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Intravenous Hydralazine in Hospitalized Children and Adolescents with Hypertension

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Objectives To explore the efficacy and safety of intravenous (IV) hydralazine in hospitalized children with hypertension.

Study design Data were retrospectively collected on hospitalized children treated with IV hydralazine. Percent changes in blood pressure (BP) were calculated, and linear regression was used to investigate associations between BP change and pertinent clinical and demographic variables. Bivariate logistic regression was used to investigate associations between the same covariates and the outcomes of ideal clinical response (ICR), a 10%-25% reduction in mean arterial pressure (MAP), and excess response (ER), a 25% reduction in MAP.

Results A total of 141 initial doses of IV hydralazine (median dose, 0.10 mg/kg [IQR, 0.09-0.11; range, 0.02-0.37]) were analyzed. Median age was 8 years (IQR, 2-15; range, 0-24); most patients had renal disease, malignancy, or were organ transplant recipients. The mean MAP reduction was 19% ± 12%. An ICR occurred in 66 patients (47%). Higher initial MAP and increased hydralazine dose were associated with greater percentage decrease in MAP. No association was found between ICR and the covariates of interest; higher initial MAP was associated with greater odds of ICR. ER occurred in 44 children (31%). Among this group, higher initial MAP and higher hydralazine dose were associated with increased odds of ER, and administration of other antihypertensive drugs was associated with decreased odds of ER. Four adverse effects possibly related to IV hydralazine, including 2 episodes of hypotension, were recorded.

Conclusions IV hydralazine reduced BP in the majority of children. However, a substantial proportion of children experienced potentially excessive BP reduction. *(J Pediatr 2016;168:88-92)*.

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The Fourth Report on high blood pressure (BP) in children and adolescents[1] recommends prompt initiation of intravenous (IV) therapy for acute severe hypertension, defined as a symptomatic BP elevation well in excess of stage 2 hypertension (>99th percentile plus 5 mm Hg). In children, acute severe hypertension most often leads to encephalopathy, which may manifest with headache, nausea, vomiting, confusion, visual changes, altered mental status, seizure, focal neurologic deficits, and coma; if left untreated, it may result in cerebral infarction or hemorrhage.[2] Therefore, prompt therapy is indicated.

At present, there are no IV agents specifically labeled by the US Food and Drug Administration or other regulatory bodies for treatment of acute severe hypertension in children.[3] Most published treatment recommendations are based upon expert opinion and include a variety of agents, some given as intermittent IV boluses, and some by continuous infusions.[1-3] The most frequently recommended intermittently administered IV agents are labetalol and hydralazine. Hydralazine is a direct-acting vasodilator with an unknown mechanism of action, most likely an alteration of intracellular calcium metabolism, leading to vasodilatation and subsequent reduction in BP.[4,5]

Despite the literature recommendations for use of IV hydralazine for treatment of pediatric acute severe hypertension, there are few published data on its efficacy and safety, and the effective pediatric dose has never been established in a prospective clinical trial. A need exists for better information on pediatric dosing of this commonly used agent. As a first step toward better understanding of the role of IV hydralazine in treatment of acute severe hypertension in children, we conducted a single-center, retrospective study of the results of IV hydralazine administration to hospitalized children and adolescents with hypertension. The goals of the study were to establish the BP reduction produced by currently used doses of IV hydralazine, and to look for safety signals.

BP	Blood pressure
DBP	Diastolic blood pressure
ER	Excess response
ICR	Ideal clinical response
IV	Intravenous
MAP	Mean arterial pressure
SBP	Systolic blood pressure
SCH	Seattle Children's Hospital

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Methods

This was a single center retrospective observational study of IV hydralazine use at Seattle Children's Hospital (SCH) between February 2012 and June 2013, inclusive. Inclusion criteria included hospitalized patients receiving IV hydralazine in any SCH inpatient unit for treatment of acute BP elevations as determined by the treating clinicians, and availability of BP recordings in the SCH electronic medical record. Exclusion criteria were lack of BP readings within 6 hours of IV hydralazine (pre or post), and IV hydralazine given for a reason other than hypertension. Electronic pharmacy dispensing records were used to identify potentially eligible patients, and eligibility was confirmed by review of the medication administration record in the electronic medical record. A Research Electronic Data Capture (REDCap) database (http://www.project-redcap.org/) was created for data collection. The Institutional Review Board at SCH approved retrospective data collection for this study.

The extremity used for BP measurement was determined according to the patient's clinical status. Any available BP recording regardless of extremity used was accepted for inclusion in the study data collection. Oscillometric BP devices were used for BP determination throughout the hospital, with cuff sizes selected according to current consensus recommendations.[1]

We limited data collection to the initial IV hydralazine administration for each patient in an attempt to ensure consistency and extract clinically relevant data reflecting the BP response to IV hydralazine. From the electronic medical record we extracted demographic and clinical information, including age, sex, weight, primary diagnosis, IV hydralazine dose administered, BP, and heart rate immediately prior to IV hydralazine, all BP and accompanying heart rate values recorded within 6 hours after the dose, and use of concurrent chronic and acute anti-hypertensive medications, including any additional doses of IV hydralazine given within 6 hours after the first dose. The time between the first hydralazine dose and the lowest BP within 6 hours following IV hydralazine was calculated and used as the time to response in our analysis. The administered IV hydralazine dose in milligrams was divided by the patient weight in kilograms to determine the dose given in mg/kg. Electronic nursing documentation of events and new symptoms within 6 hours following the dose was reviewed to look for potential adverse effects of IV hydralazine.

Statistical Analyses

The primary outcomes were calculated as percent change between the most recent BP measurement prior to hydralazine administration and the lowest BP measurement within 6 hours following, for each BP measurement (mean arterial pressure [MAP], systolic BP [SBP], and diastolic BP [DBP]). Ideal clinical response (ICR) to hydralazine was defined as a 10%-25% BP decrease, and excess response (ER) was defined as any decrease greater than 25%. Demographic and clinical characteristics of the entire cohort were summarized using counts and percentages, except for pre-hydralazine heart rate and BP for which we calculated means and SDs. Means and 95% CI were calculated for percent change in MAP, SBP, and DBP both for the entire cohort and by prespecified demographic and clinical categories including age, race, diagnosis, hydralazine dose, and administration of other antihypertensive medications. CI were calculated for the percentage of patients experiencing an ICR for each BP outcome (MAP, SBP, and DBP).

Associations between percent change in BP and prespecified covariates were investigated using bivariate linear regression. Results were estimated separately for each BP outcome (as above). Covariates investigated included age (birth to 12 months, 1 to <6 years, 6 to <12 years, 12 years and older), sex, BP prior to administration of hydralazine, hydralazine dose (<0.08 mg/kg, 0.08-0.15 mg/kg, >0.15 mg/kg), administration of other antihypertensive drugs before hydralazine (yes/no), administration of other antihypertensive drugs after hydralazine (yes/no), and diagnosis (renal disease, renovascular disease, cardiac disease, malignancy, hematologic disorders, non-renal post-transplant, respiratory failure, other). Covariates found to be significant at the 0.1 level of significance were further investigated in multivariable models. Bivariate logistic regression was used to investigate associations between an ICR for each outcome and the same covariates, as well as between ER for each BP outcome and the same covariates. Overall significance of categorical variables in multivariable models was assessed using likelihood ratio tests.

All testing was 2-sided and conducted at the 0.05 level of significance. All statistical analyses were performed using Stata ver. 12 (StataCorp., College Station, Texas).

Results

A total of 141 first doses of IV hydralazine given during the time frame above were analyzed. Demographic and clinical characteristics of the cohort are summarized in **Table I**. Median age was 8 years (IQR 2-15 years, range 0-24 years). The most common diagnosis was non-renal organ transplant (39), followed by renal disease (27), malignancy (23), respiratory failure (8), and cardiac disease (8). Before hydralazine administration, 76 children were receiving other antihypertensive medications. The most commonly used classes of antihypertensive agents included calcium channel blockers, diuretics, and angiotensin converting enzyme inhibitors.

Mean (SD) BP prior to hydralazine was 102 (15) mmHg for MAP, 140 (20) mmHg for SBP, and 86 (16) mmHg for DBP. The median first dose of IV hydralazine was 0.10 mg/kg (IQR 0.09-0.11 mg/kg, range 0.02-0.37 mg/kg).

Post-hydralazine mean (SD) BP reduction was 19% (12%) for MAP, 16% (10%) for SBP, and 22% (15%) for DBP (**Table II**). The distribution of change in MAP following hydralazine administration is illustrated in the **Figure**;