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IF THERE IS ANY EFFECT OF LOW DOSE AND HIGH DOSE INTRAVENOUS METHYLPREDNISOLONE FOR TREATMENT RELAPSES OF MULTIPLE SCLEROSIS ON ELECTROLYTES 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 effect of low dose intravenous methylprednisolone (500mg) and high dose (1000mg) for treatment of patients with relapses of multiple sclerosis on electrolytes. **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. Serum sodium, serum calcium and serum potassium before and after 1 and 6 weeks of the study. **Results:** The results showed that a non-significant difference in serum sodium and serum calcium, while there was a significant decrease in serum potassium level in group 2 after one week of treatment with 1000mg IV methylprednisolone for 5 days in comparison with pretreatment. However, there was a non-significant difference in serum sodium, serum calcium and potassium level in group 1 after one week of treatment with 500mg IV methylprednisolone for 5 days in comparison with pretreatment. After six weeks of treatment, there was a non-significant change in serum

sodium serum calcium and serum potassium level for patients in both treated groups compared to pre-treatment. In general, after one and six week there were statistically non-significant difference among groups in serum sodium, serum calcium and serum potassium level. **Conclusion:** It seems from this short study that methylprednisolone in a dose of 500mg (IV) daily for 5day to patient with multiple sclerosis had no effect on electrolytes while a dose of 1000mg (IV) for 5 days could cause hypokalemia.

KEYWORLD: Multiple Sclerosis (MS), methylprednisolone, serum sodium, serum calcium and serum potassium.

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 effect of low dose intravenous methylprednisolone (500mg) and stander dose (1000mg) for treatment of patients with relapses of multiple sclerosis on electrolytes.

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
Urine strips test	Chungdo pharm , Korea

Table (2) Instruments used in this study and their suppliers.2.2 EDSS measurement.

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

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 serum sodium, serum calcium and serum potassium level.

2. 4 Biochemical Assay Methods

2. 4.1 Measurement of electrolytes

A basic metabolic panel measures was sodium, potassium and calcium.[11]

2.4.1.1 Principle of electrolytes measurement

A process known as potentiometry measures electrolytes this method measures the voltage develops between the inner and outer surfaces of an ion selective electrode. The electrode (membrane) made of a material that is selectively permeable to the ion measured. This potential measured by comparing it to the potential of a reference electrode. Since the potential of the reference electrode held constant, the difference in voltage between the two electrodes attributed to the concentration of an ion in the sample.

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. Effect of methylprednisolone on serum sodium

Table 6 and fig. 1 showed a non-significant difference in serum sodium among treated groups at pretreatment (p= 0.421). After one week, there was a non-significant difference in serum sodium level in group1and group2 (P= 0.477), (P= 0.922) respectively compared to pretreatment value. After six weeks of treatment, also there was a non-significant change in serum sodium level in both treated groups compared to pre-treatment (P= 0.285), (P= 0.378) respectively.

Statistically, there was a non-significant difference in serum sodium among groups after one and six weeks of treatment (P= 0.112), (P= 0.294) respectively.

Sodium is the most noticeable cation in extracellular fluid. Sodium is an essential nutrient that controls blood volume, blood pressure, osmotic balance and pH.[12] These findings agree with the previous study, which showed that methylprednisolone had a non-significant effect on serum sodium.[13]

Furthermore, Fardet L, *et al*. in his study mentioned that methylprednisolone had a non-significant effect on serum sodium.[14]

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

Group	sodium level mg/dl			% of Change
	Pre- Treatment	After 1wks	After 6wks	
Group 1	138.95 ± 0.67	139.65 ± 0.71	138.40±0.77	0.39%
Group 2	139.75 ± 0.72	141.10 ± 0.60	138.90± 0.63	0.6%

Data are expressed as Mean±SEM

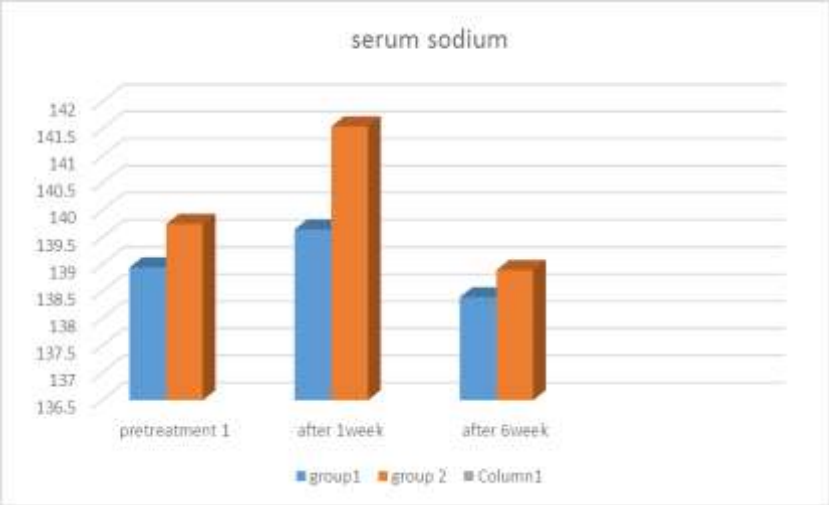

Fig.1: Histogram showing the effect of treatment with 500 mg and 1000 mg IV methylprednisolone on serum sodium in patients with MS after 1and 6 weeks of treatment.

3.2. Effect of methylprednisolone on serum calcium

Table 7 and fig. 2 showed a non-significant difference in serum calcium among treated groups at pretreatment (p= 0.770). After one week, a non-significant difference in serum calcium in group 1and group 2 (P= 0.648), (P= 0.346) respectively compared to pretreatment value. After six weeks of treatment, there was a non-significant change in serum calcium for patients in both treated groups compared to pre-treatment (P= 0.728), (P= 0.166) respectively.

Overall, there were statistically non-significant difference in serum calcium among groups after one and six weeks (P= 0.450, (P= 0.057) respectively. At the end of one to six weeks of the study, the results showed a non-significant difference in serum calcium among treated groups. That means, blood calcium was not affected by the treatment in agreement with previous study by Zorzon M, *et al*. who found that treatment with intravenous methylprednisolone pulses not associated with significant change in serum calcium level.[15]

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

Group	Calcium level mg/dl			% of Change
	Pre- Treatment	After 1wks	After 6wks	
Group 1	9.350 ± 0.131	9.260 ± 0.145	9.415 ±0.131	0.695%
Group 2	9.295 ± 0.132	9.090 ±0.169	8.985±0.181	3.335%

Data expressed as Mean±SEM

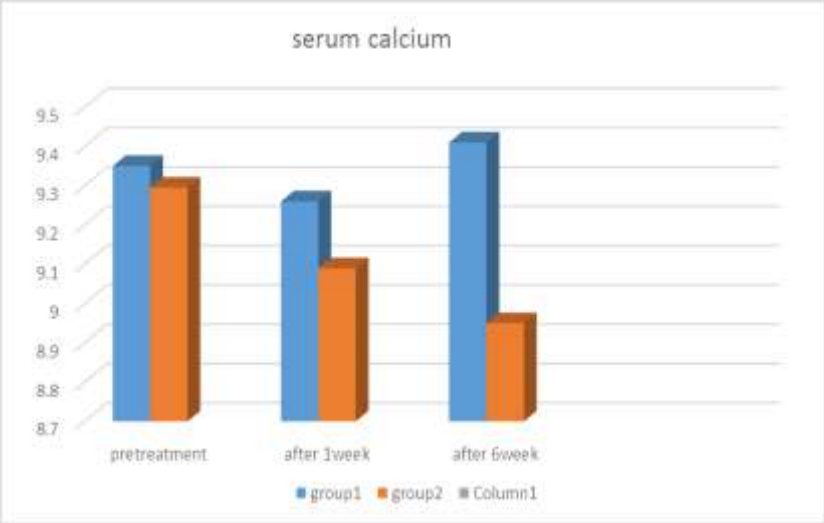

Fig.2: Histogram showing the effect of treatment with 500 mg and 1000 mg IV methylprednisolone on serum calcium in patients with MS after 1 and 6 weeks of treatment.

3. 3.Effect of methylprednisolone on serum potassium

Table 8 and fig. 3 showed a non-significant difference in serum potassium level among treated groups at pretreatment (p= 0.344). One week after therapy, a non-significant difference in serum potassium level for group 1 (P= 0.067) while significant decrease of serum potassium level in group 2 (P= 0.015) compared to pretreatment value. After six weeks of treatment, there was a non-significant change in serum potassium for patients in both treated groups compared to pre-treatment (P= 0.120), (P= 0.528) respectively.

In general, after one and six week there were statistically non-significant difference in among groups in serum potassium level (P= 0.961), (P= 0.215) respectively. Most of the body's potassium is intracellular (about 98%), the intracellular-extracellular potassium gradient is vital to sustaining resting membrane potential, and normal nerve and muscle function. Small declines in extracellular potassium can have severe effects on the heart and skeletal muscles. Mild hypokalemia is frequently asymptomatic, but severe hypokalemia related with life-

threatening arrhythmias and sudden cardiac death.[16] This result was in agreement with the results of Tamez-Pérez HE, who reported that mild and moderate hypokalemia was about 18.18% in the patients treated with 1000mg methylprednisolone without clinical or electrocardiographic concerns.[17] On the other hand, Regina Berkovich found that methylprednisolone in a dose 1000mg induced hypokalemia.[18] Hypokalemia occurred due to mineralocorticoid effect, which increase excretion of potassium.

Table 8: Effect of treatment with 500 mg and 1000 mg IV methylprednisolone on serum potassium in patients with MS after 1and 6 weeks of treatment.

Group		Serum Potassium level mg/dl			% of Change
	Pre- Treatment	After 1wks	% of Change	After 6wks	
Group 1	3.9250±0.934	3.7200±0.0555	-5.223%	4.145±0.102	5.606%
Group 2	4.060 ± 0.105	3.7700±0.0641*	-7.143%	3.9700±0.0941	-2.217%

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

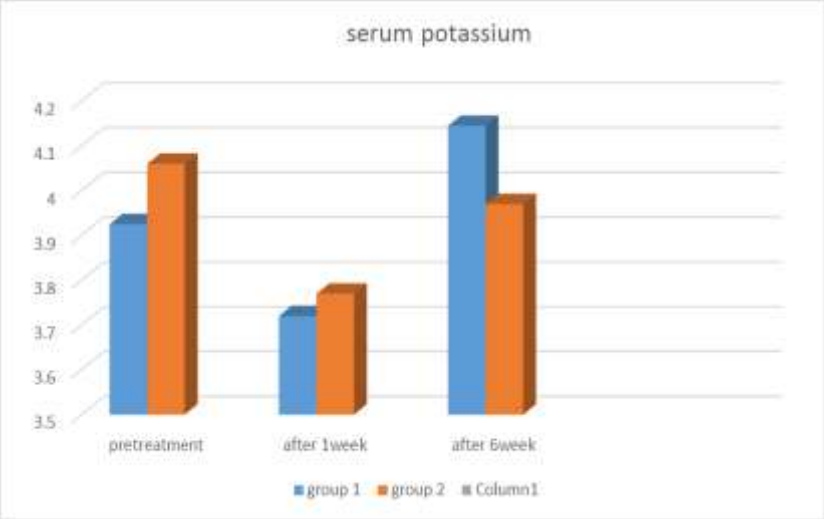

Fig.3: Histogram showing the effect of treatment with 500 mg and 1000 mg IV methylprednisolone on serum potassium in patients with MS after 1 and 6 weeks of treatment.

CONCLUSIONS

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

1. Methylprednisolone in a dose 1000mg and 500mg had no effect on serum sodium.
2. Methylprednisolone in a dose 1000mg and 500mg had no effect on serum calcium.
3. Methylprednisolone in a dose 1000mg cause hypokalemia in some patient while 500mg had no effect on serum potassium.

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