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Neonatal Hypotension: What Is the Efficacy of Each Anti-Hypotensive Intervention? A Systematic Review

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Abstract

Purpose of review There is no consensus in the treatment of hemodynamic instability in the preterm newborn. Blood pressure is one of the few measurable objective parameters for hemodynamic evaluation in this population. However, little is known about the efficacy of anti-hypotensive treatments in newborns. The objective of this review is to identify and analyze the efficacy of a given anti-hypotensive intervention in improving the hypotensive preterm newborn.
Recent findings With the increase in survival of the preterm newborns, there was an augmentation in the interest for the treatment of hypotension in this population. However, as there are doubts regarding the efficacy in anti-hypotensive treatment, new drugs are being used to reverse the hypotensive state in preterm infants: epinephrine, norepinephrine, vasopressin, and steroids.
Summary We have identified that classically used medications in the treatment of hypotension have little evidence of efficacy in rescuing the preterm infant from the hypotensive state. New therapies are emerging with potential benefits, especially in refractory hypotension such as epinephrine and norepinephrine, but more prospective studies are needed. Literature review should be careful, considering the definition

used for hypotension, the time of onset, the intravascular volume status of each patient, and if the drug was used as a first or second line of treatment.

Introduction

Until now, there is no consensus in the treatment of hemodynamic instability in neonates, especially in preterm infants [1]. This lack of agreement, with a high mortality rate population [2], demands immediate new studies, so that we can understand what, how, and when to treat hemodynamic instability in preterm infants.

In the pediatric population, blood pressure is a notable parameter for assessing the patient's hemodynamic status [3]. Unfortunately, in the neonatal period, there are doubts about what, when, and how to treat hypotension. In addition, there are uncertainties regarding the ability of anti-hypotensive treatment to reduce morbidity and mortality [4, 5] and their effect on blood pressure. Several studies show that many of them are effective in improving blood pressure and other hemodynamic parameters [6] but are they effective in withdrawing the patient from the hypotension condition?

We conducted a review of the literature in order to understand if an anti-hypotensive therapy is effective or not in treating hypotension in premature newborns. We also examined the recent therapies used in these preterm infants.

Definition of hypotension in the neonatal period

Currently, the most commonly used definition for hypotension is a mean arterial pressure (MAP) lower than gestational age (GA) [7]. This definition gained importance from a 1992 recommendation by the Joint Working Group of the British Association of Perinatal Medicine [8], and since then has been widely used to diagnose hypotension. The preference for this definition could be due to the fact that there is strong evidence that the value of blood pressure varies with gestational age [9].

But there are several different definitions, such as MAP lower than 30 mmHg [10•] or MAP lower than pre-defined percentile for gestational age [11–13].

The use of the 30 mmHg cutoff started from a study which showed that MAP < 30 mmHg in extremely premature infants was associated with severe intraventricular hemorrhage and mortality [14]. A recent study by Munro et al. showed that in extremely low birth weight preterm infants, MAP < 30 mmHg is associated with decreased cerebral blood flow [15]. However, the problem of using a pre-set value of 30 mmHg is that essentially gestational age is rejected in the analysis [16], and ends up considering that all preterm infants have the same cardiovascular maturity, which may not be correct. In addition, there are also studies that did not find the association between MAP < 30 mmHg and adverse events. Limperopoulos et al. used 3 different definitions of hypotension in their study (MAP < GA, MAP < 30 mmHg, and MAP < p10 Watkins), and none of them were related to abnormal brain abnormalities on ultrasound [17].

Therefore, there are several studies attempting to associate a cutoff value for hypotension with adverse outcomes, and the results are controversial among them. This lack of consensus in the definition of hypotension creates a great variety in the clinical management and difficulty in interpreting several existing studies.

Why to treat hypotension?

In the newborn, especially in premature infants, there are several factors that end up disturbing the interpretation of blood pressure and this is due to the preterm infant unique physiology [18]. However, in this population, there is great difficulty in measuring cardiac output, tissue perfusion, and systemic blood flow. Therefore, although blood pressure is not a so reliable marker of systemic blood flow [18] as in the pediatric and adult population, it is currently one of the few hemodynamic parameters obtainable.

Literature has recently questioned whether hypotension should be treated or not in preterm patients. Some studies have shown that hypotension is a serious factor of worse prognosis for premature infants [9, 19••]. Other authors, however, report that treatment of hypotension could be detrimental [20, 21] and do not reduce morbidity or mortality [22]; therefore, some authors defend a permissive hypotension in patients without signs of cardiovascular impairment [4].

However, in a recent study, Durrmeyer et al. [19••] showed in a prospective study of a national cohort in France that newborns with treated hypotension, even in those without signs of poor perfusion, had a better outcome and less severe cerebral lesions than those who underwent permissive hypotension. Thus, until new evidence comes to light, it does not seem advisable to abstain from treating hypotension in preterm infants.

How to treat hypotension?

This review selected 19 studies (29 interventions) that analyzed the efficacy of a given intervention in the treatment of hypotension (Table 1). The interventions identified were as follows: volume resuscitation with saline solution 0.9%; volume resuscitation with albumin; use of dopamine, dobutamine, epinephrine, norepinephrine, vasopressin, and postnatal steroids. No studies have been identified evaluating the effect of milrinone or levosimendan in the treatment of hypotension in preterm infants.

We identified that the most studied intervention was dopamine (11 studies), followed by dobutamine and postnatal steroids with 4 studies each. It is noteworthy that the intervention with few studies (only 1 study identified) is the use of saline solution 0.9%, which is the most commonly used intervention [7]. In the last decade, we have noticed an increase in the use of epinephrine, vasopressin, and norepinephrine for neonatal hypotension management.

Definitions for hypotension identified

In the 29 interventions analyzed, we identified 13 different definitions for hypotension, which is extremely alarming and making quite difficult the interpretation of these results. The most commonly used was mean blood pressure less than gestational age (8 studies, representing only 27.5% of the total studies). Which means that only a quarter of studies used the currently most accepted definition for hypotension. In addition, the first study that used the definition of hypotension as MAP < GA was published in 2005 [29]. For example, there is no study analyzing dobutamine with the definition of hypotension as MAP < GA. The second most common definition (five studies) was mean arterial pressure less than 30 mmHg.

Moment of intervention with anti-hypotensive treatment

A fact that must be cautious with is the clinical status in which the patient was at the time when the intervention was started. We observed a heterogeneity regarding the fluid balance of the patient at the time of the therapy initiation: in 16 interventions, 100% of the patients received volume resuscitation prior to the medication studied; in 7 interventions, there were patients who received and patients who did not receive previous volume resuscitation; and in only 5 interventions, the patients did not receive previous volume resuscitation (3 of them, the interventions were precisely volume resuscitation). That is, in only 2 interventions, volume resuscitation was not used before the intervention. Therefore, to follow the recommendations of these studies, it would be necessary to perform previous fluid resuscitation in all patients. But what is the evidence for volume resuscitation?

Another point to be emphasized is if at the time of the intervention, the patient was already using some other anti-hypotensive measures, excluding volume resuscitation. We found that in 22 interventions, the studied drug was the first line of treatment for hypotension. On the contrary, in 7 interventions, the drug was not the first line of treatment making the interpretation of these studies rather confusing. Did the MAP increased due to the intervention studied, or due to the combination of them?

Classic anti-hypotensive treatment (volume resuscitation, dopamine, dobutamine)

According to the inclusion criteria of this review, from 1993 to 2018, 19 studies looking at the treatment of neonatal hypotension were identified. Although volume resuscitation with 0.9% saline solution is the most used strategy, this approach was present in only 85% of cases according to Stranak et al. There was only one publication that analyzed this intervention and its efficacy in reverting hypotension in preterm infants. This study was conducted in 1997, including infants in the first 2 h of life, with a low success rate (42%). A 2004 Cochrane review states that there is no evidence to use volume expansion in preterm infants with no evidence of cardiovascular impairment and there are insufficient data to determine whether preterm infants with evidence of cardiovascular impairment could benefit with volume resuscitation [42]. Considering the physiological peculiarities of the neonatal population, the difficulty in managing fluid overload and the lack of evidence of benefit, it is surprising that the use of volume resuscitation has been seldom studied.

Among all the interventions, dopamine was the most cited by the authors, with great variation in the

Table 1. Anti-hypotensive intervention in newborns: a systematic review

Year	Author	Study design	Number of patients	Population	Birth weight (mean or median)	Hypotension definition
Dopamine						
1993	Gill et al. [23]	Case control	19	BW < 1500 g	887 g (599–1420)	MAP < p10 (Watkins 1989)
1993	Rozé et al. [24]	Case control	10	GA < 32 weeks	1140 ± 105 g	MAP < 30 mmHg
1993	Greenough et al. [25]	Case control	20	GA < 37 weeks	886 g (678–1980)	SAP < 40 mmHg
1994	Klarr et al. [26]	Case control	31	GA < 34 weeks + RDS	1079 ± 330 g	MAP < 30 mmHg
1995	Hentschel et al. [27]	Case control	10	GA < 37 weeks	1145 g (835–2610)	MAP < p10 (Weindling 1989)
1997	Bourchier et al. [28]	Case control	19	BW < 1500 g	1043 ± 184 g	MAP < 25 mmHg (< 750 g) MAP < 30 mmHg (750–999 g) MAP < 35 mmHg (1000–1499 g)
2005	Pellicer et al. [29]	Case control	27	GA < 32 weeks OR BW < 1500 g	1008 ± 286 g	MAP < GA
2006	Valverde et al. [30]	Case control	28	BW < 1500 g OR GA < 32 weeks	1008 ± 286 g	MAP < GA
2013	Lightburn et al. [31]	Cohort study	15	BW < 1000 g + MV	625 ± 174 g	MAP < GA
2013	Catenacci et al. [32]	Cohort study	159	GA < 28 weeks	No info	MAP < p3 (Zubrow 1995) OR MAP < GA less 4 mmHg
2015	Rios et al. [33]	Case control	10	BW < 1000 g AND GA < 30 weeks	675 ± 148 g	MAP < GA less 4 mmHg OR MAP < GA + hypoperfusion
Volume resuscitation with saline solution 0.9%						
1997	So et al. [34]	Case control	31	GA < 34 weeks + BW < 2000 g + MV	1163 g ± 66 g	MAP < 25 mmHg (< 1000 g) MAP < 30 mmHg (1000–1499 g) MAP < 35 mmHg (1500–1999 g)
Volume resuscitation with albumin						
1993	Gill et al. [23]	Case control	20	BW < 1500 g	867 g (604–1452)	MAP < p10 (Watkins 1989)
1997	So et al. [34]	Case control	32	GA < 34 weeks + < 2000 g + MV	1123 ± 81 g	MAP < 25 mmHg (< 1000 g) MAP < 30 mmHg (1000–1499 g) MAP < 35 mmHg (1500–1999 g)
Dobutamine						

Table 1. (Continued)

Year	Author	Study design	Number of patients	Population	Birth weight (mean or median)	Hypotension definition
1993	Rozé et al. [24]	Case control	10	GA < 32 weeks	1110 ± 80 g	MAP < 30 mmHg
1993	Greenough et al. [25]	Case control	20	GA < 37 weeks	860 g (552–1650)	SAP < 40 mmHg
1994	Klarr et al. [26]	Case control	32	GA < 34 weeks + RDS	1168 ± 450 g	MAP < 30 mmHg
1995	Hentschel et al. [27]	Case control	10	GA < 37 weeks	965 g (830–2570)	MAP < p10 (Weindling 1989)
Epinephrine						
2002	Heckmann et al. [35]	Cohort study	31	BW < 1500 g	690 g (390–1310)	MAP < 23 mmHg (< 750 g) MAP < 25 mmHg (750–999 g) MAP < 30 mmHg (1000–1500 g)
2005	Pellicer et al. [29]	Case control	32	GA < 32 weeks OR BW < 1500 g	944 ± 281 g	MAP < GA
2006	Valverde et al. [30]	Case control	32	BW < 1500 g OR GA < 32 weeks	944 ± 281 g	MAP < GA
Norepinephrine						
2016	Rowcliff et al. [36•]	Cohort study	48	GA < 32 weeks	952 g (726–1450)	MAP < GA
2017	Rizk et al. [37•]	Cohort study	30	GA < 34 weeks	903 ± 437 g 827 g (450–2550)	MAP < p10 (Nuntnarumit 1999)
Vasopressin						
2010	Ikegami et al. [38]	Cohort study	22	BW < 1000 g	658 ± 142 g	MAP < GA OR MAP < p10 (Watkins 1989)
2014	Rios et al. [33]	Case control	10	BW < 1000 g and GA < 30 weeks	640 ± 109 g	MAP < GA less 4 mmHg OR MAP < GA + hypoperfusion
Corticoid						
1997	Bourchier et al. [28]	Case control	21	BW < 1500 g	923 ± 188 g	MAP < 25 mmHg (< 750 g) MAP < 30 mmHg (750–999 g) MAP < 35 mmHg (1000–1499 g)
1999	Gaissmaier et al. [39]	Case control	8	GA < 37 weeks	698 g (450–2650)	MAP < 23 mmHg (< 750 g) MAP < 25 mmHg (750–999 g) MAP < 30 mmHg (1000–1500 g)
2006	Ng et al. [40]	Case control	24		918 g (729–1223)	MAP < GA

Table 1. (Continued)

Year	Author	Study design	Number of patients	Population	Birth weight (mean or median)	Hypotension definition
2011	Mizobuchi et al. [41]	Case control	12	GA < 32 weeks + BW < 1500 g GA < 27 weeks	554 ± 100 g	MAP < 30 mmHg OR MAP < 25 mmHg if GA < 25 weeks

Year	Time of onset	Prior volume resuscitation	First line	Success definition	Failure rate
Dopamine					
1993	< 24 h	No	Yes	MAP > p10 (Watkins 1989)	10.5%
1993	No info	Yes (100%)	Yes	MAP > 30 mmHg	0%
1993	1 (1–6) days	Yes (100%)	Yes	SAP > 40 mmHg	50%
1994	< 24 h	Yes (100%)	Yes	MAP > 30 mmHg	0%
1995	No info	Yes (100%)	Yes	MAP > p10	10%
1997	15.1 ± 10.1 h	Yes (100%)	Yes	MAP > 25/30/35 mmHg	0%
2005	< 24 h	Yes (37%)	Yes	MAP > GA + 15% GA	33.3%
2006	5.3 ± 3.9 h	Yes (35.71%)	Yes	MAP > GA + 15% GA	36%
2013	< 24 h	No	Yes	MAP > GA + 15% GA	6%
2013	< 24 h	Yes (100%)	Yes	MAP > GA – 4 mmHg OR > p3 (Zubrow 1995)	37.7%
2015	< 24 h	Yes (30%)	Yes	MAP > GA + 2 mmHg	20%
Volume resuscitation with saline solution 0.9%					
1997	< 2 h	No	Yes	MAP > 25/30/35 mmHg	58%
Volume resuscitation with albumin					
1993	< 24 h	No	Yes	MAP > p10 (Watkins 1989)	55%
1997	< 2 h	No	Yes	MAP > 25/30/35 mmHg	59.3%
Dobutamine					
1993	No info	Yes	Yes	MAP > 30 mmHg	60%
1993	1 (1–6) days	Yes	Yes	SAP > 40 mmHg	85%
1994	< 24 h	Yes	Yes	MAP > 30 mmHg	16%
1995	No info	Yes	Yes	MAP > p10 (Weindling)	20%

Table 1. (Continued)

Year	Time of onset	Prior volume resuscitation	First line	Success definition	Failure rate
Epinephrine					
2002	3 (1–21) days	Yes (100%)	No	MAP > Hypotension definition + 5 mmHg	0%
2005	< 24 h	Yes (34.37%)	Yes	MAP > GA + 15% GA	37.5%
2006	5.2 ± 3.3 h	Yes (34.37%)	Yes	MAP > GA + 15% GA	37%
Norepinephrine					
2016	1.5 (1–14) days	No info	No	MAP > GA	2%
2017	18.4 (1–116) days	Yes (73%)	No	MAP > p10 (Nuntnarumit 1999)	20%
Vasopressin					
2010	11 (0–34) days	Yes (100%)	No	25% increase in SAP or DAP	36.6%
2014	< 24 h	Yes (70%)	Yes	MAP > GA + 2 mmHg	30%
Corticoid					
1997	11.4 ± 13 h	Yes	Yes	MAP > 25/30/35 mmHg	19%
1999	2 (1–20) days	Yes	No	Epinephrine cessation	37.5%
2006	11 (8–15) hours	Yes	No	MAP > GA	8.3%
2011	25 (24–52) hours	Yes	No	MAP > 30 mmHg OR MAP > 25 mmHg if GA < 25 weeks	33%

GA, gestational age; *BW*, birth weight; *RDS*, respiratory distress syndrome; *MV*, mechanical ventilation; MAP, mean arterial pressure; *SAP*, systemic arterial pressure

definition of hypotension. We observed eight different definitions among 11 studies, with only three using the MAP < GA criteria. This fact, the early onset of dopamine in most of the cases and the wide variation of the failure rate (0 to 50%), makes it hard to tell whether dopamine is actually successful in rescuing the premature infant from its hypotensive condition. Likewise, in relation to dobutamine, the last study evaluating its impact was performed in 1995, yet no study used the definition of hypotension based on MAP < GA. The failure rate of dobutamine ranged from 16 to 85%. These data with the use of dobutamine are alarming, since this is the most chosen second-line drug to treat hypotension in the preterm infant [7].

New anti-hypotensive treatment (epinephrine, norepinephrine, vasopressin, and corticoid)

Three studies evaluating the impact of epinephrine on blood pressure of preterm newborns were identified, one of them being a retrospective study. In this study, epinephrine was not used as a first-line treatment, and every patient had a high dose of dopamine (15 mcg/kg per minute), which could explain the 100% success rate. The two other studies were prospective and used the same definition for hypotension (MAP < GA), with epinephrine beginning in the first 24 h of life. Both analyzed epinephrine as the first line of treatment and had similar failure rate. As the definition of success of the intervention was MAP 15% higher than gestational age, the failure rate of 37% may be overestimated. Although the number of studies is small, the potential use of epinephrine as an alternative for the treatment of refractory hypotension in preterm infants who are receiving the maximum dose of dopamine can be highlighted.

We did not find prospective studies analyzing the impact of norepinephrine in the hypotensive status, with only two retrospective studies with different definitions of hypotension. One of them used the definition of hypotension as MAP < GA, but the onset time of the intervention was later and it was not the first-choice treatment, which may have contributed to a low failure rate (2%). Prospective studies using norepinephrine to evaluate its potential use as an alternative in refractory hypotension are needed, especially after Saini et al. suggested that septic shock in preterm infant is primarily due to vasoregulatory failure [43••].

Regarding vasopressin, there is only one prospective study, with a very small number of patients [10•]. The absence of other prospective studies, the different definition of hypotension, and the small number of cases make it difficult to interpret the results in these publications.

Regarding the use of corticosteroids, we identified four studies, each of them using different definitions of hypotension. The only one that used the definition of MAP < GA was a prospective study that used hydrocortisone for dopamine-refractory hypotension, with a low failure rate (8.3%). Because of the small population of the study, more prospective studies are needed, but hydrocortisone may be a potential alternative for the treatment of dopamine-refractory hypotension.

Conclusion

We evaluated the drug's efficacy in removing the premature baby from the hypotensive state. Each therapy has its own side effects (known and yet to be confirmed), and the choice of anti-hypotensive therapy should be individualized, considering the possible short-term and long-term consequences.

Additionally we identified that classically used medications (volume resuscitation, dopamine, and dobutamine) in the treatment of hypotension have little evidence of efficacy in rescuing the preterm infants from the hypotensive state. We only found one study analyzing saline solution 0.9%, with a low success rate. No study analyzing dobutamine has been identified using the most commonly used definition of hypotension. New therapies are emerging with potential benefits, especially in refractory hypotension such as epinephrine and norepinephrine, but more and bigger prospective studies are needed.

The number of studies exploring the management of hypotension in preterm infants over 26 years was small, and with a wide variation in their results. The lack of consensus in the definition of hypotension in this population makes it difficult to interpret the findings described by the authors. The literature review should be careful, considering the definition used for hypotension, the time of onset, the volume status in which the patient was, and if the drug was used as the first line of treatment or not. Considering the increase in the rate of prematurity in developed and developing countries, with frequent need for hospitalization of these infants in the Intensive Care Unit, research on this topic is highly recommended.

Compliance with Ethical Standards

Conflict of Interest
Felipe Y. Matsushita, Vera L. J. Krebs, and Werther B. de Carvalho declare no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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This study demonstrate that preterm newborns with septic shock have an increased cardiac output with a normal ejection fraction. This suggests that the cause of the shock is more related to a vasoplegia.

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