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COMPARISON BETWEEN LOW DOSE AND HIGH DOSE INTRAVENOUS METHYLPREDNISOLONE FOR TREATMENT RELAPSES OF MULTIPLE SCLEROSIS IN IRAQI PATIENTS

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ABSTRACT

Background

Multiple Sclerosis, a chronic inflammatory and neurodegenerative disease of the central nervous system, characterized by recurrent relapses of central nervous system inflammation ranging from mild to severely disabling. Relapses have treated with steroids to reduce inflammation and hasten recovery. However, the commonly used intravenous methylprednisolone in a dose 500mg_1000mg for 5days. **Objectives:** The possible effect of use low dose intravenous methylprednisolone (500mg) against stander dose (1000mg) for treatment of patients with relapses of multiple sclerosis. **Methods:** A prospective case controlled study was carried on 40 patients who had multiple sclerosis relapse confirmed by kuratzke expanded disability status scale. Patients were divided into 2 groups first group involved 20 patients treated with (500 mg IV methylprednisolone) for 5 days. The second group involved 20 patients treated with (1000mg IV methylprednisolone) for 5days. Expanded disability status score, random blood sugar, blood urea nitrogen and serum creatinine before and after 1 and 6 weeks of the study. **Results:** The results showed that significant decreased in expanded disability status score, ($p<0.05$) and increase in recovery percentage after one and six weeks of treatment with 500mg and 1000mg IV methylprednisolone for 5 days in comparison with pretreatment. Regarding blood urea nitrogen and serum creatinine there were non-significant difference between both groups. **Conclusion:** It seems from this short study that methylprednisolone in

a dose of 500mg (IV) daily for 5day to patient with multiple sclerosis could have the same therapeutic effect than a dose of 1000mg (IV) for 5 days, with lower side effect.

KEYWORLD: Multiple Sclerosis (MS), methylprednisolone, Expanded Disability Status Score (EDSS).

1. INTRODUCTION

Multiple sclerosis, also known as disseminated sclerosis or encephalomyelitis disseminate. The insulating covers of nerve cells in the brain and spinal cord damaged in an inflammatory disease. This damage disrupts the ability of parts of the nervous system to communicate and resulting in a wide range of signs and symptoms.[1, 2] Lesions of MS typically occur at different times and in different central nervous system CNS locations (i.e., disseminated in time and space). Multiple sclerosis takes several forms, with new symptoms in either isolated attacks (relapsing forms) or building up over time (progressive forms). Between attacks, symptoms may disappear completely; or permanent neurological problems often occur, especially as the disease advances.[3] The main symptoms of MS was optic neuritis, sensory loss, weakness and paresthesia.[4] Measure disability and severity by the expanded disability status scale (EDSS).[5]

Relapsing defined as ‘‘ the patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in absence of fever or infection.’’.[6]

Mild acute exacerbations that do not produce functional decline may not require treatment. When functional ability is affected, the standard intervention is intravenous injection of high-dose corticosteroids.[7] Intravenous methylprednisolone has been show to shorten the duration of acute exacerbations.[8] The mechanism of action of corticosteroids used for acute relapses is not completely clear, but may involve the following actions:

Prevention of inflammatory cytokine activation, Inhibition of T-cell activation, prevention of immune cells from entering the CNS and Increased death of activated immune cells. Corticosteroids hasten functional recovery after relapses.[9, 10]

1.1 Aim of the study

The present study designed to evaluate the possible use of low dose intravenous methylprednisolone (500mg) against stander dose (1000mg) for treatment of patients with relapses of multiple sclerosis.

2. PATIENTS AND METHODS

2.1 Patient

Forty MS patients with relapse (8 male, 32 female) were participated in this study, ethical clearance to conduct the research was sought and obtained from the patients. Data were collected through direct interview with the patient with the following inclusion criteria mean age 31.725 ± 0.914 years and mean duration of MS 3.179 ± 0.505 years. They assigned to receive either 500mg or 1000mg methylprednisolone. The study is carried out in Baghdad medical city during the period from November 2014 to May 2015. Patients undergoing clinical examination by measure (EDSS) in the multiple sclerosis unit of the hospital as well as in private clinic; a senior physician selected patients .The exclusion criteria includes if patients have other diseases like diabetic mellitus, cardiovascular, CNS, renal diseases and lactating or pregnant women.

Table (1) Chemicals, Drugs and their suppliers.

Chemicals	Suppliers
Methylprednisolone vial (5oomg IV)	Pfizer
Glucose kit	Biocon Diagnostik, Germany
Urine strips test	Chungdo pharm , Korea

Table (2) Instruments used in this study and their suppliers.

Instruments	Suppliers
Auto vortex	Stuart Scientific , U .K
Blood collection plain tube	AFMH, England
Centrifuge-Universal 16A	Hettich, Germany
Distiller	Gallenkamp, U.K
EDTA containing tubes	AFMH, England
ELx 800 universal micro plate reader	Bio-Tek instruments, INC. USA
Fine and adjustable micropipettes and multichannel micropipettes	Gilson, France
Hamilton syringes	Hamilton PB 600, Bonaduz AG , Switzerland
Incubator	Gallenkamp, U.K
Oven	Memmert, Germany
pH meter	Jenway, Germany
Printer Epson	UK
Refrigerator	Arcelik, Turkey
Shaker	Khan Shaker , Italy
Spectrophotometer-CE 1011	Cecil, England
Water-bath	K&K, Korea

2.2 EDSS measurement

We can measure the disability of patient in acute attack MS and response to the treatment by calculate the kuratzke expanded disability status scale (EDSS) [5]

Table (3) expanded disability status scale (EDSS).

0.0	Normal neurologic exam (all grade 0 in functional status [FS})
1.0	No disability, minimal signs in one FS (i.e., grade 1)
1.5	No disability, minimal signs in more than one FS (more than one grade 1)
2.0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0	Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4.0	Ambulatory without aid or rest for ~500 m
4.5	Ambulatory without aid or rest for ~300 m
5.0	Ambulatory without aid or rest for ~200 m
5.5	Ambulatory without aid or rest for ~100 m
6.0	Unilateral assistance required to walk about 100 m with or without resting
6.5	Constant bilateral assistance required to walk about 20 m without resting
7.0	Unable to walk beyond about 5 m even with aid; essentially restricted to wheelchair; wheels self and transfers alone
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid to transfer
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5	essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	totally helpless bed patient; unable to communicate or eat
10.0	Death due to MS

Functional Status (FS) Score

Table (4) Functional Status (FS) Score.

A. Pyramidal functions	
0	Normal
1	Abnormal signs without disability
2	Minimal disability
3	Mild or moderate Paraparesis or hemiparesis, or severe monoparesis
4	Marked paraparesis or hemiparesis, moderate quadriparesis, or monoplegia

5	Paraplegia, hemiplegia, or marked quadriparesis
6	Quadriplegia
B. Cerebellar functions	
0	Normal
1	Abnormal signs without disability
2	Mild ataxia
3	Moderate truncal or limb ataxia
4	Severe ataxia all limbs
5	Unable to perform coordinated movements due to ataxia
C. Brainstem functions	
0	Normal
1	Signs only
2	Moderate nystagmus or other mild disability
3	Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves
4	Marked dysarthria or other marked disability
5	Inability to swallow or speak
D. Sensory functions	
0	Normal
1	Vibration or figure-writing decrease only, in 1 or 2 limbs
2	Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in 1 or 2 limbs, or vibratory decrease alone in 3 or 4 limbs
3	Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in 1 or 2 limbs, or mild decrease in touch or pain, and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs
4	Marked decrease in touch or pain or loss of proprioception, Alone or combined, in 1 or 2 limbs or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than 2 limbs
5	Loss (essentially) of sensation in 1 or 2 limbs or moderate Decrease in touch or pain and/or loss of proprioception for most of the body below the head
6	Sensation essentially lost below the head
E. Bowel and bladder functions	
0	Normal
1	Mild urinary hesitancy, urgency, or retention
2	Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence
3	Frequent urinary incontinence
4	In need of almost constant catheterization
5	Loss of bladder function
6	Loss of bowel and bladder function
F. Visual (or optic) functions	
0	Normal
1	Scotoma with visual acuity (corrected) better than 30/20
2	Worse eye with scotoma with maximal visual acuity (corrected) of 20/30 to 20/59
3	Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 60/20 to 20/99
4	Worse eye with marked decrease of fields and maximal acuity (corrected) of

	20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less
5	Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less
6	Grade 5 plus maximal visual acuity of better eye of 60/20 or less
G. Cerebral (or mental) functions	
0	Normal
1	Mood alteration only (does not affect EDSS score)
2	Mild decrease in mentation
3	Moderate decrease in mentation
4	Marked decrease in mentation
5	Chronic brain syndrome—severe or incompetent

2.3 Blood sample

Blood sample was taken before and after one and six weeks of the study to analyze random blood sugar (RBS), blood urea nitrogen and serum creatinine.

2. 4 Biochemical Assay Methods

2. 4.1 Measurement of Serum Glucose Level

Serum glucose level evaluated using a ready-made kit for this purpose, according to the method of Borham and Trindoer.[11]

2. 4.2 Measurement of blood urea nitrogen

Urea kit enables end point enzymatic determination of urea concentrations (Urease – modified Berthelot action) in human urine, serum or plasma.[12]

2. 4.3 Measurement of serum creatinine

Kinetic 2 – point mode is used to measure the red orange complex formed with picric acid in an alkaline medium (jaffes method).[13]

2.5 Statistical Analysis

Data are expressed as means ± SE. Statistics were performed using statistical software (Minitab17). Differences from baseline were assessed by the paired student's t test. P-value of <0.05 was considered significant.

RESULTS AND DISCUSSION

Forty patients presented to treatment, 20 in group1 (500mg methylprednisolone), and 20 in group2 (1000mg methylprednisolone). There were no apparent differences between the three groups with respect to demographic data. (Table5).

Table (5): Demographic data and baseline characteristics of the patients.

Data	Group 1	Group 2	P-value
Age (yrs.)	30.95±1.42	33.00 ± 1.35	0.303
No. of subjects	20	20	------
Gender	17 female 3 male	15 female 5 male	------
EDSS	2.650±0.206	2.450 ± 0.248	0.539
Dose	500 mg	1000mg	------
Duration of therapy	5 days	5 days	------
MS Duration(yrs.)	3.508 ± 0.867	2.850 ± 0.535	0.522
Weight (kg)	70.80 ± 2.10	73.30 ± 2.09	0.403

Data are expressed as Mean±SE * significant when $p<0.05$

3.1. Age and incidence of multiple sclerosis

The results in table (5) showed that the majority of MS patient were older than 30 years old. These results were in agreement with the results of Ilana B, *et al*. [14] and Koch-Henriksen N, *et al*. [15] reported that onset of disease is typically between ages 20 and 40.

3.2. Sex and incidence of multiple sclerosis

The results in table (5) showed that the majority of MS patient were female that data disclose that women are more likely than men to get MS in ratio of female: male 4:1. These results were in agreement with the results of Orton SM, et al.[16] who reported that an increase prevalence ratios approaching 3.2:1, revealing a clear female tendency. The same results were found with a studies performed by Alonso A, et al,[17] Sadovnik AD.,[18] and Debouverie M.[19] who confirmed the markedly significantly increased the incidence rates in women but not in men.

3.3. Effect of methylprednisolone on EDSS in treated patients with MS

Table 6 and fig. 1 show non-significant difference in EDSS among treated groups at pretreatment (p= 0.539). Both group1 and group2 showed a highly significant decrease in EDSS (P= 0.003), (P= 0.026) respectively after one week of treatment compared to pretreatment values. After six weeks of treatment there is highly significant decrease in EDSS for group 1(40.566%) and (37.775%) for those in group2 compared to pre-treatment (P=0.001), (P=0.008) respectively.

In general, there is highly significant effect in both group1 and group2 on EDSS compared to pretreatment (P=0.000), but statistically non-significant difference in EDSS observed after one and six weeks between group1 and group2 (P=0.870), (P=0.866) respectively.

These results confirmed previously studies by Oliveri et al. and Miller et al.,[20, 21] who had revealed in their study that there was no difference in the efficacy of the low dose and the high dose of methylprednisolone in terms of clinical recovery. Similar results were also reported by others studies,[22, 23]

Table (6): Effect of treatment with 500mg and 1000mg IV methylprednisolone on EDSS in patients with MS after 1 and 6 weeks of treatment.

Group	EDSS score			% of Change
	Pre-Treatment	After 1week	After 6weeks	
Group 1	2.650±0.206	1.725±0.204*	1.575±0.196*	–40.566%
Group 2	2.450±0.248	1.675±0.224*	1.525±0.219*	–37.775%

Data are expressed as Mean±SE;*significantly difference compare to pretreatment within the same group ($p<0.05$).

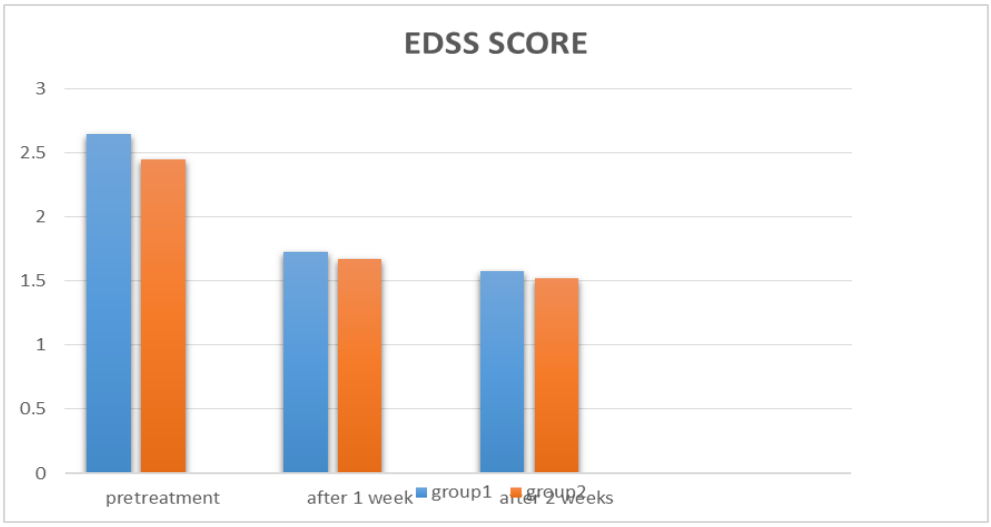

Fig. (1): Histogram showing effect of treatment with 500mg and 1000mg (IV) methylprednisolone on EDSS in patients with MS after 1and 6 weeks of treatment.

3.4. Effect of methylprednisolone on random blood sugar (RBS) in treated patients with MS

Table 7 and fig. 2 show non-significant difference in RBS among treated groups at pretreatment (P= 0.303). One week after treatment group1 showed non-significant difference (P= 0.251). However significant increase in RBS was observed in group2 (P= 0.022) after one week of therapy compared to pretreatment value. After six weeks of treatment there is non-significant change in RBS for patients in both treated groups compared to pre-treatment (P= 0.888), (P= 0.551) respectively.

Over all, there was statistically non-significant variation in RBS after one and six weeks of treatment among groups (P= 0.363), (P= 0.742) respectively.

Fardet L et al. and Martinelli V et al.,[24, 25] they found high dose (1000mg) of methylprednisolone cause significant increase in RBS.

Table (7): Effect of treatment with 500mg and 1000mg IV methylprednisolone on RBS in patients with MS after 1 and 6 weeks of treatment.

Group	RBS mg/dl				
	Pre-Treatment	After 1week	% of Change	After 6weeks	% of Change
Group 1	90.15 ± 2.56	98.40± 6.60	9.15%	89.70±1.86	0.4995%
Group 2	86.30 ± 2.66	108.70±9.02*	25.95%	88.60±2.75	2.66%

Data are expressed as Mean±SE;*significantly difference compare to pretreatment within the same group (p<0.05);

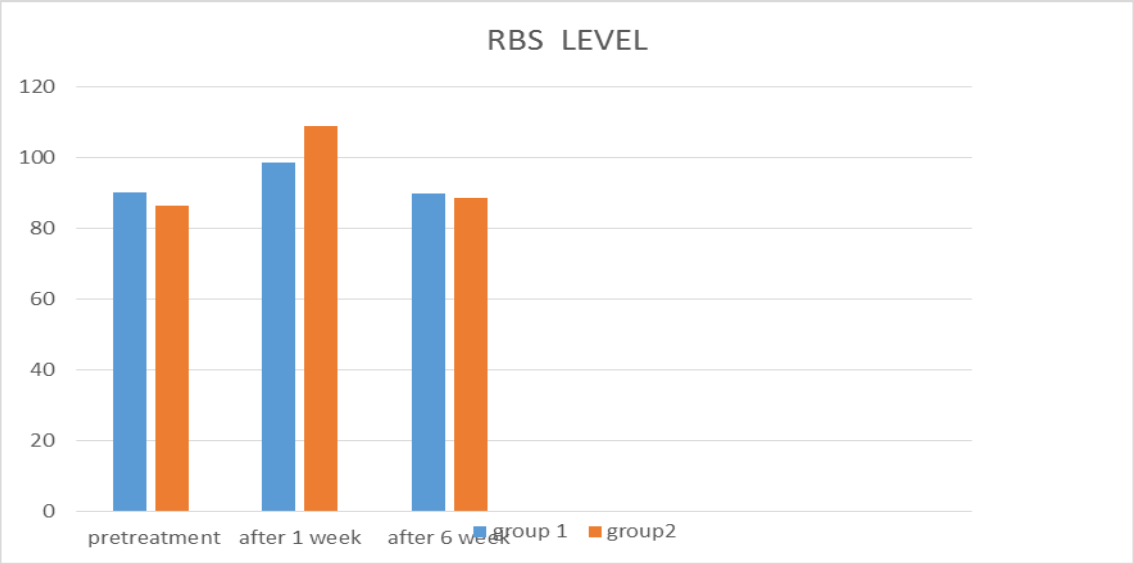

Fig. (2): Histogram showing effect of methylprednisolone on random blood sugar (RBS) in treated patients with MS after 1 and 6 weeks of treatment.

3.5. Effect of methylprednisolone on Blood urea nitrogen

Table 8 and fig. 3 show non-significant difference in blood urea among treated groups at pretreatment (p=0.738). Post treatment non-significant difference in group1 and group2 (P=0.941) (P= 0.343) compared to groups at pretreatment respectively.

In general, there is statistically non-significant difference in blood urea among groups post treatment compared to groups at pretreatment (P=0.823).

Slotman GJ1,[26] showed that blood urea nitrogen was increased from baseline values in a significantly greater proportion of the 1000mg methylprednisolone-treated patients compared 500mg methylprednisolone-treated patients.

Table (8): Effect of treatment with 500mg and 1000mg methylprednisolone on blood urea in patients with MS pre and post treatment.

Group	Blood urea nitrogen		% of Change
	Pre-Treatment	Post treatment	
Group 1	13.65±1.00	13.550±0.896	-0.73%
Group 2	13.200±0.881	14.400±0.887	9.09%

Data expressed as Mean±SEM

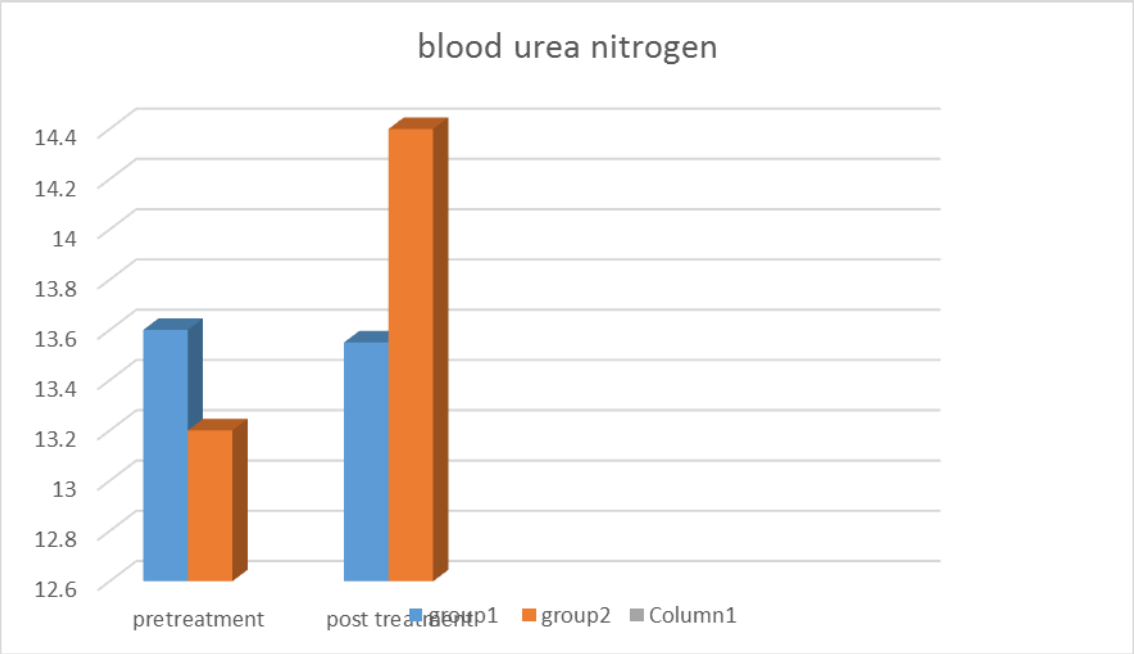

Fig. (3): Histogram showing effect of treatment with 500mg and 1000mg IV methylprednisolone on blood urea nitrogen in patients with MS pre and post treatment.

3.6. Effect of methylprednisolone on serum creatinine

Table 9 and fig. 4 show non-significant difference in serum creatinine among treated groups at pretreatment (p= 0.601). Post treatment non-significant difference in group1 and group2 (P= 0.907) (P= 0.420) compared to groups at pretreatment respectively.

Over all, there is statistically non-significant difference in serum creatinine among groups post treatment compared to groups at pretreatment (P= 0.469).

Slotman GJ1.[26] found that no effect of methylprednisolone on serum creatinine which agree with present results.

Table (9): Effect of treatment with 500mg and 1000mg methylprednisolone on serum creatinine in patients with MS pre and post treatment.

Group	Serum creatinine		% of Change
	Pre-Treatment	Post treatment	
Group 1	0.9070±0.0378	0.9125±0.0275	0.606%
Group 2	0.9355±0.0385	0.9795±0.0378	4.703%

Data expressed as Mean±SEM

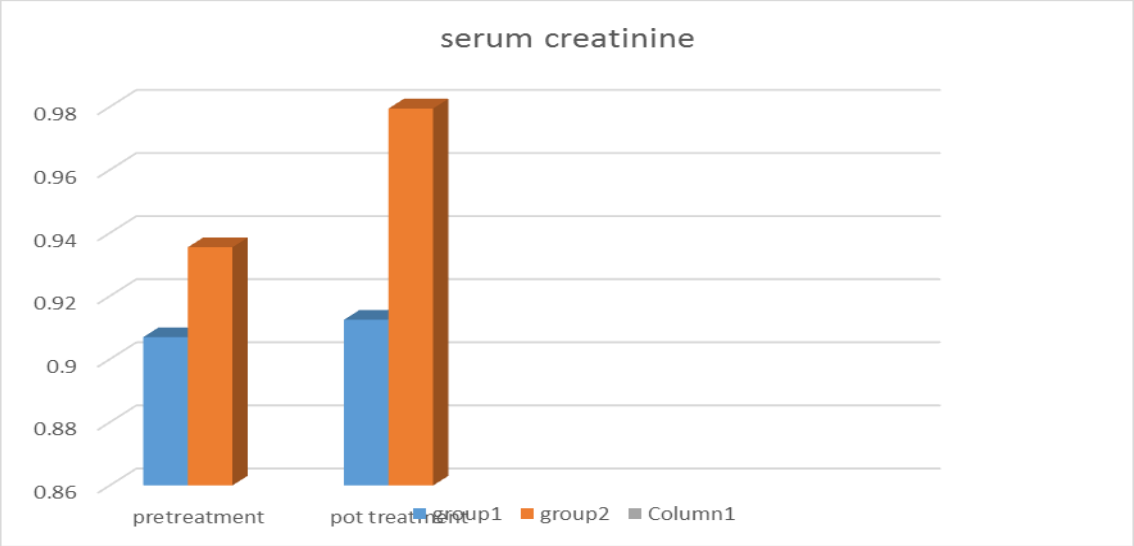

Fig. (4): Histogram showing effect of treatment with 500mg and 1000mg IV methylprednisolone on serum creatinine in patients with MS pre and post treatment.

CONCLUSIONS

According to the data of the present study, we can conclude that

1. Onset of disease is typically between ages 20 and 40.
2. Majority of MS patient were female.
3. 500mg methylprednisolone could have the same therapeutic effect (probably better) then a dose of 1000mg (IV) for 5 days.

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