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Hematological and Biochemical Changes among Visceral Leishmaniasis (Kala-Azar) Patients Under Sodium Stibogluconate (SSG) and Ambisome Therapy

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ABSTRACT

Visceral leishmaniasis (VL) remains one of the most serious public health concerns owing to its increased morbidity and mortality in untreated cases. The current study aimed to estimate hematological and chemical parameters among VL Sudanese patients in ElGadarif State Whole blood samples of 39 VL patients were collected for complete blood count and clinical chemistry parameters, Complete Blood Count (CBC) was performed, and clinical chemistry parameters were carried out via chemical analyzer Biosystem, as well as reagents for different analytical parameters measurements. Data was analyzed with the statistical package of social science (SPSS) version 22. A significant decrease in Hemoglobin (Hb), (Packed Cell Volume) PCV, Mean Cell Hemoglobin (MCH), White Blood Cells (WBCs), and platelets (PLT) were decreased, while Mean Corpuscular Hemoglobin Concentration MCHC was increased among case group than control, MCV has no difference between groups. Liver Function Tests (LFT) enzymes and Renal Functions Tests (RFTs) showed that there was a significant increase in urea, (Aspartate transaminase) AST, and Alanine aminotransferase (ALT) when compared to the control group while creatinine and Alkaline phosphatase (ALP) were insignificantly increased among case group than the control. A non-significant increase in urea, creatinine, ALT, AT, and ALP levels among the Ambisone group more than Sodium Stibogluconate (SSG) group (p-value ≤0.05) VL patients suffering from thrombocytopenia, leukopenia and anemia, and significant mild increased in levels of urea, creatinine and liver enzyme, Ambisone treatment was associated with the significantly increased level of urea and a mild increase in creatinine and AST than SSG treatment.

Key words: *Ambisone, Complete blood count, Sodium Stibogluconate (SSG), Visceral leishmaniasis*

INTRODUCTION

Leishmaniasis is a poverty-related disease, in which a mammalian host gets infection with the obligate, intracellular Leishmania parasite that exists in two main clinical forms: visceral and cutaneous leishmaniasis [1,

2]. About 0.7–1 million are infected worldwide, with 350 million at risk, reportedly, leishmaniasis is endemic in 98 countries including Sudan [3]. The incidences of visceral leishmaniasis have declined significantly over the years as a result of greater access to care and prognosis, and other more rigorous vector control as part of an Asian eradication effort, while climate change may play a significant role in incidence rates. Nevertheless, the incidence rate of this fatal illness keeps rising in eastern Africa. In Sudan mostly affected are the Blue Nile, Upper Nile, Al-Qadarif, Jonglei, and Kassala regions, as well as in the area north of the capital, Khartoum [4, 5].

Anti-leishmaniasis treatment in Africa, South America, Bangladesh, Nepal, and India has been mainly done by the effectual and more well-known Pentavalent antimonial compounds (Sb^v) which block the effects of amastigotes' glycogen synthesis and oxidative fatty acid pathways. Amphotericin B deoxycholate is suggested as an initial line of treatment if there is a high Sb^v resistance. However, this recommendation is yet to be implemented and remains in transition because of the lack of proper infrastructure and administration procedures [6, 7].

A dis-regulation in chemical and hematological values has been correlated to VL patients, which can be a significant cause of death and comorbidities [8]. Anemia, leukopenia, thrombocytopenia, and pancytopenia are the most frequently reported clinical and laboratory symptoms. Variations in hematological profile pictures induced by neutropenia have been related to bleeding disorders and also steadily increasing host vulnerability to pathogenic bacteria [9, 10]. Anemia has been associated with RBC hemolysis, poor nutritional status, and the presence of various co-morbidities including such chronic condition and opportunism infection, since amastigote proliferates and multiplies in the mononuclear phagocytic system, then lead to consequences of hematological defects that is ascertained by the spleens size and illness' course of action. A huge expansion of phagocyte-bearing organs such as the spleen and hematological manifestations can be caused by the provocation of the mononuclear phagocytic system's hyperplasia [11-13]. As well as chemical alterations of liver function that may lead to hepatic dysfunction, VL infected patients have an enlarged liver and increased level of ALT, AST, and ALP, and the condition is also categorized by serious hypertriglyceridemia with reduced concentration of total cholesterol, LDL-cholesterol, and High-density lipoprotein. It also has an influence on the renal, which is linked to high morbidity and mortality. Acute kidney injury may lead to renal dysfunction that occurs as a consequence of the deposition of immune complexes leading to the damage of the glomerulus [14-16].

Increasing disease activity has also been noted in the eastern state of Al-Qadarif, where an increased rate of death despite treatment protocol implemented within years, patients suffer from intensified symptoms even during the treatment course, giving a query about the effectiveness of drugs used over there. So this study was conducted among Sudanese patients infected with Visceral leishmaniasis to evaluate some hematological and chemical parameters to navigate the authority responsible for drug protocol to ensure about patient's states.

MATERIALS AND METHODS

Study design

This study was conducted as a descriptive cross-sectional study performed in Al- Qadarif State-Eastern of Sudan during the study period from April to December 2021. patients with visceral leishmaniasis diagnosed patients only were recruited in the study as a case group while healthy subjects were set as the control group, and patients with malaria and other disorder affecting hematological parameters and chemical ones did not involve in the study. This study was approved by the ethical committee of Alzaeim Alazhary University- and governmental hospital administration; moreover, the patients were informed of the study and its importance before sample collection. Data was collected through a direct questionnaire containing questions on age, gender, spleen, and liver state.

Sampling collection

Whole blood samples were collected during the study period from April to December 2021, from 39 VL patients under hygienic conditions in Ethyl di-amine tetra acetic acid (EDTA) for complete blood count and heparin added blood container for clinical chemistry parameters.

Method

Complete Blood Count (CBC) was performed by Mindray hematology analyzer BC3000 plus (China)^{TM}, provided with suitable reagents and clinical chemistry parameters via chemical analyzer Biosystem (Spectrophotometer-Germany) ^{TM}, as well as reagents for different analytical parameters measurements.

Data analysis

The statistical package of social science (SPSS) version 22 was employed for data analysis. Independent (T-test) was used to calculate (p-value), P-value < 0.05 was considered significance. Also, the Chi-square test was used to find the association between parameters.

RESULTS AND DISCUSSION

This descriptive case study was conducted in El-Gadarif state- regions of Kala-Azar, 39 professionally diagnosed patients with VL were included, with a mean age of ±SD (21.2+14.3) years. 21 (53.80%) were males and 18 (46.20%) were females, in parallel 39 healthy individuals were set as the control group.

Hematological parameters result

A significant decrease in Hb, PCV, MCH, WBCs, and platelets was revealed, while MCHC was increased among the case group than control as for each (p-value< 0.05), MCV has no difference between groups as p-value >0.05, considering genders, comparing parameters revealed that a significant decrease was found only in Hb as it was decreased among females than males bringing the p-value <0.05 while other parameters (PCV, RBCs indices, WBCs, and platelets) decreased among the case group than the control however with no significant difference since the p-value >0.05 as in **Table 1**.

Table 1. Comparison of hematological parameters among study group

Parameters	Case group n=39 Mean ±S.D.	control group n=38 Mean ±S.D.	p value
Hb	9.50±3.60	12.4±2.07	0.000*
PCV	25.50± 0.60	37±5.50	0.000*
MCV	74.20±10.30	84.20±13.70	0.731
MCH	28.90±9.06	28.40±2.50	0.001*
MCHC	34.80±3.14	32.80±1.30	0.016
WBCs	4.40±5.20	6.7±2.10	0.000*
Platelet	141.70±77	268.90±105	0.001*

*significant difference p-value <0.05.

Table 2 illustrates the comparison of hematological parameters according to treatment**, a**nemia (Hb <10g/dl) presented among 24 (61.5%), and the microcytic hypochromic picture presented among 28 (71.8%). thrombocytopenia among 18 (46.2%) and leukopenia among 32 (82.1%). Regarding treatment, the patients were sorted into two groups, one of Ambisone protocol, which included 22 patients and the other group contained 17 patients, they were under SSG (Sodium Stabo-Glyconate) treatment protocol, when comparing hematological parameters among both groups, there was no change of parameters levels between the two groups since there was no significant difference for each parameter as p-value >0.05.

Table 2. Comparison of hematological parameters according to treatment

parameters	AMBISONE (n=22) Mean ±S.D.	SSG (n=17) Mean ± SD	p-value
Hb	9.70±4.50	9.20±20	0.62
PCV	25±7.10	26.30±5.80	0.62
MCV	74.40±8.80	74.10±12.40	0.93
MCH	27.80±5.20	30.30±12.30	0.43
MCHC	35.20+3.60	34.20±2.30	0.32
WBCs	3.70±3	5.40±7.20	0.37
Platelet	144.10±81.80	138.70±72.60	0.83

* significant difference p-value <0.05.

In the association analysis between hematological parameters and hepatosplenomegaly, the study demonstrated no association between the variables as in **Table 3**.

Table 3. Association of hematological parameters with hepatosplenomegaly

Parameters		hepatosplenomegaly		chi-square	p-value
		Yes	no		
Hb	Normal	2 (5.40%)	4 (10.80%)	0.010	0.65
	Decrease	11(29.70%)	20 (54.10%)		
PCV	Normal	2 (5.40%)	4 (10.80%)	0.038	0.60
	Decrease	11 (29.70%)	20 (54.10%)		
MCV	Normal	3 (8.10%)	5 (13.50%)	0.025	0.59
	Decrease	10 (27.00%)	19 (51.40%)		
MCH	Normal	8 (22.90%)	7 (20.00%)	2.9	0.08
	Decrease	5 (14.30%)	15 (42.90%)		
MCHC	Normal	13 (36.10%)	21 (58.30%)	1.1	0.40
	Decrease	0 (0.0%)	2 (5.60%)		
WBCs	Normal	3 (8.10%)	4 (10.80%)	0.22	0.47
	Decrease	10 (27.0%)	20 (54.10%)		
Platelet	Normal	4 (10.80%)	14 (37.80%)	2.5	0.10
	Decrease	9 (24.30%)	10 (27.0%)		

significant difference p-value <0.05

VL patients suffered from microcytic hypochromic anemia (28, 71.8%), as lowHb, MCV, and indices indicated that, while others (11, 28.2%) presented with no anemia signs comparing the presence of low Hb and MCV showed that increased significant difference (p-value <0.05)

Chemical parameters

The results of RFTs and Liver enzymes showed that there was a significant increase in urea, AST, and ALT in the case group compared to the control (p-value < 0.05) while the levels of creatinine and ALP were increased among the case group than the control but no difference found (p-value >0.05) as in **Table 4**.

Table 4. Comparison of Liver & Renal function parameters among study group

parameters	**Case (n=39)** Mean ±SD	**Control (n=38)** Mean ±SD	**p-value**
Urea	39.30 ± 46.50	23 ± 7.10	0.03
Creatinine	1.30 ± 1.80	0.93 ±.20	0.21
AST	108.80 ± 128.20	36.10±5.20	0.001
ALT	87.30 ± 114.10	30.18±10.42	0.004
ALP	88.50 ± 55.20	92.90±46.01	0.65

Comparing parameters among treatment types groups (Ambisone and SSG)revealed that there was an increase in urea (significant difference p-value <0.05), creatinine, and ALT, each has no significant difference (p-value >0.05), ALT and ALP decreased among Ambisone group than SSG but no significant difference asp-value for each >0.05 as **Table 5**.

Table 5. Comparison of LFT enzymes& RFT according to treatment

Parameters	**AMBISONE**	**SSG**	**p-value**
Urea	52.30 ± 58.20	22 ± 8.90	0.03
Creatinine	1.70 ± 2.3	0.74 ± 0.29	0.11
AST	94.10 ± 125.20	78.8 ± 101.9	0.68
ALT	103.80 ± 134.10	114.60 ± 124.70	0.80
ALP	75.80 ± 44	104.70 ± 65.10	0.16

No statistical difference with **comparison of LFT enzymes & RFT** and **gender** of participants, all data were summarized in **Table 6**.

Table 6. The comparison of LFT enzymes & RFT according to gender

parameters	Male (n=19) Mean ± S.D.	Females (n=16) Mean ± S.D.	p-value
Urea	37.40 ± 29.30	41.60 ± 62.10	0.79
Creatinine	1.30 ± 1.70	1.20 ± 1.80	0.76
AST	115.60 ± 146.50	55.80 ± 48.80	0.10
ALT	142.60 ± 158.50	73 ± 74.50	0.09
ALP	97.70 ± 69.10	78 ± 32.80	0.30

Table 7 illustrates the association analysis between liver enzymes and renal function parameters with Hepatosplenomegally, the study demonstrated no association between the variables.

Table 7. Association of Liver enzymes & Renal function with hepatosplenomegaly

Parameters		Hepatosplenomegaly		chi-square	p-value
		Yes	No		
Urea	normal	9 (26.50%)	20(58.80%)	0.15	0.52
	Increase	2(5.90%)	3(8.80%)		
Creatinine	normal	6(18.20%)	15(45.50%)	0.54	0.3
	Increase	5(15.20%)	7(21.20%)		
AST	normal	5(13.90%)	11(30.60%)	0.05	0.5
	Increase	7(19.40%)	13(36.10%)		
ALT	normal	4(11.40%)	10(28.60%)	0.33	0.4
	Increase	8(22.90%)	13(37.10%)		
ALP	normal	5(16.70%)	10(33.30%)	1.00	0.6

Global warming is having a major effect on our ecosystems, and it has shifted the way individuals interact, availability, and allocate resources, increasing the risk of occurrences with zoonosis' communicable diseases. As climate change continues, they affect human health, migration, and food security, as well as the subsequent increase in disease-carrying vectors in new surroundings. Steadily increasing forest or native environment discharge for reusing of land, industrialization, and management of water resources are associated with the emergence of vector-borne potential pathogens [17]. As a result of the steady increase in leishmaniasis cases in Sudan, particularly in eastern Sudan, we decided to conduct the current study among Sudanese patients diagnosed with VL and undergoing treatment to evaluate the hematological and chemical parameters.

This descriptive case study was conducted in ElGadarif state- regions of Kala- zar, case group included 39 professionally diagnosed patients with VL were included, with mean age's 21.2±14.3 S.D. years. 21 (53.80%) were males and 18 (46.20%) we females. 14 (35.90%) were suffering from hepatosplenomegaly. LV patients were under treatment protocol of Sodium Stabo Glyconate (SSG) 17 (46.20%) and Ambisone 22 (53.80%), data of the case group compared with data of healthy individuals set as the control group. Interestingly such findings are similar to the result reported by an Ethiopian study as an institution-based retrospective cross-sectional study among 141 patients with visceral leishmaniasis reported that males were influenced 13-fold more than females [12]. The majority of them were workers who traveled to endemic regions during the winter season. Anemia was shown in 95% of the cases, thrombocytopenia in 90%, leukopenia in 86%, and pancytopenia in 79%. Co-infection was observable in 50 % of patients. As well as finding documented by Kindie *et al.* [18].

The results of hematological parameters revealed that there was a significant decrease in Hb, PCV, MCH, WBCs, and platelets were decreased, while MCHC was increased among the case group than the control for each (p-value< 0.05), MCV has no difference between groups as p-value >0.05. Considering the type of treatment, comparing hematological parameters among both groups, showed no significant difference for each parameter a p-value >0.05. Considering genders, comparing parameters revealed that only a significant decrease was found in Hb as it was decreased among females than males bringing the p-value <0.05 while other parameters (PCV, RBCs indices, WBCs, and platelets) were decreased among the case than control but no significant difference was obtained for each one p-value >0.05. VL patients suffered from microcytic hypochromic anemia (28, 71.80%), as low Hb, MCV, and indices indicated that, while others (11, 28.20%) presented with no anemia

signs comparing the presence of low Hb and MCV showed that increased significant difference (p-value <0.05). In the association analysis between hematological parameters and hepatosplenomegaly, the present study demonstrated that there is no association between such variables. Anemia (Hb <10g/dl) presented among 24 (61.50%), microcytic hypochromic picture presented among 28 (71.80%). thrombocytopenia among 18 (46.20%) and leukopenia among 32(82.10%).

On the other hand, the findings of LFT enzymes and RFTs showed that there was a significant increase in the levels of urea, AST, and ALT in the case group compared to the control group (p-value > 0.05) while creatinine and ALP were increased among case group than control but no difference was found.

Comparing parameters among treatment types groups (Ambisone and SSG) revealed that there increased urea level (significant difference p-value <0.05), creatinine, ALT, AT, and ALP among Ambisone group than SSG but no significant difference as P-value for each >0.05. Considering gender, both LFT enzymes and RFT gave no difference as the p-value for each parameter>0.05. In the association analysis between liver and renal function parameters with Hepatosplenomegally, the study demonstrated no association between the variables. The SSG (antimony regimen) was revealed fewer side effects as well as liver and renal toxicity than Ambisone, our finding is conflicts with that reported in the literature which stated that liposomal Amphotericin B (LAB) has effectively therapeutic efficacy and is more active at low dosage, minimizing toxic side effects [19].

Our result is in agreement with a study conducted by Tesfanchal *et al*. [14] who revealed an average serum AST, ALA, ALP, total bilirubin, and triglyceride levels were markedly larger in visceral leishmaniasis patients than in apparently control subjects. A consensus was reached concerning hematological characteristics retrieved from the laboratory records before and after the intervention. The levels of hemoglobin, WBCs, and platelets after the treatment were notably higher excluding the absolute count of neutrophils. When statistically checked, the parasite burden was noted to have a deeply negative relation to the white blood cell and red blood cell parameters [15, 20].

Present findings also a partial agreement with the study, which noted that clinical, hematological, and biochemical features of pediatric visceral leishmaniasis (PVL), were bearing mild to significant microcytic hypochromic anemia (67.70% Hb less than 8 fl oz). 66.70% of them were leukopenic (WBC: less than $5\times 10^3/\mu L$) and 24.20% had decreased platelet counts. As well as pancytopenia which was revealed in 18.2% of their cases. While the levels of MCH, MCV, and MCHC were less than normal values in 90%, 88%, and 85.10% of the patients consequently. Furthermore, there was a 53.33% and 6.66% elevation of the levels of aspartate transaminase (AST) and alanine transaminase (ALT) in the respective patients [16]. In agreement with the study whereby diagnostic facilities were lacking, conducted in india by [19] Sundar *et al*. The existence of Leishmania parasites (Leishmania Donavani bodies) (LD bodies) in bone marrow aspiration confirmed the diagnosis of VL, and it remains a gold standard technique. Some information that was noted down included physical signs at presentation, demographic information, and results of complete blood count whereas for LD bodies bone marrow aspirations were performed. The average patient age was 30 months, comprising 33 females and 31 males. 100% of children experienced fevers periodically before the diagnosis of 56 days. While hepatomegaly was present at 84.40%, all cases showed Splenomegaly with the average spleen and liver enlargements being 9.3cm and 3.5 cm, respectively. Mean hemoglobin level, white blood cell, and platelet counts were 6.6 g/dl, 3.58x109 /L, and 71.7x109 /L, respectively [21].

Eventually, an Ethiopian study was performed among VL patients and controls whose blood samples were evaluated for liver function tests, for estimation of AST, ALT, total bilirubin, albumin, and total protein. they revealed a statistically significant elevation in the level of AST, ALT, and total bilirubin among cases as compared to control. (p-value <0.001) [22].

Interestingly VL is still a complicated clinical problem, so new treatments, such as liposomal amphotericin, may use as effective regimens with less toxicity than currently used regimens, but must be tested in various leishmania endemic countries such as Sudan. The new drug implementation may offer critical safeguards and not to be used in ways that promote the development of resistance as an integral part of VL patient administration [23]. Patients with VL could be supported with erythropoietin to correct anemia. Further investigation may be applied to determine the cause of leukopenia and thrombocytopenia like bone marrow and tests for DIC respectively. The resistance of the Leishmania parasite to the drugs currently used in Sudan in the treatment protocol is mandatory.

CONCLUSION

This study showed that most patients with VL were suffering from thrombocytopenia, leukopenia, anemia, and

significant mild increases in the levels of urea, creatinine, and liver enzyme. Regarding the type of treatment used; there was no difference in hematological parameters but Ambisone treatment was associated with a significantly increased level of urea and a mild increase in creatinine and AST levels than SSG treatment.

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