

Changes in Hemoglobin Level and Mean Corpuscular Volume During the Convalescent Phase of Acute Febrile Illness in Children: A Study of the Possible Role of Hemolysis

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Abstract- Fever is one of the most common clinical manifestations in children. During the early days of acute febrile illness, some decrease in hemoglobin levels occurs due to unspecified cause. 64 children aged 6 months to 12-year-old with a fever higher than 38° for more than one day and with a diagnosis of acute febrile illness were admitted. The values of MCV, ESR, CRP, and hepcidin were measured at baseline and then 7 to 10 days after the improvement of the fever. The levels of reticulocytes, LDH, and bilirubin were also measured in two stages. Data analysis was done using SPSS software. The mean hemoglobin level in the acute phase of febrile illness was significantly increased 7-10 days after discontinuation of the fever by 12.87±1.09 g/dl ($P<0.001$). The MCV level also significantly increased ($P<0.001$), and levels of CRP, ESR, LDH, bilirubin, and hepcidin showed significantly decreased during the convalescent phase compared to acute febrile phase, but the level of erythrocyte increased. The present study confirmed the decrease in hemoglobin in children with acute febrile illness. Increasing of bilirubin, LDH, hepcidin, level, and no bleeding was observed during acute febrile infection in children.

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Introduction

Fever in children is a very commonly noted symptom that is associated with a viral infection most of the time. However, fever without source, in 7% of children, is the first symptom of a serious bacterial infection such as meningitis, pneumonia, pyelonephritis, or bacteremia (1).

Acute febrile illness is manifested by the immune system's response to the pathogen (infectious diseases) and a sudden increase in body temperature and lasts less than one week (2,3).

Anemia prevalence is related to fever duration and inflammation, and (4). Hemoglobin (Hb) level is the most reliable index of anemia in all people. Anemia is a main public health issue that may occur at any stage of life but is more common in pregnant women and young children suffering from iron deficiency (5).

Reduced immunity, reduced rate of growth, and the adverse and irreversible effects of anemia in children can

be the main incentive for screening anemia among children. When the hemoglobin concentration reaches below 7 g/dL, anemia can be life-threatening (6,7).

Studies have shown that low hemoglobin level is associated with inflammatory bowel disease in children, (8) lower respiratory tract infection (9-11) and urinary tract infection (12) in children.

During the infection with bacterial, viral, and fungal pathogens, a type of anemia, namely, anemia of inflammation occurs, and during the first week of development of acute illness, a marked drop in hemoglobin levels occurs (13).

The causes of anemia of acute infection have not yet been adequately determined. Data regarding the pathophysiology of anemia associated with acute infections are scant (14,15). In a patient, usually a child without a history of exposure to the virus, the degree of anemia depends on whether the child suffers simultaneously from hemolytic anemia or is healthy. In

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the latter case, the anemia may be left undetected because the sharp decrease in hemoglobin occurs very slowly; there is a rapid recovery of erythropoiesis within 1-2 weeks. However, in a child with congenital or acquired hemolytic anemia, the clinical conditions can be dramatically exacerbated, requiring transfusions of red blood cells (16).

The most important symptom of anemia of inflammation is systemic iron homeostasis disorder. The beneficial effect of this inflammatory response is a reduction in access to microbes and infectious agents to iron during the infection (17,18).

During infectious processes, changes in the serum concentrations of acute-phase proteins (APP), including C-reactive protein (CRP), occur (19). The plasma CRP concentration increases rapidly in response to acute inflammation and infection, reaching its maximum level at approximately 48 h and decreasing within one week; therefore, these variables serve as an important indicator of infection (19,20).

CRP is synthesized in response to cytokines, especially IL-6, from liver cells, and facilitates phagocytosis by macrophages. In healthy subjects, CRP levels are usually lower than 2 mg/L but can increase up to 10 mg/L (21,22).

Erythrocyte sedimentation rate (ESR) also begins to increase within 24-48 hours after the onset of the infection and slowly decreases after recovery (22).

Hemoglobin is the most important clinical indicator of anemia and indicates the presence of hemolytic disease. Other laboratory indices include hemolysis, reticulocytes, lactate dehydrogenase (LDH), and bilirubin (23).

Reticulocytes are nucleus-free precursors of red blood cells, which represent hematopoiesis of bone marrow and usually increase in hemolysis (24). Levels of LDH and bilirubin also increase in hemolytic states and decrease after recovery of hemolysis (25).

Although in the study of Ballin *et al.*, hemoglobin drop in the acute phase of febrile illness in children was not related to hemolysis (14), a rapid drop in hemoglobin levels associated with acute infection in the absence of obvious bleeding may suggest mild hemolysis during acute febrile illness.

Therefore, the changes in hemolytic indices were also studied in this study. It was also reported in the study of Sales *et al.*, that the probable impact of the community and the health status of the population also affected hemoglobin changes during the infection (23).

Therefore, in different populations of the present study, different results may be observed.

However, in previous studies during the acute phase of febrile illnesses in children who did not have a chronic inflammatory disease, hemoglobin decreased, and some MCV changes were observed [16,23,14-16], but few reports on the cause of hemoglobin decrease during acute infections of children are available (23).

It is not clear exactly whether we have a hemolytic condition.

Considering the proven effects of anemia on increased mortality, growth impairment and immunodeficiency in children, identifying the mechanism by which this hemoglobin drop occurs helps prevent or treat the acute phase of febrile illness, as well as prevents the effects of these complications, reduces the days of hospital stay, prevents hospital occupancy, reduces costs, and helps provide better clinical services.

If the hemolytic hypothesis is proven or ruled out, unnecessary diagnostic treatments and measures can be prevented during the acute phase of febrile illness, and an appropriate treatment protocol can be chosen.

Therefore, in this study, changes in hemoglobin and MCV levels in the acute phase of febrile illness (in comparison with the beginning of the acute phase of the illness), as well as changes in levels of hepcidin, bilirubin, LDH, and erythrocyte in convalescent phase, were investigated.

Materials and Methods

In this descriptive-analytic study, the population of the study included children aged 6 months to 12 years admitted to Hajar Hospital in Shahrekord, southwest of Iran, due to acute febrile illness (fever greater than 38 degrees for more than one day) in 2017.

The inclusion criteria included: having suffered from acute febrile illness for at least 24 hours, no history of blood transfusion in the last six months, hemoglobin levels of 7 mg/dl or higher in the initial test, no nutritional supplementation or iron-containing compounds, lack of history of anemia before the onset of acute febrile illness, absence of neutropenia or thrombocytopenia, and exclusion criteria were receiving blood during admission, using a nutritional supplement or iron-containing compounds during and after admission.

After approving the study protocol at the ethics committee of Shahrekord University of Medical Sciences (approval code: IR.SKUMS.REC.1395.133), sampling was conducted by convenience sampling.

To determine the sample size in a pilot study, a pilot group of 10 children aged 6 months to 12 years admitted for acute febrile illness was selected, and the variables in

question were measured at admission and 10 days later.

Assuming that the hemoglobin changes during the study were equal to 1 ± 1.8 , the sample size was determined to be 58 using the sample size calculation formula considering the 99% confidence interval and 95% test power. To increase the precision of the study, 64 patients were enrolled.

Blood samples were taken and mean corpuscular volume (MCV), Hemoglobin (Hb), complete blood count (CBC), ESR, CRP, LDH, reticulocytes, hepcidin, and bilirubin levels were measured in all subjects at the time of presentation using standard methods.

Before enrollment in the study, the child's parents were given explanations about the purposes and the protocol of the study, and then they provided written consent for their child's participation in the study. In this study, the cost of non-therapeutic tests was paid from research costs.

Data were recorded on the checklist according to age and sex. During 7-10 days of admission, every effort was made not to use nutritional supplements and iron-containing compounds for the child.

One week to ten days after the improvement of the patient's fever, the factors were again measured and recorded. Statistical analysis was performed by the SPSS.

In addition to descriptive statistics and mean (standard deviation) values, Kolmogorov test was first performed and based on the results of this test for the data on hemoglobin and MCV that were normally distributed paired t-test; and for comparison of other variables that were not normally distributed, Wilcoxon signed-rank test was used.

Results

In this study, a total of 64 children with febrile illness participated, of whom 33 were female (51.6%), and 31 were boys (48.4%). The age of children ranged from 7 to 144 months, with an average of 37.7 ± 2.04 months.

The mean hemoglobin level in the acute phase of the febrile illness was 12.31 ± 1.21 g/dL, which reached 12.87 ± 1.09 g/dL without treatment or supplementation, 10-7 days after discontinuation of the fever.

In four (6.2%) of the 64 patients who participated in the study, hemoglobin did not change during the convalescent phase of acute febrile illness compared to the acute phase.

In 7 patients (10.9%), hemoglobin decreased, and in 53 cases (82.8%), it increased. According to the paired t-test, hemoglobin values increased significantly during the convalescent phase of acute febrile illness ($P < 0.001$).

The MCV level also had a significant difference during the acute phase of febrile illness and recovery phase ($P < 0.001$), with an average MCV of 75.4 ± 5.31 femtoliter at baseline compared to 80.37 ± 6.48 femtoliter in the convalescent phase.

In 2 cases (3.12%), the MCV index in the convalescent phase and the acute phase of the fever was not significantly different. In 4 cases (6.25%), this index decreased, and in 58 (90.62%) cases, it increased.

Levels of CRP, ESR, LDH, bilirubin, and hepcidin significantly decreased in the convalescent phase of febrile illness compared to the acute phase, but the level of erythrocyte increased (Table 1).

Table 1. Laboratory Indicators Investigated before and after study

Statistical index		min	max	Mean \pm SD	Middle (Mid-quartile domain)	Changes after study			P
Index	Phase					Increased cases	Decreased cases	No change	
Hb (g/dL)	before*	8.8	15.6	12.31 \pm 1.21	12.3(11.62-13.2)	53(82.8%)	7(10.9%)	4(6.3%)	<0.001****
	after**	9.8	15.9	12.87 \pm 1.09	12.9(12.3-13.7)				
MCV (femtoliter)	before	56.4	89.5	75.4 \pm 5.31	75.7(72.5-78)	2(3.1%)	4(6.3%)	58(90.6%)	<0.001****
	after	60.5	93.8	80.37 \pm 6.48	80.4(77-83.6)				
CRP (mg/l)	before	1	109	20 \pm 21.95	12(5-29)	10(15.6%)	51(79.7%)	3(4.7%)	<0.001***
	after	2	13	4.62 \pm 2.26	4(3-5)				
ESR (mm/h)	before	4	69	21.25 \pm 16.52	15(9-27)	11(17.2%)	51(79.7%)	2(3.1%)	<0.001***
	after	3	69	13.2 \pm 10.53	10(6-19)				
LDH (U/L)	before	119	825	394 \pm 144	398(334-487)	20(31.2%)	44(68.8%)	0	0.002***
	after	132	679	319 \pm 117	308(223-372)				
erythrocyte (%)	before	0.3	1.4	0.59 \pm 0.19	0.5(0.5-0.6)	52(82.3%)	7(10.9%)	5(7.8%)	<0.001***
	after	0.1	1.3	0.8 \pm 0.19	0.8(0.7-0.9)				
hepcidin (ng/ml)	before	224	7311	3240 \pm 2185	3870(1049-5268)	17(26.6%)	47(73.4%)	0	0.007***
	after	234	2693	2674 \pm 2294	1928(636-4078)				
bilirubin (mg/dl)	before	0.2	1.5	0.61 \pm 0.26	0.6(0.4-0.8)	5(7.8%)	6(9.4%)	53(82.8%)	<0.001***
	after	0.1	0.9	0.36 \pm 0.18	0.3(0.2-0.5)				

* a admission (acute phase of febrile illness), ** 7-10 days after recovery of fever, *** Paired t-test, **** Wilcoxon signed-rank test

Discussion

The present study showed that hemoglobin levels increased significantly after the acute phase of febrile illness without supplement or medication, which is consistent with the study of Ami Ballin *et al.* in children aged 6-18 years, where Hgb and hematocrit (Hct) were significantly higher in prehospitalization or posthospitalization than hospitalization values, and acute illness was associated with anemia. The mean Hgb value in the infection group was 10.9 ± 1.27 g/L, and the rate of hemoglobin drop throughout the acute phase was more severe in children with bacterial infections (14,15).

The results of another study also showed that the prevalence of anemia was significantly higher in the presence of an acute phase response because of reduced serum iron concentrations and therefore impaired Hb synthesis (23).

A study by Viana MB *et al.*, to investigate the association between infection and anemia in children showed a strong correlation between the acute phase of infection (CRP greater than or equal to 6) and a decline in hemoglobin (16).

The etiology of anemia during the acute phase of infectious febrile illness has not yet been adequately determined and, due to limited studies in this regard, information on the pathophysiology of anemia related to fever and acute febrile illness is not sufficient.

This is likely to be related to the benign nature of this type of anemia. During the process of acute inflammation, the concentration of hemoglobin is reduced by about 13%, usually within a week, and then increases by about 25% during the inflammatory convalescent phase of the infection (26).

Several factors, such as reduced red blood cell production and iron deficiency due to reduced reuptake or hemolysis, may contribute to this clinical presentation.

It should be born in mind that children with iron deficiency are predisposed to infectious disease due to decreased hemoglobin production and subsequent reduction in the level of defense of the body; (11,27).

Therefore, adequate attention should be paid to the provision of balanced and adequate nutrition for growing children. In addition, early diagnosis and prevention of anemia are important to reduce the incidence of infections in children (9-11).

In addition, the present study, LDH, reticulocytes, and bilirubin during febrile illness and 7-10 days after fever convalescence were investigated to investigate the potential role of hemolysis in the development of anemia

during fever and acute febrile infections.

In the convalescent phase, LDH and bilirubin decreased significantly, but the level of reticulocytes increased significantly. Due to increased bilirubin and LDH during the acute febrile phase and their decrease after fever convalescence, it can be hypothesized that during fever, transient hemolysis occurs that is spontaneously resolved after healing of acute febrile illness, and hemoglobin levels increase.

In contrast, in the investigations of Ballin *et al.*, all parameters of hemolysis, namely reticulocytes, bilirubin, LDH, and haptoglobin, were normal, and it is argued that hemolysis and iron metabolism are unlikely to play a role in the development of anemia in children during fever.

In these studies, it was argued that the possible cause of a rapid drop in hemoglobin during the acute phase of febrile infections was the reduction in red blood formation and sequestration, and an increase in the binding of red blood cells to the endothelium of the blood vessels of the liver and spleen, which prompted the rapid removal of red blood cells by the reticuloendothelial system (14,15).

Consistent with the present study, the results of another study suggested that erythrophagocytosis played a role in the anemia of acute infection. Authors suggest that anemia associated with acute infection represents the scarifying of a small number of erythrocytes in the process of clearing invading organisms in the body (27).

In the study of Abshire *et al.*, in the United States to investigate hemoglobin and ESR levels in children hospitalized due to moderate to severe inflammatory processes, the results showed that hemoglobin levels in decreased by two points of standard deviation in 83% of the children during the acute phase of inflammation, and hemoglobin concentration increased by more than 1.3 mg/dL in 79% of these cases.

In contrast to the present study, none of these children had evidence of bleeding, hemolysis, or excessive hydration. Usually, this mild to moderate anemia improves without treatment (26).

In another study, in children of 6 months to 12-year-old with severe ESR (ESR 50), hemoglobin levels were under 11 in the 91% and under 10% in 52% of them, while anemia was rarely seen in the group of under 20 ESR. Anemia has an extremely strong association with inflammation. An association between anemia and childhood infections has also been observed (4).

In the present study, the Wilcoxon signed-rank test showed a decrease in the inflammatory parameters of ESR and CRP 7-10 days after the discontinuation of the

infection, and the hemoglobin increased accordingly.

In the study of Cristina *et al.*, a drop in hemoglobin level in children with elevated CRP levels was significantly higher than in those with normal CRP levels (23).

The study of Shinoda *et al.*, showed that the more marked the inflammation and increase in acute phase proteins, including CRP, are, the more severe anemia occurs (28).

In our study, the level of MCV in the phase after the convalescence of acute febrile illness was quite increased obviously.

However, in the process of hemolysis, the MCV index is expected to be normal or increase. In the study of Ballin *et al.*, despite the decrease in hemoglobin during the acute phase of the illness, the MCV index remained unchanged (15).

In addition, in the present study, the study of hepcidin levels during the convalescent phase of acute febrile illness showed a statistically significant relationship between fever healing and hepcidin levels, which means that in the acute phase of the illness, the level of hepcidin has increased.

This result is similar to the findings of Kossiva *et al.*, in children. In that study, hepcidin was found to rise during the acute infection and fall post-infection, including both viral and bacterial infections (29).

Considering the increase in hepcidin levels during the acute phase of a febrile illness that in turn reduces the available iron for the synthesis of hemoglobin and reduces the production of erythrocytes, it seems that in addition to the hemolysis process, there may be some levels of erythropoietic suppression in the bone marrow, but considering that the life span of red blood cells is about 100-120 days, this effect will not lead to an acute presentation, and the hypothesis of hemolysis as the cause of anemia is still likely during the acute phase of febrile illness.

On the other hand, with the increase of the hepcidin, iron decreases, (30) leading to a lack of increase in reticulocyte (despite the incidence of hemolysis) and a decrease in the MCV index in our study, and as a result, a partial decrease in MCV in red blood cells produced during the acute phase of febrile illness.

Hepcidin is an acute-phase protein and is a 25-amino acid peptide synthesized by hepatocytes, which plays a major role in iron homeostasis. Hepcidin expression is controlled by iron and inflammation, peaking at approximately 6 h after inflammation. In states of inflammation, high hepcidin levels block iron release from enterocytes and decrease iron availability (8,29-32).

However, there are no adequate data on pediatric cases to guarantee the use of hepcidin levels in clinical algorithms to diagnose acute infection (29).

In this study, hemoglobin levels in the acute phase of the illness were 0.57 lower than the convalescent phase, i.e., equal to 12.3 g/dL, which should be taken into consideration because the anemia was determined by hemoglobin values <11.0 g/dL (9,23). However, to obtain more reliable results, it is necessary to conduct studies with a larger sample size. Other limitations of this study include the lack of evaluation of iron levels to diagnose iron-deficiency anemia associated with infection.

In addition, the association between the type of acute bacterial or viral infection and the rate of hemoglobin decline was not investigated in this study. In future studies, the association between the degree of fever and the rate of hemoglobin loss can also be evaluated.

The results of this study confirm hemoglobin decline in acute febrile illness in children that resulted in transient and reversible anemia without the use of complementary therapy and became febrile spontaneously after the convalescence of the illness. Evidence of mild hemolysis (including increased bilirubin, LDH, hepcidin, and no bleeding) was observed during acute febrile infection in children. Therefore, in children with acute infection, the likelihood of anemia due to hemolysis should not be ignored.

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