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Research Article

Early Markers of Mesenteric Artery Ischemia in Rats

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Abstract

Acute mesenteric ischemia (AMI) is a disease with high mortality (60%-80%). Although it has different etiological causes, the common outcomes are intestinal necrosis and gangrene. The survival rate is reported to be 30-40% on average. Therefore, there is a need for biomarkers to assist the diagnosis. In this study, the early diagnostic values of procalcitonin, lactate, amylase and ferritin levels in AMI were investigated. The rats were divided into two groups:: Control group (Group 1, n=8) consisted of rats which underwent laparotomy only, Study group (Group 2, n=8) consisted of rats who underwent ligation of the superior mesenteric artery (SMA) from the aortic outflow tract to create an experimental ischemia model. Blood samples were taken from both groups at hours 0, 2, 6, 12, and 24, and procalcitonin, lactate, amylase and ferritin levels were compared. Lactate and amylase levels increased in blood in the study group, starting at the 6h after SMA ligation until 24h. Amylase and lactate levels can be used early diagnostic biomarkers in AMI. Increase in procalcitonin level was only significant at the 6h. Ferritin levels did not change in the first 24h and hence can not be considered as an acute phase reactant.

Keywords: *Acute mesenteric ischemia, Procalcitonin, Lactate, Amylase, Ferritin*

Ratlarda Oluşturulan Mezenterik Arter İskemisinin Erken Belirteçleri

Öz

Akut mezenterik iskemi (AMI) potansiyel olarak ölümcül bir hastalıktır (%60-80). Farklı etiyolojik nedenleri olmasına rağmen, mezenterik iskeminin ortak sonuçları bağırsak nekrozu ve gangrendir. Hayatta kalma oranı ortalama %30-40'tır. Bu nedenle tanıda rehberlik edecek biyobelirteçlere ihtiyaç vardır. Bu çalışmada AMI'deki prokalsitonin, laktat, amilaz, ferritin düzeylerinin erken tanısal değerleri araştırıldı. Sıçanlar sadece laporotomy yapılan kontrol grubu (Grup 1, n=8) ve aortik çıkış yolundan superior mezenterik arterin bağlanması ile deneysel bir iskemi modeli oluşturulan deneysel grup (Grup 2, n=8) olarak iki gruba ayrıldı. Sıçanlardan 0., 2., 6., 12. ve 24. saatte alınan kan örneklerindeki PCT, Laktat, Amilaz, Ferritin seviyeleri iki grup arasında karşılaştırıldı. Laktat ve Amilaz'ın kan düzeyleri SMA (Superior Mezenterik Arter) oklüzyonun 6. saatinden başlayarak 24. saate kadar artış gösterdi. Amilaz ve laktat, AMI'de erken tanısal belirteçler olarak kullanılabilir. Prokalsitonin artışı sadece 6. saatte anlamlıydı. Ferritin ise ilk 24 içinde hiç artış göstermediğinden AMI için erken faz belirteci olarak kabul edilmedii.

Anahtar sözcükler: *Akut mezenterik iskemi, Prokalsitonin, Laktat, Amilaz, Ferritin*

INTRODUCTION

Acute mesenteric ischemia (AMI) is a life-threatening acute abdominal disease that occurs as a result of sudden insufficiency in the blood flow of mesenteric vessels in the intestine [1-4]. Dramatically, AMI, appears as a frightening surgical problem [5]. The clinical signs and symptoms seen as a result of the sudden obstruction of the superior mesenteric artery constitute the most common clinical form, with the most common cause being the embolism of the superior mesenteric artery or its branches [6-10]. It presents with arterial spasm, insufficient collateral circulation, and decreased perfusion pressure ischemia. Venous mesenteric thrombosis is the cause of acute mesenteric ischemia in about 10-15% of all cases [1,2]. Superior mesenteric artery embolism is the most common known underlying cause of acute occlusive mesenteric ischemia, seen at a rate of 50% [11,12]. Luther et al.[13] retrospectively examined a total of 91 patients who had undergone endovascular treatment over a period of 11 years. A stent was applied in 78 (85.7%) patients, and angioplasty was performed in 13 (14.3%), principally of the superior

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mesenteric artery (n=81/91, 89%). Despite favorable early results, the outcome of endovascular treatment deteriorates over time, reaching a one-year patency rate of 63%, as reported by a multicenter analysis. This leads to secondary procedures in 30% of cases. A surgical conversion carries a risk of high mortality and a very high rate of superior mesenteric artery embolism, such as 86% [13,14]. In another study, the overall perioperative mortality was found to be 59% (192 patients), and cumulative survival was reported as 30.8%, 26% and 23% for the first, third and fifth years, respectively [15]. Since the superior mesenteric artery diameter is wider and oblique exits from the aorta, emboli are frequently seen in this artery [13,16]. Many laboratory parameters, such as serum d-lactate, amylase, ferritin, and procalcitonin have been tested for this purpose, but no clinically useful result has been obtained [5,8-10]. Most available tests are not specific and require severe tissue damage to be detected in serum. This has to be translated into surgical practice, there is a delay in diagnosis until irreversible bowel damage occurs. Therefore, it is very important to identify a specific and rapidly rising marker to diagnose intestinal ischemia in the early stage of the disease to increase the chance of successful surgery and survival. In light of this finding, in this experimental, controlled study based on a rat model, we investigated the blood lactate, amylase, ferritin and procalcitonin levels in the diagnosis of acute mesenteric ischemia.

MATERIAL and METHODS

Ethical Approval

Experimental applications in rats were performed after obtaining the approval of the Local Ethics Committee of Kobay Experimental Animals Laboratory Company (Approval number: 2020-471). Sixteen, male Wistar-Albino rats weighing 250-300 grams were randomly divided into two groups of eight animals in each group. The rats that had been used in prior studies/experiments and that had signs/symptoms of illness, such as dehydration, decreased body weight, and abnormal posture were excluded from the study. The rats were housed individually at an environmental temperature of 20-25°C, with 40% relative humidity under a 12-h light/dark cycle and were provided free access to food and water. After the 12 h fasting period, general anesthesia was induced by applying 50 mg/kg ketamine and 5 mg/kg xylazine intramuscularly.

Surgical Procedure

The abdominal aorta has three main branches that provide vascularization of the abdominal organs. The first of these, truncus coeliacus, provides blood from the distal esophagus to the second continent of the duodenum. The main branches of this artery are splenic, left gastric and main hepatic arteries. The celiac artery, which is short and large, has widespread collateral circulation, and acute mesenteric artery at this level is the most important reason for ischemia to be rare. The second branch of the abdominal aorta is the superior mesenteric artery. This artery provides vascularization of the intestines starting from the second continent of the duodenum to the distal of the transverse colon and anastomoses with the inferior mesenteric artery through Drummond's marginal artery and the arc of Riolan. The superior mesenteric artery is separated from the abdominal aorta at an angle of about 45 degrees and creates a suitable path for thrombi. This explains, albeit partially, why many mesenteric emboli occur at this level. Although there is a decrease in the blood flow of up to 75%, due to the high adaptation rate to increase oxygen extraction, the intestines can reach 12 h without serious damage and can preserve their viability in this period. However, if ischemia lasts long and is severe, the protective properties of compensatory mechanisms are impaired.

In this study, all rats were given 3 mL intraperitoneal saline. The mesenteric ischemia was created by ligating the superior mesenteric arteries (SMAs) from the aortic outlet area in the experimental group (Group 2). Blood samples were taken at hours 0, 2, 6, 12 and 24. The rats in the control groups (Group 1) were subjected to laparotomy only, and blood samples were collected and examined at the same intervals. In order to easily obtain sufficient blood, the samples were taken from the abdominal aorta and placed in tubes containing citrate. The tubes were centrifuged at 1.000 rpm for 15 min, and the plasma procalcitonin, lactate, amylase and ferritin levels were measured in the separated serum. At the end of the study, all rats were killed by decapitation. Blood samples were studied in the central biochemistry and hormone laboratory of Ankara City Hospital. The Atellica Solution Chemistry 930 analyzer and Atellica Solution Immunassay 1600 modular system analyzer (Erlangen, Germany) were used to test the blood samples.

Statistical Analysis

The control laparotomy and ischemia groups were analyzed separately. SPSS v. 13 for Windows (SPSS Inc., Chicago, IL, USA) was used to analyze all data obtained in the study. The procalcitonin, lactate, amylase and ferritin levels of the groups were investigated using the Kruskal-Wallis analysis of variance (Bonferroni-corrected Mann-Whitney U test). $P<0.05$ was regarded as statistically significant.

RESULTS

The biochemical parameters were compared between the ischemia and control groups at the same evaluation times. The basal mean biochemical values of the groups are shown in *Table 1*. In Group 2 (experimental group), the amylase values significantly increased at 6 h, 12 h and 24 h ($P<0.001$ for all) *(Fig. 1)*, the lactate values showed a significant increase at 2 h, 6 h and 12 h ($P=0.001$, $P=0.001$, and $P<0.001$, respectively) *(Fig. 2)*, ferritin maintained

Table 1. Comparison of the baseline marker levels of the groups			
Parameters	**Group 1 n=8**	**Group 2 n=8**	**P-value**
Amylase (U/dL)	996.9±199.1 (846-1316)	1015.0±172.7 (865-1345)	0.382
Lactate (mg/dL)	30.7±3.2 (26.9-35.6)	30.9±4.6 (25.6-38.3)	0.878
Ferritin (ng/mL)	0.50±0.00 (0.50-0.50)	0.50±0.00 (0.50-0.50)	0.999
Procalcitonin (pg/L)	0.17±0.14 (0.03-0.30)	0.06±0.10 (0.03-0.30)	0.234
Data are given as mean ± standard deviation and (min-max)			

started to increase from the 6 h and continued significantly until the 12 h. Among these rats with mesenteric ischemia, the amylase values continuously and significantly increased from the 6 h to the 24 h while the procalcitonin value peaked at the 6 h *(Table 2)*. There was no significant increase in the level of blood ferritin within 24 h.

DISCUSSION

Acute mesenteric ischemia is a life-threatening condition, which occurs as a result of the sudden insufficiency of blood flow of mesenteric vessels in the intestine, causing damage to not only the intestines but also other vital

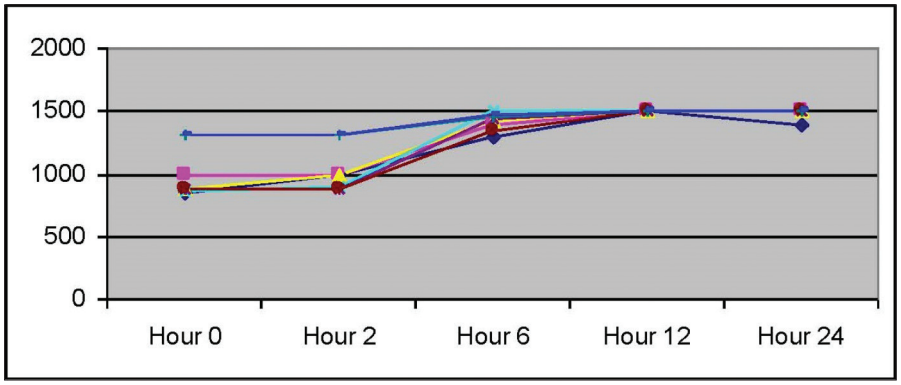
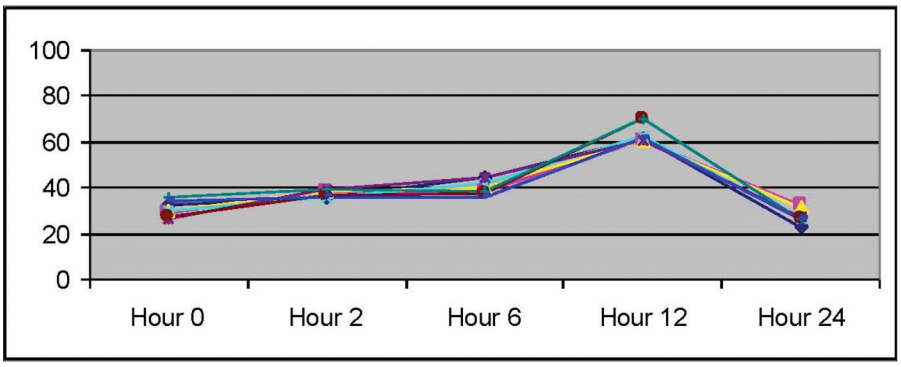


Fig 1. Changes in the amylase level of the AMI-induced rats over 24 h

Fig 2. Changes in the lactate level of the AMI-induced rats over 24 h



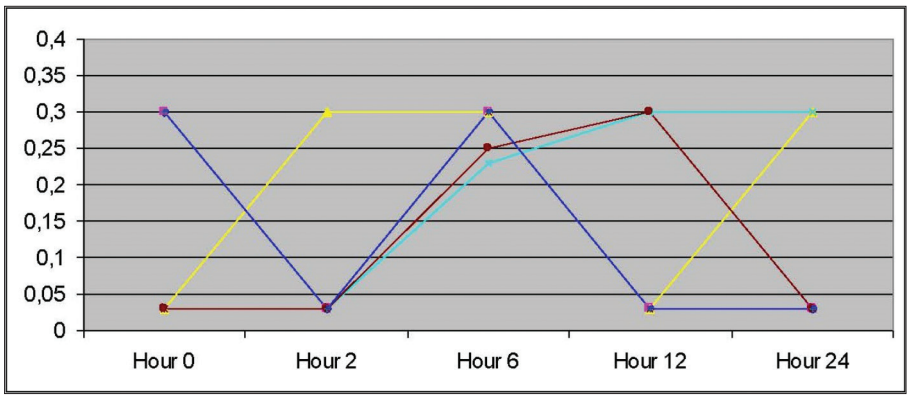


Fig 3. Changes in the procalcitonin level of the AMI-induced rats over 24 h

at the same level with no significant increase at any measurement time, and the serum procalcitonin level statistically significantly increased only at 6 h (P=0.035) *(Fig. 3)*. In addition, in Group 2, the mean of d-lactate levels

organs. AMI is an acute abdominal disease [10,16-18] remains to have a generally fatal outcome. The mortality rates of this disease are reported to be between 70 and 90% in recent years, which are very similar to those published

Table 2. *Changes in the marker levels of Group 2 compared to the baseline values*

Time Period	Amylase	Lactate	Ferritin	Procalcitonin
0 hour	996.9±199.1	30.7±3.2	0.50±0.00	0.17±0.14
2 hour	1.034.5±178.9 P= 0.121	37.5±1.5# p= 0.001	0.50±0.00	0.06±0.10 P= 0.197
6 hour	1.417.9±66.5* P<0.001	40.1±3.2# p= 0.001	0.50±0.00	0.29±0.03□ P= 0.035
12 hour	1.500.0±0.0* P<0.001	63.4±4.1# p<0.001	0.50±0.00	0.10±0.12 P= 0.451
24 hour	1.486.5±38.2* P<0.001	27.6±2.9 p= 0.111	0.50±0.00	0.10±0.12 P= 0.451
P value	0.034	0.001	0.999	0.033

Data are given as mean ± standard deviation. Values with different superscripts are significantly different at P<0.05 (, #, □)*

by Hibbert et al.[11] in 1933. The most important step in the management of AMI is, undoubtedly, to diagnose mesenteric ischemia before intestinal infarction develops. While the probability of life is 60% in patients diagnosed within 24 h, this rate drops to 30% in those diagnosed after this period. For this reason, studies on AMI and diagnostic investigations have increased in recent years [12]. The endovascular treatment of intestinal artery disease cannot be considered as the treatment of choice; it is rather an alternative method in patients with functional or local contraindications to surgery [13]. The common result of previous studies is that AMI lacks a sensitive and specific marker that can help achieve early diagnosis to increase survival. There are several different reasons why a sufficiently good diagnostic biochemical marker could not be detected. The first problem is due to the intestine consisting of mucous membranes, submucosa and smooth muscle layers. An ideal marker should be able to reflect this complex structure [5,10,14]. This marker should also ensure that damage to the mucosa is diagnosed before its progression into a full-thickness infarction. The second problem is that the vascular pathway that provides intestinal blood flow passes through the portal vein through the liver. Venous blood from the intestines can participate in systemic circulation after being exposed to the first transition effect in the liver. Lastly, the overlapping protein expression of the liver and intestine makes it difficult to identify an organ-specific marker [15,19,20].

Elevated serum lactate concentration also predicts mortality in mesenteric infarction cases [6,21]. Metabolic acidosis has been used as a biochemical parameter in the diagnosis of acute mesenteric ischemia for nearly three decades [7,16]. Accordingly, lactate levels were found to be high in approximately 90% of patients with AMI in the late period [8,19,20]. When the biochemical structure of lactate is evaluated, there are two isomers, D and L-lactate, according to the position of the alpha hydroxyl radical on the molecule, and both are products of anaerobic metabolism. Conflicting results have been reported in recent experimental studies regarding the use of lactate as a screening test in the early diagnosis of AMI, although pyruvate is reduced by specific lactate dehydrogenase [11,12,20]. Lactic dehydrogenase, amylase, alkaline phosphatase, creatinine phosphokinase, and ammonia were found to have no specificity for mesenteric ischemia. In mesenteric ischemia, the best marker evaluated to date remains serum lactate. Several clinical and experimental studies have shown that the serum lactate level increases following superior mesenteric artery occlusion [8,20]. Lange and Jackel have reported 100% sensitivity, but only 42% specificity for serum lactate as a marker for mesenteric ischemia. In another clinical study, the measurement of serum lactate was diagnostically helpful, although not confirmative [8,10,20]. Lactate is simply an indicator of an anaerobic state [8,9,21]. In our study, in the rats with mesenteric ischemia (Group 2-experimental group), the mean lactate level started to increase from the 6h, and this increase continued until 12 h *(Table 2)*.

In chronic experiments on dogs, soon after the ligation of the pancreatic duct, amylase increases in the peripheral blood, as well as the release of total amylase and lipase in the liquid and solid portions of the secretion from the isolated parts of the small intestine [9,12,20]. The α-amylase release was shown to depend on the level of blood amylolytic activity and the secretory activity of the small intestine. The α-amylase and lipase release is more increased upon mechanical rather than chemical stimulation of the small intestine. After the secretory function of the pancreas is excluded, two stages of compensatory adaptive changes occur in the secretory activity of the small intestine: consuming processes due to lower energy (secretion of blood enzymes) and involvement of the small intestine. In the diagnosis of AMI, many studies have been conducted to investigate the role of amylase for the last few decades. In a mesenteric ischemia model in dogs, Aydın et al.[21] reported that the amylase values significantly increased. Wilson et al.[22] evaluating 52 patients diagnosed with mesenteric ischemia, determined that 27 had higher amylase levels than normal. Aslan et al.[23] found that the amylase values of patients diagnosed with AMI started to increase at the third hour. The progresses in our understanding of the pathophysiology, diagnosis and treatment of the

acute occlusions of SMA or the superior mesenteric vein have made it possible to save lives and recover intestinal function in most patients with mesenteric ischemia [24]. In another previous study, amylase was found to be 42% specific and 68% sensitive in patients presenting with acute abdomen and diagnosed with mesenteric ischemia [25]. In our study, the amylase values in Group 2 increased steadily from 6 h to 24 h; thus, they exhibited an increasing trend. Based on these results, it can be commented that amylase rises in many diseases that play a role in the acute etiology of the abdomen, as well as AMI, as determined in our study. However, different studies have identified fluctuations in amylase levels and questioned whether this parameter is sufficiently specific to eliminate other causes of abdominal pain. Therefore, the use of amylase alone in the diagnosis of AMI remains controversial, and it should still be assessed together with other parameters due to its low sensitivity and specificity.

There are many laboratory parameters that are used in the diagnosis of inflammatory diseases based on their ability to show immune response. It is also known that inflammation-induced procalcitonin is released from neuroendocrine cells in the lung, liver, intestines, and pancreas. Bacterial endotoxins and TNF-α are the strongest procalcitonin inducers in experimental conditions [26,27]. The procalcitonin levels were previously found to be high in the early period in patients with acute myocardial infarction [28]. In recent years, procalcitonin has emerged a new parameter among infection markers in recent years [29]. It is a simple and practical marker that can be used in the early diagnosis of severe acute pancreatitis and monitoring of clinical prognosis [9,30]. PCT, as an inflammatory response parameter, it appears as an early and better marker in sepsis and serious infections [10,29,30]. In another study, the serum procalcitonin levels were evaluated in patients with acute stroke. In patients with acute stroke, the serum procalcitonin levels were found to be elevated starting from the first day, and it was observed to reach the highest levels on the seventh day [31]. Procalcitonin levels were also shown to increase in intestinal strangulation [32,33]. The procalcitonin levels were reported to be increased in the strangulated group compared to the controls. An increase in the procalcitonin levels was observed at the 30th and 60th min of the study, and a serious elevation was detected at the 120th min [32]. The high mortality seen in cases of mesenteric ischemia is also often caused by septic complications [2,32]. It is commonly agreed that in almost every situation, systemic inflammatory response syndrome and septic complications can develop. Plasma procalcitonin levels significantly increase in bacterial, fungal and parasitic infections, sepsis, and multi-organ failure syndrome [27,31,32]. Oruc et al.[33] found that the blood procalcitonin levels were higher in Crohn's disease, one of the inflammatory bowel diseases, compared to normal human blood levels. Procalcitonin can be used to monitor prognosis and response to treatment in this patient group [32,33]. In addition, increases in procalcitonin level does not change in autoimmune, viral and allergic diseases. Studies have shown that a small amount of bacterial endotoxin injection stimulates procalcitonin production in healthy individuals [34]. At two to three hours, procalcitonin rises to a level that can be measured, and then it increases rapidly from the sixth to eighth h, reaching its highest value at the 12th h. After this period, procalcitonin remains approximately the same for a further 12 h and returns to its normal level within the next two days. The half-life of procalcitonin varies from 20 to 24 h [27,34]. Procalcitonin measurement presents as an easy method and can be a marker for the diagnosis and follow-up of AMI and sepsis [29,34]. In our study, the PCT value in Group 2 was significantly increased only at 6 h. Since there is no study in the literature investigating procalcitonin in AMI, there is a need for research with larger series to confirm our results.

Ferritin has generally been considered to function as a "housekeeper" storage protein which can release iron required for cellular proliferation (e.g., ribonucleotide reductase) and metabolic renewal (e.g., cytochrome synthesis) [35]. The period of reperfusion after ischemia is thought to be a critical period of oxidant damage in many tissues, including the heart, brain, gut, and other organs [36]. The antioxidant properties of ferritin are likely mediated by the sequestration and storage of iron, thus preventing ferryl or hydroxyl radical generation [37,38], playing a key role in maintaining iron homeostasis. During the postischemic reoxygenation of the rat liver, early ferritin degradation was counteracted by enhanced ferritin transcription. It was suggested that this might act to re-establish ferritin levels and limit reperfusion damage [39]. Indeed, hypo-transferrinemic mice, which have high levels of ferritin and lactoferrin, are resistant to hyperoxia-induced lung injury [40]. Although serum ferritin levels usually correlate with total body iron stores, several physiologic conditions, such as inflammatory and infectious states can increase serum ferritin as one of the acute-phase proteins [41,42]. Rogers et al.[43] also reported that the inflammatory induction of ferritin synthesis was different from iron-dependent ferritin gene expression. Serum ferritin levels may increase solely as a consequence of cellular necrosis or damage [44]. This possibility is supported by previous clinical findings of an association between serum ferritin levels and the injury severity score [45]. Ferritin, a highly conserved iron-binding protein, plays a key role in the maintenance of cellular iron homeostasis and protection from oxidative stress. Ferritin mitigates oxidant stress by sequestering iron and preventing its participation in reactions that generate reactive oxygen species [46]. In our study, there was no statistically significant increase in the ferritin level of Group 2, which suggests that ferritin may be a late-phase reactant.

Çakır et al.[47] measured five parameters (White blood count,

Lactic dehydrogenase, Creatine Kinase, lactate, and D-dimer) in the blood of 92 AMI patients over 24 h. They detected cumulative percentages for amylase in 68 (73.9%) patients and lactate in 47 (51.1%). They also found that white blood cell count, creatine kinase, lactate dehydrogenase, lactate, and D-dimer levels increased in patients with acute mesenteric ischemia [47]. In our animal experiment, we simultaneously evaluated four early markers. We found similar blood values using different or same blood parameters in a more controlled rat model. The results of our animal study are consistent with clinical practice. We observed that the levels of blood amylase *(Fig. 1)* and d-lactate *(Fig. 2)* obtained from the SMA of the rats constantly increased from the 6 h to the 24 h. The amylase and lactate blood values reached their highest at the 12 h. On the other hand, we did not find a significant and stable increase in the procalcitonin and ferritin levels. Although the procalcitonin value peaked at the 6 h in the rats with mesenteric ischemia, we observed that the changes in the procalcitonin level were not consistent *(Fig. 3)*. Thus, we conclude that the lactate and amylase levels can be used as early diagnostic markers to achieve rapid and accurate results in patients with suspected SMA obstruction.

Author Contributions

FA designed the project, wrote the main paper. BA carried out data acquisition and statistical analyses. All authors contributed to the critical revision of the manuscript for important intellectual content and have read and approved the final version.

Conflict of Interest

All authors declare that they have no conflict of interest to disclose.

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