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Management of Neonatal Emergencies: Current Evidence from Chrane / Other Systematic Reviews

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Abstract

Hypotension in neonates, particularly preterm, is a matter of debate in all its aspects (definition, monitoring and treatment).The neonate is uniquely at risk of hypotension and low systemic blood flow states due to failure or delay in the normal transition of circulatory processes.While managing the hypotensive neonate, it is not clear whether the issue to be addressed is low blood pressure or low flow states. With the development of newer technologies to assess this issue; the subject becomes more challenging and interesting.Most of the neonatal units use a stepwise approach for managing hypotension in neonates. Although the understanding of cellular mechanisms of action of inotropes is well founded, there is little information on their clinically relevant long-term benefits in the neonatal patient population. Also data regarding their safety and efficacy are lacking. The current clinical query tries to answer the issue of use of dopamine versus dobutamine as first line inotrope of choice in this group of neonates. This would hopefully help the clinician to apply the evidence based practice for management of hypotension in preterm neonate and would provide insight for future well designed studies.

Keywords: Hypotension; Preterm; Dopamine; Dobutamine.

Clinical question

You are a resident in neonatal intensive care, taking care of a 34 week neonate at 14 hours of life diagnosed as a case of severe birth asphyxia with shock. The neonate has low blood pressure as measured by the oscillometric method and you plan to give normal saline,fluid bolus (10ml/kg). The administration of fluid bolus increased the blood pressure but it was still below the 5th centile. You repeat the bolus (10ml/kg), which leads to no improvement in blood pressure. You plan to start inotropes fearing the chances of heart failure on giving more fluid boluses. You ask the staff on duty to prepare dopamine as it would help to raise the blood pressure, but your colleague warns you that dobutamine would be better in cases of shock caused by birth asphyxia. You get confused as the blood pressure will drop further on administration of dobutamine. So youplan to start dopamine in emergency and in the meantime read the evidencefortreatment of shock in preterm neonates, in order to review the treatment.

You are now confronted with the following questions:

1. What is the first line drug treatment for the newborn with shock associated with birth asphyxia?
2. Is there any evidence for dopamine versus dobutamine for such a situation?
3. Does evidence suggest decrease in blood pressure with dobutamine?

You plan to review the treatment and inform your colleague after reading the available literature.

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Table 1: Drugs used in treatment of hypotension[5]

Name	Category	Mode of action	Dose
Dopamine	Inotrope/ Vasopressor	α and β adrenergic effects	2-20µg/kg/min
Dobutamine	Inotrope	α adrenergic effects	5-20µg/kg/min
Adrenaline	Inotrope/ Vasopressor	α and β adrenergic effects	0.05-2.5µg/kg/min
Noradrenaline	Vasopressor	α and (some) β adrenergic effects	0.05-2.5µg/kg/min
Hydrocortisone	Steroid	Multiple	2.5 mg/kg 6 hourly

Background

hedefinition of hypotension in the preterm infant has been a contentious issue.[1]Besides, there are wide differences in the practice of monitoring, timing of intervention, measurement of outcomes and treatment strategies for hypotension. With its varied pathophysiology added to the inherent immaturity of the preterm infant; these issues assume greater significance. The main goal of achieving the normal tissue oxygenation requires maintenance of systemic blood flow and normal blood oxygen levels.[2,3] Reduction in either of these physiological parameters may result in organ damage.To maintain these parameters the clinician uses the volume expansion (filling the pump), inotropes (tightening the pump), and hydrocortisone (compensating for an immature pump). The accurate treatment of hypotensive and low cardiac output states in the preterm infant requires a proper understanding of the actions of various drugs on the immature cardiovascular system.Despite our limited understanding of the pathophysiology of hypotension and the benefits of therapeutic intervention in the preterm infant, a significant number of preterm newborns receive cardiovascular support. [4]None of the current treatments for hypotension, including the use of inotropic agents (Table 1), have been well studied in the preterm population, and data regarding safety and efficacy are lacking. The injudicious use of inotropes in preterm neonates may be hazardous rather than supportive. In this clinical query, we have tried to review the evidence behind use of dopamine versus dobutamine as a first line drug of choice in preterm neonates with shock.

Evidence

With the updated current evidence, there are two cochrane reviews[6,7]and another single systematic review[8]addressing the issue of dopamine versus dobutamine as first line drug treatment of shock in neonates:

Cochrane review:[6,7]

(a) Thereview by *Subhedar et al* (2003),[6,7]comparing the effectiveness and safety of dopamine versus dobutamine in the treatment of systemic hypotension in preterm infants. It included five studies that enrolled a total of 209 hypotensive preterm neonates.There was no evidence of a significant difference between dopamine and dobutamine in terms of neonatal mortality (3 trials, 103 patients; RR 1.17 95% CI 0.47, 2.92), no difference in incidence of periventricular leukomalacia (3 trials, 103 patients, RR 0.43 95% CI 0.12, 1.52), or severe intraventricular haemorrhage (2 trials, 83 patients; 0.73 95% CI 0.15, 3.50). Dopamine was more successful than dobutamine in treating systemic hypotension, with fewer infants having treatment failure (4 trials, 189 patients; RR 0.41 95% CI 0.25, 0.65; NNT = 4.4, 95% CI 2.9 to 7.7). Treatment with dobutamine was associated with a significantly greater increase in left ventricular output in the single study reporting that outcome. There was no evidence of a significant difference between the two agents with respect to the incidence of tachycardia (RR 0.74 95% CI 0.26, 2.08).

(b) The other cochrane review by *Osborn et al*[4]updated in year 2007 included one study (n=43). The study compared the dopamine versus dobutaminegroup enrolled patients who had low superior vena cava (SVC) flow. They reported the short term as well as the

long term neurological outcomes of the surviving neonates. No significant difference was reported in mortality to discharge, intraventricular haemorrhage (IVH) grade 3 or 4 IVH or NEC. At three years follow up (n=13), there was no significant difference in cerebral palsy(RR 0.16 95% CI 0.01, 2.64), deafness, developmental quotient > 2 SD below norm or combined disability. But the surviving infants treated with dobutamine had a significantly higher development quotient (RR35.0, 95% CI:17.68, 52.32). There was no significant difference in death ordisability at follow up (RR 0.95, 95% CI: 0.66, 1.38).

Other systematic review

The review by *Higgins et al*[8] in the year 2011 includedseven trials, comparing the effect of dopamine versus dobutamine;(a)Dopamine administration was associated with a significantly greater overall therapy efficacy than dobutamine in terms of increase in blood pressure in hypotensive preterm infants (n=251; RR 0.26; 95% CI 0.20 to 0.32). (b) Secondly, dopamine was associated with a trend towards a lower incidence of short term adverse neurological outcome than dobutamine (three studies; n=118; r = -0.13; 95% CI -0.31 to 0.059), however, this comparison did not reach statistical significance($P_{one\text{-}tailed}$= 0.10).

To summarize, using dopamine versus dobutamine for hypotensive preterm neonates

- *Dopamine administration is associated with significant increasesin blood pressure in the hypotensive preterm infants as compared to dobutamine*
- *Possibly reduces short term adverse neurological outcome than dobutamine, reassuring that dopamine has good safety profile.*
- *Long term neuro-developmentaloutcome is possibly better in patients treated with dobutamine if they had low SVC flow(n=13).*

Discussion

The available evidence seems to favor either of the inotropes depending upon the clinical situation and the cause of hypotension in the hypotensive preterm neonate. The above mentioned studies enrolled infants with low blood pressure (B.P) as defined by their gestation in weeks, though there is no consensus on definition of hypotension in preterm infants. So treating the numerical values (B.P) has always been an issue and as stated above the SVC flow may be better indicator of organ perfusion rather than the systemic blood pressure. In the single study[3]using SVC flow as a marker; dobutamine had a better long term developmental quotient, although C.P rates were similar. So, it depends upon which parameter we are using to assess the hypotension, pressure or flow.

There are concerns while making general statements regarding this issue in regards of the available studies. They need to be addressed before a definite recommendation regarding dopamine or dobutamine is made.The concerns include:

Methodological issues

The trials included in cochrane review are not blinded (except one)[9] in regards to intervention. Though the Cochrane review did not find any significant heterogeneity between the results from trials using different randomizationmethods, the possibility of biascannot be completely ruled out. Similarly, lack of blinding - though unlikely to affect a 'hard' outcome like mortality - could result in different level of care in the two groups thus affecting the observed results.

Lack of proper and adequate long-term follow-up data

Thisis the major problem in accepting the results of the systematic reviews as such. The follow-up data available comes from a single study[3], is incomplete with a small sample size

(n=13), and points toward better developmental quotient in dobutamine treated infants, although the cerebral palsy rates were same. Given that the particular study was not powered enough to detect a small difference in the incidence of long-term outcomes, one has to be really cautious in interpreting this data.

Ethical considerations

The studies have looked at either dopamine or dobutaminefor hypotension in preterm infants. Some studies would have used the epinephrine or corticosteroids as a back up for dopamine or would have combined the two after failing to achieve the desired pressure level. Using strict criteria for the using of either drug may not be feasible as the neonates with shock are at a risk of organ damage and this may not be ethical feasible to use a single drug.

Generalization of results

Since the studies have been done in preterm population with varied reasons for shock. The reasons can vary from septic shock to shock due to persistent pulmonary hypertension or asphyxia (myocardial depression).The result may not apply to all preterm neonates where the causes of shock may be different. So extrapolating the results in all neonates with shock should be done with caution.

Proposed Recommendations (Table 2)[2,7–11]

Based on above discussion we could formulate that the patho-physiological factors which predominate in the first 24 hours are mainly related to vasoconstriction as seen by low SVC flow, normal or low BP and poor myocardial contractility. Those which affect subsequently are predominately vasodilatation associated with low BP, normal SVC flow and myocardial function. Since the babies on the first day are more likely to have low SVC flow and poor myocardial contractility, dobutamine would be the first choice of inotropes.Dopamine and epinephrine may be added as second and third line medications to titrate to blood pressure.

Summary

Systematic research on the effectiveness of inotropic agents points toward the superiority of dopamine at improving blood pressure in these neonates. [2,9,15–17]However, some studies in preterm infants using dopamine at doses >5 µg/kg per min suggest that dopamine exerts its effects byincreasing systemic vascular resistance, which could be counterproductive for the myocardium.[17,18]In fact, dobutamine[2,6,17]have had a better effect on

Table 2: Proposed treatment options for dopamine versus dobutamine in treatment of preterm shock

Interventions	Evidence	Recommendations
Dopamine / Dobutamine in treatment of neonatal shock[2,7–11]	Five RCTs[2,6,12–14] comparing dopamine with dobutamine with metaanalysis: Dobutamine is less effective than dopamine in increasing BP, But in 30-84% of babies, dobutamine is more effective in maintaining cardiac output. Dobutamine is also more effective than dopamine in maintaining SVC flow (68% Vs 45%) 40% of babies with low flows failed to maintain SVC flows despite use of both inotropes.	*In states of myocardial dysfunction, PPHN and low flow states, dobutamine may be a better choice.* *In states of normal SVC flow with hypotension, dopamine would be the choice.*

cardiac performance, probably because of a predominant â-effect. Aside from information about the short-term effects of these drugs on the cardiovascular system in preterm infants, little data are available on the systematic evaluation of the effects of catecholamines on neonatal morbidity and mortality, [6,19]and long term neurodevelopmental effect[3], so it is difficult to document specific recommendations for treatment strategies. Currently, many infants receive potentially toxic therapies based solely on simplistic criteria, such as a mean blood pressure less than the gestational age in weeks, in the absence of any evidence that such an approach is beneficial. Good clinical practice requires a careful assessment of the risks and benefits of an intervention before starting it. Also, on the another hand, it is important, on those promoting a more interventionist approach to perform the requisite randomized controlled trials to prove that clinical outcomes are improved.

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