

# Intraarterial Infusion of Lidocaine is Superior to the Subcutaneous Injection of Low Molecular Weight Heparin for Improving the Course of Cerulein-Induced Acute Pancreatitis in Rats

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## Abstract

This study aimed to determine the efficacy of low molecular weight heparin (LMWH) and lidocaine combined with LMWH for improving the course of acute pancreatitis (AP). A total of 30 rats were divided into three groups: the NaCl group, which received an intraarterial infusion of 0.9% sodium chloride; the Heparin group, which received a subcutaneous injection of LMWH; and the Lidocaine–Heparin group, which received an intraarterial infusion of 1% lidocaine, with subsequent subcutaneous injection of LMWH. AP was triggered using 80 µg/kg body weight of cerulein. Serum amylase and lipase levels were evaluated before induction of AP (measurement 0 – M0), after triggering AP (measurement 1 – M1), 1 h (measurement 2 – M2), 3 h (measurement 3 – M3), and 5 h (measurement 4 – M4) after treatment. After euthanasia, pancreatic tissues were collected for pathological analysis. No intergroup differences in serum amylase and lipase levels were observed between the NaCl and Heparin groups in all post-treatment evaluation points (M2, M3, and M4). Conversely, the Lidocaine–Heparin group showed significantly lower amylase values than the NaCl and Heparin groups in all post-treatment evaluation points. Furthermore, the Lidocaine–Heparin group showed significantly lower lipase values compared with the NaCl group in the first post-treatment evaluation point (M2), as well as compared with the Heparin group in the first (M2) and second (M3) post-treatment evaluation points. No significant intergroup differences were observed in pathological pancreatic tissue evaluation. Subcutaneous injection of LMWH did not impact the natural course of AP. However, the addition of intraarterially administered 1% lidocaine solution significantly reduced the severity of AP.

## Keywords

Experimental • Microcirculation • continuous regional arterial infusion • Vasodilation • Anticoagulation

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## Abbreviations

AP, acute pancreatitis; IL, interleukin; LMWH, low molecular weight heparin; M0, measurement 0; M1, measurement 1; M2, measurement 2; M3, measurement 3; M4, measurement 4; PAF, platelet-activating factor; TNF, tumor necrosis factor.

## 1. Introduction

Acute pancreatitis (AP) represents one of the most prevalent acute gastrointestinal disorders, with a globally increasing

incidence. Most commonly, AP is caused by gallstones and alcohol abuse (Iannuzzi et al. 2022). Pancreatic duct obstruction and increased intraductal pressure trigger the transformation of inactive trypsinogen into trypsin, thus inducing the cascade of biochemical events promoting the course of AP. Damage to the acinar cells as a result of autodigestion processes causes an inflammatory reaction in the damaged pancreatic tissue; infiltration of neutrophils and macrophages; and the release of cytokines, interleukins, and tumor necrosis factor (TNF)-α that eventually result in microcirculatory disturbances in the pancreatic tissue (Antkowiak et al. 2022). The mechanism underlying the disorders of pancreatic microcirculation and progressive damage to the pancreas consists of early vasoconstriction, with subsequent vascular permeability, and eventually activation of the coagulation system as the result of a local and systemic inflammatory response, which in turn leads to systemic microcirculation disorders and the development of multi-organ failure in the course of AP (Qiu et al. 2019; Tozlu et al. 2019). Therefore, microcirculatory disturbances are considered to be a crucial step in AP development, thus warranting therapeutic approaches to improve pancreatic microcirculation (Antkowiak et al. 2022). Lidocaine is an amide-type anesthetic that, apart from its widely known antiarrhythmic properties, has also been found to have vasoactive and anti-inflammatory properties. It has

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been found that lidocaine induces vasodilation at concentrations higher than 10–100 µg/mL (Satoh et al. 2015; Arsyad and Dobson 2016). Theoretically, lidocaine may induce vasodilation in pancreatic microcirculation, acting in the early stages of AP development, and thus relieving the severity of AP. The results of our previous study showed that regional, intraarterial infusion of 1% lidocaine solution (acting as a strong vasodilator through the concentration of 10,000 µg/mL) improves the course of cerulein-induced AP in rats (Antkowiak et al. 2020). Although the evidence on the actual efficacy of lidocaine in AP in the clinical settings remains unknown, further research aiming at vasodilation in pancreatic microcirculation needs to be encouraged.

Apart from the microcirculatory vasoconstriction, which is the early pathological mechanism responsible for further AP progression, subsequent vascular disturbances in AP consist of activation of the coagulation system and its consequences. Therefore, much effort has been put into studying the role of low molecular weight heparin (LMWH) for treating AP. LMWH is characterized by its anticoagulatory and anti-inflammatory effects, which are crucial in the later steps of AP development. LMWH reduces the release of cytokines and inflammatory mediators, inhibits leukocyte adhesion to vascular endothelial cells, reduces platelet activation, activates antithrombin III, and inhibits coagulation factors IIa and Xa, ultimately inhibiting the formation of fibrin clots. Moreover, it has been found that a complex of LMWH and antithrombin III reduces trypsin and chymotrypsin activity, thus reducing trypsinogen activation (Qiu et al. 2019; Tozlu et al. 2019). Some studies have shown that LMWH inhibits the development of AP triggered by the ischemia-reperfusion phenomenon (Cuthbertson and Christophi 2006; Podda et al. 2024). Considering complex mechanisms of microcirculatory disturbances, we hypothesized that combined, multi-target therapy with LMWH and lidocaine may positively impact the course of AP, enhancing vasoactive properties. Therefore, the present study aimed to determine the efficacy of LMWH and lidocaine combined with LMWH for improving the course of cerulein-induced experimental AP in rats.

## 2. Methods

### 2.1. Ethical approval

The protocol for this study was approved by the 2nd Local Institutional Animal Care and Use Committee of the Institute of Pharmacology, Polish Academy of Sciences in Krakow (Approval No. 351/2022). All procedures were performed under the Polish Law Act of 15 January 2015 on protecting animals used for scientific or educational purposes. The paper preparation strictly adhered to the “Animal Research: Reporting of In Vivo Experiments” guidelines (Percie du Sert et al. 2020).

### 2.2. Study cohort

The study was conducted at the Experimental and Innovative Medicine Center at the University of Agriculture in Krakow. Following ethical approval, male albino Wistar rats were obtained from the Animal House of the Faculty of Pharmaceuticals, Jagiellonian University Medical College in Krakow. The details of animal care were consistent with those presented in our previously published paper (Antkowiak et al. 2020). A total of 30 subjects included in the present study were randomly divided into three consecutive groups: the NaCl group (Group 1–10 rats), which received intraarterial infusion of 0.9% sodium chloride solution; the Heparin group (Group 2–10 rats), which received subcutaneous injection of LMWH (Clexane 100 mg/mL, Sanofi-Aventis, Warsaw, Poland); and the Lidocaine–Heparin group (Group 3–10 rats), which received intraarterial infusion of 1% lidocaine (Lidocainum Hydrochloricum WZF 1%, Polfa Warszawa, Warsaw, Poland), with subsequent subcutaneous injection of LMWH.

### 2.3. Study design

The experiment began with blood tests for baseline amylase and lipase levels evaluation from the greater saphenous or caudal vein (measurement 0 – M0). Afterwards, to trigger experimental AP, a 20 µg/kg body weight of cerulein (Ceruletide, MCE, Monmouth Junction, NJ, USA) was subcutaneously injected every hour for four consecutive hours (80 µg/kg body weight in total) in each animal. To determine the severity of experimental AP, blood tests for amylase and lipase levels were retaken (measurement 1 – M1) 6 h following the last cerulein injection (10th hour after the first injection). The surgical intervention was performed within 1 h after the M1 blood tests were taken. The surgical procedure was performed in rats from the NaCl and lidocaine–heparin groups. The details of the surgical technique are described in our previously published paper (Antkowiak et al. 2020). Briefly, regional intraarterial infusions were made slowly with a 26G venous cannula introduced precisely into the celiac trunk via direct perpendicular puncture of the abdominal aorta at the level at which the celiac trunk branches off. After that, subjects from the NaCl group received a slow intraarterial infusion of 0.9% sodium chloride at a dose of 5 mg/kg body weight in a bolus. In rats from the lidocaine–heparin group, lidocaine was administered at a dose of 5 mg/kg body weight in a bolus. After a successful intraarterial infusion, the surgical procedure was terminated. Subsequently, rats constituting the lidocaine–heparin group received subcutaneous injection of LMWH at a dose of 1.5 mg/kg body weight in a bolus. Subjects from the heparin group did not undergo the abovementioned open surgical procedure – their treatment protocol consisted of subcutaneous injection of LMWH at a

dose of 1.5 mg/kg body weight in a bolus. Both lidocaine and LMWH doses were based on maximally safe therapeutical doses reported in the Medical Product Characteristics. Post-intervention blood tests were performed 1 h (measurement 2 – M2), 3 h (measurement 3 – M3), and 5 h (measurement 4 – M4) after termination of the last therapeutical procedure (surgical procedure in the NaCl group, and LMWH injection in the lidocaine–heparin and heparin groups). Following the last blood test, all animals were euthanized using 300 mg/kg body weight pentobarbital (Morbital, Biowet Pulawy, Pulawy, Poland). Pancreatic tissue and the surrounding adipose tissue were collected for post-mortem pathological examination.

## 2.4. Histopathological examination

Following post-mortem tissue preparation, the pancreas with the surrounding adipose tissue of each rat was fixed in a 10% formalin solution and embedded in paraffin blocks. After that, 5 µm-thick slices were cut and stained with hematoxylin and eosin (H&E). All histopathological examinations were performed by an experienced pathologist (B.D.) who remained blinded to the distribution of rats in each group. The following features were evaluated: (1) pancreas: necrosis, edema, hemorrhagic foci, acute inflammatory response, and chronic inflammatory response; and (2) adipose tissue: necrosis, hemorrhagic foci, acute inflammatory response, and chronic inflammatory response. Additionally, the number of veins and arteries, as well as the number of capillaries, were calculated in each pancreatic tissue sample. The following scale was used to assess the severity of observed features: 0 – feature was not observed, no changes, 1 – mild changes, 2 – moderate changes, and 3 – severe changes (Kim et al. 1996, 2020; Ethridge et al. 2002; Antkowiak et al. 2020).

## 2.5. Statistical analysis

An ANOVA analysis was performed to assess intergroup differences in amylase and lipase levels. If differences occurred, *post hoc* tests were done. Pearson's chi-square independence analysis was conducted to determine the relationship between the severity of histopathological features and the study group. Kruskal–Wallis test was used to evaluate the differences in quantitative variables. Values with  $p < 0.05$  were considered statistically significant. All analyses were performed using the Statistica 13.3 software (StatSoft Polska, Krakow, Poland).

# 3. Results

## 3.1. Study cohort

A total number of 29 rats completed the study protocol and were further analyzed. One rat from the lidocaine–heparin

group presented with significant hypothermia and hypovolemia postoperatively. While the blood test could not have been collected correctly, the subject was excluded from the study. Consequently, there were 10 rats in the NaCl group, 10 in the heparin group, and 9 in the lidocaine–heparin group.

## 3.2. Pancreatic enzymes levels

### 3.2.1. Amylase levels

Amylase levels measured at baseline (M0), as well as those measured after AP induction, were comparable among the three groups ( $p > 0.05$ ). Similarly, no intergroup differences in serum amylase levels were observed between the NaCl group and the heparin group in all post-treatment time points (M2, M3, and M4) ( $p > 0.05$ ).

Conversely, the lidocaine–heparin group showed significantly lower amylase values than the NaCl group in all post-treatment time points (M2  $p < 0.001$ , M3  $p = 0.002$ , and M4  $p = 0.025$ ). Moreover, the lidocaine–heparin group achieved significantly lower amylase values than the heparin group in all post-treatment time points (M2  $p < 0.001$ , M3  $p < 0.001$ , and M4  $p = 0.001$ ).

All intergroup differences in amylase levels are depicted in Table 1 and Figure 1.

### 3.2.2. Lipase levels

Lipase levels measured at baseline (M0), as well as those measured after AP induction, were comparable among the three groups ( $p > 0.05$ ). Similarly, no intergroup differences in serum lipase levels were observed between the NaCl and heparin groups in all post-treatment time points (M2, M3, and M4,  $p > 0.05$ ).

Conversely, the lidocaine–heparin group showed significantly lower lipase values compared with the NaCl group in the first post-treatment time point (M2,  $p = 0.032$ ), while comparable values were observed in the second (M3,  $p = 0.712$ ) and the last post-treatment time points (M4,  $p = 0.907$ ). Moreover, the lidocaine–heparin group achieved significantly lower lipase levels compared with the heparin group in the first (M2,  $p < 0.001$ ) and the second (M3,  $p = 0.039$ ) post-treatment time points, while values achieved at the last post-treatment time point were comparable between those two groups (M4,  $p = 0.147$ ). All intergroup differences in lipase levels are depicted in Table 2 and Figure 2.

## 3.3. Pathological examination of the pancreatic tissue

Pancreatic tissue and surrounding adipose tissue specimens were available for all 29 rats included in the study. The severity of all observed features, if present, was determined as grade 1 (mild changes), except for two rats from the NaCl

**Table 1.** Comparison of amylase levels between the control groups

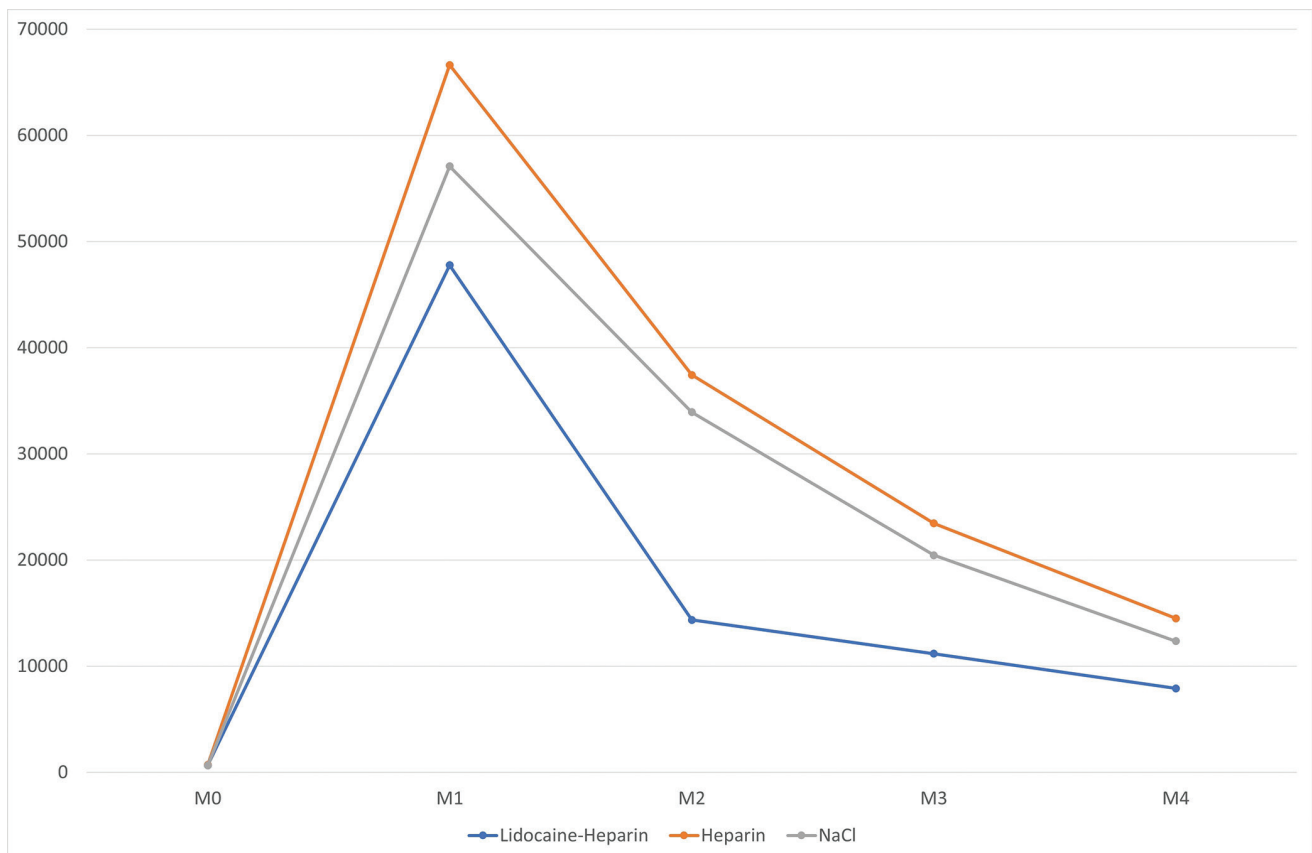
Measurement	Mean amylase levels in the NaCl group [U/L]	Mean amylase levels in the heparin group [U/L]	Mean amylase levels in the lidocaine-heparin group [U/L]	p-value		
				NaCl vs. heparin	NaCl vs. lidocaine-heparin	Heparin vs. lidocaine-heparin
M0	644.5	708.20	658.0	0.093	0.894	0.234
M1	57,083.4	66,622.0	47,766.22	0.457	0.492	0.069
M2	33,927.0	37,428.0	14,346.89	0.557	<b>&lt;0.001***</b>	<b>&lt;0.001***</b>
M3	20,444.4	23,452.30	11,171.67	0.406	<b>0.002*</b>	<b>&lt;0.001***</b>
M4	12,358.3	14,504.40	7914.56	0.361	<b>0.025*</b>	<b>0.001**</b>

Heparin and the lidocaine-heparin group within the whole course of the study.

Legend: \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

Values presented in bold refer to statistically significant differences in the respective comparative analysis.

M0, measurement 0; M1, measurement 1; M2, measurement 2; M3, measurement 3; M4, measurement 4.



**Fig 1.** Amylase levels in the NaCl, heparin, and lidocaine-heparin groups over the entire preoperative (M0–M1) and postoperative (M2–M4) course. M0 – initial amylase levels, M1 – amylase levels after the induction of pancreatitis – just before the operation, M2 – amylase levels 1 h after drug administration, M3 – amylase levels 3 h after drug administration, M4 – amylase levels 5 h after drug administration. M0, measurement 0; M1, measurement 1; M2, measurement 2; M3, measurement 3; M4, measurement 4.

group (grade 2 pancreatic edema), one rat from the lidocaine-heparin group (grade 2 pancreatic edema), and one rat from the heparin group (grade 2 pancreatic necrosis). However, no statistically significant differences in all evaluated features were observed between groups. Detailed histopathological analysis is depicted in Table 3.

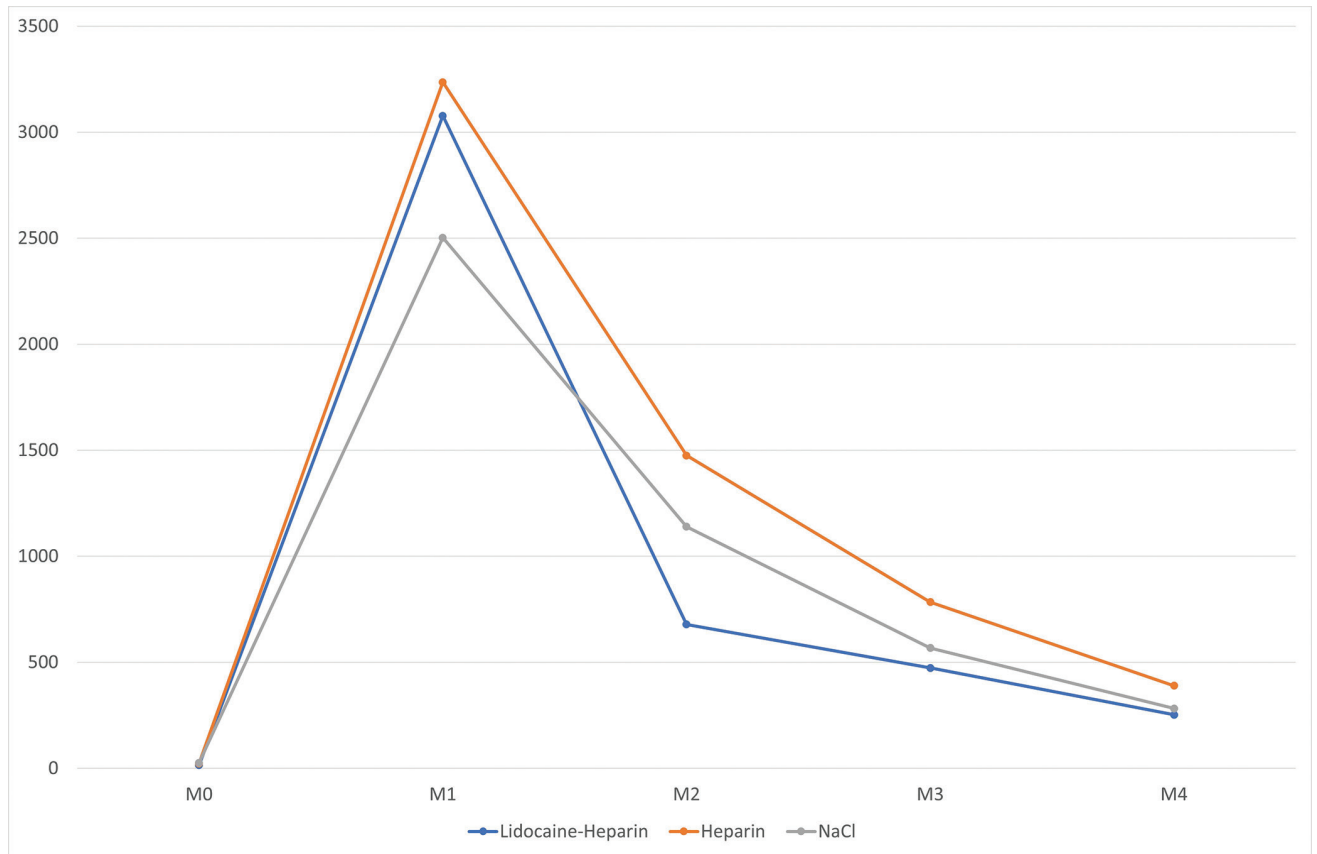
## 4. Discussion

Abnormalities in pancreatic microcirculation constitute the foundation of AP development and progression (Cuthbertson and Christophi 2006; Antkowiak et al. 2022). The pathogenesis of AP begins with activating trypsinogen in the acinar

**Table 2.** Comparison of lipase levels between the control groups

Measurement	Mean lipase levels in the NaCl group [U/L]	Mean lipase levels in the heparin group [U/L]	Mean lipase levels in the lidocaine–heparin [U/L]	p-value		
				NaCl vs. heparin	NaCl vs. lidocaine–heparin	Heparin vs. lidocaine–heparin
M0	25.99	23.10	14.67	0.909	0.267	0.473
M1	2502.20	3236.28	3077.04	0.116	0.273	0.901
M2	1139.61	1475.14	678.70	0.127	<b>0.032*</b>	<b>&lt;0.001**</b>
M3	567.48	783.49	472.91	0.171	0.712	<b>0.039*</b>
M4	281.98	389.79	252.21	0.280	0.907	0.147

Heparin and the lidocaine–heparin group within the whole course of the study.  
Legend: \* $p < 0.05$ ; \*\* $p < 0.001$ .  
Values presented in bold refer to statistically significant differences in the respective comparative analysis.  
M0, measurement 0; M1, measurement 1; M2, measurement 2; M3, measurement 3; M4, measurement 4.



**Fig 2.** Lipase levels in the NaCl, heparin, and lidocaine–heparin groups over the entire preoperative (M0–M1) and postoperative (M2–M4) course. M0 – initial lipase levels, M1 – lipase levels after the induction of pancreatitis – just before the operation, M2 – lipase levels 1 h after drug administration, M3 – lipase levels 3 h after drug administration, M4 – lipase levels 5 h after drug administration. M0, measurement 0; M1, measurement 1; M2, measurement 2; M3, measurement 3; M4, measurement 4.

cells, promoting the inflammation process, and consequently, autolysis of the pancreas and peripancreatic adipose tissue (Antkowiak et al. 2022). As a result of the inflammatory process development, platelet-activating factor (PAF) bradykinin and thromboxane A2 are released. The PAF is a strong pro-inflammatory factor that activates monocytes and

neutrophils, responsible for thrombus formation and endothelin release (Tozlu et al. 2019). The release of endothelin – serving as a strong vasoconstricting factor – as well as an increase in vascular permeability, leads to an increase in the blood viscosity and reduction of the pancreatic blood flow, increasing the risk of thrombus formation, resulting in the



**Table 3.** Comparison of histopathological findings between three groups

Feature	NaCl group	Heparin group	Lidocaine–heparin group	p-value
Pancreatic tissue				
Necrosis	0/10 (0%)	2/10 (20%)	3/9 (33%)	0.163
Edema	8/10 (80%)	6/10 (60%)	5/9 (56%)	0.530
Hemorrhagic foci	0/10 (0%)	1/10 (10%)	1/9 (11%)	0.565
Acute inflammation	0/10 (0%)	0/10 (0%)	2/9 (22%)	0.092
Chronic inflammation	7/10 (70%)	9/10 (90%)	9/9 (100%)	0.152
Mean number of veins and arteries (SD)	19.5 (7.25)	17.1 (2.51)	15.0 (8.34)	0.094
Mean number of capillaries (SD)	36.0 (8.76)	27.9 (5.65)	29.44 (6.35)	0.080
Adipose tissue				
Necrosis	0/10 (0%)	0/10 (0%)	2/9 (22%)	0.092
Hemorrhagic foci	0/10 (0%)	1/10 (10%)	1/9 (11%)	0.565
Acute inflammation	0/10 (0%)	0/10 (0%)	1/9 (11%)	0.316
Chronic inflammation	2/10 (20%)	4/10 (40%)	6/9 (67%)	0.119

SD, standard deviation.

pancreatic tissue swelling and hypoxia. It has already been found that vasoconstriction appears in the early phase of AP development, followed by increased vessel permeability and thrombi formation (Cuthbertson and Christophi 2006). Considering the complexity of mechanisms involved in AP development and progression, vasoactive, anti-thrombotic, and anti-inflammatory approaches are believed to be needed in order to achieve satisfactory control of AP. It has been hypothesized that LMWH, harboring anti-inflammatory, anti-thrombotic, and as a result of those also vasoactive effects, may positively counteract the cascade of AP pathogenesis (Ke et al. 2014; Ning et al. 2015). LMWH activates antithrombin III, leading to the reduction of leukocyte–endothelium interaction and decreases the level of endothelin-1, TNF- $\alpha$ , and interleukin (IL)-6, leading to inhibition of the early inflammatory response.

Furthermore, heparin prevents microvascular constriction in the pancreas by inhibiting complement system activation and endothelin release from the endothelial cells (Dobosz et al. 2004; Hackert et al. 2004). Perfusion analysis showed that administering heparin significantly improved microcirculation in the pancreas and other organs, which may significantly impact the treatment and prevention of local and systemic complications of AP (Dobosz et al. 2004). Considering the multiplicitous mechanism of LMWH action, we aimed to evaluate the impact of LMWH applied subcutaneously on the pancreatic enzyme levels. Our study showed that LMWH did not significantly reduce the severity of AP compared with untreated controls in terms of pancreatic enzyme levels and pathological changes in the pancreatic tissue.

Given the importance of vasoconstriction of the pancreatic vasculature in the development of AP, we hypothesized that early pharmacologically induced vasodilation may improve the course of AP. Lidocaine, an amide-type anesthetic agent, has been found to have concentration-dependent vasoactive properties, with concentrations of 1  $\mu\text{g/mL}$  inducing vessel contraction, while concentrations of 10–100  $\mu\text{g/mL}$  show vasodilatory effects (Sato et al. 2015). In our previous experimental study on cerulein-induced AP, we demonstrated that 1% lidocaine solution (lidocaine concentration of 10,000  $\mu\text{g/mL}$ ), acting as a strong vasodilating substance, significantly improved the course of AP, reducing the levels of pancreatic enzymes and slightly improving the severity of pathological changes in the pancreatic tissue, as compared with untreated controls. Although that study did not directly evaluate the influence of lidocaine on the microcirculation (through imaging tools like Doppler flowmetry), we hypothesized that given the vasoactive effects of lidocaine, its therapeutic mechanism could have resulted from pancreatic microcirculation dilation.

In the present study, we evaluated the efficacy of subcutaneously injected LMWH combined with intraarterial infusion of 1% lidocaine solution in treating cerulein-induced AP in rats. Consequently, in rats receiving combined treatment, we observed significantly lower amylase values compared with both untreated controls and rats receiving only subcutaneous injection of LMWH without the intraarterial preinfusion of 1% lidocaine solution. Conversely, rats receiving combined treatment with LMWH and lidocaine showed significantly lower lipase levels compared with untreated controls only in the first post-treatment evaluation point (M2). However, rats receiving combined treatment presented significantly lower lipase levels than the heparin group in both the first (M2) and second (M3) post-treatment evaluation points. Lipase is more sensitive than amylase in diagnosing AP (Ismail and Bhayana 2017). It is worth noting that the protocol of our study involved the induction of AP using a total dose of 80  $\mu\text{g/kg}$  cerulein, which led to the development of edematous AP instead of severe AP (Ding et al. 2003; Buyukberber et al. 2009). However, the presented study constituted the continuation of our effort to determine the role of lidocaine in experimentally induced AP (Antkowiak et al. 2020). When designing these studies, we hypothesized that if severe AP was induced, the therapeutical role of lidocaine (which has never been studied in AP before – therefore, its actual impact on AP has been unknown) could have been challenging to observe. Hence, initially, edematous AP was induced in order to detect even subtle changes in pancreatic enzyme levels as a result of lidocaine infusion. However, given that both our studies reflected the efficacy of lidocaine in relieving the course of mild edematous AP, it is our future aim to design an experimental study on severe AP to define further the actual

therapeutical role of lidocaine in a more advanced stage of AP. Based on the foregoing results, considering the tendency of pancreatic enzymes to naturally decrease, as observed in the untreated controls, we conclude that the addition of lidocaine may influence the course of AP while lacking the impact on the final AP outcomes. Moreover, the dynamics of pancreatic enzymes stay in line with the histopathological findings, which did not differ significantly between groups. Theoretically, if the severe AP was induced instead of the mild edematous one, the histopathological findings could have shown the differences caused by one treatment, supporting its efficacy.

Lidocaine and LMWH act at different stages of AP. Since vasoconstriction represents an early and crucial event in AP development, followed by vascular permeability and thrombi formation, lidocaine is believed to prevent further progression of AP. On the contrary, LMWH is thought to act at the later stages of AP, when irreversible changes induced by vasoconstriction have occurred. These discrepancies may stand for lack of LMWH efficacy compared with lidocaine. Consequently, it may be hypothesized that the superior efficacy of additional lidocaine infusion to the LMWH compared with LMWH alone stands for the significance of vasoactive (vasodilatory) management in the early phases of AP.

#### 4.1. Limitations

Although being the first report on the efficacy of lidocaine combined with LMWH in treating AP, the present study has some major limitations that need to be highlighted. First, this experimental study was performed on a scarce number of Wistar rats. Furthermore, the use of 80 µg/kg cerulein did not trigger severe AP, precluding a conclusion on the impact of lidocaine on the AP outcomes. We encourage researchers to perform further studies involving swine models triggering severe AP to define the role of lidocaine and LMWH in AP and eventually conclude on their efficacy in that setting. Moreover, the effectiveness of each treatment scheme was evaluated merely through the dynamics of amylase and lipase levels. It should be mentioned that additional evaluation of TNF-α, IL-1, IL-6, or endothelin-1 could have given more insight into the impact of each treatment strategy on the AP course. However, in our setting, technical issues precluded the evaluation of the abovementioned markers.

## 5. Conclusions

Subcutaneous injection of LMWH does not impact the natural course of AP in an experimental setting. However, the addition of intraarterially administered 1% lidocaine solution significantly reduces the severity of AP. Through the comparison

of two drugs acting at different stages of AP development, both targeting pathological cascade occurring in the pancreatic microcirculation, it can be stated that lidocaine-triggered vasodilation appeared as a crucial step in relieving the course of AP.

### Compliance with ethical standards

#### Funding

No funding was received.

#### Conflict of interest

RA and LA have patent #P.433511 issued to the Patent Office of the Republic of Poland. Other co-authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Ethics approval

Ethical approval was obtained from the 2nd Local Institutional Animal Care and Use Committee (IACUC) of the Institute of Pharmacology, Polish Academy of Sciences in Krakow (approval no. 351/2022). In accordance with Polish law, the animals used in the study were obtained from the Animal House of the Faculty of Pharmaceutics, Jagiellonian University Medical College in Krakow, following ethical approval.

#### Availability of data and material

The data generated during this study are available within the article. The datasets analyzed during the current study preparation are available from the corresponding author upon reasonable request.

#### Consent for publication

Not applicable.

#### Author contributions

Conceptualization: RA, LA, and ZA; Methodology: RA, LA, and ZA; Formal analysis: RA, LA, BD, and AK; Investigation: RA, LA, and ZA; Resources: RA, LA, ZA, BD, and AK; Writing – Original Draft: RA, LA, and AK; Writing – Review and Editing: JB, AP-F, PD, and AC-B; Visualization: RA, and LA; Supervision: PD, AC-B, and MK All the authors have approved the final version of the manuscript.

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