

Intraoperative Hypotension and Long-term Neurodevelopmental Outcomes in Children Undergoing Inpatient Surgery

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Introduction: Recent meta-analyses evaluating children following surgery and anesthesia have reported worse outcomes in some neurodevelopmental domains. [1, 2] There are a number of hypothesized reasons for these differences besides the anesthetic exposure including intraoperative hypotension, which has been associated with adverse outcomes in adult populations.[3-7] The purpose of this retrospective observational study was to explore the association between intraoperative hemodynamics and subsequent neurodevelopmental disorders, evaluating whether an increased risk of mental disorder diagnoses (MDD) will be seen in children with the lowest intraoperative blood pressures during inpatient surgery.

Methods: A retrospective observational study was performed including children ≥ 28 days and <18 years with intraoperative electronic anesthetic records between January 1, 2009, and April 30, 2017, who underwent inpatient surgery at our institution. Hospital and physician records were also evaluated with International Classification of Disease, Ninth revision, (ICD-9), and Tenth revision (ICD-10) diagnosis codes used to identify medical conditions prior surgery including baseline MDD. Children with prior MDD, who had a gap of >10 minutes in intraoperative blood pressure, were missing gas analyzer data, or who had multiple anesthetic records were excluded from analysis. The remaining children were categorized based on their mean intraoperative mean arterial pressure (MAP) relative to other children of the same sex and similar age: category 1 (very low) included children with the lowest blood pressures, with mean MAP value <10 th percentile, category 2 (low) with mean MAP ≥ 10 th and <25 th percentiles, category 3 (reference) with mean MAP ≥ 25 th and <75 th percentiles, category 4 (high) with mean MAP ≥ 75 th and <90 th percentile, and category 5 (very high) with the highest blood pressures, with mean MAP ≥ 90 th percentile. Cumulative probabilities of time to MDD diagnosis stratified by intraoperative blood pressure category were evaluated. Cox proportional hazard regression models adjusting for covariates including demographic characteristics, intraoperative covariates (ASA status, procedure type, anesthetic duration, technique, agents, and airway type), end-tidal CO₂, cardiopulmonary bypass, and presence of any chronic conditions were then performed to evaluate the hazard of subsequent MDD in each intraoperative blood pressure category. All analyses were performed using SAS 9.4.

Results: A total of 6533 children received anesthesia for inpatient surgery. The median duration of anesthesia was 141.5 minutes (IQR 81.5-237.5). The blood pressure thresholds for classification into each category can be seen in Table 1. Differences in ethnicity, ASA status, chronic conditions, and procedure type based on blood pressure category were observed (Table 2) Unadjusted cumulative probability curves reported an increased probability of MDD in the children in the lowest blood pressure category approximately 1 year after the procedure. (Figure 1) In unadjusted analyses, compared to the reference category (mean MAP ≥ 25 th and <75 th percentiles) children in the lowest blood pressure category (mean MAP <10 th percentile) had an elevated risk of MDD (HR, 1.53; [95% CI, 1.07-2.19]). (Table 3) While these differences persisted after adjusting for demographic characteristics, they were no longer statistically significant after adjustment for demographic and clinical characteristics including ASA status, procedure type, and comorbidities (HR, 1.26; [95% CI, 0.86-1.825]). Statistically significant differences were not seen in any other blood pressure category relative to the reference category.

Conclusions: While an increased risk of MDD was observed in children with the lowest intraoperative blood pressures in unadjusted analyses, after adjustment for demographic and clinical characteristics, the differences were no longer observed. This suggests that the higher levels of MDD in children with lower blood pressures may stem from baseline comorbidity and surgical complexity. However, given the uncertainty regarding what constitutes hypotension in pediatric patients, significant differences may be seen when evaluating other blood pressure thresholds or when evaluating larger cohorts of children.

Figure 1: Cumulative probability of Mental Disorder Diagnosis by Intraoperative Blood Pressure Category

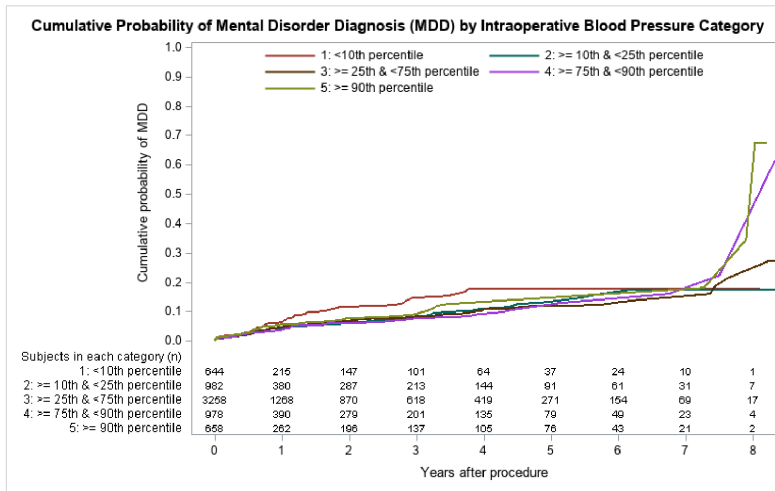


Table 1: Mean intraoperative MAP categories.

Age	Sex	n	Mean intraoperative MAP values (mmHg)				
			10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
≥28 days to <3 months	Female	195	39.5	43.7	48.7	54.8	62.0
	Male	379	39.3	42.9	49.2	54.9	61.3
≥3 to <6 months	Female	190	44.2	47.9	52.5	57.7	63.3
	Male	284	43.4	47.3	53.0	58.6	64.3
≥6 months to <1 year	Female	165	47.4	50.9	55.9	62.6	69.4
	Male	179	45.2	50.6	55.9	61.0	66.4
≥1 to <2 years	Female	225	49.6	52.7	57.2	62.4	67.7
	Male	220	49.4	52.3	56.5	61.9	68.0
≥2 to <4 years	Female	339	50.1	54.4	58.9	64.5	69.7
	Male	341	50.7	54.8	59.3	64.2	70.4
≥4 to <6 years	Female	240	52.1	55.8	60.4	66.2	72.3
	Male	287	51.9	54.9	61.5	67.9	76.0
≥6 to <9 years	Female	284	55.2	59.1	64.9	71.1	80.0
	Male	344	54.8	59.4	65.6	73.0	79.1
≥9 to <12 years	Female	344	58.4	63.2	68.3	74.9	80.9
	Male	417	58.5	63.1	69.7	74.7	80.6
≥12 to <15 years	Female	494	60.3	63.7	69.3	74.5	80.8
	Male	498	60.5	65.0	69.9	75.4	81.5
≥15 to <18 years	Female	579	60.3	64.7	69.6	76.1	82.0
	Male	529	61.7	66.1	71.1	77.5	84.4

Mean intraoperative MAP categories:	1: Very Low	2: Low	3: Reference	4: High	5: Very High
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Table 2: Selected Patient Characteristics

		Blood Pressure Category				
		<10th percentile n (%)	≥10th & <25th percentiles n (%)	≥25th & <75th percentiles n (%)	≥75th & <90th percentiles n (%)	≥90th percentile n (%)
Sex	Female	303 (46.8)	459 (46.7)	1526 (46.8)	458 (46.7)	309 (46.8)
	Male	345 (53.2)	523 (53.3)	1737 (53.2)	522 (53.3)	351 (53.2)
Race	Asian	19 (2.9)	31 (3.2)	88 (2.7)	21 (2.1)	16 (2.4)
	Black	44 (6.8)	63 (6.4)	232 (7.1)	78 (8)	54 (8.2)
	WHITE	203 (31.3)	342 (34.8)	1245 (38.2)	354 (36.1)	209 (31.7)
	Declined/Unknown	382 (59)	546 (55.6)	1698 (52)	527 (53.8)	381 (57.7)
Ethnicity	Hispanic	80 (12.4)	117 (11.9)	536 (16.4)	207 (21.1)	122 (18.5)
	Non-Hispanic	190 (29.3)	303 (30.9)	954 (29.2)	266 (27.1)	166 (25.2)
	Declined/Unknown	378 (58.3)	562 (57.2)	1773 (54.3)	507 (51.7)	372 (56.4)
ASA Status	1	132 (20.4)	199 (20.3)	876 (26.9)	296 (30.2)	186 (28.2)
	2	290 (44.8)	413 (42.1)	1377 (42.2)	438 (44.7)	277 (42)
	3	197 (30.4)	303 (30.9)	830 (25.4)	194 (19.8)	155 (23.5)
	4 or 5	29 (4.5)	67 (6.8)	180 (5.5)	52 (5.3)	42 (6.4)
Chronic Conditions	Congenital genetic	49 (7.6)	53 (5.4)	224 (6.9)	40 (4.1)	25 (3.8)
	Cardiovascular	239 (36.9)	365 (37.2)	903 (27.7)	202 (20.6)	136 (20.6)
	Gastrointestinal disease	30 (4.6)	53 (5.4)	152 (4.7)	64 (6.5)	40 (6.1)
	Hematological/Immunologic	15 (2.3)	29 (3)	73 (2.2)	25 (2.6)	18 (2.7)
	Malignancy	25 (3.9)	39 (4)	124 (3.8)	31 (3.2)	28 (4.2)
	Metabolic	16 (2.5)	20 (2)	97 (3)	25 (2.6)	28 (4.2)
	Neonatal	37 (5.7)	26 (2.7)	66 (2)	21 (2.1)	18 (2.7)
	Neuromuscular	44 (6.8)	73 (7.4)	245 (7.5)	75 (7.7)	43 (6.5)
	Renal	26 (4)	28 (2.9)	110 (3.4)	35 (3.6)	21 (3.2)
	Respiratory	24 (3.7)	37 (3.8)	141 (4.3)	57 (5.8)	34 (5.2)
	Technology dependence	24 (3.7)	50 (5.1)	110 (3.4)	33 (3.4)	24 (3.6)
	Organ transplant	5 (0.8)	4 (0.4)	14 (0.4)	3 (0.3)	3 (0.5)
	Scoliosis	22 (3.4)	57 (5.8)	319 (9.8)	75 (7.7)	42 (6.4)
Procedure Type	Brain procedure	12 (1.9)	17 (1.7)	57 (1.8)	17 (1.7)	9 (1.4)
	Endocrine procedure	8 (1.2)	10 (1)	25 (0.8)	4 (0.4)	7 (1.1)
	Urology procedure	20 (3.1)	36 (3.7)	107 (3.3)	28 (2.9)	24 (3.6)
	Gynecological procedure	5 (0.8)	8 (0.8)	27 (0.8)	14 (1.4)	5 (0.8)
	Ophthalmologic procedure	5 (0.8)	9 (0.9)	27 (0.8)	3 (0.3)	4 (0.6)
	Musculoskeletal procedure	104 (16.1)	140 (14.3)	460 (14.1)	102 (10.4)	42 (6.4)
	Skin procedure	14 (2.2)	22 (2.2)	103 (3.2)	29 (3)	22 (3.3)
	Organ transplant	2 (0.3)	-	5 (0.2)	-	-
	Diagnostic imaging procedure	25 (3.9)	37 (3.8)	63 (1.9)	10 (1)	6 (0.9)
	Oral/otolaryngologic procedure	27 (4.2)	52 (5.3)	245 (7.5)	119 (12.1)	97 (14.7)
	Vertebral procedure	16 (2.5)	53 (5.4)	349 (10.7)	85 (8.7)	38 (5.8)
	Respiratory system procedure	22 (3.4)	27 (2.8)	114 (3.5)	42 (4.3)	28 (4.2)
	Misc. spine procedure	6 (0.9)	8 (0.8)	60 (1.8)	17 (1.7)	11 (1.7)
	Cardiac open heart procedure	152 (23.5)	252 (25.7)	600 (18.4)	89 (9.1)	78 (11.8)
	Cardiac non-open heart procedure	57 (8.8)	95 (9.7)	193 (5.9)	49 (5)	25 (3.8)
	Vascular procedure	32 (4.9)	42 (4.3)	72 (2.2)	20 (2)	14 (2.1)
	Hematologic procedure	12 (1.9)	21 (2.1)	27 (0.8)	9 (0.9)	7 (1.1)
	Upper GI procedure, Endoscopic	19 (2.9)	14 (1.4)	39 (1.2)	15 (1.5)	11 (1.7)
	GI procedure, Non-endoscopic	44 (6.8)	63 (6.4)	477 (14.6)	267 (27.2)	188 (28.5)
	Miscellaneous GI procedure	23 (3.6)	40 (4.1)	140 (4.3)	51 (5.2)	36 (5.5)
	Hernia repairs	43 (6.6)	36 (3.7)	73 (2.2)	10 (1)	8 (1.2)

Table 3: Hazard Ratios for Mental Disorder Diagnoses Associated with MAP Category, MAP as Continuous Variable, and Time Under Threshold

Exposure	n	<u>Unadjusted Hazard Ratio</u>		<u>Adjusted Hazard Ratio*</u>		<u>Adjusted Hazard Ratio**</u>	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
MAP Category							
1: Very Low	644	1.53 (1.07, 2.19)	0.02	1.51 (1.06, 2.16)	0.02	1.26 (0.86, 1.82)	0.23
2: Low	982	1.06 (0.76, 1.47)	0.73	1.05 (0.76, 1.46)	0.76	1.03 (0.73, 1.43)	0.88
3: Reference	3258	-		-		-	
4: High	978	0.97 (0.69, 1.36)	0.84	0.95 (0.68, 1.34)	0.78	0.93 (0.65, 1.32)	0.68
5: Very High	658	1.17 (0.81, 1.69)	0.39	1.15 (0.79, 1.66)	0.46	1.08 (0.74, 1.58)	0.69

HRs compared each blood pressure category to the “Reference” category in the same statistical model.

*Adjusted for gender, race, and ethnicity.

**Primary analysis adjusted for gender, race, ethnicity, ASA status, procedure type, cardiovascular comorbidity, other comorbidity.