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

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Abstract

Objective: - To ascertain the adverse events and changes in vital signs (heart rate (HR), systolic (SBP), diastolic blood pressure (DBP), and serum potassium level during and after intravenous methylprednisolone (IVMP) in multiple sclerosis exacerbation.

Design: retrospective review study conducted at Hamad General Hospital (HGH), all patients who are admitted 2019-2020 with MS exacerbation without any other comorbidities will be categorized into 2 groups depending on infusion rate, one group received conventional intravenous methylprednisolone pulse dose over 30minutes to one hour, while the second group received methylprednisolone pulse dose intravenously over an extended period)(four to six hours). Multiple readings of vital signs and, potassium level through steroid administration time will be assessed to determine if there is an infusion-related significant difference in adverse events between both groups.

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

Results: 74 patients with MS included in the study, 61 patients (83.6%) were received methylprednisolone dose 500 mg -1000 mg in conventional infusion rate while 12 patients (16.4%) were received pulse steroid in extended duration. There was no significant difference in mean blood pressure before and after IVMP in both groups. There was a small but statistically significant increase in mean heart rate in the conventional group immediately after 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 is a non-significant decrease in potassium level in the extended group ($P=0.72$).

Conclusion: IVMP is considered safe and effective in the treatment of 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 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 that potassium level monitoring should be only restricted to patients with other risk factors of hypokalemia.

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 is the standard of care for the treatment of MS relapse
- IVMP is relatively safe and effective in the treatment of 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 typically 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 is the standard of care for the treatment of 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, but due to lack of guidelines or standards with regards to infusion duration, there is an always inconsistent practice between physicians regarding infusion rate and duration with some of them prefer administering over 30 minutes to one hour, whereas others prefer extended infusion over 4-6 hours due to conception of more adverse events such as cardiac arrhythmias and hypokalemia associated with a short infusion. Extended infusion time will increase the length of hospital stay, additionally, it increases the possibility of steroid infusion interruption due to patient's mobility.

Methylprednisolone manufacturing company mentioned that there are reports of cardiac arrhythmias and/or cardiac arrest following the rapid administration of large intravenous doses (greater than 0.5 gram administered over less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate and may be unrelated to the speed or duration of infusion. When a high steroid dose is wanted, the recommended dose must be administered over at least 30 minutes (2,7).

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

There is only one retrospective study aimed to analyze the changes in vital signs (including heart rate (HR), systolic (SBP), and diastolic blood pressure (DBP)) during and after IVMP infusion in Thyroid eye disease, which showed that IVMP is safe and associated with mild and noncumulative effects on vital signs when IVMP given over 60 minutes, this study attributed the occurrence of hypertension or bradycardia to individual factors such as those with underlying hypertension and uncontrolled thyroid dysfunction or due to medications e.g. Beta-blockers (4).

For the above reasons, this retrospective comparative study is conducted to investigate the impact of MP infusion duration on vital signs and serum potassium level in MS patients.

Seventy-four patients with MS relapse with no other comorbidities were reviewed and classified into 2 groups, one group received pulse methylprednisolone at a conventional rate over 1 or 2 hours, whereas the other group received extended infusion, both groups were monitored frequently during steroid infusion and potassium level, blood pressure (BP), heart rate(HR) readings were recorded during hospitalization, these readings were analyzed to determine the effect of infusion duration of steroids on potassium level, HR, BP among the 2 groups.

Methods

We performed a retrospective review of seventy-four electronic medical records of MS patients who were administered methylprednisolone pulse therapy for MS flare through 2019 at Hamad General Hospital (HGH). Inpatients aged 18 years or older with MS exacerbation without any other comorbidities were categorized into 2 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 hospital stay which is varied from 2-5 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 medical research centre (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 another reading later during the day (1st reading). Serum potassium was measured on admission before pulse MP and after infusion before discharge.

Patients who had 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 package SPSS 27.0 (IBM SPSS Inc. NY). Descriptive statistics were used to summarize and determine the sample characteristics and distribution of data 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 at 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 outcome measured across different time points. All P values presented were two-tailed, and P values <0.05 were considered statistically significant.

Results

61 (83.6%) out of 74 MS patients included in the study were received methylprednisolone dose 500 mg -1000 mg in conventional infusion rate (group 1), while 12 patients (16.4%) received pulse steroids in extended duration (group 2), 688 blood pressure measurement readings and 685 readings of heart rate are 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 received pulse infusion methylprednisolone 1000 mg over 1hour, (Table 1).

Table 1
parameters of Participants

Characteristics	Conventional infusion rate *n*= 62 (83.6%)	Extended infusion rate *n*= 12 (16.4%)
Sex	Male n=29 (39.2%)	Male n= 4 (5.4%)
Male *n*=33 (44.6%)	Female n= 33 (44.6%)	Female n=8 (10.8%)
Female *n*=41 (55.4%)		
Methylprednisolone dose	500 mg N= 2	500 mg N=2
500 mg N= 4	1000 mg N=60	1000 mg N= 10
1000 mg N=70		
Infusion time rate	1hr n=37	3hr *n*=1
	2hr n=25	4hr *n*=9
DAY 1		6hr *n*=2
BP baseline	61	12
BP post-infusion immediately	61	12
BP 1ST reading post-infusion	42	11
heart rate baseline before infusion	60	12
heart rate post-infusion immediately	60	12
heart rate 1ST reading post-infusion	48	10
DAY 2		
BP baseline	56	10
BP post-infusion immediately	56	11
BP 1ST reading post-infusion	41	8
heart rate baseline before infusion	55	11
heart rate post-infusion immediately	55	11
heart rate 1ST reading post-infusion	44	6
DAY 3		
BP baseline	49	10
BP post-infusion immediately	47	10
BP 1ST reading post-infusion	29	8
heart rate baseline before infusion	48	9
heart rate post-infusion immediately	48	9
heart rate 1ST reading post-infusion	29	7
DAY 4		
BP baseline	32	4
BP post-infusion immediately	32	4
BP 1ST reading post-infusion	19	3
heart rate baseline before infusion	31	4
heart rate post-infusion immediately	32	4
heart rate 1ST reading post-infusion	20	3
DAY 5		
BP baseline	22	2
BP post-infusion immediately	22	2

Characteristics	Conventional infusion rate *n*= 62 (83.6%)	Extended infusion rate *n*= 12 (16.4%)
BP 1ST reading post-infusion	11	1
heart rate baseline before infusion	21	2
heart rate post-infusion immediately	21	2
heart rate 1ST reading post-infusion	13	1
	580 BP measurement readings	108 BP measurement readings
	585 HR measurement readings	103 HR measurement readings
Baseline potassium level	39	7
Post pulse steroid potassium level	39	7

Overall, during five days of IVMP, there is no significant difference in systolic and diastolic blood pressure changing between the conventional and extended groups, tables (2-6) illustrated the daily mean blood pressure and heart rate measurement readings during five days of receiving pulse steroid.

Methylprednisolone pulse causes fluctuation in heart rate from baseline (increasing or decreasing) (figures 1, 2 showed the variation in heart rate over five days from the baseline then post IVMP infusion immediately and 3rd reading during the day). Our study found a change in the mean heart rate over five days in 3-time points (baseline, immediately after infusion, and another reading during the day). Overall, the mean heart rate was not significantly different between both groups (Tables 2-6). Due to the limited number of patients who all prescheduled vitals readings have been measured and documented during all five days, we performed a subgroup analysis comparing the mean heart rate in 2-time points(at baseline and immediately after IVMP) from day1 to day 3 (results illustrated in table A, B)

Table 2
The variation in blood pressure and heart rate in day 1 between both 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 1st reading (mmHg)	118.7+/- 12.1	116.3+/-7.7	0.537
Diastolic 1st 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 1st reading (BPM)	78.6+/- 11.2	81.00+/-15.7	0.563

Table 3
The variation in blood pressure and heart rate in day 2 between both 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 variation in blood pressure and heart rate in day 3 between both 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 variation in blood pressure and heart rate in day 4 data between 2 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 variation in blood pressure and heart rate in day 5 between both groups

Day 5	Conventional infusion rate	Extended infusion rate	P-value
systolic BP baseline (mmHg)	121.45+/- 11.7	111.00+/-1.4	0.230
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	112.00	0.241
Diastolic 1st reading (mmHg)	70.73+/- 6.9	74.00	0.660
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	63.00	0.302

There was a statistically significant increase in heart rate mean in the conventional group immediately after 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 no statistically significant increase in heart rate mean from baseline and after IVMP infusion completed in extended group after 1st,2nd, and 3rd dose.

The maximum and lowest heart rate post-Methylprednisolone pulse dose documented were 102 BPM, 45 BPM respectively. Both readings were found when Methylprednisolone was administered over 1 hour, only 1 patient was found to have tachycardia which is not related to steroid infusion.

A total of 6 patients developed bradycardia (less than 60 BPM), 5 out of 6 were in a conventional group on days 1,3,4, and 5, while 1 patient on the extended group developed bradycardia on day 1. For all patients, bradycardia resolved spontaneously.

46 out of 74 participants' blood potassium level was collected before and after Methylprednisolone pulse administration (Table 7). The Mean baseline potassium level in the conventional and extended group was 4.05+/- 0.26 and 4.16 +/-0.35 mmol/L respectively. After Methylprednisolone infusion, potassium level was found 4.1+/-0.3 mmol/L in the conventional group which is not statistically significantly different from potassium level in the extended group 4.07+/-0.3 mmol/L (P= 0.72).

Table 7
arrhythmia comparison between conventional and extended infusion.

	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%

There is a minimal increase in potassium level in the conventional group but not a statistically significant p-value (0.17), whilst there is a non-statistically significant decrease in potassium level in the extended group p-value (0.72). (Table 7). No incidence of hypokalemia/hyperkalemia in both groups.

Discussion

Pulse methylprednisolone infusion was found to be relatively safe when given over 1 hour or extended up to 6 hours. Our data showed that there is no significant difference in vital signs readings before and after infusion between different infusion rates, while there was a change in blood pressure and heart rate readings before and after the administration of IVMP however, this variation remains within normal range and does not move far 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. Out of 74 patients, 8 patients developed bradycardia(as defined by heart rate less than 60 beats per minutes9), 2 of them were baseline HR < 60 BPM which increased after IVMP, while the remaining 6 patients developed Bradycardia after receiving IVMP, 5 patients (8%) were in the conventional group and 1 patient (8.3%) was on the extended group, although no significant difference in the incidents of bradycardia between different infusion rate of IVMP.

On the other hand, tachycardia (as defined by a heart rate of more than 100 BPM (8)), was documented in 8 patients (7 patients in conventional group and 1 patient in extended group) out of 74 patients. Seven out of those 8 patients had developed tachycardia at baseline before IVMP was administered on days 1 and 2, while only 1 patient who was in the conventional group developed mild tachycardia after being given IVMP. We believe the tachycardia happened due to individual factors as patients were initially and persistently tachycardiac even before IVMP was given.

As this is a retrospective study, only a limited number of patients completed all vital signs readings during the whole 5 days, in addition, the majority of patients have received only 3 doses of IVMP in hospital and completed the steroid course in outpatient settings, therefore, we performed sub-analysis comparing the mean of heart rate in 2-time points(at baseline and immediately after IVMP) from day1 to day 3, the results illustrated in table A, B.

This sub-analysis interestingly showed a statistically significant increase in the heart rate means in the conventional group immediately after 1st and 2nd doses despite being still in the normal range. This increase in heart rate does not reflect any clinical symptoms, while in the extended infusion group there was a non-statistically significant increase in heart rate before and after IVMP possibly due to the long duration of infusion.

Yong, Kai-Ling et al. (4) found that IVMP led to a significant percentage drop in HR at 60 minutes which is contradictory to our sub-analysis results, this might be explained by the effect of comorbidities and medications of the included subjects, which were excluded in our study as we included only healthy subjects without comorbidities.

Generally, we found there is a mild increase in the mean BP after receiving IVMP but without inducing hypertension, the possible mechanisms are sodium retention, volume expansion (5), and interrupting nitric oxide system. Steroids may also mediate vascular vasoconstrictor sensitivity to catecholamines and other vasoconstrictor hormones systems [4].

Hypokalemia is one of the possible side effects of IVMP which is defined as a serum potassium level less than 3.5 mEq/l. The normal range of serum potassium is 3.5 to 5 mEq/l, out of 46 patients who were potassium level checked before and 24-72 following IVMP administration, only one patient developed mild hypokalemia (3.4 mEq/l). Interestingly, in comparison with baseline, 23 patients (50%) their potassium level had increased

within normal range after receiving IVMP, however, it was not statistically significant (P = 0.17, 0.72) in the conventional group and extended group respectively (Table 8).

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 A. 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 B. 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

Our study findings support the suggestion of Kai-Ling Yong El who discouraged regular potassium checking after IVMP administration in relatively well patients with normal potassium at baseline, while restricting its measurement for those patients with other risk factors., such as renal failure or use of 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 the treatment of MS exacerbation regardless of intravenous infusion duration whether administered over 1 hour or up to 6 hours. There was no significant difference in vital signs fluctuation between different infusion rates. Moreover, there was a statistically significant increase in heart rate mean in the conventional group immediately after first and second but not 3rd dose of IVMP compared to baseline. We found that there is no significant difference in potassium level variation before and after IVMP, monitoring potassium levels should be restricted only to patients with other risk factors.

Declarations

Ethics approval and consent to participate:

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 in accordance with all the relevant sections of the Rules and Regulations for Research at HMC and with the 1964 Helsinki declaration ethical standards. All methods were conducted in accordance with relevant guidelines and regulations. As it is retrospective date review study, the need for informed consent was waived by the Institutional Review Board (IRB) of Hamad Medical Corporation.

Consent for publication:

Not applicable.

Availability of data and materials:

The data that support the findings of this study are available from Hamad Medical Corporation, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Hamad Medical Corporation.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

HA conceived the research idea. HA and ME designed the initial study protocol submitted to MRC. PC is responsible for the statistical design and analysis. HA and ME have done data collection. HA, LB, BS, and MK wrote the manuscript. All other authors (HA, LB, BS, PC, MK, and ME) critically reviewed the initial draft and approved the final version for publication.

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References

1. Serhan Sevim(2016)' Relapses in Multiple Sclerosis: Definition, Pathophysiology, Features, Imitators, and Treatment' Turk J Neurol 22:99-108: https://jag.journalagent.com/tjn/pdfs/TJN_22_3_99_108%5BA%5D.pdf
2. http://online.lexi.com/lco/action/doc/retrieve/docid/multinat_f/4669835?cesid=7WS8FnH6gQ3&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3DmethylPREDNISolone%26t%3Dname%26va%3DmethylPREDNISolone#
3. Heidrich E, Greene G, Weberding J, Lin L, McGee S. Effects of methylprednisolone infusions on vital signs in children with headaches. J Pediatr Pharmacol Ther. 2013 Jan;18(1):39-44. doi: 10.5863/1551-6776-18.1.39. PMID: 23616734; PMCID: PMC3626064.
4. Yong KL, Chng CL, Htoon HM, Lim LH, Seah LL. Safety Profile and Effects of Pulsed Methylprednisolone on Vital Signs in Thyroid Eye Disease. Int J Endocrinol. 2015;2015:457123. doi:10.1155/2015/457123.
5. Kelly JJ, Mangos G, Williamson PM, Whitworth JA. Cortisol and hypertension. Clin Exp Pharmacol Physiol Suppl. 1998 Nov;25:S51-6. doi: 10.1111/j.1440-1681.1998.tb02301.x. PMID: 9809193.
6. A. E.McLuckie and R. W. Savage, "Atrial fibrillation following pulse methylprednisolone therapy in an adult," Chest, vol. 104, no. 2, pp. 622–623, 1993.
7. van den Berg, J S et al. "Anaphylactoid reaction to intravenous methylprednisolone in a patient with multiple sclerosis." Journal of neurology, neurosurgery, and psychiatry vol. 63,6 (1997): 813-4. doi:10.1136/jnnp.63.6.813.
8. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NA 3rd, Field ME, Goldberger ZD, Hammill SC, Indik JH, Lindsay BD, Olshansky B, Russo AM, Shen WK, Tracy CM, Al-Khatib SM; Evidence Review Committee Chair‡. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2016 Apr 5;133(14):e506-74. doi: 10.1161/CIR.0000000000000311. Epub 2015 Sep 23. Erratum in: Circulation. 2016 Sep 13;134(11):e234-5. PMID: 26399663.
9. Spodick DH. Normal sinus heart rate: sinus tachycardia and sinus bradycardia redefined. Am Heart J. 1992 Oct;124(4):1119-21. doi: 10.1016/0002-8703(92)91012-p. PMID: 1529897.
10. B Bonnotte, B Chauffert, F Martin, B Lorcerie, Side-effects of high-dose intravenous (pulse) methylprednisolone therapy cured by potassium infusion., Rheumatology, Volume 37, Issue 1, Jan 1998, Page 109, https://doi.org/10.1093/rheumatology/37.1.109a .

Figures

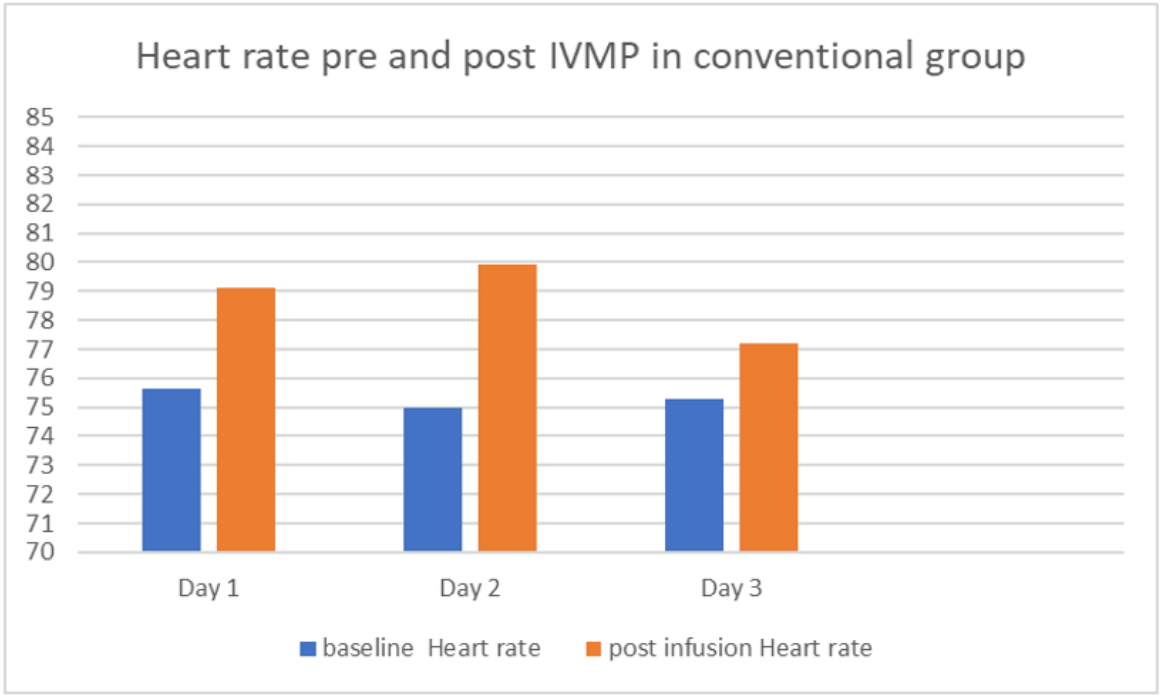

Figure 1

Heart rate comparison pre and post IVMP in the conventional group from day 1-3

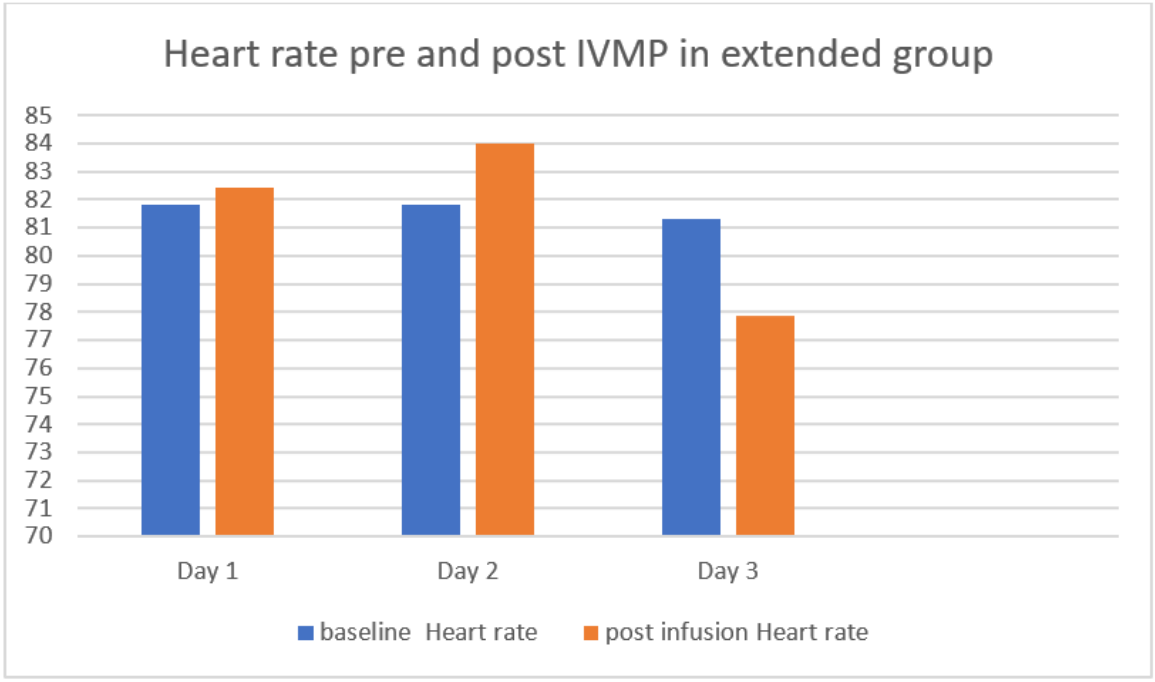

Figure 2

Heart rate comparison pre and post IVMP in the extended group from day 1-3