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Can galectin-3 be used to predict the severity of vasoocclusive crisis in patients with sickle cell anaemia?

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ABSTRACT

Objective: The number of markers showing the severity of the disease and the number of drugs that can be used in the treatment is very low in vasoocclusive crises seen in patients with sickle cell anemia. This study aims to evaluate the levels and changes of serum galectin-3 levels, which are known to have many roles in the body, during a painful crisis.

Material and Methods: In addition to the 0th and 48th hour galectin-3 levels in patients hospitalized for a painful crisis, galectin-3 measurements were also performed in stable patients with sickle cell anemia and healthy individuals.

Results: Galectin-3 levels were statistically significantly different in patient groups (p=0.001). It was observed that galectin-3 levels at the 48th hour were markedly higher than at the 0th hour in patients with painful crises. It was found that galectin-3 levels at both 0th and 48th hours were correlated with the duration of hospitalization due to painful crisis and the period of intravenous opioid use.

Conclusion: Galectin-3 levels, which are elevated during the painful crisis in patients with sickle cell anemia, are associated with the severity of the painful crisis

Keywords: sickle cell disease, vasoocclusive crisis, galectin-3

INTRODUCTION

Sickle cell anaemia is characterized by chronic hemolytic anaemia and recurrent painful crises. The most common reason for hospitalization in these patients is painful vasoocclusive crises.

The frequency and severity of painful crises vary among patients. Apart from pain treatment, the number of drugs used in vasoocclusive crises is very limited today (1).

The pathophysiology of vasoocclusive crises is quite complex. It is believed that clinical symptoms occur with endothelial activation, increased adhesion of erythrocytes and leukocytes to endothelial cells, and increased oxidative stress conditions causing vascular occlusion (2).

Galectin-3, which is known to have a role in many places such as cell adhesion, activation, chemotaxis, growth and differentiation, and resistance to oxidative stress, is a molecule belonging to the galectin family (3).

Due to these features of galectin-3, which may have a role in the pathophysiology of vasoocclusive crisis, its use as a marker showing the clinical course of these patients and as a treatment target may be on the agenda.

The objective of this study is to examine the levels and changes of serum galectin-3 during the painful crisis in patients with sickle cell anaemia, and to evaluate whether or not these levels and changes are related to the severity of the painful crisis.

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MATERIAL AND METHODS

Patients aged 18 years and older hospitalized in Mersin University Hematology and Pediatric Hematology clinics and Adana City Training and Research Hospital Hematology clinic between February 2021 and June 2021 due to vasoocclusive crisis were included in the study. For the sickle cell anaemia control group, stable patients with sickle cell anaemia who applied to the outpatient clinic in the same centers were included. For the healthy control group, healthy individuals who applied to the haematology outpatient clinic in the same centers were included.

For measurement of galectin-3, blood samples were collected twice from patients hospitalized with vasoocclusive crisis, immediately before the start of opioid infusion therapy (hour 0) and at 48 hours of infusion. A blood sample was collected once for the sickle cell anaemia control group and once for the healthy control group. The collected blood samples were centrifuged, and then the serum samples obtained were kept at -80 0C until the study was completed, and galectin-3 levels were studied in the samples at the end of the study. Galectin-3 measurements were made with ELISA kits, and results are shown in ng/mL.

Routine hemogram values, HbS and HbF percentages in haemoglobin electrophoresis, ferritin levels, number of days of hospitalization, and intravenous opioid days of patients hospitalized for the painful crisis were recorded.

Patients under 18 and whose vasoocclusive crisis duration was less than 48 hours were excluded from the study.

A signed informed form was obtained from all patients and healthy volunteers participating in the study. This study was approved by Mersin University Clinical Research Ethics Committee (2021/13).

Statistical Method: NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analysis.

Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used to evaluate study data.

The conformity of the quantitative data to the normal distribution was tested with the Kolmogorov-Smirnov, Shapiro-Wilk test, and graphical evaluations. The Student's t-test was used to compare normally distributed quantitative data between two groups, and the Mann Whitney U test was used for two-group comparisons of non-normally distributed quantitative data. Pearson Chi-Square test was used to compare qualitative data. In evaluating the relations between the variables, Pearson Correlation Analysis was used for normally distributed variables, and Spearman's Correlation Analysis was used for non-normally distributed variables. Significance was evaluated at the $p<0.05$ level at least.

RESULTS

The distribution of the descriptive characteristics of the patients included in the study is given in Table-1. Galectin-3 levels were statistically significantly different in patient groups (p=0.001). According to the results of the pairwise comparisons made to determine the difference, the Galectin-3 value of the individuals in Group 1 was significantly higher than the subjects in Group 2 and the control group (p=0.001). Likewise, the Galectin-3 levels of Group 2 individuals were significantly higher than those in the control group (p=0.001). The Galectin-3 levels of the patient groups and control group are given in Figure-1.

When Table-2 is examined, it is observed that serum Galectin-3 levels are correlated with both the duration of the crisis and the number of days that require intravenous opioids. It is noteworthy that the correlation degrees of Galectin-3 levels at the 48th hour are stronger than galectin levels at the 0th hour.

When Table-3 is examined, it is observed that there is no statistically significant relationship between Galectin-3 values at 0th and 48th hours and Hb, HbA2, HBS, HBF and Ferritin values of the individuals participating in the research.

Table 1: Distribution of descriptive features

		Total	Group 1	Group 2	Control	
		n (%)	n (%)	n (%)	n (%)	*p*
Gender	*Female*	*61 (49,2)*	20 (16,1)	18 (14,5)	23 (18,5)	[a]***0,675***
	Male	*63 (50,8)*	20 (16,1)	23 (18,5)	20 (16,1)	
Age (years)	*Mean±Sd*	*32,82±10,95*	30,37±9,77	33,92±9,69	34,04±12,84	[b]***0,214***
Galectin-3 levels (ng/mL)	*Median (Min-Max)*	*11,9 (6,4-25,7)*	19,6 (12,1-25,7)	11,9 (6,7-18,9)	8,4 (6,4-13,1)	

A Pearson Chi-Square Test b Kruskal Wallis Test
Group 1: Patients with sickle cell anemia hospitalized with a painful crisis
Group 2: Patients with sickle cell anemia without painful crisis
Control: Healthy adult patients participating in the study

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Table 2: Evaluations of the duration of the painful crisis and the number of days of intravenous opioid

	Crisis Period		Number of Iv opioid Days	
	r	*p*	*r*	*p*
Age (years)	-0,096	[d]*0,558*	-0,029	[d]*0,861*
Galectin-3 at 0th hour	0,442	[d]*0,007***	0,509	[d]*0,001***
Galectin-3 at 48th hour	0,828	[d]*0,001***	0,896	[d]*0,001***
Hb	0,014	[d]*0,930*	0,017	[d]*0,916*
HbA2	0,090	[d]*0,581*	0,047	[d]*0,774*
HBS	0,030	[c]*0,856*	0,084	[c]*0,608*
HBF	0,156	[c]*0,336*	0,179	[c]*0,269*
Hematocrit	0,049	[c]*0,763*	0,031	[c]*0,848*
Platelet	0,119	[c]*0,463*	0,142	[c]*0,381*
Leukocyte Count	0,200	[d]*0,217*	0,241	[d]*0,135*

Table 3: Relationship between serum Galectin 3 levels and some laboratory parameters in the patient group with painful crisis

	Galectin3 at 0th hour		Galectin3 at 48th hour	
	r	*p*	*r*	*p*
Hb	-0,058	[d]*0,609*	0,024	[d]*0,885*
HbA2	0,034	[d]*0,765*	-0,083	[d]*0,610*
HBS	-0,086	[c]*0,444*	0,124	[c]*0,445*
HBF	0,106	[c]*0,346*	0,136	[c]*0,401*
Ferritin	0,046	[c]*0,682*	0,362	[c]*0,022**

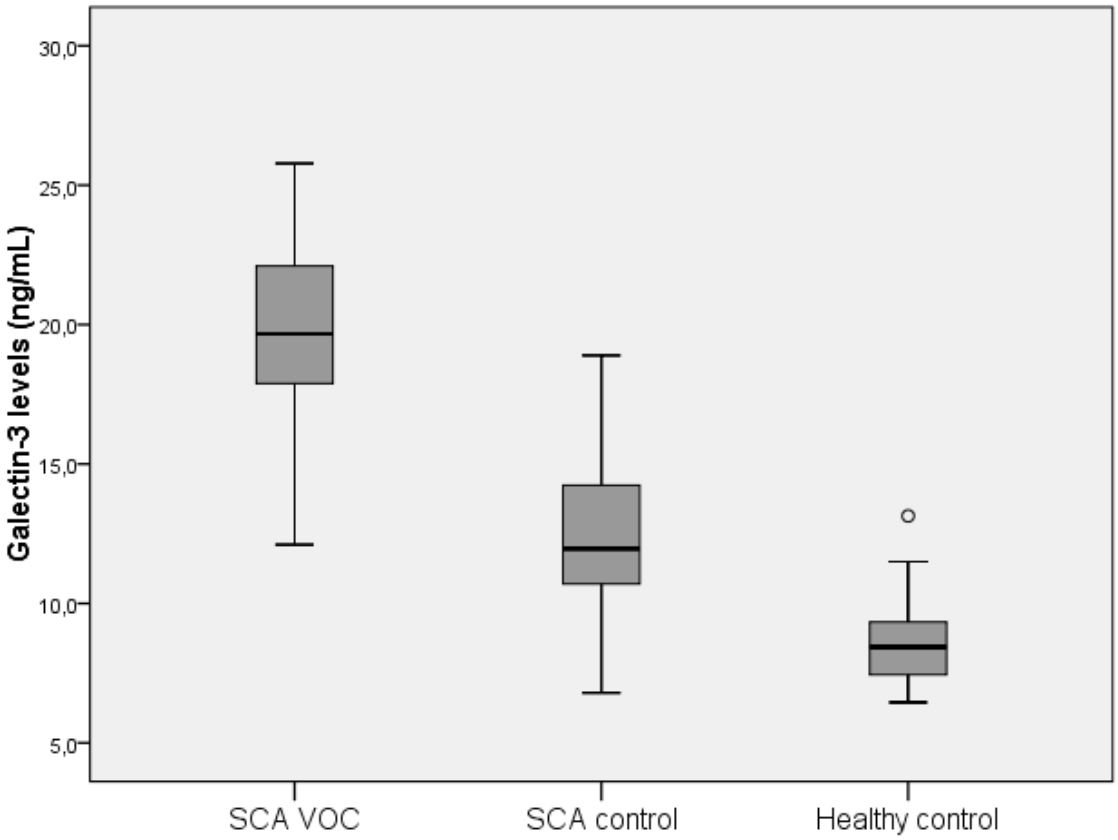

Figure 1: Galectin-3 levels. **SCA:** Sickle cell anaemia, **VOC:** Vasoocclusive crisis

DISCUSSION

This prospective and controlled study demonstrates that galectin-3 levels are higher in patients with painful crises than stable patients with sickle cell anaemia and healthy individuals. Moreover, it was determined that Galectin-3 levels continued to increase in the 48th hour of the painful crisis and were better correlated with the duration of the painful crisis and the duration of an intravenous opioid requirement compared to the 0th-hour measurements.

Sickle cell anaemia is the most common hemoglobinopathy globally and presents with severe organ damage with advancing age and recurrent transfusions (4). These patients mostly apply to the emergency department with a painful crisis and suffer from severe pain (5). There are many ongoing studies to reduce the duration and severity of the painful crisis in hospitalized patients. However, an ideal molecule has not been found yet (6). Hydroxyurea therapy has been used for a long time to increase HbF levels in these patients. Still, despite using hydroxyurea, there are many patients who are admitted to the hospital with severe painful crises.

Two molecules with proven effectiveness in preventing painful crises in recent years stand out. The first of these, L-glutamine, has been shown to reduce the frequency of painful crises. It is believed that this molecule acts by reducing oxidative stress in erythrocytes (7). Crizanlizumab, which has recently been approved by the FDA and acts by inhibiting P-selectin, is another molecule. It has been found that this molecule also reduces the frequency of painful crises in patients with sickle cell anaemia and does this independently of hemolysis (8). Despite the current developments in this regard, the need for biomarkers that will enable the prediction of the severity of the painful crisis as well as the search for molecules that reduce the frequency and severity of painful crises continues.

Galectin-3 is involved in various biological processes such as cellular adhesion, activation, chemotaxis, growth and differentiation, resistance to oxygen and nitrogen radicals, damage and apoptosis (9). In many disease groups, especially malignant diseases, chronic inflammatory diseases and diseases with fibrosis, Galectin-3 levels were studied. It has been shown by Aksan et al. that Galectin-3 levels are high in patients with coronary atherosclerosis and can be used in risk classification. (10). It has been observed that Galectin-3 may have a role in the pathogenesis of pulmonary hypertension in mouse models and it is predicted that it can be used for treatment in the future (11). Studies are showing that Galectin-3 can be used for diagnostic and prognostic purposes in patients with gastric cancer (12). It has been stated that this marker is also increased in peripheral arterial disease, and that it also correlates with oxidative stress markers and inflammation markers (13). It has been shown by Jiang et al. that Galectin-3 is associated with poor prognosis in patients with primary hepatocellular cancer (14). Moreover, Galectin-3 has been shown to have a role in the metastases of some cancers and it has been stated that Galectin-3 inhibitors can be used to reduce metastasis in metastatic cancer patients (15). Many ongoing phase studies are investigating the use of Galectin-3 inhibitors in fibrosis and metastatic cancers.

Although few in number, there are also studies in the literature on the role of Galectin-3 levels in the development of pulmonary hypertension and pulmonary fibrosis in patients with sickle cell anaemia (9, 16). However, no study examining the relationship between Galectin-3 and painful crisis in these patients was found in the literature review. In this respect, what makes this study important is that it is the first to show the relationship between Galectin-3 level and the severity of painful crisis in patients with sickle cell anaemia.

As for the limitations of the study, first of all, we can say that the number of patients was relatively small. Second, although we did examine the relationship between the number of days of intravenous opiod and Galectin-3 levels; since patients were not evaluated daily with pain scores, the relationship with the degree of daily pain was not examined. Third, in patients with sickle cell anaemia who were discharged after a painful crisis attack, Galectin-3 levels could not be examined when they were stable. If they had been examined, we guess we could have found more precise results.

CONCLUSION

In conclusion, in patients with sickle cell anaemia, Galectin-3 may be one of the indicators of disease severity during the painful crisis. Phase studies of Galectin-3 inhibitors are ongoing for many diseases, and the use of these drugs in patients with sickle cell anaemia in painful crisis may also be considered in the light of future studies involving more patients.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. The Ethics Committee of the Mersin University approved the study.

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