Clinical Investigation

Effects of Methylprednisolone Infusions on Vital Signs in Children With Headaches

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OBJECTIVES Intravenous methylprednisolone (IVMP) infusions have been associated with adverse cardiovascular effects. Inconsistent monitoring practices in a pediatric hospital led to questions about patient safety and allocation of nursing resources. This study describes vital sign changes in children and monitoring practices related to IVMP.

METHODS This retrospective chart review received Institutional Review Board approval. Children aged 5 to 17 years receiving IVMP from January 2006 to January 2009 were included. Seventy-four patients with 94 hospital admissions were evaluated. Data collected included systolic blood pressure, diastolic blood pressure, and heart rate, as well as the time and dosage of IVMP. Frequency of vital sign monitoring as ordered and as performed was described. Interrater reliability was calculated, and descriptive statistics were used in the data analysis.

RESULTS At baseline, about half of the patients had vital signs out of normal range for age. After the first dose, vital signs fluctuated, with a majority having greater than 10% changes from baseline as increases, decreases, or both. Time of initial 10% change in vital signs ranged from immediately after the dose to 135.5 hours later. Increased vital sign changes were seen in the older patients and in patients receiving higher doses. Monitoring of vital signs occurred more frequently than was ordered. Only 1 patient had a specific order for monitoring with IVMP.

CONCLUSIONS The patients included in this study experienced documented fluctuations in vital signs. A prospective study to evaluate the relationship of IVMP and patient safety will assist in standardizing vital sign monitoring guidelines.

INDEX TERMS adverse effects, children, headache, methylprednisolone, vital signs

J Pediatr Pharmacol Ther 2013;18(1):39–44

INTRODUCTION

A wide range of medications are used to treat acute migraine headaches including antiemetics, ergot alkaloids and derivatives, non-steroidal anti-inflammatory drugs, and triptans.[1] While not an acute treatment, corticosteroids, including intravenous methylprednisolone (IVMP) (15–30 mg/kg/dose, maximum 1000 mg/day), have been shown to be effective in reducing the rate of headache recurrence.[2] IVMP infusions have been associated with adverse effects including hypotension, hypertension, bradycardia, tachycardia, and some reports of unexplained death.[3-7] Inconsistent ordering and monitoring of vital signs when patients received IVMP for migraine headaches were identified on the neuroscience unit at a 525-bed university affiliated children's hospital. Questions about the frequency of vital sign changes that can be attributed to IVMP led to this study.

National Guideline Clearinghouse was searched for guidelines on administering high dose steroid infusions; none were found. Medline, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, and Scopus databases were searched using the keywords: methylprednisolone, pulse dosing, children, adverse effects or events, migraine, acute disseminated encephalomyelitis, acute spinal cord injury, asthma, and optic neuritis. No studies were found that focused on children with neuroscience diagnoses. Three studies were identified concerning children with any diagnosis and vital

sign changes related to high dose (30 mg/kg up to a maximum of 1000 mg/24 hours) IVMP infusions.[8-10] A prospective study evaluated adverse reactions associated with high dose corticosteroids in children (n=214) and identified 9 patients who experienced vital sign changes.[8] An efficacy study compared hydrocortisone to IVMP in 19 children with rheumatic diseases. This study did not look at adverse reactions specifically but did report hypotension, hypertension, and tachycardia.[9] A series of case reports described one institution's experience over a 6-month period with 5 children with rheumatic diseases who developed sinus bradycardia after IVMP infusions.[10]

Adult case reports described unexpected cardiac arrest and death following high dose IVMP infusions.[4-6] Most of these patients had multisystem disease, but several had no evidence of pre-existing cardiac disease. One adult and 1 pediatric case report identified severe bradycardia associated with the infusions.[10-11]

The pediatric studies had variation in vital signs with minimal clinical significance in common. However, the adult case reports that describe unexpected cardiac arrest and death raise concern about the safe administration of IVMP. None of these studies specifically addressed the need for frequent monitoring of vital signs during the IVMP infusions, or the duration of adverse effects and the need for follow-up monitoring after the infusions. Frequent monitoring of vital signs requires a large commitment of nursing time. The purpose of this study was to describe heart rate (HR) and blood pressure (BP) of children being treated for headaches before, during, and after IVMP infusions and evaluate factors that may increase the risk for fluctuations in HR and BP. The anticipated results of this study may assist practitioners in setting a standard of practice for monitoring these patients.

MATERIALS AND METHODS

Institutional Review Board approval was obtained. A retrospective descriptive study was conducted to evaluate the frequency of HR and BP changes related to IVMP infusions during a 3-year time period. Patients aged 5 to 17 years old who were admitted to a pediatric hospital and received IVMP for headaches were eligible for this study. The charts were reviewed for data available from 24 hours before the first IVMP infusion until 7 days after the last infusion, unless the patient was discharged earlier. Exclusion criteria were concomitant disease states that could affect HR or BP, admission to cardiology, hematology/oncology, and nephrology services, liver disease, spinal cord injury, or IVMP administered within 48 hours after surgery. Patients were also excluded if they were currently taking antihypertensive medications, inotropes, or vasopressors.

Data collected included patient demographics, active medication orders at the time of the infusions, the dose of IVMP, the number of infusions each patient received, and the timing and length of the infusions. Vital sign monitoring orders were compared with actual monitoring performed. The association of HR and BP changes with IVMP and the relationship to age, dose (mg/kg), and number of infusions were examined. Normal vital signs for children based on age were used in this study.[12] Patient temperatures and pain scores were also recorded. Two reviewers independently collected data for 12 randomly selected patients to assess the interrater reliability.

Quantitative variables were described by median, mean ± SD, interquartile range, and range depending on data distribution. Categorical variables were described by frequency and proportions. The correlation coefficient was calculated to examine the relationship between vital sign changes and age. A t-test was used to compare mean differences between subgroups. A paired t-test was applied to compare mean differences after IVMP infusions. The data distribution of each variable was checked by histogram, boxplot, and normality test. The 2-sided significance level was set at 0.05. All the analyses were conducted using SAS 9.2.

RESULTS

One hundred twenty-two patients were identified as being admitted for headaches and treated with IVMP from January 2006 to January 2009. Thirty-four of these were excluded for not meeting inclusion criteria: 12 patients did not receive the ordered dose (refused, lost access, or not charted); 16 had headaches with other indications (rheumatology, nephrology, tumor, allergic reaction); and 2 were receiving antihypertensive medications (clonidine and lisinopril). Other exclusions were due to intramuscular injection (n=1) and age (n=3). An additional 14 patients

Table 1. Patient Demographics (n=74)

Age (years)	
Median (range)	15 (5–17)
IQR	13–16
Weight (kg)	
Median (range)	57 (18.9–122.9)
IQR	48.4–67.5
Female, n (%)	56 (75.7)

IQR, interquartile range

were excluded due to missing baseline or after dose data. Finally, a total of 74 patients with 94 admissions were evaluated. Analysis was completed for a single admission for 60 patients and for more than 1 admission for the other 14 patients.

The interrater reliability of the chart review was 98.9% (95% confidence interval = 0.983–0.993). The first admission with complete data available for each patient (n=74) was used in analysis of vital sign changes and monitoring orders and practices to ensure the independence of the data. In examining the relationship of vital sign changes to age, dose, and number of infusions, all 94 admissions were included.

The subjects' ages ranged from 5 to 17 years. This sample was primarily female (75.7%) with median age of 15 years and median weight of 57 kg. The single most common dose of IVMP was 1000 mg (77%). Although weight-based dosing is standard practice, the dose for most patients in this study exceeded the guidelines and they received the maximum 1000 mg dose. The number of vital sign measurements available ranged from 1 to 81 (mean=10). Table 1 presents a detailed description of the sample and study. Infusion times varied from 15 minutes to 60 minutes. No children were noted to have fever.

HR and BP changes

At baseline, approximately half of the patients had vital signs out of the normal range for age. After the first dose, the number of patients with vital signs out of the normal range increased to over three-fourths (Table 2). The vital signs fluctuated around the baseline with about one-third experiencing both increases and decreases in vital signs during the observation window (Figure 1). The time of initial 10% change in vital signs ranged from immediately after the dose to 135.5 hours after. The median time between

Table 2. Vital Signs out of Normal Range for Age (n=74)

Vital Sign	Baseline	After First Dose
SBP, n (%)	42 (56.8)	61 (82.4)
DBP, n (%)	30 (40.5)	59 (79.7)
HR, n (%)	48 (64.9)	59 (79.7)

DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure

the dose and the first incidence of 10% change from patients' baseline varied from 1.37 hours to 4.49 hours (Figure 2). The most common concurrent headache medication was dihydroergotamine (DHE) (60.8%). HR after the first dose (mean=83.0, SD=13.9) was significantly higher than baseline (79.9 ± 10.7) in this group (one-sided p=0.0274, paired t-test). Those who did not receive DHE (n=29, 39.2%) had a baseline HR of 86 ± 15.6, and showed a slight decrease in HR after the first dose (84.3 ± 12.7). Changes in BP for both groups were similar and not statistically significant.

Relationship among vital sign changes, age, dose amount, and number of IVMP infusions

Systolic BP (SBP) changes were slightly correlated to HR changes (r=0.23). SBP changes were strongly positively related to diastolic BP (DBP) changes (r=0.67). Age was positively correlated with BP. Greater changes in BP were observed in older children (SBP r=0.23, p=0.04; DBP r=0.27, p=0.02). Greater decreases in HR (r= −0.26, p=0.03) were seen in patients receiving higher milligram doses. These were generally the older patients who received the maximum dose of 1000 mg. As expected, due to dosing based on weight, age was correlated with dosage in milligram (r=0.57). The relationship between vital sign changes and dose per kilogram could not be accurately identified due to the large number of subjects who received the maximum dose. For the 14 patients receiving 2 doses, the trend was toward increases in HR after the second dose. This did not reach statistical significance (p=0.18) (Figure 3).

HR and BP monitoring practice versus written order

There were 26 different orders for vital sign monitoring. Of the 74 patients, 3 had no vital sign monitoring orders, and some had more than 1 order. The most common orders were "every 4 hours" (55.6%) and "every shift" (29.2%) (Figure

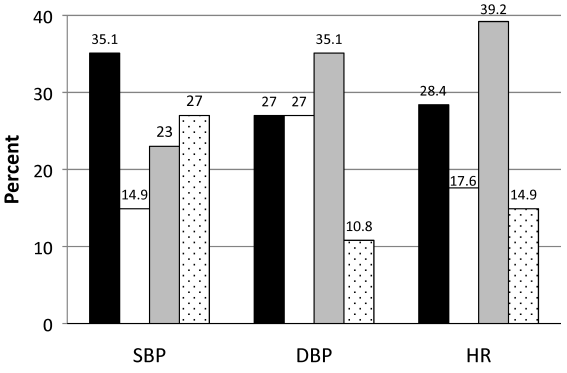

Figure 1. Patients with greater than 10% change in vital signs after first dose of methylprednisolone.

DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure

Black bar, >10% increase only; white bar, >10% decrease only; gray bar, >10% increase and decrease; dotted bar, < 10% change

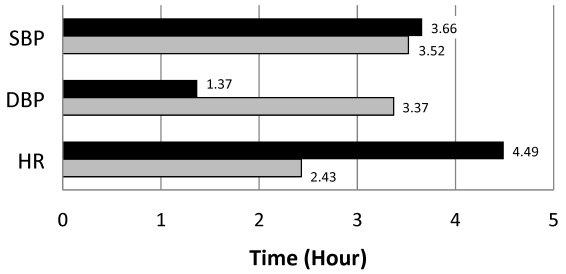

Figure 2. Median time to 10% change after first dose.

DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure

Black bar, decreased; gray bar, increased

4). Only 1 patient had a specific order for vital sign monitoring with IVMP infusion. The mean time between actual vital sign observations was less than 3 hours, regardless of the ordered frequency. The vital sign monitoring frequency was higher for patients given 1000 mg (every 2.11 ± 1.12 hours) than for patients given less than 1000 mg (2.41 ± 1.23 hours) but did not reach statistical significance (p=0.38). The patients also receiving DHE had more frequent vital sign monitoring than patients who were not (p=0.034 for BP and p=0.23 for HR, 2-sample t-test).

DISCUSSION

Few studies addressed the incidence of adverse events related to vital sign changes in children receiving high dose IVMP infusions (30 mg/kg to a maximum of 1000 mg). In 1 prospective study in which high dose IVMP was administered over 60 minutes, the incidence of vital sign changes was 4.2 % (9/214). The changes experienced by the 9 patients included hypertension (n=5), hypotension (n=2), and tachycardia (n=2). The study report did not identify the severity of these reactions. One patient with hypotension and tachycardia was treated with a fluid bolus, while the second patient's hypotension resolved spontaneously. Five patients experienced transient hypertension, which responded to decreased rate of infusion (n=2), diuretics (n=2), and/or antihypertensive medication (n=2).[8] In a study of 19 children who received high dose IVMP (30 mg/kg in 100 mL of 5% dextrose in water infused over 20–30 minutes), 2 experienced transient hypotension and 1 transient tachycardia. None required treatment, and all reactions lasted less than 30 minutes.[9] In a series of case reports over a 6-month period, 5 children with rheumatic diseases developed sinus bradycardia with IVMP (30 mg/kg to a maximum of 1000 mg in 100 mL of 5% dextrose in water or 5% dextrose/0.2% normal saline infused over 30–60 minutes). Specific information was reported for 2 patients whose baseline HRs were 93 and 95 beats per minute with bradycardia of 35 and 45 beats per minute, respectively. All patients were asymptomatic and received no treatment but continued to have bradycardia for at least 72 hours after it was first noted. All patients were continuously on cardiac monitoring before, during, and after their infusions.[10]

This current study confirmed that IVMP infusions have some impact on vital signs. Fifty percent of the patients had vital signs out of normal range before the first dose, and approximately 80% had vital signs recorded out of the normal range for age after the dose. A higher incidence of vital sign changes was identified in this study than in the literature reviewed, although bradycardia found in other pediatric studies could not be determined with this study design.[8-10] Only 14.9% of the patients maintained a HR within 10% of their baseline. It is unclear how many patients experienced clinical bradycardia. Decrease in HR took the longest time to appear. Similar results were found in BP with about a quarter of the patients staying within 10% of their baseline

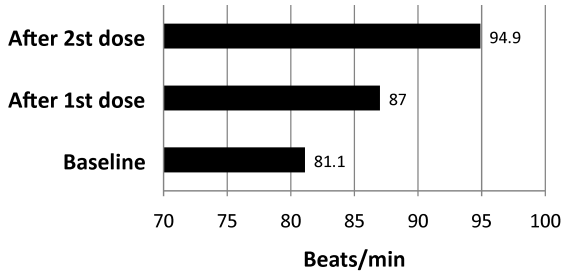

Figure 3. Mean heart rate for patients receiving two doses of methylprednisolone.

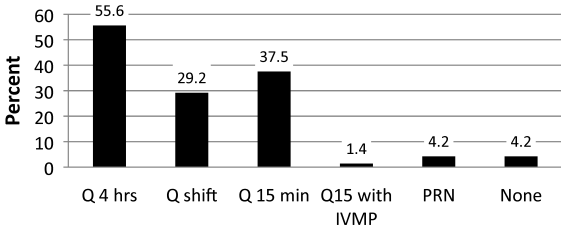

Figure 4. Orders for vital signs monitoring.

*Percentages do not equal 100% due to multiple orders per patient.

SBP. DBP changes were even greater with only 10% staying within 10% of their baseline.

A wide variation existed in both the monitoring frequency ordered and actual monitoring practices. Nurses consistently monitored the patients more frequently than ordered, which reflects nurses' assessment and judgment in patient care. In the current study sample, older pediatric patients and those with higher doses per kilogram of body weight appeared to have a greater risk of vital sign changes. Adult studies support that age may increase the risk of patients demonstrating vital sign changes during corticosteroid pulse therapy.[13,14] A literature review noted that few studies addressed nursing care to patients undergoing corticosteroid pulse therapy, and there is no consensus about the frequency of monitoring needed to maintain the safety of these patients. The authors emphasized the importance of standardized care to provide for early identification and treatment of the side effects of this therapy.[14] Care guidelines that address specific risk factors such as age and dosage may further support nurses in providing safe monitoring during corticosteroid therapy.

This study had a number of limitations, many related to the study design. Retrospective chart reviews allow no control over the data available. With this retrospective design, clinical significance of vital sign changes could not be determined. In addition, there was variability in the length of stay and the frequency of monitoring. Many children were discharged shortly after the infusion, while others stayed several days, contributing to the wide range of vital sign measurements available for analysis. The observation window ranged from 0 to 161 hours, with a mean of 20.8 hours. The literature suggests that complications could occur or persist up to 8 days after infusion.[5] Charts were reviewed for subsequent admissions. Readmissions for headache treatment were noted, but no IVMP infusion related complications were documented.

The infusion times varied and were not available for all patients. Cardiac arrhythmias, circulatory collapse, and/or cardiac arrest have been reported with rapid infusions of IVMP.[13] Shorter infusion times could possibly have a greater effect on vital sign changes, but this was not able to be evaluated. Administration guidelines from Lexicomp[15] recommend infusing low dose IVMP (<2 mg/kg up to 125 mg total) over 15 minutes; moderate dose (>2 mg/kg up to 500 mg) over 30 minutes; high dose (>15 mg/kg up to 1 g) over 60 minutes. As a result of this study, these guidelines have been added to the computerized order entry program at this hospital.

Concurrent medications administered to the sample during the study period posed additional limitations. Antihypertensive medications used as preventative headache treatment may have excluded some patients from the study. The most common concurrent medication was DHE. Significant increases in BP, life-threatening disturbances of cardiac rhythm, and death have been reported with DHE administration, although the incidence is extremely low.[16] In this institution, an order set includes vital sign monitoring during DHE infusions. Therefore, these patients had more vital signs ordered and recorded, with a greater opportunity to identify changes in HR and BP. Many other uncontrolled factors can contribute to changes in vital signs, such as family stress, fear of being in the hospital, missed school/work, fever, and pain.

These results suggest that monitoring of vital signs after IVMP infusions is part of providing safe care. Standard of care should balance patient safety, time requirement of nursing staff, and

overall healthcare expenses. There were frequent vital sign changes with a wide variation in the time of occurrence related to dose administration. No untoward effects were recorded. Practitioner judgment and practice guidelines will assist in setting a standard for the monitoring needed for these patients. A prospective study to evaluate the relationship of IVMP and patient safety is needed to further evaluate the monitoring frequency needed to identify clinically significant vital sign changes.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ACKNOWLEDGMENTS This study was presented as a Poster Presentation at 2 national conferences: American Association of Neuroscience Nurses, March 18, 2011, Kansas City, MO; Pediatric Pharmacy Advocacy Group, March 18, 2011, Memphis, TN.

ABBREVIATIONS BP, blood pressure; DBP, diastolic blood pressure; DHE, dihydroergotamine; HR, heart rate; IVMP, intravenous methylprednisolone infusions; SBP, systolic blood pressure

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