example, water, sodium phosphate buffer solution, phosphate buffered saline solution, normal saline or Ringer solution or other physiological buffer saline, or other solvent or vehicle such as glycol, glycerol, and oil such as olive oil or injectable organic ester.

Pharmaceutically acceptable carriers may include physically acceptable compounds, such as for stabilizing or enhancing the absorption of INGAP-PP peptide, HIP peptide, or their analogs of the invention. These physically acceptable compounds include carbohydrates such as glucose, sucrose or dextrans, etc.; antioxidants such as ascorbic acid or glutathione, etc.; chelating agents such as ethylenediaminetetraacetic acid (EDTA), etc., that can disrupt microbial membranes; divalent metal ions such as calcium or magnesium; low molecular weight proteins; or other stabilizers or excipients. One skilled in the art would know that the choice of pharmaceutically acceptable carriers, including physiologically acceptable compounds, depends, for example, on the route of administration of the composition. Suitable carriers and formulations are well known in the art (see, for example: *Remington: The Science and Practice of Pharmacy*, 19th ed., ed. A. R. Gennaro, Mack Publishing Company, Easton, PA (1995); and *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton PA (1990)). Typically, an appropriate amount of pharmaceutically acceptable salt is used in formulations to render the formulation isotonic. The pH of the solution is generally from about 5 to about 8, for example, from about 7 to about 7.5.

Pharmaceutically acceptable carriers are known to those skilled in the art. These typically would be standard carriers for administration of drugs to humans, including

solutions such as sterile water, saline, and buffered solutions at physiological pH, as described above. Pharmaceutical compositions may include carriers, thickeners, diluents, buffers, preservatives, surfactants, and a substance that increases the selection possibility of INGAP-PP peptide, HIP peptide, or their analogs.

5 Further carriers may include carriers for sustained or controlled release preparations, such as semipermeable matrices of solid hydrophobic polymers covalently or non-covalently bound to the INGAP-PP peptide, HIP peptide or their analogs, which matrices are in the form of shaped articles, for example, films,, liposomes, non-liposome lipid complexes or microparticles, and the like, or other biocompatible
10 polymers well known to those skilled in the art (see, for example, U.S. Patent No. 6, 824, 822 and 8, 329, 648). Liposomes, which consist of phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer. (Gregoriadis, *Liposome Technology*, Vol. 1 (CRC Press, Boca Raton Fla., 1984). Various drug delivery methods are well known to those
15 skilled in the art (Langer, *Nature* 392 (Suppl): 5-10 (1998); Langer et al., *Nature* 428:487-492 (2004)). It will be apparent to those persons skilled in the art that certain carriers can be selected depending upon, for instance, the route of administration and concentration of composition being administered.

The pharmaceutical compositions can be administered in many ways depending on the
20 need for local or systemic treatment and on the area to be treated. It can be understood that various routes of administration are available for INGAP-PP peptide, HIP peptide, or their analogs, and methods of the invention. Such routes of administration encompass systemic and local routes of administration, and include ,without limitation, intravenous or intraperitoneal injection, intramuscular injection, subcutaneous
25 injection, transdermal delivery, percutaneous diffusion or electrophoresis, inhalation administration, oral administration, local injection, intracavitary administration, and extended release delivery devices, including local implantation of extended release devices, such as bioerodible or reservoir-based implants. Administration may be
30 topically (ophthalmically, vaginally, rectally, intranasally), orally, by inhalation, or parenterally, for example by intravenous drip, subcutaneous injection, intraperitoneal injection or intramuscular injection.

Preparations for parenteral administration include sterile aqueous solutions or non-aqueous solutions, suspensions and emulsions. Examples of non-aqueous solvents
35 include propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered

media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid, nutrient replenishers, electrolyte replenishers (such as Ringer's dextrose), and the like. Preservatives and other additives can be present such as, for example, antimicrobials, antioxidants, chelating agents, and inert gases and the like. Insulin is a well known peptide therapeutic, so methods used for delivery of insulin particularly amenable as a delivery method for peptides or analogs of the invention, including but not limited to syringes, pens, infusion pumps, inhalers, mouth sprays, tablets, and the like.

5
10 In one aspect, the invention provides a method for treating acute pancreatitis in patients, including administering to the patient a pharmaceutical composition comprising INGAP-PP peptide, HIP peptide, or analogs thereof. In one embodiment, the INGAP-PP peptide analog is Ac-IGLHD PSHGT LPAGS-OH.

15 In another aspect, the invention provides a method for reducing blood amylase and lipase levels in patients with acute pancreatitis, including administering to the patient a pharmaceutical composition comprising INGAP-PP peptide, HIP peptide, or analogs thereof. In one embodiment, the INGAP-PP peptide analog is Ac-IGLHD PSHGT LPAGS-OH.

20 In a further aspect, the invention provides a method for treating patient with acute pancreatitis by reducing blood amylase and lipase levels in patients with acute pancreatitis, including administering to the patient a pharmaceutical composition comprising INGAP-PP peptide, HIP peptide, or analogs thereof. In one embodiment, the INGAP-PP peptide analog is Ac-IGLHD PSHGT LPAGS-OH.

25 In another aspect, the invention provides a method for preventing or reducing pancreatic injury caused by acute pancreatitis, including administering to the patient a pharmaceutical composition comprising INGAP-PP peptide, HIP peptide, or their analogs. In one embodiment, the INGAP-PP peptide analog is Ac-IGLHD PSHGT LPAGS-OH.

30 In another aspect, the invention provides a method for treating inflammatory pancreatic diseases or symptoms, including administering the patient a pharmaceutical composition containing INGAP-PP peptide, HIP peptide, or analogs thereof. In one embodiment, the INGAP-PP peptide analog is Ac-IGLHD PSHGT LPAGS-OH.

Accordingly, the application also provides the use of pharmaceutical compositions comprising INGAP-PP peptide, HIP peptide, or their analogs in the treatment of

patients with acute pancreatitis.

The dosage of INGAP-PP peptide, HIP peptide, or analogs thereof in pharmaceutical compositions can be selected in a broad range, including but not limited to 0.0005 mg/kg/day-100 mg/kg/day; for example, about 0.0005 mg/kg/day, about 0.001 mg/kg/day, about 0.005 mg/kg/day, about 0.01 mg/kg/day, about 0.025 mg/kg/day, about 0.05 mg/kg/day, about 0.1 mg/kg/day, about 0.25 mg/kg/day, about 0.5 mg/kg/day, about 0.75 mg/kg/day, about 1.0 mg/kg/day, about 1.25 mg/kg/day, about 1.50 mg/kg/day, about 1.75 mg/kg/day, about 2.0 mg/kg/day, about 2.5 mg/kg/day, about 5.0 mg/kg/day, about 10.0 mg/kg/day, about 15.0 mg/kg/day, about 25.0 mg/kg/day, about 50.0 mg/kg/day, about 75.0 mg/kg/day, or about 100 mg/kg/day, and the like. The exemplary dose ranges include, but are not limited to 0.0005 mg/kg/day-0.005 mg/kg/day, 0.005 mg/kg/day-0.05 mg/kg/day, 0.025 mg/kg/day-0.25 mg/kg/day, 0.05 mg/kg/day-0.5 mg/kg/day, 0.25 mg/kg/day-2.5 mg/kg/day, 0.5 mg/kg/day-5.0 mg/kg/day, 2.5 mg/kg/day-25.0 mg/kg/day, 5.0 mg/kg/day-50.0 mg/kg/day, or 25.0 mg/kg/day-100 mg/kg/day, and etc.

The INGAP-PP peptide, HIP peptide or analogs thereof of the invention can also be combined with other known or to be developed drugs for the treatment of acute pancreatitis in the same preparation for patients with acute pancreatitis, or different preparations can be administered to patients with acute pancreatitis respectively. Drugs used in combination with INGAP-PP peptide, HIP peptide, or analogs thereof for the treatment of acute pancreatitis include, but are not limited to, trypsin secretion inhibitors such as glucagon, calcitonin, growth inhibitor hormone and its analog such as octreotide and the like, protease inhibitors such as ulinastatin, gabexate and the like, tumor necrosis factor-alpha (TNF-alpha) inhibitors such as pentoxifylline, and other drugs for treating acute pancreatitis, such as antioxidants, platelet activating factor antagonists, probiotics and activated protein C, etc.

The following examples are intended to illustrate the invention and should not be interpreted in any way as limiting the invention.

Example 1: Effects of peptide NO. 12 on the model of pancreatitis induced by sodium taurocholate

After at least 7 days of accumulation period, 60 female and 70 male Sprague-Dawley (SD) rats were included in the study. Five females and eight males were randomly selected as the control group. Another five females and eight males were randomly selected as the sham group, the abdominal cavity was opened for each of the rats in the

sham group, and a cotton swab was used to gently flip the duodenum and pancreas, then the abdominal muscle and skin were sutured after the completion of the operation. The remaining animals were assigned to establish the severe acute pancreatitis (SAP) rat model using the method of retrograde injection of sodium taurocholate solution with 35 mg/kg dosage into the biliopancreatic duct. The model animals were randomly divided into 4 groups of 24 rats each (male: female=1:1) on the day after model establishment, which were the model control group (vehicle), and low dose group of peptide 12 (0.05 mg/kg), middle dose group of peptide 12 (0.25 mg/kg) and high dose group of peptide 12 (1.25 mg/kg), peptide 12 was dissolved in saline.

The animals were subcutaneously injected once on the day after the establishment of the model, once on the second day, for a total of 2 consecutive days, and the experimental period was 3 days. During the experiment, the animals were observed by cage, including if there is any animal death or near death, mental state, behavioral activities, fecal characteristics, skin, hair, eyes, ears, nose, abdomen, external genitals, anus, limbs, feet, respiration, etc. At the end of the experiment, all the surviving rats were weighed and blood samples were collected to detect the levels of amylase, calcium and lipase in serum of rats in each group. The general anatomical observation was made, focusing on the status of pancreas, gastrointestinal tract, ascites, bile duct obstruction, pulmonary congestion and saponification spots. The pancreas was preserved in 10% formalin fixative for further pathological analysis.

The survival rate of each group was shown in Table 5 and Figure 1. There was no animal death in normal control group and sham-operated control group, so the survival rate of normal control group and sham control group was 100%. The survival rate of model control group was 37.5%. The survival rate of model animals was improved in all three peptide 12 treatment groups. The improvement of survival rate was related to the dosage of peptide 12, with the animals in the peptide 12 at the dose of 1.25mg/kg showed the most significant improvement, the survival rate was 66.7% and the survival ratio was 1.78 as compared with the model control group. At the same time, the mental state and activity state of the surviving animals in the peptide 12 treatment groups were significantly better than those in the model control group. The general anatomy of the surviving animals showed that the edema and liquefaction of the pancreas, gastrointestinal obstruction, ascites volume, bile duct obstruction, pulmonary congestion and saponification spots were improved with varying degrees in the peptide 12 treatment groups compared with those in the control group.

Table 5. Survival Outcome in Each Group

Group	Survival Rate	Ratio (treatment group/model group)
Normal control	100%	/
Sham control	100%	/
Model control	37.5%	1.00
Model + peptide12 0.05mg/kg	41.7%	1.11
Model + peptide 12 0.25mg/kg	50.0%	1.33
Model + peptide 12 1.25mg/kg	66.7%	1.78

5 Compared with normal group and sham-operated group, the levels of amylase and lipase in blood of model control group increased significantly. Compared with model control group, the levels of amylase and lipase in blood of peptide 12 treatment groups decreased (see Figure 2 and Figure 3).

10 The severity of pancreatic injury was assessed by preparing HE slices of pancreas and using Schmidt's scoring standard to evaluate the pathological changes of pancreatic edema, inflammation, hemorrhage and necrosis. The hepatology scoring standard is shown in Table 6 below. The total pancreatic injury calculated as the sum of the above four items.

Table 6. Histopathology Scoring Standard

Pathologic change	Score				
	0	1	2	3	4
Edema	Absent	Diffuse expansion of inter lobular septae	1+ diffuse expansion of inter lobular septae	2+ diffuse expansion of inter acinar septae	3+ diffuse expansion of inter cellular septaes
Inflammation (HPF)	0~5 intra lobular or perivascular leukocytes	6~10 intra lobular or perivascular leukocytes	11~20 intra lobular or perivascular leukocytes	21~30 intra lobular or perivascular leukocytes	>30 intra lobular or perivascular leukocytes
Hemorrhage (HPF)	Absent	1~3 foci	4~5 foci	6~7 foci	>7 foci

Area of necrosis	Absent	1%~10% area	11%~20% area	21%~30% area	>30% area
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Note:

1. Microscopic examination of each slide was performed at both low magnification (LPF: ×100) and high magnification (HPF: ×400), and 8 visual fields were randomly selected for observation and grading;
2. Edema and area of necrosis were scoring under low magnification;
3. Inflammation, hemorrhage and necrosis cells were scoring under high magnification.

Pathological scores are shown in tables 7 and in Figure 4-8.

Table 7. Pathological scores of each group

Group	Edema	Inflammation	Hemorrhage	Area of necrosis	Total damage
Normal control	0.00±0.00	0.17±0.28	0.00±0.00	0.00±0.00	0.17±0.28
Sham control	0.22±0.27	0.56±0.72	0.06±0.14	0.17±0.41	1.00±1.33
Model control	2.22±0.65	3.56±0.53	2.41±0.76	2.11±0.44	10.30±1.87
Peptide 12-L	1.33±0.86	2.90±1.22	1.73±0.89	1.63±0.74	7.60±3.07
Peptide 12-M	1.44±0.87	2.83±0.93	1.31±0.87	1.11±0.78	6.69±2.53
Peptide 12-H	1.21±0.96	2.67±1.00	1.15±0.83	1.13±0.85	6.15±2.69

- 5 As it indicated in Figure 4 to Figure 8, one can clearly see that administration of peptide 12 can reduce the pathological changes of pancreas caused by sodium taurocholate in a dose-dependent manner.

Example 2. Effects of peptide 12 on caerulein induced pancreatitis model

- 10 Male BALB/c mice, aged 6-8 weeks, were accumulated for more than 7 days. After fasting overnight, 10 animals were randomly selected as normal control. The remaining animals were injected with caerulein 50µg/kg intraperitoneally every 1 hour

for 10 times to induce acute pancreatitis, and they were randomly divided into model control group and peptide 12 treatment groups with the dosage of 0.025, 0.25, 2.5 and 25 mg/kg respectively, there were 10 mice in each group. Mice were given corresponding doses of peptide 12 or normal saline 5 minutes before the fourth injection of caerulein.

The experiment was finished one hour after the 10th injection of caerulein, blood samples were collected for the determination of amylase and lipase levels. Pancreas were weighed and fixed in 10% formalin solution for subsequent pathological analysis.

The pancreatic index was calculated as pancreatic weight/body weight, which reflected the severity of pancreatic edema. The statistical results were shown in Figure 9, in which ### means $P < 0.001$ compared with the normal control group; ** means $P < 0.01$ compared with the model control group, *** means $P < 0.001$ compared with the model control group. As showed in Figure 9, the pancreatic index was significantly increased in the model group comparing to the normal control group, pancreatic indexes were significantly decreased at the doses of 0.025, 0.25 and 2.5 mg/kg of peptide 12 treatment groups in a dose dependent manner. As shown in Figure 10 and Figure 11, the levels of amylase and lipase were significantly increased in the model control group compared with those in the normal control group. Compared with the model control group, the levels of the amylase and lipase in the Peptide 12 at the doses of 0.025, 0.25, 2.5 and 25 mg/kg treatment groups were significantly lowered. It should be noted that in Figure 10, ### means $P < 0.001$ compared with the normal control group; *** means $P < 0.001$ compared with the model control group; in Figure 11, ### means $P < 0.001$ compared with the normal control group; *** means $P < 0.001$ compared with the model control group.

The severity of pancreatic injury was assessed by preparing HE slices of pancreas and using Schmidt's scoring standard to evaluate the pathological changes of pancreatic edema, inflammation, hemorrhage and necrosis.

Table 8. Pathological scores of each group

Group	Edema	Inflammation	Hemorrhage	Area of necrosis
Normal control	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00

Model control	2.00±0.89	2.33±0.82	0.00±0.00	0.00±0.00
Peptide 12-0.025	1.50±0.84	1.33±0.52	0.00±0.00	0.00±0.00
Peptide 12-0.25	1.67±0.82	1.17±0.75	0.00±0.00	0.00±0.00
Peptide 12-2.5	1.17±1.17	0.83±0.75	0.00±0.00	0.00±0.00
Peptide 12-25	1.50±0.55	2.17±0.75	0.33±0.82	0.00±0.00

5 The pathological scoring results showed that there was no obvious hemorrhage and necrosis in the model of caerulein-induced pancreatitis, and the scoring results of edema and inflammation were shown in Figure 12 and Figure 13. It should be noted that in Figure 12, ### means $P < 0.001$ compared with the normal control group; in Figure 13, ### means $P < 0.001$ compared with the normal control group, * means $P < 0.05$, ** means $P < 0.01$ compared with the model control group. From Figure 12 to Figure 13, it can be seen that the model group has obvious edema and inflammation damage compared with the normal control group, and the edema and inflammation of the pancreas were all alleviated with the treatment of peptide 12.

15 The representative examples disclosed herein are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. The following examples contain important additional information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

CLAIMS

1. Use of an INGAP-PP peptide, HIP peptide, or analog thereof in the preparation of medicament for treating acute pancreatitis, the peptide or analog thereof comprising the formula of:



wherein, X^1 is selected from Isoleucine(I), D-Isoleucine, L-NorValine or L-NorLeucine; X^2 is selected from Alanine(A) or Aspartic Acid(D); X^3 is selected from Serine(S) or Threonine(T); X^4 is selected from Histidine(H) or Glutamine(Q); X^5 is selected from Leucine(L) or Glutamic acid(E); and when it is established that X^1 is Isoleucine(I), X^2 is Aspartic Acid(D), X^3 is Serine(S), X^4 is Histidine(H), and X^5 is Leucine(L), then X^6 is selected from either Alanine(A), α -Amino-isobutyric acid or N-methyl-L-Alanine; and when it is not established that X^1 is Isoleucine(I), X^2 is Aspartic Acid(D), X^3 is Serine(S), X^4 is Histidine(H) and X^5 is Leucine(L), then X^6 is selected from either Alanine(A), Asparagine(N), α -Amino-isobutyric acid or N-methyl-L-Alanine.

2. Use of an INGAP-PP peptide, HIP peptide, or analog thereof in the preparation of medicament for acute pancreatitis, the peptide or analog thereof comprising the formula of:



wherein, m is 0 or 1; R^1 is selected from -H or -Ac; R^2 is selected from -OH or -NH₂; and

when it is established that R^1 is -H, R^2 is -OH and m is 0, then X^1 is selected from Glutamic acid(E), Cysteine(C) or Lysine(K); and

when it is not established that R^1 is -H, R^2 is -OH and m is 0, then X^1 is selected from Serine(S), Glutamic acid(E), Cysteine(C) or Lysine(K).

3. Use of an INGAP-PP peptide, HIP peptide, or analog thereof in the preparation of medicament for treating acute pancreatitis, the peptide or analog thereof comprising the formula of:



wherein, m is 0 or 1; R¹ is selected from -H or -Ac; R² is selected from -OH or -NH₂; and

when it is established that R¹ is -H, R² is -OH and m is 1, then X¹ is selected from Glutamic acid(E), Cysteine(C) or Lysine(K); and

5 when it is not established that R¹ is -H, R² is -OH and m is 1, then X¹ is selected from Serine(S), Glutamic acid(E), Cysteine(C) or Lysine(K).

4. Use of an INGAP-PP peptide, HIP peptide, or analog thereof in the preparation of medicament for treating acute pancreatitis, the peptide or analog thereof comprising the formula of:



wherein, X² is selected from Lysine(K) or Cysteine(C), R¹ is selected from -H or -Ac, R² is selected from -OH or -NH₂.

5. Use of an INGAP-PP peptide, HIP peptide, or analog thereof in the preparation of medicament for treating acute pancreatitis, the peptide or analog thereof comprising the formula of:



wherein, X¹ is selected from Isoleucine(I) or D-Isoleucine; X² is selected from Glutamic acid(E) or Leucine(L); and

20 when it is established that X¹ is Isoleucine(I) and X² is Glutamic acid(E), then X³ is selected from Alanine(A) or α -Amino-isobutyric acid; and

when it is not established that X¹ is Isoleucine(I) and X² is Glutamic acid (E), then X³ is selected from Alanine(A), Asparagine (N) or α -Amino-isobutyric acid.

6. Use of an INGAP-PP peptide, HIP peptide, or analog thereof in the preparation of medicament for treating acute pancreatitis, the peptide or analog thereof comprising the formula of:



wherein, X¹ is selected from -H or -Ac; X² is selected from -OH or -NH₂; and

30 when it is established that R¹ is -H and R² is -OH, then X¹ is selected from Serine(S) or Cysteine(C); and

when it is not established that R¹ is -H and R² is -OH, then X¹ is selected from

Serine(S), Glutamic acid(E) or Cysteine(C).

7. Use of an INGAP-PP peptide, HIP peptide, or analog thereof in the preparation of medicament for treating acute pancreatitis, the peptide or analog thereof comprising the formula of:



wherein, R^1 is selected from -H or -Ac; R^2 is selected from -OH or -NH₂, n is 0 or 1; X^1 is selected from Serine(S) or Cysteine(C).

8. Use of an INGAP-PP peptide, HIP peptide, or analog thereof in the preparation of medicament for treating acute pancreatitis, wherein the INGAP-PP and HIP peptide are selected from the INGAP-PP and HIP peptides of Table 1, the INGAP-PP analogs selected from Table 2, and the HIP peptide analogs are selected from Table 3,
- 10

Table 1. INGAP-PP peptide and HIP peptide

Peptide ID / SEQ ID NO.	Sequence
1 (INGAP-PP)	H-IGLHDPSHGTLPNGS-OH
2 (HIP)	H-IGLHDPTQGTEPNGE-OH

15

Table 2. Exemplary INGAP-PP Analogs

Peptide ID / SEQ ID NO.	Sequence
1	H-IGLHDPSHGTLPNGS-OH
6	H-IGLHAPSHGTLPNGS-OH
7	H-IGLHDPSHGTLPAGS-OH
8	H-IGLHAPSHGTLPAGS-OH
9	H-IGLHDPSHGTLPAGSK-OH
10	H-IGLHDPSHGTLP(Aib)GS-OH
11	H-IGLHDPSHGTLP(N-methyl-L-Alanine)GS-OH
12	Ac-IGLHDPSHGTLPAGS-OH

13	H-(D-Isoleucine)GLHDPSHGTLPAGS-OH
14	H-(L-NorValine)GLHDPSHGTLPAGS-OH
15	H-(L-NorLeucine)GLHDPSHGTLPAGS-OH
16	Ac-IGLHDPSHGTLPNGS-OH
17	H-(D-Isoleucine)GLHDPSHGTLPNGS-OH
18	H-IGLHDPSHGTEPNGS-OH
19	H-IGLHDPSQGTLPNGS-OH
20	H-IGLHDPTHGTLPNGS-OH
21	H-IGLHDPSHGTLPNGE-OH
22	H-IGLHDPSHGTLPNGK-OH
23	H-IGLHDPSHGTLPAGK-OH
24	H-IGLHDPSHGTEPAGS-OH
25	H-IGLHDPSQGTLPAGS-OH
26	H-IGLHDPTHGTLPAGS-OH
27	H-IGLHDPSHGTLPAGE-OH
28	H-IGLHDPSHGTLPAG-NH2
29	Ac-IGLHDPSHGTLPAGS-NH2
30	Ac-IGLHDPSHGTLPAG-NH2
31	Ac-IGLHDPSHGTLPNGS-NH2
32	H-IGLHDPSHGTLPNGS-NH2
33	H-IGLHDPSHGTLPNGSC-OH
34	Ac-IGLHDPSHGTLPNGSC-OH
35	H-IGLHDPSHGTLPNGSC-NH2
36	Ac-IGLHDPSHGTLPNGSC-NH2
37	H-IGLHDPSHGTLPNGC-OH
38	Ac-IGLHDPSHGTLPNGC-OH
39	H-IGLHDPSHGTLPNGC-NH2
40	Ac-IGLHDPSHGTLPNGC-NH2
41	H-IGLHDPSHGTLPAGS-NH2
42	H-IGLHDPSHGTLPAGSC-OH
43	Ac-IGLHDPSHGTLPAGSC-OH
44	H-IGLHDPSHGTLPAGSC-NH2
45	Ac-IGLHDPSHGTLPAGSC-NH2
46	H-IGLHDPSHGTLPAGC-OH
47	Ac-IGLHDPSHGTLPAGC-OH
48	H-IGLHDPSHGTLPAGC-NH2
49	Ac-IGLHDPSHGTLPAGC-NH2

73	IGLHDPSHGTLPAG
74	IGLHDPSHGTLPNG
75	Ac-IGLHDPSHGTLPNG
76	IGLHDPSHGTLPNG-NH2
77	Ac-IGLHDPSHGTLPNG-NH2
78	H-IGLHDPSHGTLPQGS-OH
79	H-IGLHDPSHGTLPDGS-OH
80	H-IGLHDPSHGTLPESGS-OH
81	H-IGLHEPSHGTLPNGS-OH
82	H-IGLHQPSHGTLPNGS-OH
83	H-IGLHNPSHGTLPNGS-OH
84	H-IGLHEPSHGTLPAGS-OH
85	H-IGLHQPSHGTLPAGS-OH
86	H-IGLHNPSHGTLPAGS-OH
87	H-IGLHDPSHGTLPQGSC-OH
88	H-IGLHDPSHGTLPDGSC-OH
89	H-IGLHDPSHGTLPESGSC-OH
90	H-IGLHEPSHGTLPNGSC-OH
91	H-IGLHQPSHGTLPNGSC-OH
92	H-IGLHNPSHGTLPNGSC-OH
93	H-IGLHDPSHGTLPQG-OH
94	H-IGLHDPSHGTLPDG-OH
95	H-IGLHDPSHGTLPESG-OH
96	H-IGLHEPSHGTLPNG-OH
97	H-IGLHQPSHGTLPNG-OH
98	H-IGLHNPSHGTLPNG-OH
99	H-IGLHEPSHGTLPAG-OH
100	H-IGLHQPSHGTLPAG-OH
101	H-IGLHNPSHGTLPAG-OH
102	H-IGLHDPSHGTLPQGE-OH
103	H-IGLHDPSHGTLPDGE-OH
104	H-IGLHDPSHGTLPESGE-OH
105	H-IGLHEPSHGTLPNGE-OH
106	H-IGLHQPSHGTLPNGE-OH
107	H-IGLHNPSHGTLPNGE-OH
108	H-IGLHEPSHGTLPAGE-OH
109	H-IGLHQPSHGTLPAGE-OH

110	H-IGLHNPSHGTLPAGE-OH
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Table 3. Exemplary HIP Analogs

Peptide ID / SEQ ID NO.	Sequence
2	H-IGLHDPTQGTEPNGE-OH
50	H-IGLHDPTQGTEPAGE-OH
51	H-IGLHDPTQGTEP(Aib)GE-OH
52	Ac-IGLHDPTQGTEPAGE-OH
53	H-(D-Isoleucine)GLHDPTQGTEPAGE-OH
54	Ac-IGLHDPTQGTEPNGE-OH
55	H-(D-Isoleucine)GLHDPTQGTEPNGE-OH
56	H-IGLHDPTQGTEPNGS-OH
57	H-IGLHDPTQGTEPAGS-OH
58	H-IGLHDPTQGTLPNGE-OH
59	H-IGLHDPTQGTLPAGE-OH
60	Ac-IGLHDPTQGTEPAG-NH ₂
61	Ac-IGLHDPTQGTEPNGE-NH ₂
62	Ac-IGLHDPTQGTEPAGE-NH ₂
63	H-IGLHDPTQGTEPNGE-NH ₂
64	H-IGLHDPTQGTEPNGC-OH
65	Ac-IGLHDPTQGTEPNGC-OH
66	H-IGLHDPTQGTEPNGC-NH ₂
67	Ac-IGLHDPTQGTEPNGC-NH ₂
68	H-IGLHDPTQGTEPAGE-NH ₂
69	H-IGLHDPTQGTEPAGC-OH
70	Ac-IGLHDPTQGTEPAGC-OH
71	H-IGLHDPTQGTEPAGC-NH ₂
72	Ac-IGLHDPTQGTEPAGC-NH ₂

9. A method for treating acute pancreatitis comprising administering to the patient having acute pancreatitis a pharmaceutical composition comprising an INGAP-PP peptide, HIP peptide, or analog thereof according to any of claims 1-8.
10. A method for lowering blood amylase and lipase levels in patients with acute pancreatitis comprising administering the patient a pharmaceutical composition

comprising an INGAP-PP peptide, HIP peptide, or analog thereof according to any of claims 1-8.

- 5
11. A method for treating acute pancreatitis by lowering the levels of amylase and lipase in the blood of the patient having acute pancreatitis comprising administering the patient a pharmaceutical composition comprising an INGAP-PP peptide, HIP peptide, or analog thereof according to any of claims 1-8.
- 10
12. A method for preventing or reducing pancreatic injury caused by acute pancreatitis comprising administering to a patient a pharmaceutical composition comprising an INGAP-PP peptide, HIP peptide, or analog thereof according to any of claims 1-8.
- 15
13. A method for treating inflammatory pancreatic disease or condition comprising administering a patient a pharmaceutical composition comprising an INGAP-PP peptide, HIP peptide, or analog thereof according to any of claims 1-8.

FIGURES

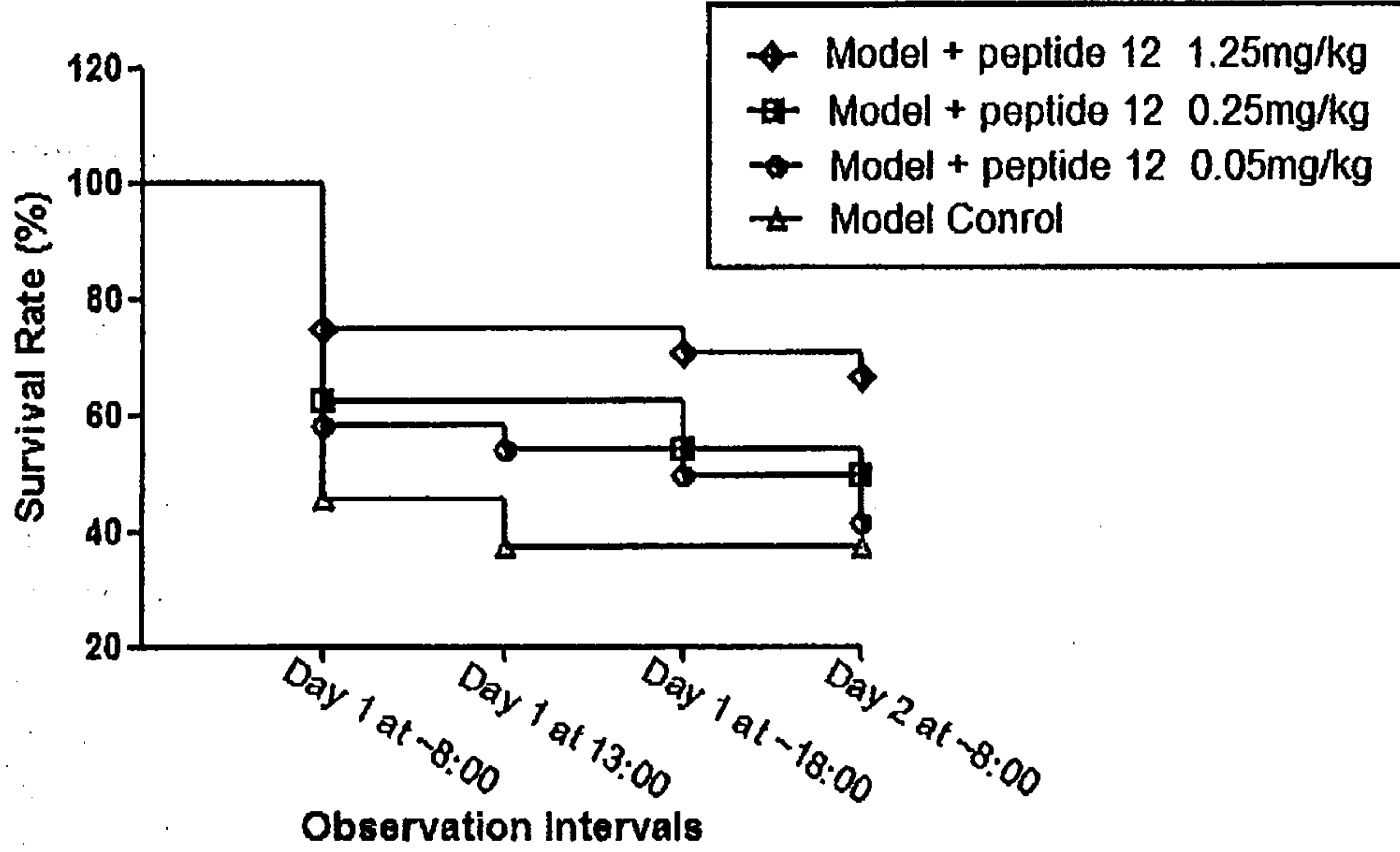


Figure 1. Beneficial effects of peptide No. 12 on the survival outcome in sodium taurocholate induced pancreatitis model

5

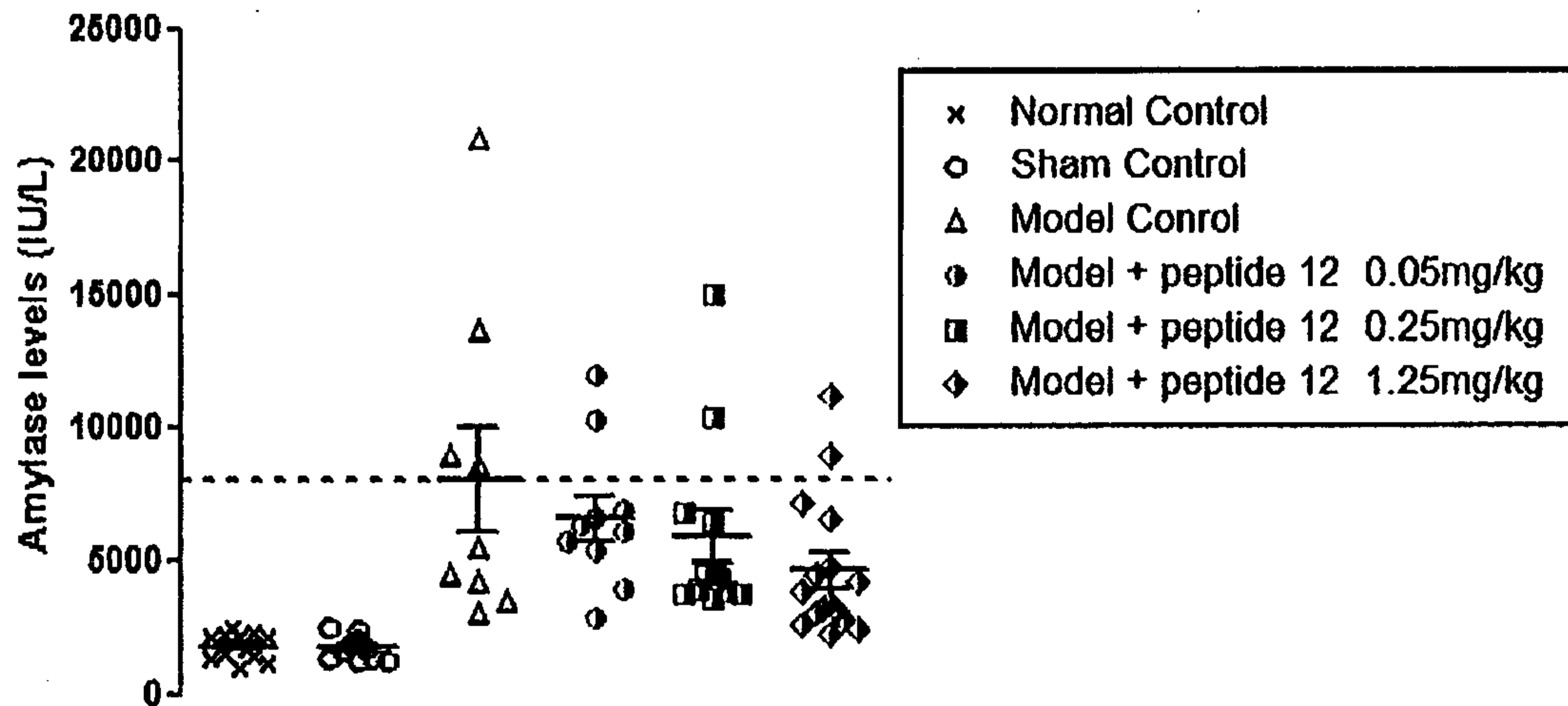


Figure 2. Beneficial effects of peptide No. 12 on the serum amylase levels in sodium taurocholate induced pancreatitis model

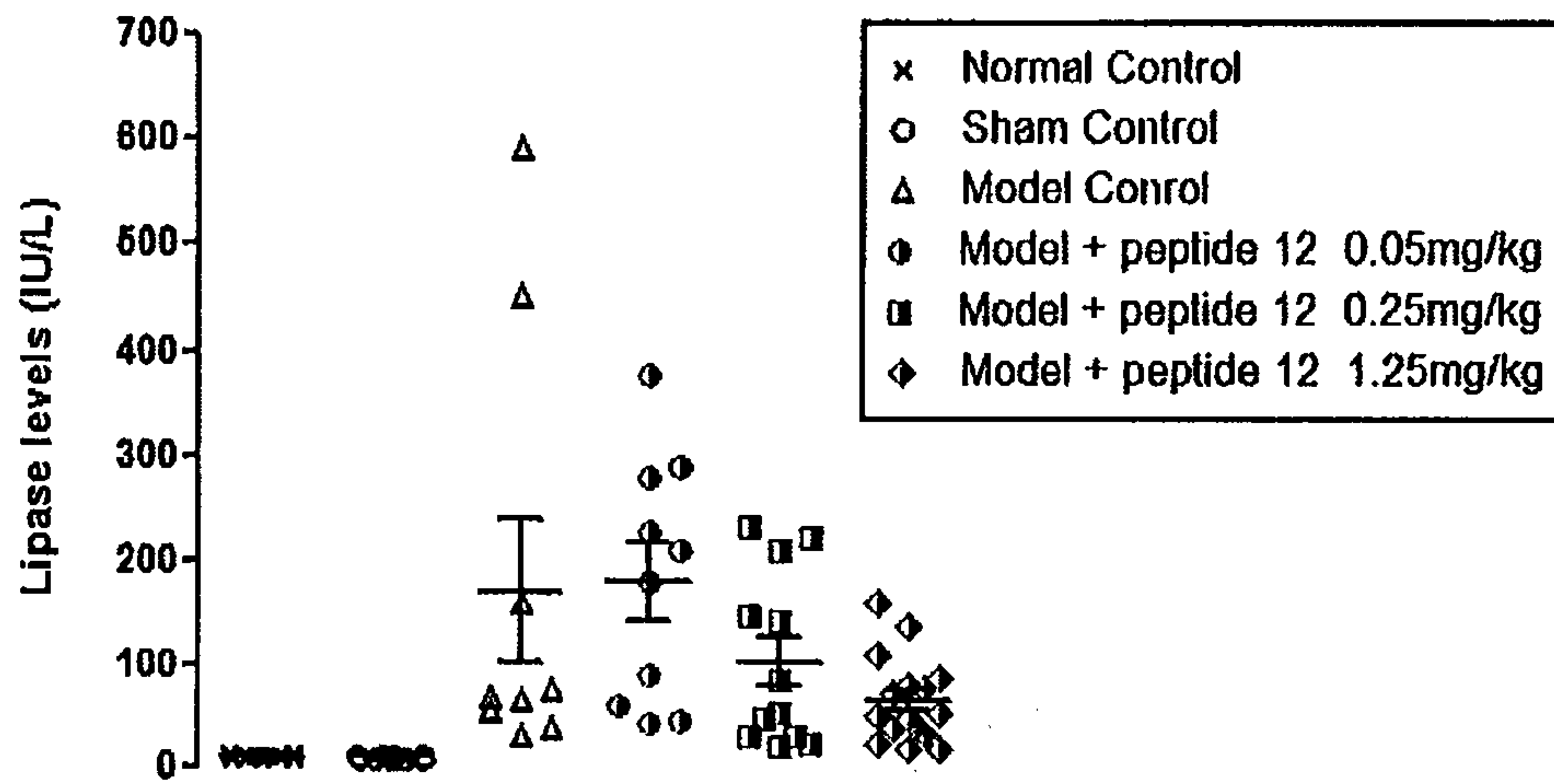


Figure 3. Beneficial effects of peptide No. 12 on the serum lipase levels in sodium taurocholate induced pancreatitis model

5

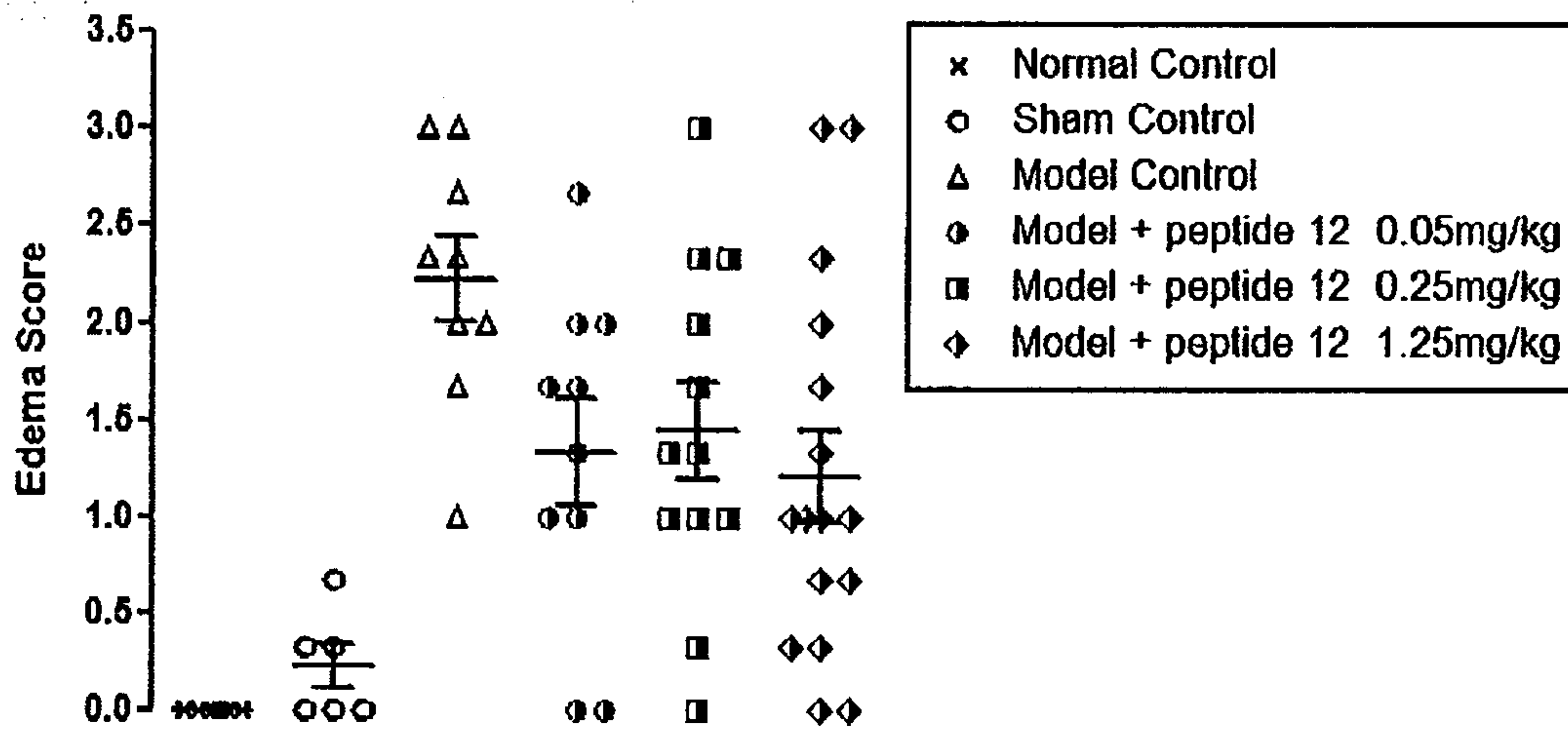


Figure 4. Beneficial effects of peptide No. 12 on the pathologic changes of edema in sodium taurocholate induced pancreatitis model

10

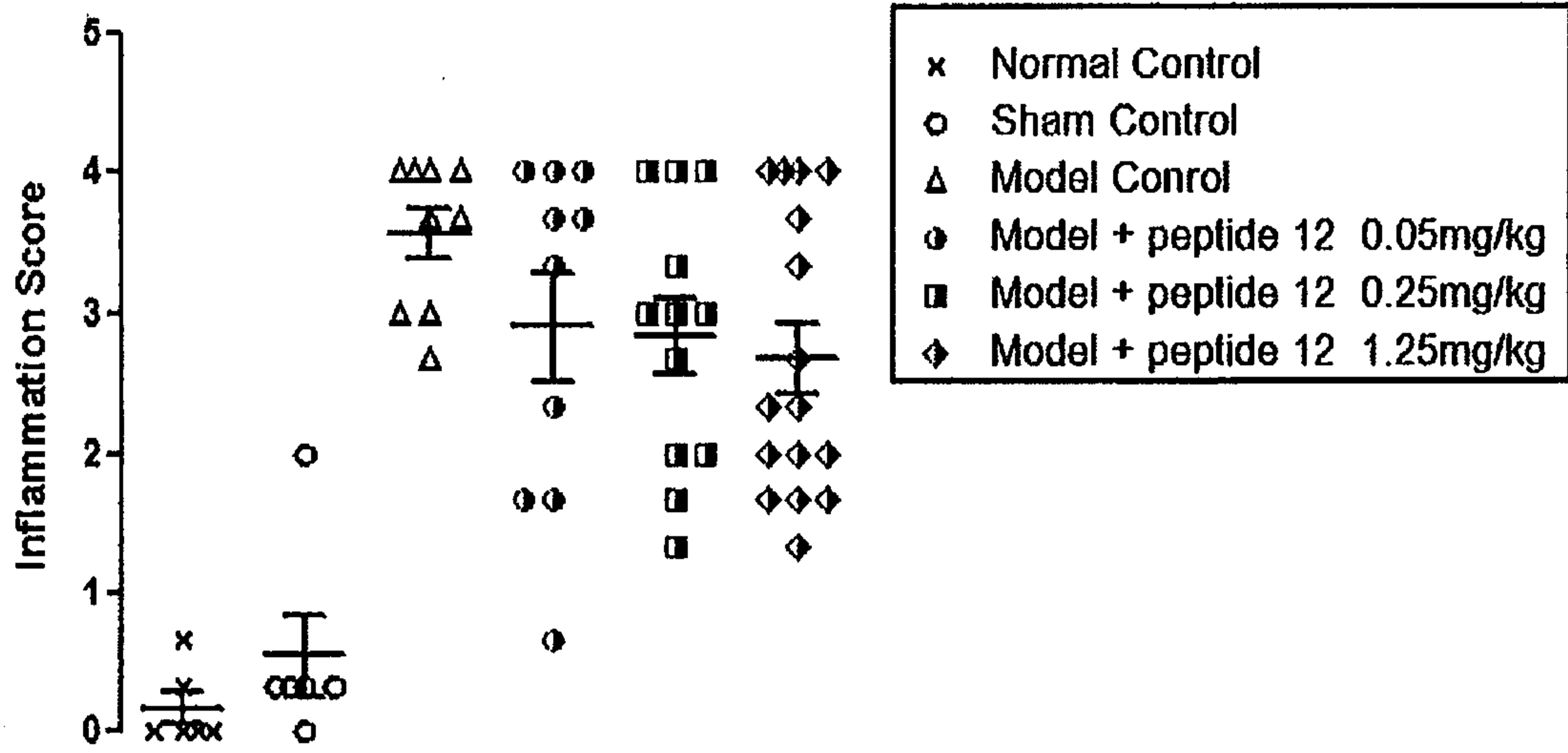


Figure 5. Beneficial effects of peptide No. 12 on the pathologic changes of inflammation in sodium taurocholate induced pancreatitis model

5

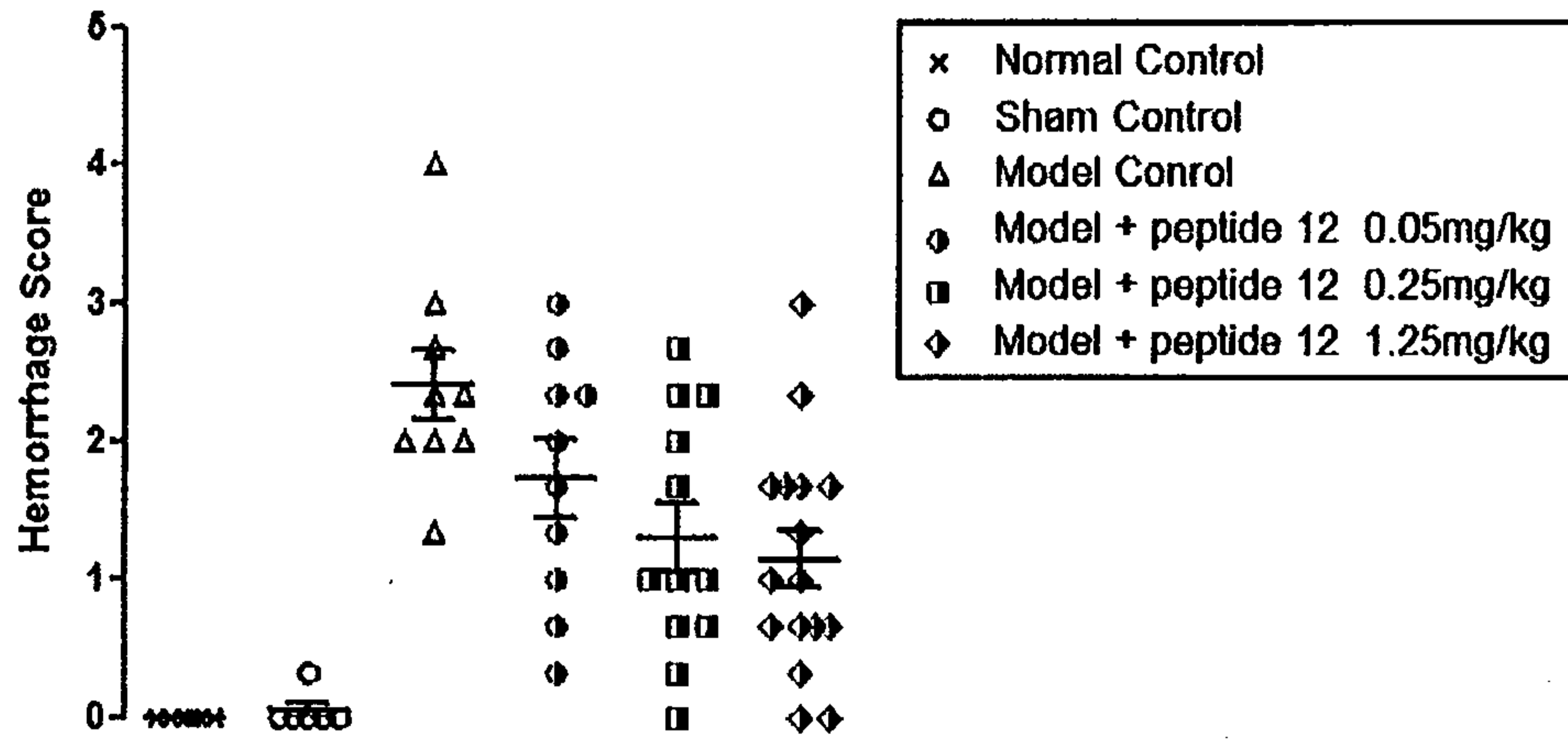


Figure 6. Beneficial effects of peptide No. 12 on the pathologic changes of hemorrhage in sodium taurocholate induced pancreatitis model

10

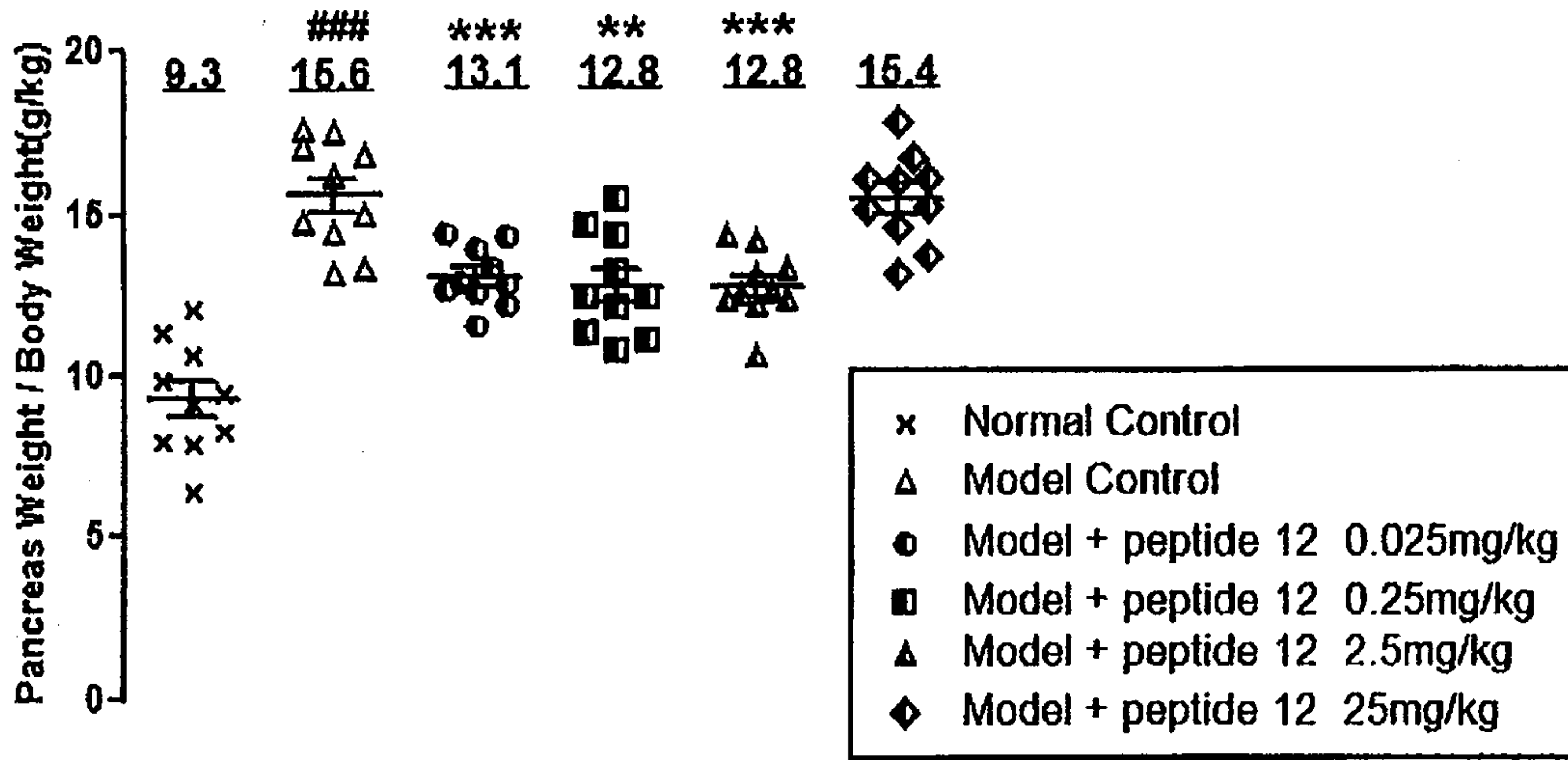


Figure 9. Beneficial effects of peptide No. 12 on the pancreatic index in caerulein induced pancreatitis model

5

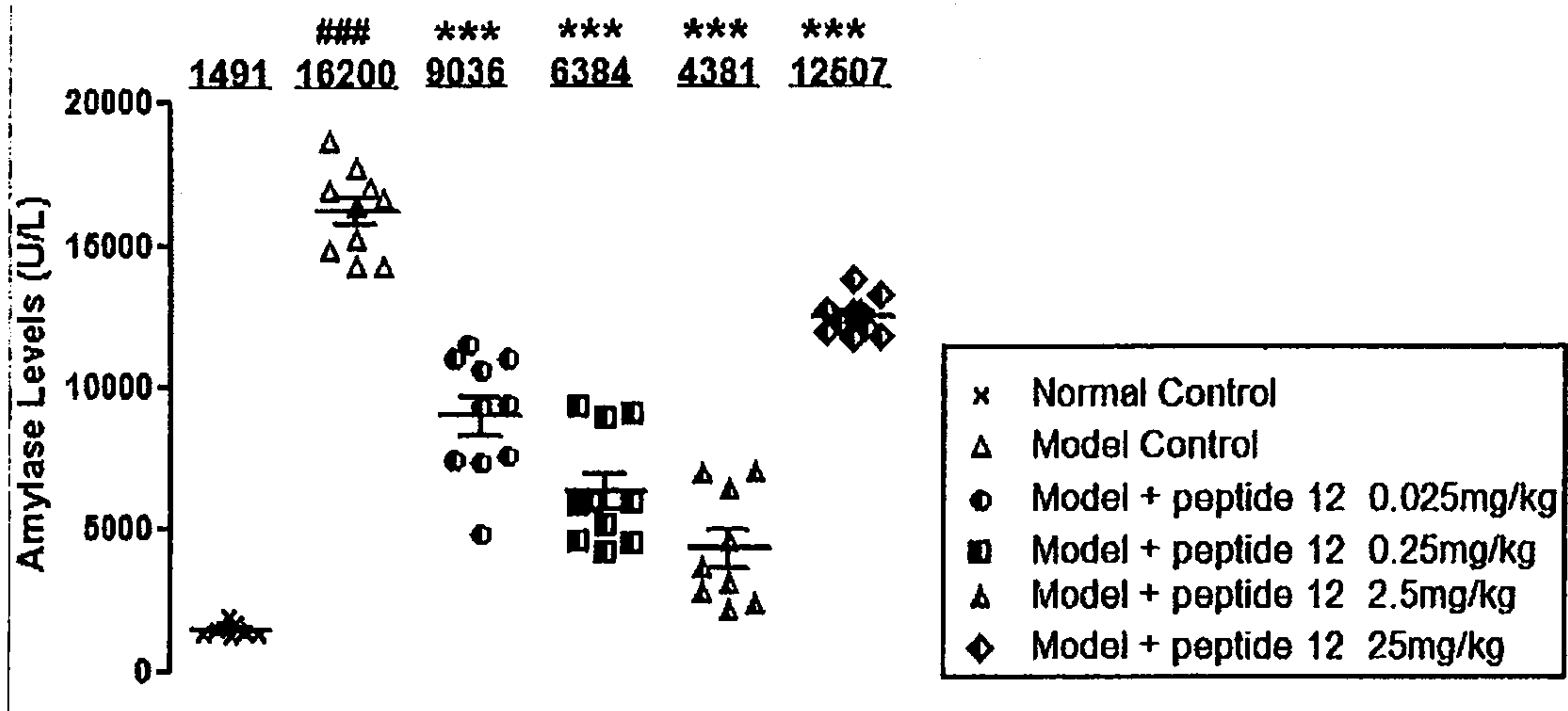


Figure 10. Beneficial effects of peptide No. 12 on the serum amylase levels in caerulein induced pancreatitis model

10

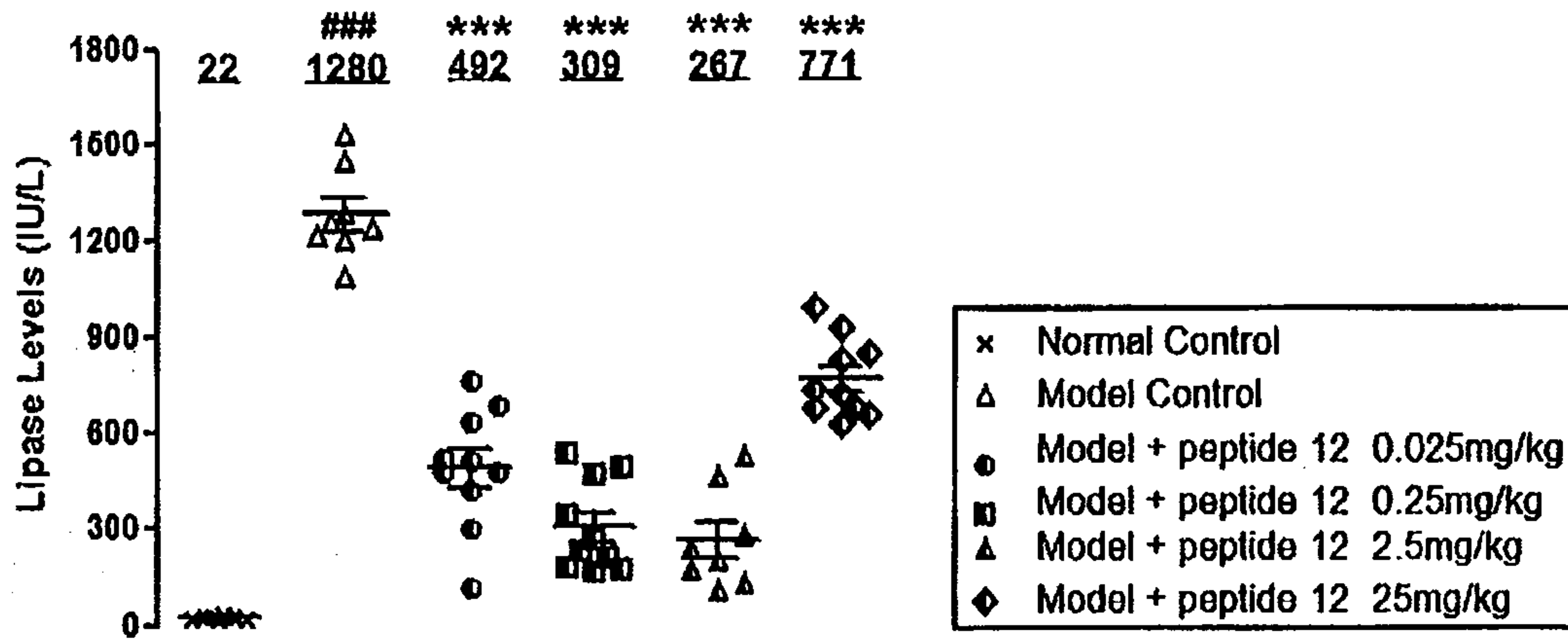


Figure 11. Beneficial effects of peptide No. 12 on the serum lipase levels in caerulein induced pancreatitis model

5

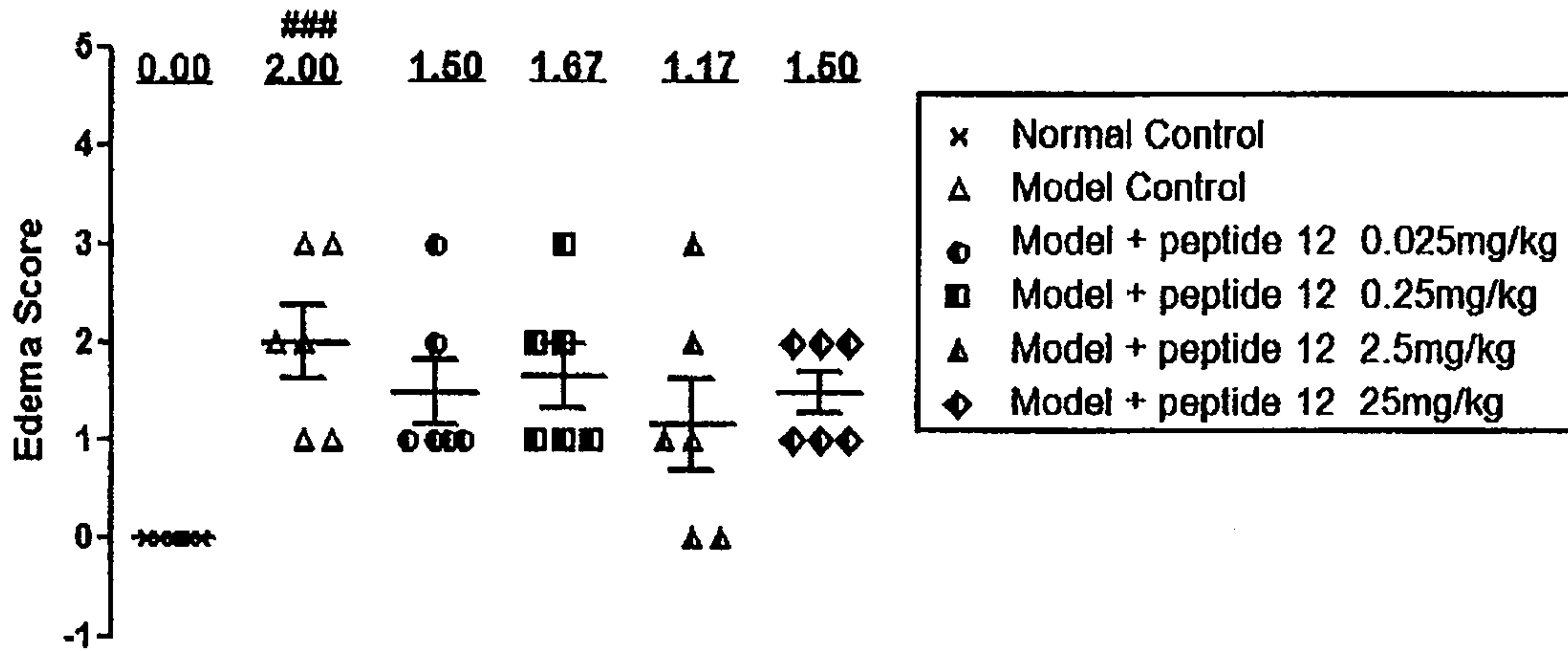


Figure 12. Beneficial effects of peptide No. 12 on the pathologic change of edema in caerulein induced pancreatitis model

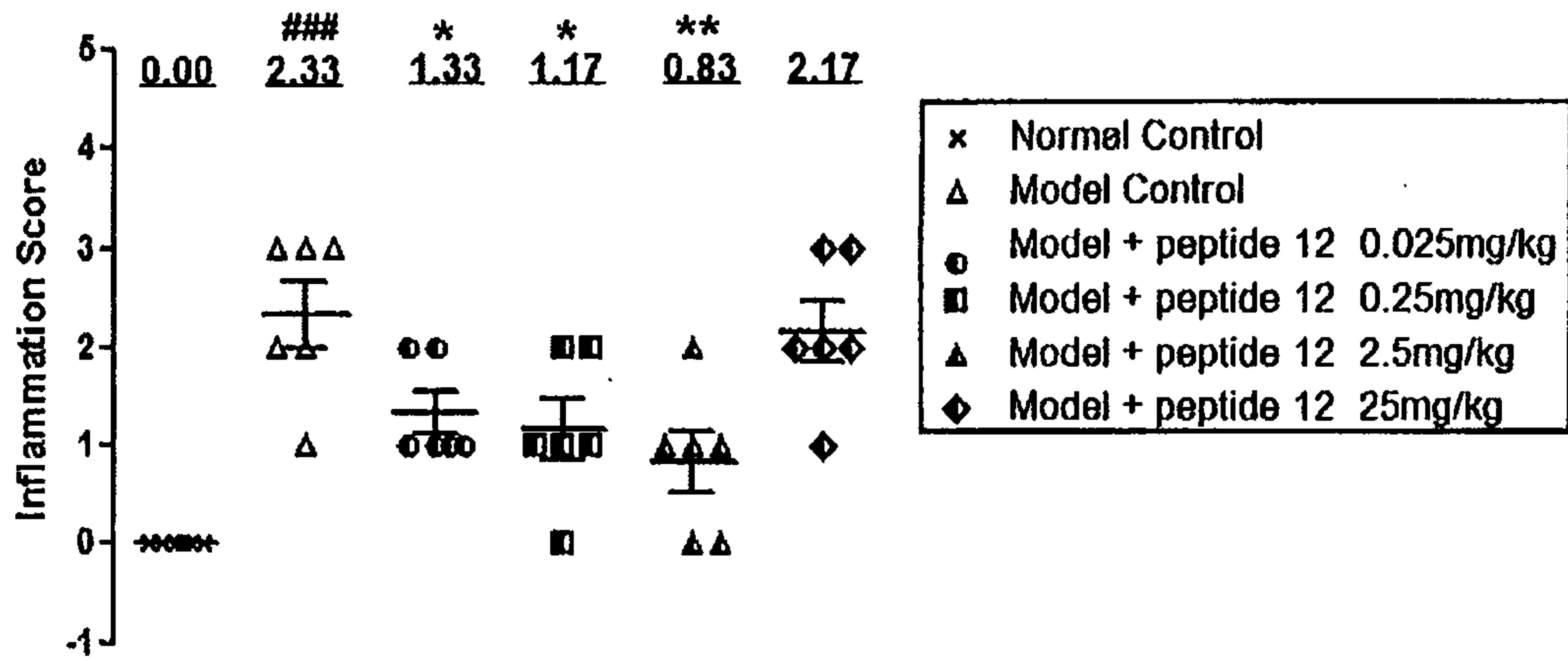


Figure 13. Beneficial effects of peptide No. 12 on the pathologic change of inflammation in caerulein induced pancreatitis model

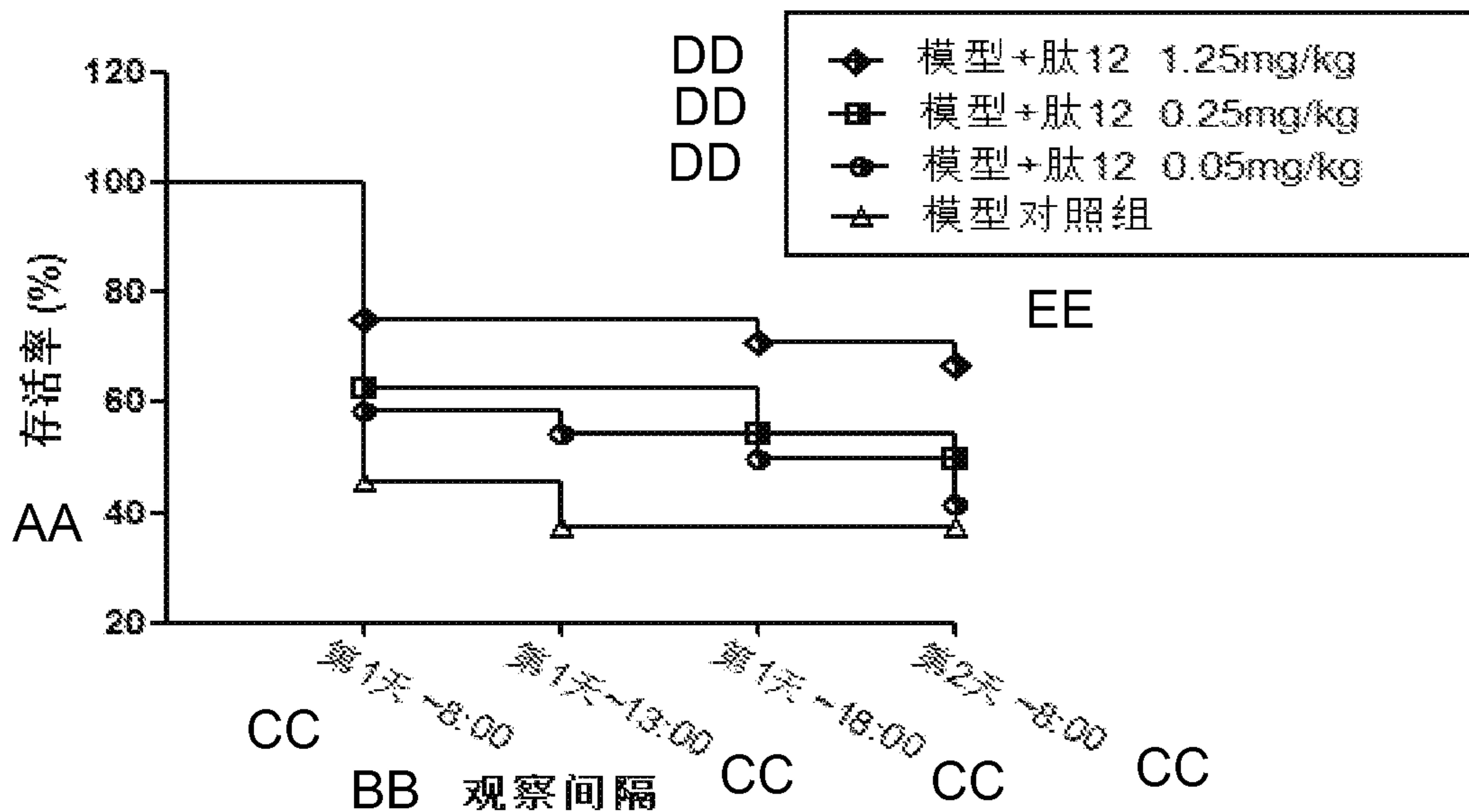


图 1. 肽 12 对牛黄胆酸钠诱导的急性胰腺炎模型动物存活率的改善情况

FIG. 1: Peptide 12 improves the survival rate of a model animal with acute pancreatitis induced by sodium taurocholate

- AA Survival rate
- BB Observation interval
- CC Day
- DD Model + peptide
- EE Model control group