


Research Article

Safety Comparison of Conventional Versus Extended Infusion of Pulse Methylprednisolone in Multiple Sclerosis Exacerbation

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Abstract

Objective: To determine the impact of Intravenous Methylprednisolone (IVMP) administration on the changes in vital signs (Heart Rate (HR), Systolic (SBP), Diastolic Blood Pressure (DBP), and serum potassium level in multiple sclerosis flare.

Design: retrospective review study conducted at Hamad General Hospital (HGH). All patients admitted in 2019-2020 with MS flare without any comorbidities were categorized into two groups depending on infusion rate. One group received a conventional IVMP dose over 30 minutes to one hour, while the second group received IVMP over an extended period (four to six hours). After that, we assessed multiple readings of vital signs and potassium levels through steroid administration time to determine if there was an infusion-related significant difference in adverse events between both groups.

Methods: 74 adult patients with MS relapse admitted to Hamad General Hospital (HGH) and satisfied pre-specified inclusion criteria were invited to participate in the study.

Results: 74 patients with MS were included in the study; 61 patients (83.6%) received a methylprednisolone dose of 500 mg -1000 mg in a conventional infusion rate, while 12 patients (16.4%) received pulse steroids in an extended duration. Both groups had no significant difference in mean blood pressure before and after IVMP. There was a small but statistically significant increase in mean heart rate in the conventional group immediately after the first and second but not 3rd dose of IVMP compared to baseline 3.5 ± 8.9 and 4.85 ± 13.9 $P < 0.003$. There was a minimal non-significant increase in potassium level in the conventional group ($P = 0.17$), while there was a non-significant decrease in potassium level in the extended group ($P=0.72$).

Conclusion: IVMP is considered safe and effective in treating MS exacerbation regardless of intravenous infusion duration. There was no significant difference in vital signs among different infusion rates. However, there was a small but statistically significant increase in mean heart rate in the conventional group immediately after the first and second but not 3rd dose of IVMP compared to baseline. No significant difference was observed in potassium levels before and after IVMP. We, therefore, recommend restricting potassium level monitoring to patients with other risk factors of hypokalemia.

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Learning points

- Multiple Sclerosis (MS) relapses are typically defined as a new or worsening neurological deficit lasting 24 hours or more in the absence of fever or infection.
- High-dose short-term parenteral steroids are the standard of care for treating MS relapse.
- IVMP is relatively safe and effective in treating MS exacerbation regardless of intravenous infusion duration.
- There was no difference in vital signs fluctuation and potassium level between different infusion rates.

Introduction

Multiple Sclerosis (MS) relapses are defined as a new or worsening neurological deficit lasting 24 hours or more in the absence of fever or infection [1]. High-dose short-term parenteral steroids are the standard of care for treating MS relapse. The most common regimen used is 500mg-1000mg of IV methylprednisolone (MP) for 3- 5 days [1]. The common practice at Hamad General Hospital (HGH) is to administer MP infusion once daily. Still, there is always an inconsistent practice between physicians regarding infusion rate and duration due to a lack of guidelines or standards regarding infusion duration. Some prefer administering over 30 minutes to one hour; in contrast, others prefer extended infusion over 4-6 hours due to the conception of more adverse events such as cardiac arrhythmias and hypokalemia associated with the short infusion. However, extended infusion time will increase the length of hospital stay. Additionally, it increases the possibility of steroid infusion interruption due to the patient's mobility. Methylprednisolone manufacturing company mentioned that there are reports of cardiac arrhythmias and cardiac arrest following the rapid administration of large intravenous doses (greater than 0.5 grams administered over less than 10 minutes). In addition, Bradycardia has been reported during or after administering large doses of IVMP and may be unrelated to the speed or duration of infusion. Therefore, when a high steroid dose is wanted, the recommended dose must be administered over 30 minutes [2,7].

Adult case reports described unexpected cardiac arrest and death following high-dose IVMP infusions [6]. Most of these patients had a multisystem disease, but several had no evidence of a pre-existing cardiac condition. One adult and one pediatric case report developed severe Bradycardia associated with the infusion [3]. There is no established consensus on monitoring patients during and after IVMP administration.

One retrospective study analyzed the changes in vital signs, including heart rate (HR), systolic (SBP), and diastolic blood pressure (DBP) after IVMP infusion in Thyroid eye disease,

which showed that IVMP is safe and associated with mild and non-cumulative effects on vital signs when administered over 60 minutes. This study attributed the occurrence of hypertension or bradycardia to individual factors such as underlying hypertension, uncontrolled thyroid dysfunction, or medication usage, e.g., Beta-blockers [5]. For the above reasons, this retrospective comparative study is conducted to investigate the impact of IVMP infusion duration on vital signs and serum potassium levels in MS patients. Seventy-four patients with MS relapse with no other comorbidities were reviewed and classified into two groups; one group received pulse IVMP at a conventional rate over 1 or 2 hours, whereas the other group received extended infusion; both groups were monitored frequently during steroid infusion. Potassium level, blood pressure, and heart rate readings were recorded during hospitalization. These readings were analyzed to determine the effect of infusion duration of steroids on potassium level, HR, and BP among the two groups. This study protocol was approved by the Institutional Review Board (IRB) of Hamad Medical Corporation (MRC number: 01-18-024).

Method

We performed a retrospective review of seventy-four electronic medical records of MS patients administered methylprednisolone pulse therapy for MS flare through 2019 at Hamad General Hospital (HGH). Inpatients aged 18 years or older with MS flare without other comorbidities were categorized into two groups. Group 1 received intravenous methylprednisolone pulse therapy (500 -1000 mg) for 2-5 days over 1 – 2 hours, while group 2 received it over an extended period (3-6 hours). Blood pressure, heart rate, and potassium level were measured according to study protocol before, during, and after infusion of IVMP during the hospital stay, which varied from 2-to 5 days. Subsequently, data were analyzed to determine the effect of infusion duration on blood pressure, Heart rate, and potassium level variation between both groups. This study was approved by the Medical Research Center (MRC) of Hamad Medical Corporation (MRC number: 01-18-024). The mean value of the three measurements of systolic blood pressure, diastolic blood pressure, and pulse rate were included in the analysis. All subjects had their daily vital signs (HR, SBP, and DBP) recorded before infusion (baseline), after infusion immediately (post-infusion), and at a later point during the day (1st reading). Serum potassium was measured on admission before pulse MP and after infusion before discharge. Patients with hypertension, diabetes mellitus, chronic renal disease, cardiac disease, hyperthyroidism, and pregnant women were excluded from the study. Statistical analyses were performed using statistical software and the package SPSS 27.0 (IBM SPSS Inc. NY). We used Descriptive statistics to summarize and determine the sample characteristics, data distribution, and results. The normally distributed data and

results were reported with mean and standard deviation (SD); the remaining results were reported with median and Inter-Quartile Range (IQR). Quantitative outcomes measured on each specific day between the two groups (conventional infusion rate vs. extended infusion rate) were compared using unpaired t or Mann-Whitney U tests as appropriate. Repeated measure analysis of variance (ANOVA) was performed to determine and assess differences in quantitative outcomes measured across different time points. All P values presented were two-tailed, and P values <0.05 were considered statistically significant.

Results

In the study, 61 (83.6%) out of 74 MS patients received a methylprednisolone dose of 500 mg-1000 mg through a conventional infusion rate (group 1). Conversely, 12 patients (16.4%) received pulse steroids for an extended duration (group 2), 688 blood pressure readings and 685 heart rate readings were collected. The mean baseline blood pressure before pulse steroid administration was (systolic 118.93±16.04 mmHg, diastolic 70.42±9.44 mmHg), and baseline heart rate 76.66 ± 11.2 beat per minute (BPM). The majority of patients underwent pulse infusion of methylprednisolone at a dosage of 1000 mg over 1hour [Table 1]. Throughout the five days of intravenous methylprednisolone (IVMP) administration, there weren't any notable variations in systolic or diastolic blood pressure changes between the conventional and extended groups (Tables 2-6 illustrate the daily mean blood pressure and heart rate readings throughout the five days of pulse steroids administration).

Methylprednisolone pulse administration had led to fluctuation in heart rate through either increasing or decreasing compared to the patient's initial or baseline measurements. [Figures 1, 2]. Our study's results showed that there was a change in the mean heart rate across three specific time points over the span of five days: at baseline, immediately following the infusion, and at an additional reading taken later in the day. The mean heart rate was not significantly different between both groups [Tables 2-6]. A

limited number of patients whose vital signs readings were measured and documented across all five days of the study period. Therefore, we conducted additional analysis focusing on the mean heart rate at two specific time points: baseline and immediately after IVMP administration. Our findings indicated a statistically significant increase in the mean heart rate in the conventional group immediately after the first and second but not the third dose of IVMP compared to baseline [Table 9, 10].

On the contrary, our analysis revealed no statistically significant difference in the mean heart rate following IVMP administration compared to the baseline within the extended group after the first, second, and third doses. The maximum and lowest patient's heart rate obtained following IVMP administration were 102 BPM and 45 BPM, respectively. Even though methylprednisolone was administered over a one-hour period in both cases, only one patient exhibited tachycardia. However, this increase in heart rate was not attributable to the steroid infusion itself, suggesting an unrelated cause for the observed tachycardia in that patient. Six patients developed bradycardia (< 60 BPM); five out of six were in a conventional group on days 1,3,4, and 5, while one patient experienced bradycardia at day one in the extended group. For all patients, bradycardia resolved spontaneously. We collected 46 out of 74 participants' blood potassium levels before and after Methylprednisolone pulse administration [Table 8]. The mean baseline potassium level in the conventional and extended group was (4.05±0.26), and (4.16 ±0.35) mmol/L, respectively. Following Methylprednisolone administration, the potassium levels observed in the conventional group, averaging at 4.1±0.3 mmol/L, did not demonstrate any statistically significant difference compared to the potassium levels noted in the extended group, which averaged at 4.07±0.3 mmol/L (P= 0.72). There was a minimal increase in potassium level in the conventional group but not statistically significant p-value (P= 0.17). There was a non-statistically significant decrease in potassium level in the extended group p-value (P= 0.72). [Table 8]. No incidence of hypokalemia/hyperkalemia in both groups.

Table 1: Baseline characteristics of the patients along with HR and BP readings before and after IVMP administration.

Characteristics	Conventional infusion rate n= 62 (83.6%)	Extended infusion rate n= 12 (16.4%)
Sex		
Male n=33 (44.6%)	Male n=29 (39.2%)	Male n= 4 (5.4%)
Female n=41 (55.4%)	Female n= 33 (44.6%)	Female n=8 (10.8%)
Methylprednisolone dose		
500 mg N= 4	500 mg N= 2	500 mg N=2
1000 mg N=70	1000 mg N=60	1000 mg N= 10
Infusion time rate		
	1hr n=37	3hr n=1
	2hr n=25	4hr n=9
		6hr n=2
DAY 1		
BP baseline	61	12
BP post-infusion immediately	61	12
BP first reading post-infusion	42	11

Heart rate baseline before infusion	60	12
Heart rate post-infusion immediately	60	12
Heart rate first reading post-infusion	48	10
DAY 2		
BP baseline	56	10
BP post-infusion immediately	56	11
BP first reading post-infusion	41	8
Heart rate baseline before infusion	55	11
Heart rate post-infusion immediately	55	11
Heart rate first reading post-infusion	44	6
DAY 3		
BP baseline	49	10
BP post-infusion immediately	47	10
BP first reading post-infusion	29	8
Heart rate baseline before infusion	48	9
Heart rate post-infusion immediately	48	9
Heart rate first reading post-infusion	29	7
DAY 4		
BP baseline	32	4
BP post-infusion immediately	32	4
BP first reading post-infusion	19	3
Heart rate baseline before infusion	31	4
Heart rate post-infusion immediately	32	4
Heart rate first reading post-infusion	20	3
DAY 5		
BP baseline	22	2
BP post-infusion immediately	22	2
BP first reading post-infusion	11	1
Heart rate baseline before infusion	21	2
Heart rate post-infusion immediately	21	2
Heart rate first reading post-infusion	13	1
Total BP and HR readings in 5 days		
BP readings	580	108
HR readings	585	103
Baseline potassium level (Number of readings)	39	7
Post pulse steroid potassium level (Number of readings)	39	7

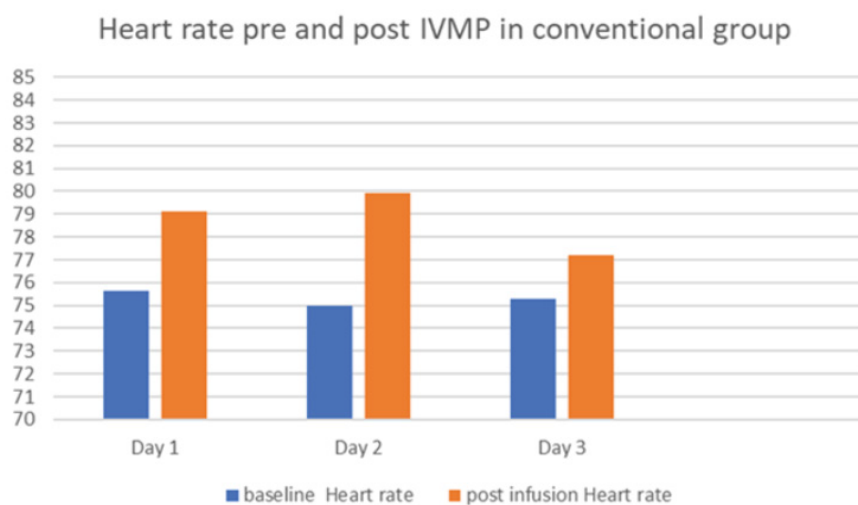


Figure 1: The comparison of heart rates before and after IVMP administration in the conventional group was conducted from day 1 to day 3.

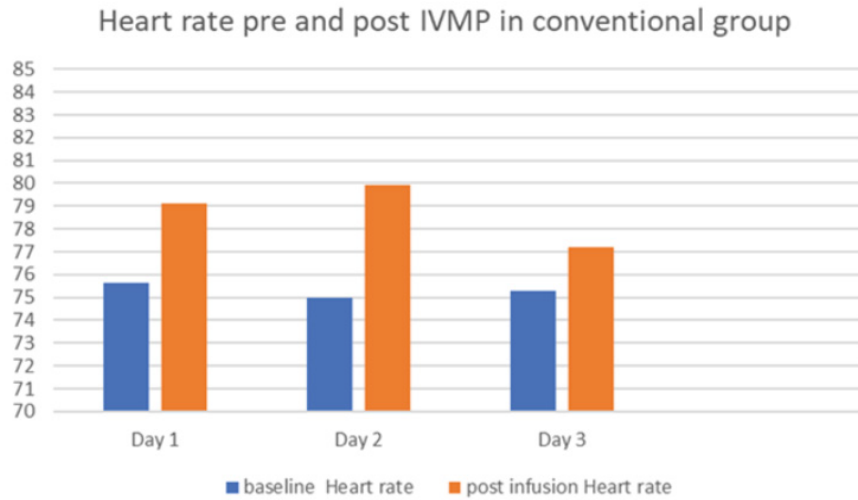


Figure 2: The comparison of heart rates before and after IVMP administration in the extended group was conducted from day 1 to day 3.

Table 2: The differences in blood pressure and heart rate on day 1 between the two groups.

Day 1	Conventional infusion rate	Extended infusion rate	P-value
Systolic BP baseline (mmHg)	118.3+/- 15.7	122.9+/-18.3	0.372
Diastolic BP baseline (mmHg)	70.3+/- 9.8	70.5+/- 7.914	0.942
Systolic post infusion (mmHg)	120.2+/-14.3	117.08+/-10.31	0.478
Diastolic post infusion (mmHg)	70.95+/- 8.4	69.58+/-6.571	0.598
Systolic first reading (mmHg)	118.7+/- 12.1	116.3+/-7.7	0.537
Diastolic first reading (mmHg)	69.6+/- 8.2	68.5+/-5.7	0.661
Baseline Heart rate (BPM)	75.6+/- 10.1	81.8+/- 15.3	0.081
Heart rate post-infusion (BPM)	79.1+/-10	82.4+/-14.0	0.335
Heart rate first reading (BPM)	78.6+/- 11.2	81.00+/-15.7	0.563

Table 3: The differences in blood pressure and heart rate on day 2 between the two groups.

Day 2	Conventional infusion rate	Extended infusion rate	P-value
Systolic BP baseline (mmHg)	118.7+/- 11.8	121.1+/-10.5	0.541
Diastolic BP baseline (mmHg)	70.3+/- 6.8	70.0+/- 7.6	0.914
Systolic post infusion (mmHg)	118.7+/-18.7	118.18+/-12.1	0.933
Diastolic post infusion (mmHg)	70.91+/- 10.7	66.73+/-8.0	0.224
Systolic 1st reading (mmHg)	119.17+/- 10.7	122.88+/- 11.2	0.378
Diastolic 1st reading (mmHg)	69.73+/- 8.0	68.75+/-8.0	0.753
Baseline Heart rate (BPM)	79.64+/- 11.2	83.82+/- 11.2	0.264
Heart rate post infusion (BPM)	80.07+/-10.3	84.00+/-12.0	0.266
Heart rate 1st reading (BPM)	79.18+/- 11.0	84.50+/-9.2	0.268

Table 4: The differences in blood pressure and heart rate on day 3 between the two groups.

Day 3	Conventional infusion rate	Extended infusion rate	P-value
Systolic BP baseline (mmHg)	118.55+/- 11.96	116.10+/-8.13	0.540
Diastolic BP baseline (mmHg)	68.65+/- 8.243	69.60+/- 10.844	0.755
Systolic post infusion (mmHg)	121.51+/-11.84	117.00+/-12.7	0.285
Diastolic post infusion (mmHg)	70.15+/- 7.46	71.90+/-10.6	0.536
Systolic 1st reading (mmHg)	124.66+/- 12.060	119.63+/- 9.5	0.285
Diastolic 1st reading (mmHg)	71.59+/- 9.0	73.00+/-7.2	0.686
Baseline Heart rate (BPM)	79.10+/- 10.3	75.22+/- 11.0	0.309
Heart rate post infusion (BPM)	77.38+/-9.3	77.89+/-11.2	0.883
Heart rate 1st reading (BPM)	75.41+/- 11.4	81.29+/-13.9	0.249

Table 5: The differences in blood pressure and heart rate on day 4 between the two groups.

Day 4	Conventional infusion rate	Extended infusion rate	P-value
Systolic BP baseline (mmHg)	121.13+/- 12.5	121.50+/-2.4	0.953
Diastolic BP baseline (mmHg)	69.69+/- 7.9	67.25+/- 7.2	0.563
Systolic post-infusion (mmHg)	119.75+/-11.019	126.75+/-2.9	0.220
Diastolic post infusion (mmHg)	70.44+/- 7.264	72.25+/-6.7	0.639
Systolic 1st reading (mmHg)	126.05+/- 9.8	126.00+/- 7.0	0.993
Diastolic 1st reading (mmHg)	73.95+/- 9.2	72.00+/- 4.6	0.727
Baseline Heart rate (BPM)	76.45+/- 11.2	78.25+/- 14.9	0.772
Heart rate post infusion (BPM)	75.16+/-8.3	82.00+/-12.6	0.151
Heart rate 1st reading (BPM)	73.05+/- 9.5	68.33+/-1.5	0.410

Table 6: The differences in blood pressure and heart rate on day 5 between the two groups.

Day 5	Conventional infusion rate	Extended infusion rate	P-value
Systolic BP baseline (mmHg)	121.45+/- 11.7	111.00+/-1.4	0.23
Diastolic BP baseline (mmHg)	69.55+/- 8.6	64.50+/- 9.2	0.438
Systolic post infusion (mmHg)	124.14+/-13.7	116.00+/-1.4	0.419
Diastolic post infusion (mmHg)	73.36+/- 7.4	70.00+/-2.8	0.537
Systolic 1st reading (mmHg)	128.27+/- 12.5	112	0.241
Diastolic 1st reading (mmHg)	70.73+/- 6.9	74	0.66
Baseline Heart rate (BPM)	74.90+/- 9.8	67.50+/- 6.4	0.314
Heart rate post-infusion (BPM)	74.71+/-11.6	62.50+/-7.8	0.165
Heart rate 1st reading (BPM)	75.54+/- 11.2	63	0.302

Table 7: The comparison of arrhythmia occurrences between the conventional and extended infusion methods.

	Conventional	Extended
Lowest HR post-infusion	45 BPM	49 BPM (baseline 52 BPM)
Maximum HR post-infusion	102 BPM	100 BPM
Maximum increasing HR	71 BPM increased 97 (+26)	74 BPM increased 98 (+24)
Maximum decreasing HR	82 BPM decreased 62 (-20)	78 BPM decreased 54 (-24)
Incidents of bradycardia	5 patients 8%	1 patient 8.3%

Table 8: Potassium level before and after steroid pulse infusion.

Infusion group	Initial potassium level	Post infusion potassium level	P-value
Conventional group N=39	4.03+/- 0.26	4.1+/-0.3	0.17
Extended group N=7	4.16+/- 0.35	4.07+/-0.3	0.72

Table 9: Heart rate changing in the conventional group from day 1-3.

Days	Baseline heart rate	Post infusion heart rate	P-value
Day 1 n=60	75.62 ± 10.1	79.1±10	0.003
Day 2 n=54	75±10.3	79.9±10.3	0.013
Day 3 n=47	75.3±10.4	77.2±9.3	0.294

Table 10: Heart rate changing in the extended group from day 1-3.

Days	Baseline heart rate	Post infusion heart rate	P-value
Day 1 n=12	81.83± 15.314	82.42± 14.016	0.808
Day 2 n=11	81.82± 16.061	84.00± 12.058	0.563
Day 3 n= 9	81.33± 17.664	77.89± 11.230	0.322

Discussion

We found Pulse methylprednisolone infusion relatively safe when given over 1 hour or extended up to 6 hours. Our data showed no significant difference in vital signs readings before and after infusion among different infusion rates. At the same time, there was a change in blood pressure and heart rate readings before and after the administration of IVMP. However, this variation remains within the normal range and does not stray significantly from the baseline. Additionally, this variation has not been affected by the infusion rate. The variation in heart rate might be related to individual factors such as stress, the timing of vital sign measuring, and patient activity during the hospital stay. Eight patients out of 74 patients developed bradycardia (defined as heart rate below 60 beats per minute [9]). Among these, two patients had a baseline heart rate below 60 BPM, which increased after IVMP, while the remaining six patients developed bradycardia after receiving IVMP. Five patients (8%) were from the conventional group, and one patient (8.3%) was from the extended group. Despite this, there was no significant difference in the incidents of bradycardia between different infusion rates of IVMP. On the other hand, tachycardia (defined as heart rate above 100 BPM [8]) was documented in 8 patients (7 patients in the conventional group and one patient in the extended group) out of 74 patients. Seven out of those eight patients developed tachycardia at baseline before administration of IVMP on days 1 and 2. Only one patient in the conventional group experienced mild tachycardia following the administration of IVMP. Therefore, we believe the tachycardia occurred due to individual factors as patients were initially and persistently tachycardiac even before IVMP administration. As this is a retrospective study, only a limited number of patients completed all vital signs readings during

the five days; while most patients received only three doses of IVMP during their hospital stay and completed the rest of the steroid course in outpatient settings. Hence, we conducted an additional analysis comparing the average heart rate at two time points (baseline and immediately after IVMP) from day 1 to day 3. [Table 9, 10].

Interestingly, additional analysis showed a statistically significant increase in the average heart rates among the conventional group immediately after 1st and 2nd doses despite these rates remaining within the normal range. This increase in heart rate was not accompanied by any clinical symptoms. On the other hand, there was a non-statistically significant increase in heart rate before and after IVMP in the extended infusion group which could potentially be attributed to the prolonged duration of the infusion. Yong, Kai-Ling, et al.'s study showed a significant decrease in HR at the 60 minutes following IVMP administration [4] which contradicts our additional analysis results. This might be explained by the impact of comorbidities and medications on the included subjects, in contrast to our research which focused solely on healthy individuals without underlying health conditions or medications. Generally, we found a mild increase in the mean BP after receiving IVMP, but without hypertension; the potential mechanism of such finding is sodium retention, volume expansion, and potential interference with the nitric oxide system [6]. In addition, steroids increase the sensitivity of blood vessels to vasoconstrictor hormones like catecholamines and other vasoconstrictive systems [4]. Hypokalemia is a possible side effect of IVMP, defined as a serum potassium level of less than 3.5 mEq/l. The usual range of serum potassium is 3.5 to 5 mEq/l. Out of 46 patients who underwent potassium level assessments before and 24-72 hours post IVMP administration, only one patient developed

mild hypokalemia (3.4 mEq/l). In comparison with baseline, 23 patients (50%) experienced an increase in potassium levels within the normal range following IVMP administration; however, it was not statistically significant in either the conventional or extended group, with p-values of 0.17 and 0.72, respectively [Table 8]. Our study findings support the recommendation of Kai-Ling Yong El, who discouraged regular potassium checking after IVMP administration in relatively healthy patients with normal baseline potassium levels. Instead, restricting its measurement for those patients with other risk factors, such as renal failure or utilizing medications such as diuretics [4,10].

Strength and limitations

Our study included 688 vital signs (BP, HR) measurements related to 277 infusions administered. The main limitation of our study was the small number of study subjects in the extended group; in addition, there was variability in the length of stay and the frequency of monitoring.

Conclusion

IVMP is relatively safe and effective in treating MS exacerbation regardless of intravenous infusion duration, whether administered over a shorter or longer period. There was no significant difference in vital signs fluctuation between different infusion rates. Moreover, there was a statistically significant increase in the mean heart rate in the conventional group immediately after the first and second but not the third dose of IVMP compared to baseline. Additionally, the absence of significant changes in potassium levels before and after IVMP administration suggests that routine potassium monitoring might not be necessary for all patients receiving this treatment.

Acknowledgments

Not applicable.

Statement of Ethics

This study protocol was approved by the Institutional Review Board (IRB) of Hamad Medical Corporation (MRC number: 01-18-024, Email: irb@hamad.qa Tel: 00974-40256410, HMC-IRB Registration: MOPH-HMC-020, IRB-MoPH Assurance: IRB-A-HMC-2019-0014), and is therefore carried out per all the relevant sections of the Rules and Regulations for Research at HMC and with the 1964 Helsinki declaration ethical standards. Furthermore, all methods were conducted in accordance with appropriate guidelines and regulations. As it is a retrospective study, the need for informed consent was waived.

Conflict of interest

The authors declare that they have no conflicts of interest.

Consent for publication: Not applicable.

Data Statement and Author Contributions

Haider Alabd conceived the research idea. Haider Alabd and Mohamed Elshafei designed the initial study protocol submitted to MRC. Prem Chandra is responsible for the statistical design and analysis. Haider Alabd and Mohamed Elshafei have done data collection. Haider Alabd, Lolwa Barakat, Bhagya Sree, and Mohamed Khalil wrote the manuscript. Haider Alabd, Lolwa Barakat, Bhagya Sree, Prem Chandra, Mohamed Khalil, and Mohamed Elshafei critically reviewed the initial draft and approved the final version for publication.

The data supporting this study's findings are available from Hamad Medical Corporation. Still, restrictions apply to the availability of these data, which are used under license for the current research and are not publicly available. However, data are available from the authors upon reasonable request and with the permission of Hamad Medical Corporation.

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