Use of combination pulmonary vasodilator therapy in pediatric patients with bronchopulmonary dysplasia and pulmonary hypertension

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Background

Bronchopulmonary dysplasia (BPD) is a serious complication of prematurity, with multifactorial associations.[1] Associated alveolar diffusion impairment, abnormal vascular remodeling, and pulmonary vascular growth arrest results in pulmonary hypertension (PH) in about 25% of infants with moderate to severe BPD with these infants demonstrating worse physical growth, neurodevelopmental, and survival outcomes, higher rates of tracheostomy, increased use of supplemental oxygen, feeding problems, and frequent hospitalizations. [2-11]

Pharmacotherapy targeting the prostacyclin pathway, the nitric oxide pathway, and the endothelin pathway is administered to induce pulmonary vasodilation, decreasing pressure in the right ventricle in attempts to avoid right heart failure. [12-13] The phosphodiesterase-5 inhibitors (PDE5i) are frequently the first line in contemporary BPD PH therapy, demonstrating improvement in pulmonary vascular resistance and functional class.[14-18] The FDA has also approved the PDE5i tadalafil for the treatment of PH based on studies that have shown long term tolerance and efficacy in pediatric PH populations.[19-23] The use of non-selective endothelin A- and B-receptor antagonists (ERAs) like bosentan have also found support in studies such as the FUTURE-1 trial through improvement in hemodynamics and functional status class. [24-25]

Progressive disease often necessitates combination therapy, a practice that has been widely adopted in the clinical setting.[26] Meta-analyses and trials on combination therapy compared to monotherapy in adults have previously demonstrated improvement in exercise capacity, hemodynamics, and reduction of risk of clinical worsening and failure.[27-29] In the treatment of infants with BPD PH, sildenafil and bosentan, alone and in combination, are frequently used.[30-31] Evidence has shown that combination therapy is independently associated with improved survival as compared with single-agent therapy.[32] However, there is limited data published and gaps in translation to clinical practice for the use of combination therapy (utilizing multiple drug classes) in PH secondary to BPD.

Objectives

This study aims to describe the effects of combination pulmonary vasodilator therapy in children with PH secondary to BPD in comparison with monotherapy on specific echocardiogram parameters.

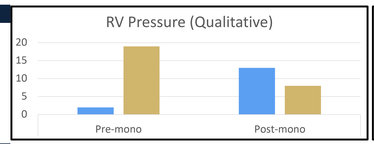
Project Design

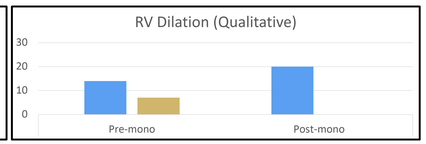
This retrospective study compares neonates with PH secondary to BPD started in the first year of life on single pulmonary vasodilator therapy with those on combination therapy. Data was obtained by identification of medication orders between 01/2010 to 11/2021 through TheraDoc and Epic Electronic Health Record system for Johns Hopkins All Children's Hospital. Demographic, therapeutic, and diagnostic data were obtained through chart review and analyzed using mean, fisher's exact test, and two-tailed paired and unpaired t-tests.

Monotherapy consists of those on sildenafil, combination therapy consists of those on sildenafil or tadalafil and bosentan, plus or minus a prostacyclin analogue (PCA) (treprostenil). Parameters include right ventricular pressure (RVP), right ventricular dilation (RVD), right ventricular function depression (RVFd), tricuspid regurgitation (TR). Baseline data was from immediately prior to initiation of PH therapy. Subsequent data was obtained after medication addition and steady state dosing reached. Infants without BPD, with complex congenital heart defects, with congenital diaphragmatic hernia, without data, or with therapy started after 365 days were excluded.

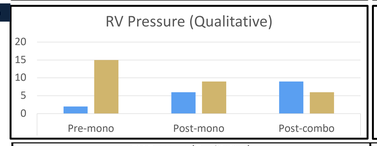
Results: Echocardiography Data

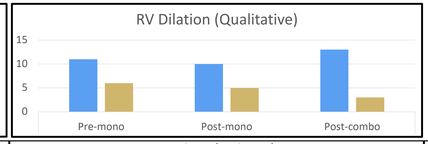
Monotherapy Group





Combo Therapy Group





	RV Pressure (Qualitative)					RV Dilation (Qualitative)					RV Function Depression (Qualitative)					TR (Qualitative)				
	Category	Score*	Baseline	Post-mono	Post-combo	Category	Score*	Baseline	Post-mono	Post-combo	Category	Score*	Baseline	Post-mono	Post-combo	Category	Score*	Baseline	Post-mono	Post-combo
Monotherapy Group																				
	≤ 1/2 systemic (n)	0 to 1	2	13		Normal to Mild (n)	0 to 2	14	20		Normal to Mild (n)	0 to 2	21	21		None to Mild (n)	0 to 2	18	20	
	> 1/2 systemic (n)	2 to 4	19	8		Mild-moderate to Severe (n)	3 to 6	7	0		Moderate to Severe (n)	3 to 4	0	0		Moderate to Severe (n)	3 to 6	2	1	
	> 1/2 systemic (%)		90%	38%		Mild-moderate to Severe (%)		33%	0%		Moderate to Severe (%)		0%	0%		Moderate to Severe (%)		10%	5%	
Difference				52%					33%					0%					5%	
P-value				0.0090					0.0086					1.0000					0.6060	
Combo Therapy Group																				
	≤ 1/2 systemic (n)	0 to 1	2	6	9	Normal to Mild (n)	0 to 2	11	10	13	Normal to Mild (n)	0 to 2	16	15	16	None to Mild (n)	0 to 2	15	14	15
	> 1/2 systemic (n)	2 to 4	15	9	6	Mild-moderate to Severe (n)	3 to 6	6	5	3	Moderate to Severe (n)	3 to 4	1	0	0	Moderate to Severe (n)	3 to 6	1	2	1
%	> 1/2 systemic (%)		88%	60%	40%	Mild-moderate to Severe (%)		35%	33%	19%	Moderate to Severe (%)		6%	0%	0%	Moderate to Severe (%)		6%	13%	6%
Difference					48%					17%					6%					0%
P-value				0.1058	0.0080				0.9072	0.4384				1.0000	1.0000				1.0000	1.0000

Comparison Data										
		Pre-therapy	Post-therapy		Pre-therapy	Post-therapy		Pre-therapy	Post-therapy		Pre-therapy	Post-therapy
P-value		1.0000	1.0000		1.0000	0.0784		0.4595	1.0000		1.0000	1.0000

*<1/2 systemic (0), 1/2 systemic (1), > 1/2 systemic (2), systemic (3), supra-systemic (4)

*normal (0), borderline (1) mild (2), mild-moderate (3) moderate (4), moderate-severe (5), severe (6)

*normal (0), borderline (1), mild (2), moderate (3), severe (4)

*none (0), trivial (1), mild (2), mild-moderate (3), moderate (4), moderate-severe (5), severe (6)

Results: Baseline Characteristics

		Mono Therapy	Combo Therapy
Total Sample: included/total		21/523	17/44
%		4.0	63.0
Sex (n)	Female	8	7
Race	Black	14	9
	White	5	7
	Asian	1	0
Ethnicity	Hispanic	1	2
	Non-Hispanic	20	14
Gestational Age (days)	Mean	26.7	26
	Comparative P-value	0.5237	
Birth weight (kg)	Mean	0.9	0.9
	Comparative P-value	0.9563	
Deceased (days)	Mean age of death	438	349
Structural Cardiac Diagnoses (n)	PDA	17	9
	PFO	7	6
	ASD	6	4
	VSD	5	3
	Coarctation	0	1
	PAPVR	1	0
	PPS	0	1
Renal disease (n)		1	1
Tracheostomy (n)		5	4
Sildenafil data (n)		21	7
	Initiation of therapy with sildenafil (n)		6
	Age at initiation, Mean (days)	129	157
	Initiation dose, Mean (mg/kg/day)	2.7	8.3
	Maximum dose, Mean (mg/kg/day)	6.6	7.1
Tadalafil data (n)			10
	Initiation of therapy with tadalafil (n)		9
	Age at initiation, Mean (days)		161
	Initiation dose, Mean (mg/kg/day)		4
	Maximum dose, Mean (mg/kg/day)		8.2
Bosentan data (n)			9
	Age at initiation, Mean (days)		212
	Initiation dose, Mean (mg/kg/day)		2.4
	Maximum dose, Mean (mg/kg/day)		3.8
Treprostenil data (n)			4
	Age at initiation, Mean (days)		166
	Initiation dose, Mean (mg/kg/day)		1
	Maximum dose, Mean (mg/kg/day)		15.3

Conclusion

The development of PH in children with BPD is associated with significant mortality and morbidity. The use of pulmonary vasodilators improves pulmonary artery (PA) pressure and may help improve outcomes. Some children with significant PH may have an insufficient response to first line monotherapy (traditionally PDE5i) and may require additional agents (such as ERAs or PCAs) to improve PA pressure and RVP. Analysis of baseline data such as gestational age, birth weight, did not demonstrated significant difference between the monotherapy and combination group. There was similarly no significant difference in concurrent therapy in the form of oxygen delivery and medications within the groups pre-therapy and post therapy and across groups pre-therapy and post-therapy.

The data shows that a significant improvement in RVP can be achieved in many infants with PH secondary to BPD, but it may require multiple agents for a subset of these patients. The baseline distribution of severity scores was not significantly different between those patients that needed only one medication versus those requiring multiple pulmonary vasodilators. More information is needed to continue better understanding risk factors for needing multiple PH targeted medications.

Good progress has been made in the past few decades in treatment of pediatric PH. A limitation to broadly extrapolating this data is the single center retrospective nature of this study. Further multi-institutional or prospective may help add more insights to risk factors and better therapeutic strategies for this challenging disease.

References

1. Allen J, Zwerdling R, Ehrenkranz R, et al. Statement on the care of the child with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med.* 2003;168(3):356-396. doi:10.1164/rccm.168.3.356
2. Lignelli E, Palumbo F, Myti D, Morty RE. Recent advances in our understanding of the mechanisms of lung alveolarization and bronchopulmonary dysplasia. *Am J Physiol Lung Cell Mol Physiol.* 2019;317(6):L832-L887. doi:10.1152/ajplung.00369.2019
3. Steinmann CG, Asnes JD, Bazzy-Asaad A, Tolomeo C, Ehrenkranz RA, Bizzarro MJ. Pulmonary hypertension in preterm infants: results of a prospective screening program. *J Perinatol.* 2017;37(5):572-577. doi:10.1038/jp.2016.255
4. Mourani PM, Sontag MK, Younoszai A, et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2015;191(1):87-95. doi:10.1164/rccm.201409-1594OC
5. Nakanishi H, Uchiyama A, Kusuda S. Impact of pulmonary hypertension on neurodevelopmental outcome in preterm infants with bronchopulmonary dysplasia: a cohort study. *J Perinatol.* 2016;36(10):890-896. doi:10.1038/jp.2016.108
6. Choi EK, Shin SH, Kim EK, Kim HS. Developmental outcomes of preterm infants with bronchopulmonary dysplasia-associated pulmonary hypertension at 18-24 months of corrected age. *BMC Pediatr.* 2019;19(1):26. Published 2019 Jan 17. doi:10.1186/s12887-019-1400-3
7. Lagatta JM, Hysinger EB, Zaniletti I, et al. The Impact of Pulmonary Hypertension in Preterm Infants with Severe Bronchopulmonary Dysplasia through 1 Year. *J Pediatr.* 2018;200:218-224.e3. doi:10.1016/j.jpeds.2018.07.035
8. Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics.* 2007;120(6):1260-1269. doi:10.1542/peds.2007-0971
9. Alhi G, Bhombal S, Feinstein J, Hopper RK, Tacy TA. Diminished right ventricular function at diagnosis of pulmonary hypertension is associated with mortality in bronchopulmonary dysplasia. *Pulm Circ.* 2019;9(3):2045894019878598. Published 2019 Oct 14. doi:10.1177/2045894019878598
10. Ong MS, Alman S, Sexton ED, et al. Racial and Ethnic Differences in Pediatric Pulmonary Hypertension: An Analysis of the Pediatric Pulmonary Hypertension Network Registry. *J Pediatr.* 2019;211:63-71.e6. doi:10.1016/j.jpeds.2019.04.066
11. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115(5):343-349. doi:10.7326/0003-4819-115-5-343
12. Hansmann G, Sallmon H, Roehr CC, et al. Pulmonary hypertension in bronchopulmonary dysplasia. *Pediatr Res.* 2021;89(3):446-455. doi:10.1038/s41390-020-0993-4
13. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med.* 2004;351(14):1425-1436. doi:10.1056/NEJMra040291
14. Tsoumani N, Farrah TE, Dhaun N, Webb DJ. Established and emerging therapeutic uses of PDE type 5 inhibitors in cardiovascular disease. *Br J Pharmacol.* 2020;177(24):5467-5488. doi:10.1111/bph.14920
15. Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. *Circulation.* 2014;129(19):1914-1923. doi:10.1161/CIRCULATIONAHA.113.005698
16. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. *J Heart Lung Transplant.* 2019;38(9):879-901. doi:10.1016/j.healun.2019.06.022
17. Kadmon G, Schiller O, Dagan T, Bruckheimer E, Birk E, Schonfeld T. Pulmonary hypertension specific treatment in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol.* 2017;52(1):77-83. doi:10.1002/ppul.23508
18. Cohen JL, Nees SN, Valencia GA, Rosenzweig EB, Krishnan US. Sildenafil Use in Children with Pulmonary Hypertension. *J Pediatr.* 2019;205:29-34.e1. doi:10.1016/j.jpeds.2018.09.067
19. Takatsuki S, Calderbank M, Ivy DD. Initial experience with tadalafil in pediatric pulmonary arterial hypertension. *Pediatr Cardiol.* 2012;33(5):683-688. doi:10.1007/s00246-012-0180-4
20. Shiva A, Shiran M, Rafiei M, et al. Oral Tadalafil in Children with Pulmonary Arterial Hypertension. *Drug Res (Stuttg).* 2016;66(1):7-10. doi:10.1055/s-0034-1395510
21. Yamazaki H, Kobayashi N, Taketsuna M, Tajima K, Suzuki N, Murakami M. Safety and effectiveness of tadalafil in pediatric patients with pulmonary arterial hypertension: a sub-group analysis based on Japan post-marketing surveillance. *Curr Med Res Opin.* 2017;33(12):2241-2249. doi:10.1080/03007995.2017.1354832
22. Small D, Ferguson-Sells L, Dahdah N, Bonnet D, Landry L, Li B. Pharmacokinetics and safety of tadalafil in a paediatric population with pulmonary arterial hypertension: A multiple ascending-dose study. *Br J Clin Pharmacol.* 2019;85(10):2302-2309. doi:10.1111/bcp.14039
23. Oudiz RJ, Brundage BH, Galie N, et al. Tadalafil for the treatment of pulmonary arterial hypertension: a double-blind 52-week uncontrolled extension study. *J Am Coll Cardiol.* 2012;60(8):768-774. doi:10.1016/j.jacc.2012.05.004
24. Barst RJ, Ivy D, Dingemanse J, et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. *Clin Pharmacol Ther.* 2003;73(4):372-382. doi:10.1016/s0009-9236(03)00005-5
25. Beghetti M, Haworth SG, Bonnet D, et al. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study. *Br J Clin Pharmacol.* 2009;68(6):948-955. doi:10.1111/j.1365-2125.2009.03532.x
26. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. *Eur Heart J.* 2014;35(11):716-724. doi:10.1093/eurheartj/eht072
27. Buckley MS, Staib RL, Wicks LM. Combination therapy in the management of pulmonary arterial hypertension. *Int J Clin Pract Suppl.* 2013;(179):13-23. doi:10.1111/ijcp.12136
28. Galie N, Palazzini M, Manes A. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. *Eur Heart J.* 2010;31(17):2080-2086. doi:10.1093/eurheartj/ehq152
29. Sitbon O, Sattler C, Bertoletti L, et al. Initial dual oral combination therapy in pulmonary arterial hypertension. *Eur Respir J.* 2016;47(6):1727-1736. doi:10.1183/13993003.02043-2015
30. Cohen JL, Nees SN, Valencia GA, Rosenzweig EB, Krishnan US, Sildenafil Use in Children with Pulmonary Hypertension. *J Pediatr.* 2019;205:29-34.e1. doi:10.1016/j.jpeds.2018.09.067
31. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol.* 2013;168(2):871-880. doi:10.1016/j.ijcard.2012.10.026
32. Zijlstra WMH, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: clues to a better understanding of outcome and optimal treatment strategies. *J Am Coll Cardiol.* 2014;63(20):2159-2169. doi:10.1016/j.jacc.2014.02.575