Pharmacological Management of Low Blood Flow State in Less than 28 weeks Neonates

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BRIEF OVERVIEW

A low blood flow state is defined as insufficient cardiac output to maintain adequate cellular metabolism at the organ level. A low blood flow state can be measured by reduced organ perfusion, such as reduced superior vena cava flow[1,2] or high resistance flow in superior mesenteric doppler scan [3]. The combination of capillary refill time of greater than 4 seconds and serum lactate greater than 4 mmol/litre has 97% sensitivity of identifying low blood flow state [4].

In the presence of the above markers of a low blood flow state, the blood pressure may be normal or high in the first 48 hours of life due to high systemic resistance [5]. Therefore, high, or normal blood pressure should be interpreted with great caution.

Literature was sourced through health care database advanced search using articles and journals from Medline, PubMed, and Embase to design evidence-based guidance on the pharmacological treatment of low blood flow state.

KEYWORDS: Preterm; Prematurity; Extreme Prematurity AND Hypotension; Low blood pressure AND Inotropes; Therapeutics; Pharmacological

MANAGEMENT OF LOW BLOOD FLOW STATES

The presence of hemodynamically significant shunt and low index of resistance to left ventricular output in early post-natal life was emphasized as a cause of low blood flow state in extremely preterm neonates [6,7]. Hence, the vital role of predominant vasopressors (Dopamine, Noradrenaline, Adrenaline, Vasopressin). There is another evidence that suggests no significant improvement in myocardial function in the first four weeks of life in extremely preterm neonates [8]. Therefore, the use of inotropes such as Dobutamine and Milrinone as first-line drugs may be considered in extreme preterm neonates with low blood flow states.

It is important to note that pharmacological treatment of low blood state in extreme preterm neonates during the first three days of life is linked to an increased risk of intraventricular

haemorrhage or mortality [9]. Hence cautious use of pharmacological treatment is advised.

Because of the overlapping causes of low blood flow state and the possible adverse consequences of pharmacological treatment in the preterm neonate, serial echocardiography is necessary to choose pharmacological treatment [10].

The international consensus on new-born resuscitation is against the routine use of fluid bolus [11].

DOPAMINE

Dopamine is more effective than Dobutamine, Colloids, and Hydrocortisone in increasing blood pressure [12]. Although, Dopamine can cause a significant increase in kidney function at a lower dose without any effect on blood pressure or heart rate [13]. It is, therefore, vital to titrate the dopamine dose to achieve the desired effect.

Dopamine provides a similar effect as low dose adrenaline on increasing the blood pressure and cerebral perfusion in hypotensive preterm neonates [14,15]. It is worth emphasizing the small numbers involved in the above studies, and the result should be interpreted with caution.

It is important to note that Dopamine at higher doses of greater than 10 microgram/kg/minutes may result in impaired cerebral perfusion [16,17]. In the above studies, the cohort that received Dopamine was significantly unwell compared to the control group, making it difficult to attribute the impaired cerebral autoregulation to Dopamine alone.

Dopamine remains the first choice of vasopressor in the preterm neonate with a low blood flow state [18]. Another concomitant vasopressor advised when approaching the dopamine dose of ten microgram/kg/minutes.

DOBUTAMINE

Dobutamine is the second most used drug in patients unresponsive to Dopamine [19]. Its use at ten microgram/kg/minute may cause increase cardiac output and superior mesenteric, renal artery, and cerebral blood flow. However, dobutamine administration causes an 8 to 10 hours delay in increasing cerebral blood flow, superior mesenteric artery, renal artery flow [20].

A similar Dobutamine and Dopamine effect at doses of 10 microgram/kg/minutes on superior mesenteric artery flow

rate has been reported [21]. It should be noted that there is a dearth of evidence on Dobutamine's impact at higher doses on superior mesenteric, renal arteries, and cerebral blood flow [22]. It is worth emphasizing the need to assess the superior mesenteric flow when using Dobutamine and consider adding another pharmacological agent to counteract the possible delay in gut perfusion.

Dobutamine use is advised in extreme preterm neonates with myocardial dysfunction secondary to pulmonary hypertension and in post ligation cardiac syndrome [23].

NORADRENALINE

Noradrenaline is tolerated safely in preterm less than 32weeks treated for sepsis and pulmonary hypertension [24]. Noradrenaline at a dose of 0.5mcg/kg/minutes caused the desired blood pressure effect in within 1 hour [24].

Noradrenaline improves post-natal pulmonary hypertension adaptation in foetal lambs by increasing systemic vascular pressure and increasing pulmonary blood flow [25]. Furthermore, noradrenaline may cause improvement in pulmonary function by increasing pulmonary/ systemic artery pressure ratio and improved cardiac function [26].

Noradrenaline use as the choice of a vasopressor is suggested in hypotensive preterm neonates with pulmonary hypertension.

ADRENALINE

The use of Adrenaline in new-born resuscitation for the return of spontaneous circulation is a recognized practice [27]. A low to moderate Adrenaline dose is as effective as a low to moderate dopamine dose in hypotension treatment in low-birth-weight neonates [28]. It is essential to emphasize the complication associated with Adrenaline, such as high heart rate, high lactate, lower base excess, and lower bicarbonates.

Furthermore, a Cochrane review suggested insufficient evidence on Adrenaline's use as the first line in preterm neonates with low blood flow state [29].

The consensus is on the use of Adrenaline when there is no spontaneous return of adequate circulation.

CORTICOSTEROID

Corticosteroids are known for treating hypotension resistant to fluid expansion and two vasopressors [30]. The routine use of

hydrocortisone as the 1st line in the treatment of hypotension is frowned upon due to sepsis complications and gut perforation [31].

Hydrocortisone might be as effective as Dopamine in treating hypotension [32]; this agreed with the prophylactic use of low dose hydrocortisone, reducing the use of vasopressors [33]. On the other hand, hydrocortisone's stress dose effectively treats refractory hypotension [34].

The use of low-dose hydrocortisone prophylaxis in extremely preterm neonates is not associated with adverse effects for either death or 2-year neurodevelopmental delay [35]. Conversely, dexamethasone's routine use in preterm hypotension is much discouraged based on lack of long-term safety profile [36].

Hydrocortisone remains a safe drug in the treatment of refractory hypotension. The use of baseline cortisol in deciding the need for prophylactic therapy is encouraged [37].

MILRINONE

Milrinone prophylaxis does not prevent low blood flow states in high-risk preterm neonates [38]. The prophylactic use of Milrinone post-patent ductus arteriosus ligation is discouraged with emphasis that prophylactic Milrinone has no impact on immediate cardiovascular or long-term outcomes [39]. Therefore, the prophylactic use of Milrinone is not suggested in everyday practice.

In contrast, a case series report suggested that Milrinone is a valuable therapy in infants with echocardiography findings of pulmonary hypertension or right heart dysfunction [40]. The administration of Milrinone to neonates with low cardiac output before PDA ligation might lead to improved postoperative stability [41].

Milrinone is encouraged as second choice inotropes when there is a suboptimal response to Dobutamine in preterm neonates with myocardial dysfunction and pulmonary hypertension.

VASOPRESSIN

Vasopressin use is associated with complications such as liver necrosis, splanchnic hypoperfusion, and high mortality [42,43]. In contrast, vasopressin's safe use and less side effect profile in preterm neonates have been reported [44,45]. The common side effects are raised lactate and hyponatremia [46].

There is insufficient evidence to recommend vasopressin's

everyday use in neonates for treatment of low blood flow state [47]. The use is reserved for a very severe low blood flow state resistant to catecholamine treatment [48].

LIMITATIONS

The quality of evidence is sub-optimal; the majority are observational studies with high heterogeneity and less representation of less than 24 weeks, hence creating a high confounding factor. Besides, there is variability between different centers in diagnosing low blood flow states, some of the studies used low mean or systolic blood pressure to determine the effect of treatment.

CONCLUSION

The pharmacological treatment of a low blood flow state should be guided by thorough clinical assessment. The prophylaxis or stress dose hydrocortisone treatment of low flow state is gaining grounds mainly when there is evidence of adrenal insufficiency.

The choice and titration of pharmacological treatment should be guided by functional echocardiography. The use of Dobutamine as first-line treatment is advised when myocardial dysfunction on echocardiography is noted.

Milrinone use is reserved for extreme preterm neonates with myocardial dysfunction before patent ductus arteriosus ligation. Dopamine and noradrenaline remain the commonly used first- and second-line vasopressors, respectively, to manage low blood flow states secondary to poor vasomotor resistance.

CONSENT

Not required.

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APPENDIX 1

Literatures were sourced through health care database advanced search using articles and journals from Embase, Medline and PubMed. Keywords used are: Preterm OR Prematurity OR Extreme Prematurity AND Hypotension OR Low blood pressure AND Inotropes OR Therapeutics OR Pharmacological. 210 articles were obtained between 1995 to 2020. 79 excluded due to duplication. 66 of the remaining 131 were published in the last 10 years. The pharmacological choice for the management of low blood flow states was obtained from publications in the last 10 years.

☐ 1	EMBASE	(preterm).ti,ab	View Results (105,797)	Edit		
☐ 2	EMBASE	exp PREMATURETY/	View Results (105,713)	Edit		
☐ 3	EMBASE	(1 OR 2)	View Results (158,035)			
☐ 4	EMBASE	(hypotension OR Low blood pressure OR haemodynamic).ti,ab	View Results (111,390)	Edit		
☐ 5	EMBASE	exp HYPOTENSION/	View Results (148,055)	Edit		
☐ 6	EMBASE	(4 OR 5)	View Results (201,833)			
☐ 7	EMBASE	(inotropes OR therapeutic OR pharmacological).ti,ab	View Results (1,726,606)	Edit		
☐ 8	EMBASE	exp "INOTROPIC AGENT"/	View Results (14,021)	Edit		
☐ 9	EMBASE	(7 OR 8)	View Results (1,736,527)			
☐ 10	EMBASE	(3 AND 6 AND 9)	View Results (348)			
☐ 11	Medline	(PRETERM).ti,ab	View Results (75,176)	Edit		
☐ 12	Medline	exp "INFANT, PREMATURE"/	View Results (56,742)	Edit		
☐ 13	Medline	(11 OR 12)	View Results (105,344)			
☐ 14	Medline	(hypotension OR Low blood pressure OR haemodynamic).ti,ab	View Results (128,422)	Edit		
☐ 15	Medline	exp HYPOTENSION/	View Results (28,011)	Edit		
☐ 16	Medline	(14 OR 15)	View Results (140,237)			
☐ 17	Medline	(inotropes OR therapeutic OR pharmacological).ti,ab	View Results (1,231,993)	Edit		
☐ 18	Medline	exp "CARDIOTONIC AGENTS"/	View Results (218,376)	Edit		
☐ 19	Medline	(17 OR 18)	View Results (1,433,341)			
☐ 20	Medline	(13 AND 16 AND 19)	View Results (208)			

☐ 21	PubMed	(preterm).ti,ab	View Results (100,876)	Edit
☐ 22	PubMed	(prematurity).ti,ab	View Results (24,706)	Edit
☐ 23	PubMed	(21 OR 22)	View Results (114,282)	
☐ 24	PubMed	(hypotension OR Low blood pressure OR haemodynamic).ti,ab	View Results (836,356)	Edit
☐ 25	PubMed	(hypotension).ti,ab	View Results (68,980)	Edit
☐ 26	PubMed	(24 OR 25)	View Results (836,356)	
☐ 27	PubMed	(inotropes OR therapeutic OR pharmacological).ti,ab	View Results (9,423,983)	Edit
☐ 28	PubMed	(inotropes agent).ti,ab	View Results (100)	Edit
☐ 29	PubMed	(27 OR 28)	View Results (9,423,983)	
☐ 30	PubMed	(23 AND 26 AND 29)	Viewing (2,684)	

APPENDIX 2

APPENDIX 3

APPENDIX 4

Hydrocortisone	Dosage
Prophylaxis	0.5 mg/kg/12 hourly for 9 days, then 0.5 mg/kg/24 hourly for 3 days
Therapeutic stress dose	1mg/kg eight hourly for five days

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