A SYSTEMATIC REVIEW OF PHARMACOLOGICAL INTERVENTIONS TO ENHANCE SYSTEMIC CIRCULATION IN LATE PRETERM (≥32 WEEKS GESTATION) AND TERM INFANTS WITH PPHN

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Background and aims: Neonates with persistent pulmonary hypertension of the newborn (PPHN) often suffer cardiac dysfunction and/or low systemic blood pressure (BP). A systematic review was performed to assess the evidence for pharmacological interventions which enhance the systemic circulation in late preterm and term infants with PPHN.

Method: EMBASE, Medline, CINAHL, Cochrane Library, Google Scholar, ScienceDirect and Web of Science were searched between November 2016 and September 2017; prospective registers and reference lists were also scanned. Quantitative studies were eligible for inclusion. The methodological quality of the studies was assessed using the *Critical Review Form – Quantitative Studies* from McMaster University. Primary outcomes were improvement of cardiac function and systemic hypotension. Secondary outcomes included adverse effects.

Results: Nine eligible studies were found; four investigated milrinone, three dopamine/noradrenaline/adrenaline and two vasopressin. Four were prospective and five retrospective; no RCT was found. Milrinone was reported to improve cardiac function but a transient drop in mean arterial BP was observed. Noradrenaline improved cardiac function and systemic BP. Vasopressin showed a significant improvement in systemic BP and left ventricular (LV) function. Study methodologies were too heterogeneous to allow meta-analysis.

Study flow chart to identify and select eligible studies

Conclusion: All nine studies were low in the evidence hierarchy. They provide some evidence that milrinone, noradrenaline and vasopressin improve cardiac function and/or systemic hypotension, although all showed some adverse effects.

Author	Population	Mean GA (weeks)	Intervention	Significant improvements were reported in:
James et al. (2016)	17 infants PPHN	39.8	Milrinone	Reduction of systolic, diastolic and mean BP (p=0.004), increase in RV basal longitudinal strain (p=0.01), systolic strain rate (p=0.002) and fractional area change (p=0.007), in LV s' and a' waves, increase in myocardial performance index (p=0.003) and LV output (p=0.004)
Patel et al. (2012)	6 infants with CDH and severe PPHN	38.6	Milrinone	Progressive increase in early diastolic (E') velocities in the RV (p<0.05)
McNamara et al. (2006)	9 full term infants with severe PPHN	39.2	Milrinone	Improvement in heart rate (p<0.001)
McNamara et al. (2013)	11 neonates with PPHN	39.2	Milrinone	Ratio of RV ejection time to pulmonary artery acceleration time (p<0.05), increased RV output (p<0.05) and LV output (p<0.05), lower proportion of right-left transductal shunting (p<0.05)
Buijs et al. (2014)	28 patients with CDH of whom 20 with PPHN	38.3-39.4	Dopamine Norepinephrine Epinephrine	Increase in heart rate after starting norepinephrine (p=0.023), increase in mean arterial BP after starting dopamine (p=0.001) and norepinephrine/epinephrine (p=0.046)
Tourneux et al. (2008)	22 term infants, 15 with PPHN	39.1	Noradrenaline	Increase in systemic BP by 40% (p<0.001), increase in heart rate (p<0.05)
Tourneux et al. (2008)	18 newborns with PPHN	37	Norepinephrine	Increase in mean systemic artery pressure (p<0.05), systolic and diastolic SAP (p<0.001), LV output increased by 22% (p<0.05), increased end diastolic LV diameter (p<0.05), mean PAP/SAP ratio decreased (p<0.001), ductus arteriosus shunting switched from bidirectional to exclusive left-right in 8 infants
Mohamed et al. (2014)	10 term infants with severe PPHN	38.8	Vasopressin	Improvement in systolic, diastolic and mean BP (p<0.001)
Acker et al. (2014)	13 infants with PPHN 6 infants did not require ECMO	36-41	Vasopressin	All results only relate to the 6 patients not requiring ECMO: drop in heart rate, in 4 out of 7 infants, LV function improved and ECMO was no longer indicated.