Isradipine treatment of acute hypertension in hospitalized pediatric patients

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Outline

- Background/Motivation
- Aims
- Methods
- Results
- Conclusion/Discussion

Background

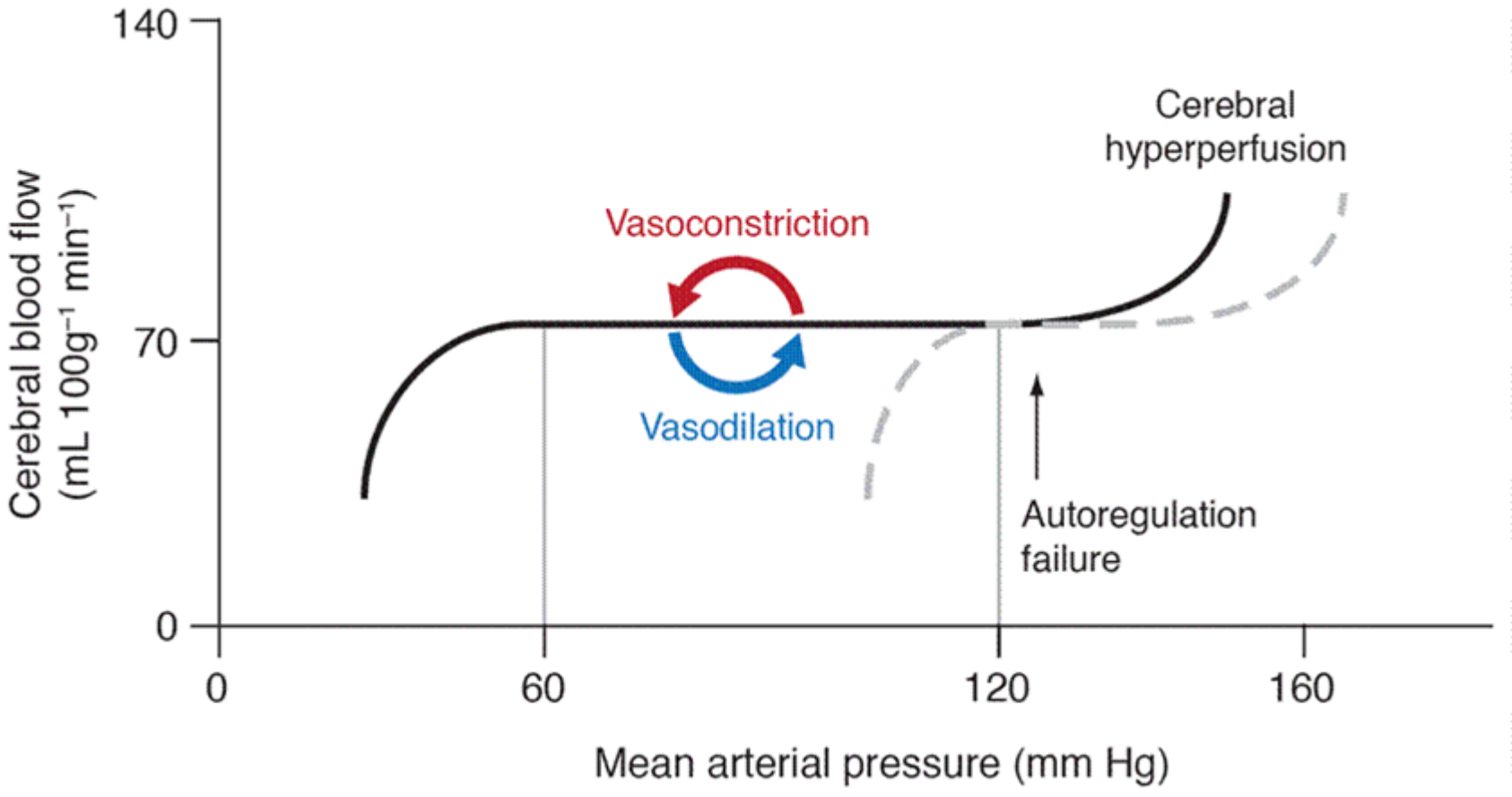
- Severe uncontrolled hypertension (HTN) most often leads to encephalopathy
  - Headache
  - Nausea/vomiting
  - Visual changes
  - Altered mental status
  - Seizure
  - Coma
  - Cerebral infarction/hemorrhage
- Prompt therapy is indicated

Therapy for acute hypertension

- There are a number of oral and IV medication recommended for acute HTN
- For patients with acute HTN with no evidence of end-organ damage, who can take oral medication, isradpine is one of a number of choices

Risk of acute blood pressure decrease

Altered cerebral autoregulation in chronic hypertension



Flynn and Tullus, Pediatr Nephrol 2008

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Short Acting Nifedipine vs. Isradipine

SA Nifedipine

- Traditionally a preferred oral agent for in pediatrics
- Contraindicated in adults
- Literature on pediatric use controversial
- Difficult to dose accurately in infants and toddlers

Isradipine

- Characteristics
  - Initial onset of action in approximately 1 hour
  - Peak serum concentration in 1-3 hours
  - Peak response in 2-3 hours
- Suspension can be made from powder from capsule
- One adult study showing efficacy in acute HTN

Aims

1. To investigate the effect on blood pressure from use of isradipine for acute HTN
   a. Blood pressure change after a dose of isradipine
   b. Identification of patient characteristics that may alter the effectiveness of isradipine
2. To describe potential adverse events following isradipine dosage including:
   a. increase in heart rate
   b. mean arterial pressure (MAP) drop > 25%
   c. other documented events

Methods

- A single center retrospective observational study
- Inclusion criteria
  - Seattle Children's Hospital inpatient and ED patients
  - Received isradipine for acute hypertension from 1/1/2006 to 12/31/2007
  - Only the first dose analyzed
- Exclusion criteria
  - No BP recording within 6 hours of isradipine
  - Isradipine given for a reason other than acute hypertension
- IRB approval obtained for data collection

Variables Collected

- Patient characteristics: age, gender, weight, diagnosis
- Formulation (capsule vs. suspension)
- BP and pulse just prior to isradipine
- Lowest BP and concurrent pulse within 6 hours of dose
- Time of the lowest BP recording
- Use of other anti-hypertensive medication
- Adverse events documented in nursing records within 6 hours of the dose

Statistical analysis

- Primary Analysis
  - Descriptive statistics and paired t-test on BP change and pulse
- Secondary analysis
  - Multiple linear regression to identify potential predictors on efficacy
  - Rank-sum test for adverse effects including MAP decrease > 25%
- STATA X, College Station, TX

Patient characteristics (N = 391)

Gender	Male			Female	
	225 (58%)			166 (42%)	
Age (years)	0 - < 2	2 - < 12		12 - < 17	≥ 17
	34 (9%)	127 (32%)		167 (43%)	63 (16%)
Dose (mg/kg)	0 – 0.05		0.05 – 0.1		≥ 0.1
	54 (14%)		234 (60%)		103 (26%)
Diagnosis	Renal	Non-renal Tx	Oncologic	Neurologic	Others
	232 (59%)	54 (14%)	56 (14%)	22 (6%)	27 (7%)
Formulation	Capsule			Suspension	
	247 (63%)			144 (37%)	
Chronic BP meds	No			Yes	
	192 (49%)			199 (51%)	
Additional acute BP meds	No			Yes	
	273 (70%)			118 (30%)	

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Overall BP response

	Median % decrease in BP (IQR)	p-value (paired t-test)	Median time of lowest BP (hours) (IQR)
SBP	15.9 (8.2, 22.8)	< 0.0001	2.5 (1.5, 4)
DBP	24.7 (12.9, 35.7)	< 0.0001	

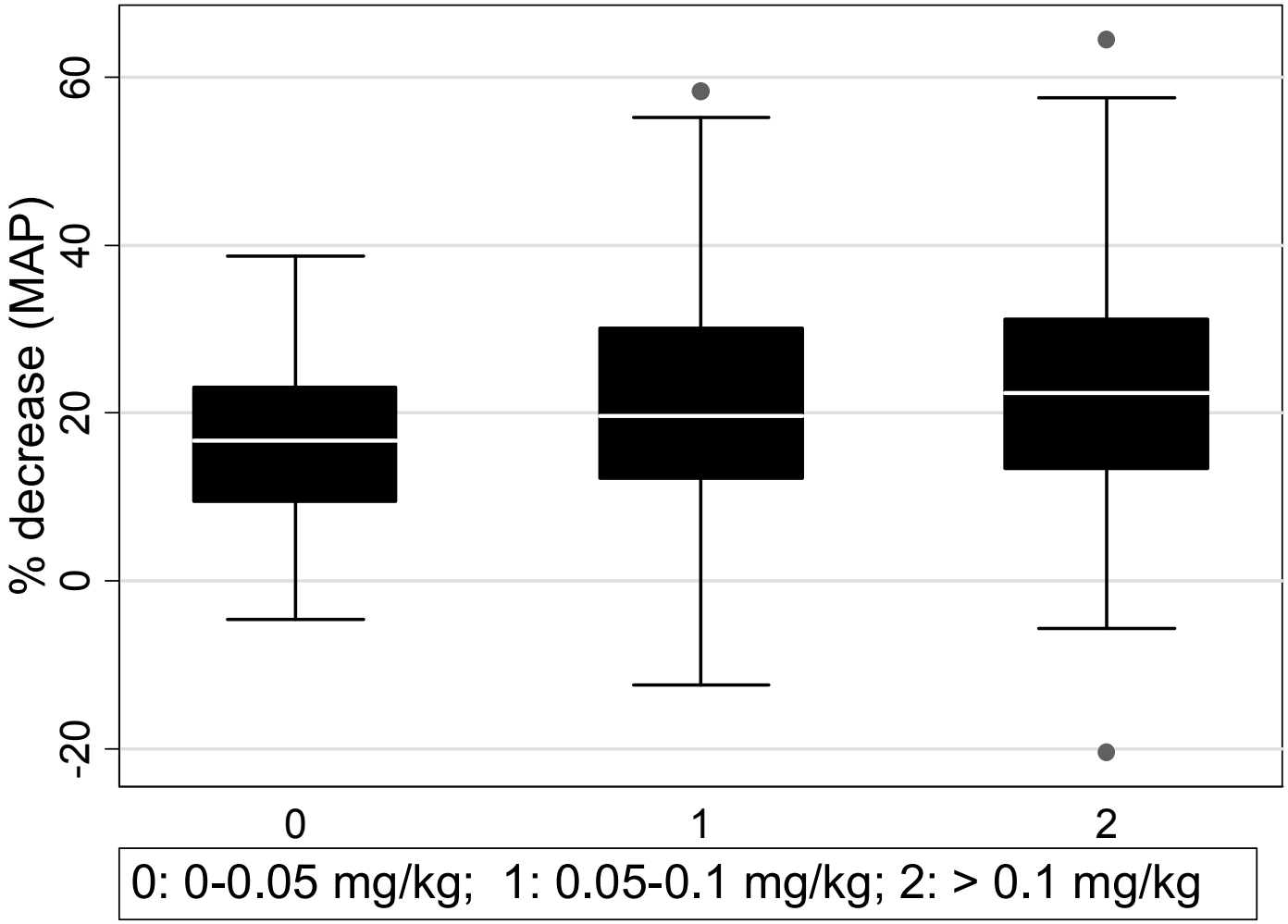
Stratified analysis

Renal disease ($p < 0.001$) and neurologic disease ($p = .03$) were associated with less MAP decrease, while non-renal transplant ($p = 0.009$) and oncologic disease ($p=0.002$) were associated with greater MAP decrease

Stratified by diagnosis	
Diagnosis	Median % decrease in MAP (IQR)
Renal	19.4 (10.1, 27.8)
Non-renal Tx	23.7 (13.9, 40.0)
Oncologic	21.7 (14.7, 33.2)
Neurologic	16.9 (10.3, 23.7)
Others	23.2 (12.2, 33.1)

Stratified by age	
Age group (years)	Median % decrease in MAP (IQR)
0 - < 2	24.0 (10.9, 30.9)
2- < 12	21.6 (13.4, 37.7)
12- < 17	18.1 (9.8, 27.7)
≥ 17	19.8 (12.3, 35.6)

Box plot of % decrease in MAP stratified by dose size (mg/kg)



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Effect on heart rate

		Median pulse increase (per min) (IQR)	p (paired t-test)
All doses		6 (-4, 16)	< 0.0001
Dose categories (mg/kg)	≤ 0.05	4 (-7, 10)	0.24
	0.05 – 0.1	6 (-3, 16)	< 0.0001
	> 0.1	6 (-5, 20)	< 0.0001
Age categories (years)	0 - < 2	2, (-11, 11)	0.48
	2 - < 12	6 (-4, 17)	0.0001
	12 - < 17	8 (-2, 20)	< 0.0001
	≥ 17	4 (-2, 12)	0.014

Documented events

There were 40 adverse events reported in 33 patients

Events	Frequency
Emesis	8
Headache	8
Nausea	5
Hypotension requiring intervention	4
Flushing/feeling hot	3
Dizziness/lightheadedness	3
Palpitations	2
Hypotension, abd pain, PVC, chest pain, irritability, confusion, itchiness	1 each

All 5 patients with hypotension were on azole antifungal

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Other adverse events

- Statistically significant difference in dose size for doses with MAP decrease > 25% vs. doses with MAP decrease < 25 %
  - 0.09 mg/kg vs. 0.08 mg/kg (p = 0.009, Mann-Whitney)
- MAP decrease > 25% most often observed in the 2 youngest age groups
- No significant association between:
  - adverse events and dose size (p = 0.21, Mann-Whitney)
  - Adverse events and MAP decrease > 25% (p = 0.12, Mann-Whitney)

Conclusions

- Isradipine lowered BP in a wide variety of patients
- BP response for individual doses quite variable
- Lower starting dose (0.05 mg/kg) may be needed for younger patients
- Change in heart rate likely clinically insignificant
- Adverse events were not necessarily dose dependent or associated with MAP decrease > 25%

Limitations

- Single center retrospective observational study with no control group
- Lowest recorded BP may not be completely representative of the efficacy
- Documented adverse events incomplete
- All potential confounders likely unaccounted

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Questions/comments?

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5 patients documented to have hypotension

Age (years)	Diagnosis	Dose (mg) (mg/kg)	Formulation	Change in pulse	Other BP meds	Intervention
18	Oncologic	10 (0.11)	Capsule	16	Hydralazine 10 mg	NS bolus
15	Oncologic	2.5 (0.06)	Capsule	48	None	NS bolus and dopamine
15	Non-renal Tx	4.8 (0.1)	Suspension	4	None	NS bolus
11	Oncologic	3.5 (0.1)	Suspension	24	None	NS bolus
14	Renal	5 (0.07)	Capsule	20	Enalapril	None

*All 5 patients on fluconazole or voriconazole

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Multiple linear regression

- Baseline model
  - Dependent variable: post-MAP
  - Independent variable: dose (mg), weight (kg), pre-MAP
- Models to test for significance
  - Introduce patient characteristics and examine the p-value of the coefficient on the variable introduced in the model

With no repeat patients (N=282)

	Median % decrease in BP (IQR)	Mean pre-BP (mm Hg)	Mean post-BP (mm Hg)	p-value (paired t-test)	Median time of lowest BP (hours) (IQR)
SBP	15.9 (7.9, 22.9)	146.7	122.5	< 0.0001	2.5 (1.5, 4)
DBP	23.8 (12.2, 34.9)	90.1	67.6	< 0.0001	

N = 282

	Median % decrease in BP (IQR)	Mean pre-BP (mm Hg)	Mean post-BP (mm Hg)	p-value (paired t-test)	Median time of lowest BP (hours) (IQR)
SBP	15.9 (8.2, 22.8)	146.6	122.2	< 0.0001	2.5 (1.5, 4)
DBP	24.7 (12.9, 35.7)	91.4	68.5	< 0.0001	

N = 391