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Multi drug therapy effects on routine laboratory parameters in Leprosy patients

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Abstract

Background: Multi Drug Therapy approved by WHO is the best treatment option for Leprosy. There is a significant decline of mortality and morbidity after the introduction of multi drug therapy. But the adverse effects causing changes in clinical and laboratory parameters to multi drug therapy are the main limiting obstacle for the treatment course completion.

Objective: The aim of this study is to find out the effects on routine laboratory parameters including hematological and biochemical changes before, during and after the treatment of multi drug therapy in leprosy.

Methodology: A descriptive cohort hospital based study on 85 multi drug therapy treated leprosy patients using standard laboratory tools for routine investigations for 18 months.

Results: During the one year multidrug treatment period, most of the routine laboratory parameters showed mild to moderate change from normal level during the first 3 months with gradual recovery in the following months. Complete blood count assessment revealed mild decline in Hb, PCV, MCH, MCHC, and moderate decline in WBC and Platelet count. A mild increase in liver function tests (Bilirubin, AST, ALT, Alkaline phosphatase) and renal function tests (S.Creatinine, b. Urea) was observed. A moderate decline in S. Sodium with mild increase in S. Potassium was found on investigating S. Electrolytes. Patients were fully recovered from all hemato-biochemical adverse effects after 6 months of completion of the multi drug therapy.

Conclusion: Despite of mild to moderate hematological and biochemical adverse reactions with multi drug therapy, recovery was excellent after 6 months of completion of therapy.

Keywords: Multi drug effect, Laboratory parameters, Leprosy

Introduction

Leprosy is an ancient infectious disease that yet represents major socio-economic burden to humanity with approximate one million cases in Asia, Africa, and South America [1]. Failure in early detection often leads to severe disability in spite of eradication of mycobacteria at a later date. Untreated the disease is progressive and results in permanent damage to the skin, nerves, limbs and eyes [2]. In most populations, over 95% of individuals are naturally immune. In spite of this the disease accounts for approximately 10 million affected people worldwide [3].

Leprosy remained an incurable disease until 1940, when the first breakthrough occurred with the development of dapsone, a drug capable of arresting the disease [4]. Today, it is widely accepted that multi-drug therapy (MDT) renders leprosy curable.

Multi drug therapy protocol in leprosy is based on combined antimicrobial effect of three drugs rifampicine, dapsone and clofazimine. This combined regimen is given for one year under partial medical supervision and daily self administration of drugs. Adverse reactions to multi drug therapy protocol are the main limiting hurdle for the treatment course completion; these side effects are mainly attributed to dapsone and to lesser extend to other medications. Agranulocytosis, hemolytic anemia, methemoglubinemia, and other hematological traits have been reported for multi drug therapy [5]. Few cases of hepatitis, pancreatitis, and renal impairments have been reported for multi drug therapy patients which warrants close biochemical assessment to follow up these side effects. Erythema nodosum is another major side effect for multi drug therapy that might lead to mortality [6]. Due to the temporary abnormal changes in laboratory parameters by multi drug regimen, it can be a confusing or misleading for the physicians which often lead to wrong diagnosis like infection, hepatitis, renal failure or even malignancy. With this point of view the study was performed to find out the routine hematological and biochemical changes with multi drug therapy in leprosy.

Materials and methods

This was a descriptive prospective hospital based study done for 1.5 years (January 2014 to July 2015) in Rangamati Sadar Hospital. A full detailed history and proper systemic and neurological examination was performed by the authors. Standard laboratory protocols were followed to find out the hematological and biochemical results. Board certified laboratory physicians and technicians were conducted for this purpose. According to WHO, diagnosis of leprosy was made by clinical parameters with having one or more of three cardinal signs: 1- Hypo pigmented or reddish patches with definite loss of sensation.2- Thickened peripheral nerves.3- Acid-fast bacilli on skin smears or biopsy materials. The disease is classified into paucibacillary (PB) and multibacilary (MB) leprosy according to WHO classification. Standard regiments of MDT according to WHO therapeutic guidelines were used for the treatment of the patients included in the study. Hematological parameters by complete blood count (Hb%, PCV, MCH, MCHC, ESR, WBC and Platelet) and biochemical parameters (S. Creatinine, B. Urea, ALT, AST, Alkaline phospahatase, S. Electrolytes) were observed for a duration of 1 year during the treatment and follow up investigation done after 6 months of completion of multi drug treatment.

Multi Drug Therapy (MDT)

MDT protocol is based on combinatorial antibacterial effect of three chemotherapeutic agents, dapsone, clofazimine, and rifampicin. This combination treatment is administered for 12 months under partial medical supervision. Side effects to MDT protocol are the main limiting hurdle for the treatment course completion; these side effects are mainly attributed to dapsone and to lesser extend to the rest of medications. **Table 1** shows the WHO recommended regimen for leprosy.

Blood sample collection

Venous blood samples (two samples per patient) were withdrawn from peripheral vein while the patient is sitting. For biochemical assessment blood samples were allowed to clot, centrifuged and the serum were kept frozen at -20°C.

Table 1: Multi drug therapy in Leprosy (WHO approved).

Monthly Supervised Drugs	Daily Self administered Drugs	Duration of treatment
Rifampicine 600 mg	Clofazimine 50 mg	12 months
Clofazimine 300 mg	Dapsone 100 mg	

Another blood samples were sent for hematological assessment in the same day sampling.

Assessment of hematological parameters

Whole blood was injected immediately after sampling into the automatic coulter counter, Sysmex™, K800 (Block Scientific Inc, NY, USA). Hemoglobin (Hb%), Packed Cell Volume (PCV), Mean Cellular Hemoglobin (MCH), and Mean Cellular Hemoglobin Concentration (MCHC), white blood cell and platelet were determined using azide free reagent mix and according the manufacturer procedures. [7]

Assessment of biochemical parameters

Biochemical assessments were assessed in isolated sera using specific kits (Dade Behring, Marburg, Germany). AST, ALT and alkaline phosphatase were assessed by standard method [8]. Bilirubin (direct, indirect and total) was determined using end point technique with blank solution correction analysis [9]. Creatinine was determined via picric acid chromophore interaction assay [10]. Serum electrolytes were determined using standard analyzer machine (IONIX).

Statistical analysis

Survey data were analyzed using the SPSS statistical program Version 16 (SPSS Inc, Chicago, IL, USA). Statistical analyses were performed and a P value <0.05 was considered statistically significant.

Ethical considerations

Institutional Review Board (IRB) approval was obtained from ethical committee of Chittagong Medical College and Hospital (CMCH No: 8732/14). Before administering the survey, investigators explained the purpose of the study to all patients. The voluntary nature of participation and the anonymous and confidential nature of the interview schedules were strongly emphasized. Verbal informed consent was obtained from all patients.

Results

Among 104 patients diagnosed as leprosy, multibacillary type was predominant (n=69, 66.3%) and remaining 25 cases were paucibacillary (n=35. 33.7%). All the patients were treated with standard multi drug regimen of leprosy. There was no defaulter or resistance case reported.

Table 2 shows the socio-demographic factors of leprosy patients. We found that 54 (51.9%) patients were middle aged between 20–40 years. Among the study subjects 65.4% were female, 58.7% were from rural area. Only 1 patient had previous history of blood disorder named Idiopathic Thrombocytopenic Purpura (ITP) 3 years back and cured completely. 2 patients had history of tuberculosis (TB) at least 5 years back and cured without any major complications. 1 patient had hypertensive nephropathy with creatinine 2.1 mg/dl. After 6 months of clinical manifestations, 61.2% were diagnosed correctly.

On investigating hematological parameters by complete blood count showed mild to moderate changes in parameters. There was a significant reduction in all the parameters after the start of therapy with marked change in the first 3 months and recovering gradually over next 9 months. WBC and platelet count showed moderate (20-30 %) decline initially.

After the completion of therapy there was a This study also reveals the biochemical parameters where tests done to assess the liver function, renal function and serum electrolytes. There was a gradual increase in liver function parameters during the treatment which was highest at one year. Among them ALT showed the highest rate complete recovery of parameters **(Table 3).** of increase **(Table 4).** On investigating the renal function there was a sudden pick of serum creatinine and blood urea level at 3 months followed by gradual decline of parameters with recovery at 12 months **(Table 5).**

Table 2: Distribution of leprosy patients according to socio-demographic factors.

Socio-demographic factors	Number	Percentage %
Age		
<20	21	20.19
20-40	54	51.9
>40	29	27.9
Gender		
Female	68	65.4
Male	36	34.6
Residence		
Rural	61	58.7
Urban	43	41.3
Previous Blood Disorder		
Yes	1	1
No	103	99
Previous Chronic Infection		
Yes	2	2
No	102	98
Chronic Liver / Renal disease		
Yes	1	1
No	103	99
Duration before diagnosis		
< 6 Month	89	85.6
>6 Month	15	14.4

Table 3: Complete blood count findings with multidrug therapy.

Parameters	0 month	3 months	6 months	12 months	18 months
Hb (g%)	12.3 ± 1.1	10.1 ± 1.8*	10.8 ± 0.8 *	11.8 ± 0.4	12.8 ± 0.4
PCV (%)	45.3 ± 3.8	41.2 ± 2.8*	42.1 ± 1.6	43.6± 0.6	44.8 ± 0.8
MCH (pg)	32.4 ± 1.2	30.1 ± 1.8*	31.6 ± 1.4	31.8 ± 0.6	32.8 ± 0.4
MCHC (g%)	33.6 ± 1.6	29.9 ± 1.4*	32.1± 0.5	32.4 ± 1.2	33.1 ± 1.1
WBC mcL	8500 ± 2400	5300 ± 1800*	5600 ± 1300 *	6400 ± 1100	7100 ± 2500
Platelets /μL	22-28 x 10^9/l	18-23 x 10^9/l *	19-21 x 10^9/l *	21-26 x 10^9/l	24-30 x 10^9/l

*Significantly different from starting reading (P <0.05)

Table 4: Liver function tests with multidrug therapy.

Parameters	0 month	3 months	6 months	12 months	18 months
S. Bilirubin	0.7 ± 0.2	1.5 ± 0.4*	1.2 ± 0.8	1.2 ± 0.5	0.8 ± 0.4
ALT	32.2 ± 6.4	54.4 ± 12.8*	48.8 ± 10.4	44.2 ± 9.8	36.5 ± 6.8
AST	29.6 ± 4.4	47.4 ± 14.5*	40.1 ± 4.2	38.8 ± 7.4	32.2 ± 2.2
Alkaline Phosphatase	58.4 ± 8.8	104.6 ±20.5*	94.2 ± 14.6	88.4 ± 18.8	64.6 ± 8.6

*Significantly different from starting reading (P <0.05)

Table 5: Renal function tests with multidrug therapy.

Parameters	0 month	3 months	6 months	12 months	18 months
S. Creatinine (mg/dl)	0.8 ± 0.2	1.5 ± 0.2 *	1.3 ± 0.4*	1.1 ± 0.5	0.7 ± 0.3
B. Urea (mmol/l)	3.5 ± 1.2	6.8 ± 1.8*	4.4 ± 1.4	4.1 ± 1.8	3.1 ± 1.1

*Significantly different from starting reading (P <0.05)

Table 6: S. Electrolytes findings with multidrug therapy.

Parameters	0 month	3 months	6 months	12 months	18 months
Sodium	137.2 ± 4.1	131.2 ± 2.8 *	132.4 ± 2.1 *	134.1 ± 3.5	139.8 ± 4.1
Potassium	3.7 ± 0.8	4.8 ± 0.5 *	4.9 ± 0.4 *	5.2 ± 0.6 *	4.1 ± 0.2
Chloride	101.2 ± 2.1	99.5 ± 4.8	102.2 ± 3.6	100.8 ± 1.8	99.2 ± 3.6
Bicarbonate	24.5 ± 2.2	23 ± 1.2	23.5 ± 1.8	25.4 ± 2.2	26 .2 ± 1.6

*Significantly different from starting reading (P <0.05)

Serum electrolytes also gave the impression of deviation of markers from normal level during treatment. There was significant reduction of S. Sodium level at 3 month followed by gradual recovery at the end of treatment. Serum level of potassium had the tendency to rise though out the treatment duration. Serum level of chloride and bicarbonate did not show any significant change **(Table 6).** All the biochemical parameters revert back to almost normal level after the end of multidrug therapy.

Discussion

This study showed progressive mild to moderate decline in most of the examined hematological parameters among leprosy patients treated with multi drug therapy. After the completion of management all the parameters reverts back to almost normal level which is similar to the previous study done in Chine [11]. First three months of therapy was the most vulnerable period where the decline was significant by 10 -30 %. Concentration of hemoglobin decreased since the first three months of multi drug treatment. In patients with normal GDP-6 (glucose dehydrogenase phosphate 6) level, non immune hemolytic anemia is common adverse effect for multidrug therapy which explains the significant drop in hemoglobin count in multi drug treatment patients. The drop in hemoglobin concentration might be also due to autoimmune hemolytic reaction or to met-hemoglobenemia. This is supported by the decrease in MCHC which might not be related to change in hemoglobin concentration. Both immune and non immune hemolytic anemia was previously reported in multidrug treated leprosy patients and might be to greater extent than reported in this study [12]. Adverse effects like agranulocytosis and immune suppression mainly due to dapsone in multi drug therapy, are commonly reported in previous studies done by different area of

the world. [13]. Two cases of complete agranulocytosis were reported in Sri Lanka in a local anti-leprosy campaign [14]. However our study had no agranulocytosis or immue deficiency state and most of hematological adverse reactions were mild to moderate in severity.

This study also showed also showed mild to moderate temporary increase in enzyme levels of biochemical parameters with multi drug therapy treated leprosy patients. There was a 15-35 % increase in enzyme levels in comparison to initial levels. Although there was significant level of increase in level of enzymes, these levels do not represent clinical value warrants treatment termination. Hepatitis caused by Dapsone has been clinically reported previously in leprosy patients with elevated ALT, AST and Alkaline phosphatase levels [15]. The higher level of Bilirubin in patients might be due to the cholestatic hormonal effect. Bilirubin level remained high until the treatment completion. However, its level does not present clinical jaundice at any time point. Multi drug therapy induced hepatitis was manifested with elevated bilirubin, ALT and AST level which was found in previous study [15]. During our study multi drug therapy was well tolerated by patients with no aggravated liver failure or damage. Serum creatinine showed progressive temporary elevation in multi drug therapy patients. However kidney function was not affected as evaluated by creatinine clearance and urinary microscopic examinations. For renal function test creatinine is a known biochemical marker for GFR (glumrular filtration rate) [16]. However, in assessing renal filtration function creatinine clearance is much more accurate. Creatinine production is related to skeletal and cardiac muscle metabolism and its clearance is related to renal function [17]. As there was no effect on creatinine clearance by multi drug therapy, mild elevation in creatinine level might be due to moderate muscle atrophy in response to multidrug therapy on leprosy.

Other biochemical parameters assessed such as S. Chloride, S. bicarbonate did not show any significant change in multi drug therapy treated patients. In contrary to our study, other study done in different demographic populations presented pancreatitis, muscle atrophy, hepatitis and other complains attributed to multi drug therapy management [18].

Conclusion

Multi drug therapy was well tolerated in leprosy patients with mild to moderate temporary hematological and biochemical adverse reactions. Physicians should aware of these reactions during treatment to consider them before diagnosing any co existing disease.

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