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Cardiovascular Drug Therapy for Human Newborn: Review of Pharmacodynamic Data

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Abstract

Background: Circulatory failure in preterm and term newborn infants is commonly treated with inotropes or vasoactive medications. In this structured literature review the available data on pharmacodynamic effects of the inotropes adrenaline, dobutamine, dopamine, levosimendan, milrinone, noradrenaline, and the vasoactive drugs vasopressin and hydrocortisone are presented. **Methods:** Structured searches were conducted to identify relevant articles according to pre-defined inclusion criteria which were human clinical trials published after 2000.

Results: Out of 101 identified eligible studies only 22 studies met the criteria for evidence based practice guidelines level I to IV. The most prevalent pharmacodynamic effects were increase in blood pressure and/or heart rate, which were also the most frequently studied circulatory parameters. **Conclusion:** This review demonstrates the need for further systematic studies on all reviewed drugs with incorporation of novel non-invasive biomarkers in this vulnerable patient group, for more timely and appropriate treatment for clinical efficacy.

Keywords: Cardiac, Circulation, Inotrope, Pharmacodynamic, Neonate, Preterm.

1. INTRODUCTION

Cardiovascular drug therapy, particularly inotrope administration, is a very common practice in neonatal intensive care units (NICU) based on a variety of clinical assessments including; low blood pressure, poor perfusion, poor cardiac functions, decreased urine output which are considered as indicators of circulatory failure. However this

practice has wide variations from centre to centre, even from clinician to clinician [1]. A national registry study of the Norwegian Neonatal Network database has provided data from newborns reporting inotrope treatment in 3 % of all NICU admissions, of whom 28 % were in the extremely low gestational age (ELGAN) population and 84 % received dopamine as first choice treatment during the first week of life [2]. Similar data from USA shows a 25 % prevalence of inotrope use in very low birth weight newborns with 83 % of those who began treatment on the first 2 days of life receiving dopamine alone [3]. In both studies the timing and choice of treatment differed amongst centres.

Neonatal circulatory failure may occur secondary to many conditions that vary according to gestational age. In preterm infants transitional circulation within the first 3 days of life may be associated with circulatory failure due to immature cardiovascular system, rarely hypovolemia, decreased cardiac function, together with relative adrenal insufficiency, or perinatal hypoxia. At a later stage patent ductus arteriosus, sepsis, necrotising enterocolitis are the conditions responsible for circulatory failure in the preterm population. Whereas in term babies perinatal asphyxia, congenital cardiac defects, sepsis or persistent pulmonary hypertension are the main causes for circulatory failure requiring treatment.

Most commonly used medications include dopamine, dobutamine, epinephrine, norepinephrine, milrinone, and levosimendan. Vasopressin and hydrocortisone although not categorized as inotropes are also used quite frequently along with inotropes for circulatory failure. Although there is a large body of evidence regarding effects of these medications in adults and children, the reported experience in newborns is not as comprehensive. The drugs are often administered according to the preference or experience of the clinician instead of solid evidence based practice. The choice of appropriate drug for the particular clinical condition, the dosing, and the evaluation of the response to treatment are still not adequately studied in the newborn population. In a feasibility study of early blood pressure management in preterm newborns it has been emphasized that it is very difficult to perform randomized placebo controlled trials with inotropes which leaves the clinician with many unknowns [4]. One drug which works well for one clinical condition may have deleterious effects in another necessitating good knowledge and careful evaluation of the patient. The clinician in the NICU is often faced with the challenge of first identifying the exact problem, second deciding about the best medication and appropriate dose for that condition and third evaluating the response to treatment. The challenge that the clinicians are facing is reflected in the wide range of variability of their choice while treating newborns with circulatory problems. A recent survey about physicians' preferences to treat hypotensive preterm newborn infants has shown the wide diversity of the clinical practice. The diversity is further exaggerated by the variable dosage regimes used in the clinical practice [5].

The purpose of this study was to conduct a structured literature review of published research on the use of medications listed above in neonates and to report pharmacodynamic (PD) effects as applicable. We believe that a thorough review of literature on PD effects of the commonly used medications may help clinicians to use an evidence based practice in the treatment of circulatory failure and reveal the knowledge gaps. This will enable better clinical trial designs and wider acceptance of the clinical equipoise. However it should be noted that this study is primarily focused on short term effects and therefore long term outcome data is not presented; mainly because it is already known that existing studies in newborn infants reporting short term PD effects do not address meaningful long term endpoints, such as mortality or neurodevelopmental impairment – this deserves to be emphasized.

2. STUDY DESIGN

2.1. Search Strategy

The following databases for studies addressing the use of cardiovascular (CV) drugs in neonates and their PD effects were searched: Medline, Embase, Web of Science, WHO ICTRP, ClinicalTrials.gov and the Cochrane Database of Systematic Reviews from 2000 to 2017 with the final search performed on 23 March 2017. References of initially selected studies were also searched for potential additional articles and thus some publications prior to 2000 were also included. Only human studies performed in newborns were included. Preclinical and animal studies were excluded. There were no language restrictions. A search strategy for the mentioned databases was devised with the help of a trained clinical librarian. The review question was broken down in its constituent entities in accordance with PICO structure to contain information on the Population, Intervention and Outcomes to be measured [6, 7]. Intervention facet included CV drugs: dopamine, dobutamine, epinephrine, norepinephrine, milrinone, levosimendan, vasopressin and hydrocortisone. Outcomes were categorized by a PD effect facet that included: blood pressure, heart rate, systemic vascular resistance, pulmonary resistance/flow, superior vena cava (SVC) flow, cardiac output, cardiac functions, renal blood flow, urine output, superior mesenteric artery flow, cerebral flow, peripheral or organ perfusion and blood lactate levels. These PD effects were selected based on the NEO-CIRC consortium activities to define neonatal shock by novel biomarkers [7]. The search covered each entity by its own facet consisting of subject headings and (free text) keywords. Search results were provided for every inotrope separately, combined from individual databases and de-duplicated.

2.2. Data Review and Analysis

Initial selection of studies by title and abstract was performed by four reviewers (EE, MCB, CK, and LM) and these studies were retrieved for full assessment. Studies were eligible for inclusion in this review when they fulfilled the following criteria: studies with participants aged between 0 and 28 days of life including preterm infants; CV drugs administered by continuous infusion, except in the case of hydrocortisone which can be administered by divided doses; inotropes administered on their own or in conjunction with another vasoactive medication; the dose or drug infusion range must be provided; no restrictions on dose, route or duration of drug administration; studies written in different languages, reports from conference proceedings and other grey literature to be considered if they met the inclusion criteria. The quality of studies was evaluated according to the rating system shown in Figure 1 [8].

---- Insert Figure 1 ----

Figure 1. Evidence rating system. *Adapted from Melnyk B.M & Fineout-Overholt E. (2011). Evidence-Based Practice in Nursing and Healthcare: A Guide to Best Practice 2nd edition (p. 12). Copyright 2011 by Wolters Kluwer Health / Lippincott Williams & Wilkins.*

3. RESULTS

A total of 1235 potential relevant studies were identified by the initial search, after duplicates removed. Of these 790 were excluded on the basis of title and abstract. The remaining 445 were fully assessed for inclusion and a further 344 papers were rejected, leaving 101 studies for final assessment.

The medications whose PD effects in newborns were searched in the literature are presented in the remainder of this section and the most relevant findings discussed. Table 1 presents those effects supported by at least a Level IV evidence. Additional tables for each medication with information about the studies included, study type, level of evidence, patient subgroup and dose range are presented as supplementary material.

The literature search process is outlined in Figure 2.

----Insert Figure 2 ----

Figure 2. Literature review process. Used abbreviations are DOB: Dobutamine, DA: Dopamine, EPI: Epinephrine, HC: Hydrocortisone, LS: Levosimendan, MIL: Milrinone, NE: Norepinephrine, VAS: Vasopressin.

3.1. Dobutamine

Physiology: Dobutamine is a synthetic, not endogenous, sympathomimetic drug used in the treatment of heart failure and cardiogenic shock. It increases myocardial contractility, stroke volume and heart rate via direct stimulation of myocardial α and β_1 receptors. It also exerts weak vasodilatory effects via β_2 receptors [9].

Dosing: The dose in neonates varies between 5-20 mcg/kg/min.

Evidence & PD Effects: Dobutamine has various pharmacodynamics effects in all age groups and is generally considered as the second most important drug after dopamine for treatment of neonatal circulatory failure.

In many clinical trials the effect of dobutamine is usually compared to dopamine for treating hypotension where the latter has been found more efficacious in increasing blood pressure [10-12]. This finding has also been reported in a Cochrane review of dopamine vs dobutamine; but none of the studies in this review reported the incidence of adverse long term neurodevelopmental outcome [13].

On the other hand one randomized clinical trial (RCT) reported that both dopamine and dobutamine increased blood pressure similarly [14].

Increase in heart rate (chronotropic effect) is another pharmacodynamic effect of dobutamine which has been shown in newborn population in one RCT [15]. The same investigators also studied cerebral perfusion by cerebral Doppler and cerebral NIRS measurements but dobutamine did not cause any change in the assessed parameters compared to placebo [15]. Another RCT comparing dobutamine to dopamine for the chronotropic effect did not reveal any significant difference between the two medications, with urine output also similar between groups [14].

Cardiac effects of dobutamine deserve particular attention and have been studied by echocardiographic assessments. It has been shown to cause more increase both in right and left ventricular output compared to dopamine. One study has reported that dobutamine caused 21% increase in left ventricular outflow (LVO) compared to 14 % decrease observed with dopamine [12, 16]. On the other hand comparison on cardiac contractility between dopamine and dobutamine has not revealed any difference [16]. One of the most important effects of dobutamine in newborn infants is the impact on SVC flow. Dobutamine has been shown to be superior to dopamine in increasing SVC flow which is considered to represent cerebral blood flow [17]. Increase in SVC flow was also shown in a placebo controlled trial [15]. This effect is particularly important for the treatment of transitional circulatory failure in the

preterm infant, as early circulatory impairment is believed to be related to an immature myocardium unable to overcome the increase in afterload in extremely low birth weight (ELBW) infants at birth.

The impact of dobutamine in peripheral circulation in newborn infants has been assessed in a few studies. In a preterm group it has resulted in increased mesenteric blood flow assessed by Doppler ultrasound [18].

Conclusion: So far the best documented effects of dobutamine in newborn infants have been increased ventricular output and increased SVC flow, but there is no information showing significant benefits of dobutamine on long term neurodevelopmental outcome compared to dopamine. There is still need for RCTs to investigate the right dose, timing and treatment impact on haemodynamics.

3.2. Dopamine

Physiology: Dopamine effects are exerted either by directly stimulating α and β adrenergic receptors and dopaminergic receptors or indirectly by its conversion to norepinephrine at sympathetic nerve endings. The cardiovascular effects of dopamine are dose related.

Dosing: Commonly used dosage regimes in clinical practice start at 2-5 mcg/kg/min and increase by steps of 5 mcg/kg/min up to 20 mcg/kg/min. Low dose dopamine at 2-5 mcg/kg/min affects mainly dopaminergic receptors and as dose is further increased β and α adrenergic effects become apparent. The increase in blood pressure is due to increase of systemic vascular resistance via vasoconstriction and increase in cardiac contractility and output [19].

Evidence & PD Effects: Dopamine is the most frequently used inotrope in newborns and therefore the most studied inotrope on different organ systems [19]. There is evidence from a systematic review of 5 RCTs, published in 2003, that dopamine is more effective than dobutamine in the short term treatment of low blood pressure in preterm infants. Number needed to treat is 4.4. However, in the absence of data assessing long term outcomes and safety of dopamine, no firm recommendations could be made [13]. A RCT comparing dopamine with low dose epinephrine has shown that both drugs had similar effects in treating hypotension in low birth weight infants but epinephrine resulted in higher heart rate compared to dopamine [20]. Another RCT shown that dopamine was superior to volume infusion with albumin 20% of 15ml/kg in increasing blood pressure [21]. In this study LVO was also increased with dopamine. In a randomized double blind trial comparing dopamine with dobutamine systemic vascular resistance was increased with both inotropes but more so with dopamine [12]. In another observational study the increase in blood pressure was related to the increase in systemic vascular resistance [22].

Impact of dopamine on heart rate was observed in various other clinical trials. In a group of patients with diaphragmatic hernia increased heart rate was reported after dopamine treatment [23]. Similar effect was observed in preterm infants who received dopamine after administration of indomethacin [24] and in preterm infants with septic shock [25].

Pulmonary pressures can be only assessed indirectly in neonates by echocardiography and the open fetal channels make these assessments even more challenging. One study found evidence for a pulmonary vasoconstrictor effect of dopamine in preterm infants with PDA. However, although increased vascular resistance appears to be a consistent effect of dopamine, the authors reported that there is no information at present that dopamine administration results in clinically relevant and significant increases in pulmonary pressures in preterm or term neonates without

significant left to right shunting across the PDA [26]. Another study reported that dopamine administered to normalise hypotension in preterm infants had variable effects on pulmonary haemodynamics and its effect should be monitored carefully and, if possible, by echocardiographic measurements of pulmonary pressures [27].

SVC flow which is considered to be an important parameter of neonatal circulation was assessed in newborn infants receiving dopamine in a few studies. A RCT comparing dopamine with dobutamine did not detect any effect of dopamine on SVC flow [21]. On the other hand an observational study found that dopamine administration in infants with patent ductus arteriosus (PDA) resulted in 30 % increase in SVC flow [17, 26].

Although dopamine is a well-known inotrope the impact on myocardial contractility is not thoroughly investigated in newborn infants. In infants developing low SVC flow in the first day after birth neither dopamine nor dobutamine increased contractility measured by mean velocity of circumferential fractional shortening versus left ventricular wall stress. However, dopamine at 20 mcg/kg/min increased LV wall stress suggesting increased afterload [16].

Dopamine is considered to have significant effects on renal function and urine output. Low dose dopamine received wide acceptance among neonatologists as treatment for low urine output. However there is only one RCT assessing renal effects of dopamine published in 1988 which showed that 2 mcg/kg/min dopamine increased urine output significantly compared to controls [28]. In normotensive oliguric preterm newborns 2.5 mcg/kg/min dopamine infusion increased urine output and the same effect was observed in sick newborns with 2 mcg/kg/min dose [29, 30]. In a group of indomethacin treated preterm infants which compromises urine output, early dopamine administration at 5 mcg/kg/min after indomethacin increased urine output [24].

The effect of dopamine on mesenteric blood flow is unclear. There is only one RCT published in 1995 reporting decreased superior mesenteric artery pulsatility index with both dopamine and dobutamine at 10 mcg/kg/min dose [18]. More recently mesenteric blood flow was found decreased in one observational study where dopamine was administered for hypotension, whereas it was found increased in the study where dopamine was given for low urine output [22, 24].

Cerebral effects of dopamine have been studied by cerebral Doppler measurements or NIRS. Among hypotensive LBW infants, cardiovascular support with low/moderate-dose dopamine or low-dose epinephrine increased cerebral perfusion, as indicated by increased cerebral tissue oxygenation [20]. Two other observational studies did not find any significant difference in cerebral blood flow velocity or middle cerebral artery pulsatility index [21, 24].

The impact of dopamine on peripheral perfusion is also unclear. In a group of newborns with congenital diaphragmatic hernia, dopamine increased blood pressure with no effect on skin microcirculation and perfusion [23]. However an observational study where dopamine was administered to hypotensive VLBW infants found that skin blood flow increased in parallel with blood pressure [31].

Dopamine has been shown to suppress pituitary function in preterm infants, resulting in decreased levels of thyroid-stimulating hormone, thyroxine and prolactin, but extensive description of dopamine related endocrine effects is out of scope of the current literature review [14, 32-35].

Conclusion: Overall dopamine is the most studied inotrope in the neonatal population. However, some of the pharmacodynamic effects are still unclear; even with respect to its use for treating hypotension where there are still

unknowns about dosing and the effect on cardiac function. There are many unresolved issues to address including the definition of circulatory failure in preterm infants, the best biomarkers to assess circulatory failure and the best biomarkers to guide the titration of the inotropic support. Dopamine effects on cerebral, mesenteric and peripheral haemodynamics and their effect on long term clinical outcomes deserve to be studied in well-designed clinical trials.

3.3. Epinephrine

Physiology: Epinephrine is a naturally occurring catecholamine that is secreted by the adrenal medulla. It exerts its effects on α and β adrenoreceptors. Epinephrine is also commonly referred to as adrenaline.

Dosing: It is prescribed in a dose range of 0.05-1.00 mcg/kg/min although higher doses up to 2.5 mcg/kg/min are also used. At lower doses it is postulated to work primarily on β receptors causing systemic and pulmonary vasodilatation whilst increasing heart rate and cardiac stroke volume. At higher doses, greater than 0.3 mcg/kg/min, it is believed to act primarily on α receptors causing intense systemic vasoconstriction [19]. It needs to be infused via long central line due to its vasoconstricting properties.

Evidence & PD Effects: A total of 5 studies, two of them RCTs, looking into the use of epinephrine in neonates were identified. The use of epinephrine in newborns is generally reported for hypotension unresponsive to dopamine and/or dobutamine, but there are in fact very few randomized controlled trials assessing the effect of epinephrine on pharmacodynamics in newborn infants. A 2004 Cochrane review identified only 2 trials [36], one of which was only available in abstract form and the other was ongoing at the time of publication [20, 37], both focusing on short term haemodynamic changes and none reporting effects on mortality or neurodevelopmental outcome. Phillipos et al. reported that epinephrine infusions between 0.125-0.5 mcg/kg/min increased blood pressure and heart rate in neonates weighing over 1750 grams [37]. Pellicer et al. [20] reported, as part of a randomized controlled trial (RCT) comparing effects of epinephrine to dopamine in low birth weight infants (less than 1500 grams) with hypotension, the existence of an association between epinephrine infusion and increased blood pressure and heart rate. In the same RCT a similar pattern with dopamine was reported; whilst cerebral near infrared spectroscopy (NIRS) revealed increased cerebral oxygenation with both drugs but with a larger increase of cerebral blood volume with epinephrine in newborns < 28 weeks gestational age. Looking at short and medium term effects of epinephrine versus dopamine in the same cohort, both medications increased blood pressure significantly and at 24-36 hours into treatment epinephrine resulted in significantly increased heart rate and lactate levels as well as glucose [38]. Two retrospective studies also reported increased blood pressure and heart rate in newborns with hypotension despite already being on dopamine and dobutamine. The starting dose of epinephrine was already on the higher range with 0.2 and 0.3 mcg/kg/min in these studies [39, 40].

The fact that epinephrine is potentially a strong vasoconstrictor (as this effect is dependent on the dose given) has led to concerns about peripheral circulatory problems in newborn infants receiving it. A prospective cohort study looking at the impact of dopamine, epinephrine and norepinephrine reported that although blood pressure and heart rate was increased significantly, microcirculation assessed by Sidestream Dark Field (SDF) imaging was unchanged. No difference was observed in lactate levels either [23].

Conclusion: Our literature search of published studies on the use of epinephrine in newborns has revealed that it is commonly used in circulatory failure when patients are unresponsive to other inotropes [41]. The possibility that

epinephrine may result in increased lactate and impair peripheral circulation is still of concern to neonatologists, particularly for very low birth weight (VLBW) newborns with circulatory failure. There is the need for more clinical trials exploring the effects of epinephrine on different pharmacodynamics parameters.

3.4. Hydrocortisone

Physiology: Cortisol is a glucocorticoid synthesized in the zona fasciculata of the adrenal gland. Glucocorticoids increase adrenergic receptor expression in the cardiovascular system and increase responsiveness to the circulating catecholamines epinephrine and norepinephrine, thereby increasing cardiac contractility and vascular tone. They also decrease catecholamine metabolism and inhibit re-uptake by receptors. Inadequate cortisol levels therefore are considered to be associated with poor cardiac functions and excessive vasodilatation from a circulatory stand point.

Hydrocortisone (HC) produces the same effects as cortisol; within hours of administration it helps to increase blood pressure by decreasing catecholamine metabolism and inhibiting reuptake. It also increases muscle cell calcium availability and suppresses vasodilator NO and prostaglandin synthesis. The later effect of HC is to upregulate adrenergic receptors by gene expression [42, 43].

Dosing: 0.5-1mg/kg/dose every 8-12 hours depending on gestational age and response of the patient.

Evidence & PD Effects: Hydrocortisone is used in catecholamine resistant shock in all age groups. It is one of the main medications in paediatric septic shock [44]. Its use is mostly based on relative adrenal insufficiency which is a potential contributing factor to circulatory failure under stressful conditions including sepsis. Relative adrenal insufficiency is defined as a random cortisol level < 15 mcg/dl in adults but it is less clear in neonates [42].

Regarding the definition a low level general approach is to accept serum cortisol level < 5mcg/dl in newborn infants although values of 9, 13 or 15 mcg/dl have also been used. Low cortisol levels have been shown in preterm and term infants requiring vasopressor support [42, 45]. This finding has led HC to be included in management of neonatal hypotension or shock unresponsive to inotropes by experts with words of caution about short term adverse effects including hyperglycaemia, increased risk of sepsis and spontaneous intestinal perforation especially if administered concomitantly with indomethacin and long term adverse effects including poor neurodevelopmental outcome [46, 47].

Several randomized controlled trials (RCT) have investigated the efficacy of HC in treatment of hypotension in newborn infants. Prophylactic use of HC in a preterm population has also resulted in less hypotension and less vasopressor requirement [48]. On the other hand first line use of HC in combination with Dopamine is effective in increasing blood pressure [49]. One RCT has used HC for refractory hypotension if Dopamine requirement was >10 mcg/kg/min and stress dose of HC produced response with increased blood pressure [50]. In another RCT HC was administered for hypotension if >14 mcg/kg/min Dopamine and/or Epinephrine was required and resulted in decreased inotrope dose [51].

Three systematic reviews including one Cochrane data analysis performed in the years 2007, 2010 and 2011 have reported that HC is effective in increasing blood pressure in preterm newborns with refractory hypotension and result in decreased inotrope requirement however without positive clinical outcome; highlighting also that potential long-term sequelae of HC administration in preterm neonates have not been adequately studied [52-54].

In an observational study of 15 preterm and 5 term newborn infants with hypotension requiring Dopamine >15 mcg/kg/min HC addition resulted in increase in blood pressure and stroke volume assessed by echocardiography [55]. There are also studies reporting the efficacy of HC in late onset circulatory failure of preterm infants and in term newborns after cardiac surgery [56, 57].

The effect of hydrocortisone is reported to start within 2-4 hours in most of the prospective studies and one retrospective case-control study [58]. This rapid response is most likely due to non-genomic effects followed by the genomic effects reflected as catecholamine receptor upregulation.

In a recent review on HC dosing Watterberg suggests to give a test dose of 1mg/kg for refractory hypotension and if there is no response within 2-4 hours to discontinue the medication. If there is a response with increased blood pressure HC should be continued with 0.5mg/kg/dose every 12 hours in preterm infants < 34 weeks gestation and every 6-8 hours in newborns ≥34 weeks gestation. If hypotension reoccurs the interval can be changed to 6 hours and the dose can be increased to 1mg/kg [59]. When to start weaning HC is also a challenge for the clinician. Neonatologists generally prefer to wean when vasopressors are off or are at a low dose of infusion. In preterm infants relative adrenal insufficiency may last for weeks and may necessitate prolonged administration however early weaning as possible is recommended.

Conclusion: Overall clinical trials on pharmacodynamic effects of HC in newborns has mainly focused on its effects on blood pressure and inotrope requirement disregarding the regional effects including cerebral, mesenteric, renal blood flow or peripheral circulation. However circulatory failure may be present despite normal blood pressure and may result in unfavourable short and long term prognosis. Now that effect of HC on blood pressure has been proven, studies investigating the effects of the medication on circulation with a broader perspective are warranted.

3.5. Levosimendan

Physiology: Levosimendan is a calcium sensitizer, which enhances the sensitivity of contractile myofilaments to intracellular calcium concentration by binding to the C cardiac troponin. It increases myocardial contractility but this effect is not mediated by adrenergic receptors [60]. It also has vasodilator effects attributed to activation of sarcolemmal K-sensitive adenosine triphosphate (KATP) channels of vascular smooth muscle cells.

Another key feature of levosimendan is the activation of mitochondrial KATP channels, which are important mediators of ischemic preconditioning, and may also be protective in other tissues, such as kidney and brain.

Dosing: The most commonly administered infusion doses of levosimendan are 0.1-0.2 mcg/kg/min in neonates.

Evidence & PD Effects: Currently levosimendan use in newborns has been limited to patients undergoing cardiac surgery who develop myocardial failure. Increased cardiac output and cardiac index has been shown in two RCTs performed with newborns after heart surgery [61, 62]. One of those studies has also reported decreased heart rate and lactate levels with treatment [61].

Cerebral and peripheral tissue oxygenation measured by NIRS have been found to be increased with levosimendan in a group of newborns undergoing corrective surgery for heart disease [63].

Conclusion: The proven effects of levosimendan currently makes it an alternative in newborns with cardiac failure and increased afterload but requires careful follow up for hypotension may occur. Low grade evidence data exists in the form of a case report about its use in preterm population with improvement in LVO post-cardiac surgery [64].

3.6. Milrinone

Physiology: Milrinone is Type III phosphodiesterase inhibitor with inotropic and lusitropic effects on the myocardium. Due to increased c-AMP levels it also has vasodilator effects both in systemic and pulmonary circulation [65].

In newborn infants milrinone has been used for postoperative cardiac failure following heart surgery and is considered as an option for persistent pulmonary hypertension of newborn [66].

Dosing: The most commonly administered infusion dose of milrinone is 0.2 -1 mcg/kg/min with or without a previous bolus of 50 mcg/kg. However, based on a recent pharmacokinetic study with mathematical simulations it has been proposed to give a bolus infusion of 0.73 mcg/kg/min for 3 h followed by a 0.16 mcg/kg/min maintenance infusion in preterm infants [67].

Evidence & PD Effects: In newborn infants milrinone has been used for postoperative cardiac failure following heart surgery and is considered as an option for persistent pulmonary hypertension of newborn [66]. In a RCT of milrinone and levosimendan in post-operative newborns undergoing cardiovascular surgery, infants who received milrinone or levosimendan showed a similar cerebral NIRS profile along the first 24h post-surgery, without differences between both groups. This effect consisted of a time-dependent increase in the cerebral tissue oxygenation index and the cerebral intravascular oxygenation (determined by oxyhemoglobin) and a decrease in the cerebral fractional oxygen fraction. However, the peripheral oxygenation differed between both groups along this time period, showing an increase in the levosimendan group and a decrease in the milrinone group. In the same study, there were no significant differences between groups regarding serial echocardiography parameters; however lactate level was increased in the milrinone group [63].

Cardiac effects of milrinone were also studied in a very preterm group and no significant difference was observed between milrinone and placebo administered prophylactically with regards to median SVC flow or right ventricular output. Infants randomized to milrinone had significantly higher heart rate and lower mean blood pressure after commencing the infusion although no significant difference was seen in incidence of hypotension in infants randomized to milrinone (50% versus 38% for placebo). Significantly more infants randomized to milrinone had tachycardia (67% versus 22%) during study drug infusion ($P < .0001$) [68].

Preterm infants at high risk of developing cardiac syndrome after surgical ligation of patent ductus arteriosus and treated with milrinone were found to have lower incidence of ventilation failure, less need for inotropes (19% vs 56%; $P = .01$), and a trend towards improved oxygenation as compared with another historic cohort of infants with similar characteristics not treated with milrinone [69].

Conclusion: Experience with milrinone in newborns points to its use in cardiac failure during the postoperative period of cardiac surgery including ductal ligation. Attention should be paid to the development of hypotension. Treatment of persistent pulmonary hypertension of newborn (PPHN) with milrinone requires further investigation

although there are some case series papers that have found some benefits (fall in oxygenation index, decrease in the inhaled nitric oxide dose, an increase in blood pressure or an increase in indicators of myocardial performance) after milrinone infusion in newborn (term and preterm) infants with pulmonary hypertension [70-74].

3.7. Norepinephrine

Physiology: Norepinephrine (NE) is a catecholamine neurotransmitter released from adrenergic nerve endings. It has strong α -mimetic and β_1 mimetic effects, and lower β_2 effects. At lower doses increased contractility and heart rate are observed, at higher doses net effects are increased vascular resistance and blood pressure [75]. Vasoconstriction may also increase afterload resulting in increased myocardial work load. Generally NE is preferred to be used with caution for it may cause decrease in organ perfusion due to strong vasoconstrictor effect.

Dosing: Dose range reported in literature varies between 0.02-1 mcg/kg/min [76].

Evidence & PD Effects: Norepinephrine is used in children particularly in dopamine unresponsive shock however data in newborns is extremely scarce [44]. In a group of children including newborn infants NE has been shown to increase blood pressure on a dose dependent fashion [77]. One prospective cohort study has shown increased blood pressure with NE in newborns with congenital diaphragmatic hernia with no change in microcirculation measured by SDF imaging where peripheral microvascular bed is assessed [23]. In one observational study in term newborns with septic shock NE use has resulted in increase in blood pressure and urine output and decrease in lactate levels [78]. Surprisingly NE has a pulmonary vasodilator effect which may make it an alternative in newborn infants with refractory PPHN [79]. This effect is present if pulmonary vascular tone is already increased. Possible mechanisms for the pulmonary vasodilatory effect are the stimulation of nitric oxide (NO) synthesis via α_2 receptors.

One retrospective cohort study in 48 preterm newborns has reported that NE is effective in increasing blood pressure however 31% of patients experienced tachycardia. Poor neurodevelopmental outcome was also reported for this cohort [80].

Conclusion: Literature regarding NE use in human newborns is limited to observational studies presented above possibly due to strong vasoconstrictor effect which may result in decrease in organ blood flow. Adequate fluid replacement is necessary before starting NE to avoid ischemia and drug should be administered through central line.

Current data suggests cautious use of NE in newborn infants particularly with regards to tachycardia and hypertension and clinical trials are warranted.

3.8. Vasopressin

Physiology: Vasopressin (VP) or arginine vasopressin (AVP) is an endogenous peptide produced in the hypothalamus. It is synthesized as a prohormone called preprovasopressin which is then converted to provasopressin and finally to vasopressin in pituitary gland [81]. There are three types of vasopressin receptors; the V1 (V1a) receptors are expressed in vascular smooth muscles and are responsible from the vasoconstrictor effect, while V2 receptors are present on the basolateral membrane of the tubular epithelium of collector ducts of kidney and mediate antidiuretic and osmoregulatory effects by increasing c-AMP levels. V3 (V1b) receptors are present in the pituitary gland only. Additionally, VP also exerts some action via oxytocin (OTR) and purinergic receptors [81, 82].

Vasopressin causes vasoconstriction via V1 receptors through several mechanisms; by releasing calcium from sarcoplasmic reticulum, potentiation of vasoconstrictive effects of norepinephrine, inactivation of ATP-gated potassium channels and inhibition of nitric oxide and atrial natriuretic peptide-induced cGMP production [83].

However unlike catecholamines, VP induces vasodilatation in pulmonary, renal and cerebral circulation through V2 or OTR mediated NO release. Vasodilator effect is exhibited particularly at low doses [83, 84].

Although it is known as antidiuretic hormone (ADH) paradoxically VP has a diuretic effect in patients with septic shock possibly through V1 receptor mediated selective renal efferent arteriolar constriction, NO mediated afferent arteriolar vasodilatation, and down regulation of V2 receptors [82].

Vasopressin has a short half-life (5-15 minutes) and its pressor effect lasts for 30-60 minutes necessitating continuous intravenous infusion. It is metabolised by renal and hepatic vasopressinase enzymes [81]. Terlipressin (TP) is a synthetic analogue of vasopressin which has a longer half-life making it possible to deliver in boluses every 4-12 hourly [81].

Dosing: Dose for VP is variable and is reported at a range of 0.00001-0.003 unit/kg/min. Optimal dose for TP and timing have not been clearly established, and dosing has been variable in literature; 2-20 mcg/kg every 4-6 hourly bolus or continuous infusion of 4-20 mcg/kg/h.

Evidence & PD Effects: Low-dose vasopressin therapy has been considered as a rescue therapy for shock unresponsive to catecholamines and/or steroids in paediatric population [44].

It has a more selective effect on V1 receptors and may be more effective as a vasoconstrictor in septic shock. However there are some disadvantages including potentially greater untoward effects on peripheral perfusion [85-87].

Many studies have reported that infusion of low-dose vasopressin decreases catecholamine requirements, maintains blood pressure and cardiac output, decreases pulmonary vascular resistance (PVR), and increases urine output. However currently there are very few controlled trials investigating the role of AVP/TP in newborns with circulatory failure or shock.

A Cochrane systematic review in 2013 has not identified any RCT for AVP/terlipressin use in newborns. In case series both medications were reported to be effective in increasing blood pressure, urine output and decreasing inotrope requirements [88].

A recent systematic review, meta-analysis and trial sequential analysis of literature published on AVP use in paediatric and neonatal shock has reported increased mean arterial pressure (MAP) and decreased heart rate with AVP without positive effect on mortality [89].

Experience with AVP/TP in neonates has been more focused on term newborns with congenital heart disease who develop hypotension after surgery, newborns with PPHN or with septic shock all reporting increased blood pressure, most reporting increased urine output and some reporting decreased lactate levels coming from retrospective studies or case series [85, 90-95].

In the preterm population the data is even scarcer. One small RCT of vasopressin use in preterm infants during transitional circulation (< 24 h of age) has shown that vasopressin increased blood pressure in a similar fashion like dopamine [96].

Other reports on VP use in preterm infants have been observational studies or case series with low grade of evidence and therefore discussed only briefly in the following.

In a case series of 6 preterm newborns with catecholamine/steroid refractory hypotension AVP has increased blood pressure and urine output. However the effects were sustained in the 3 patients with septic shock and not sustained in the non-septic group [97]. In adult population patients in septic shock tend to have lower levels of VP as disease progresses due to depletion of neurohypophyseal stores also due to an increase in the levels of NO and norepinephrine, however this has not been proven in children. In fact in a group of children with septic shock AVP levels have been found elevated compared to patients without shock [98]. The course of AVP levels in newborns with shock remains to be investigated since low levels of AVP during shock regardless of the cause has been found to be associated with a better response to exogenous AVP/TP treatment [99].

In a retrospective analysis of 33 separate VP infusions in 20 ELBW infants with refractory shock unresponsive to catecholamines/corticosteroids VP has resulted in increased blood pressure and decrease in inotrope requirement [100]. In a case series of 4 preterm patients low dose vasopressin (0.3-0.8mU/kg/min) has been effective in increasing blood pressure, renal blood flow and urine output.

One observational study has reported 22 preterm infants with 75 % response in the septic shock group and 50 % response in the group with other causes of hypotension. In this group 4 patients were in the transitional circulation period. All patients responded with increase in BP and urine output but mortality was 100% [101].

The reason underlying rare use of AVP in the neonatal population may be the fear of potential untoward effects of the medication characterized with peripheral ischemia due to severe vasoconstriction, decreased mesenteric or renal blood flow, hyponatremia, elevated liver enzymes and effects on platelet aggregation which have been reported in adults [102]. These effects could be more overt if AVP is co-administered with another potent vasoconstrictor norepinephrine [82, 87]. Most of the case series from newborns have not reported any of these effects. Good fluid replacement prior to initiation of AVP/TP may help to overcome the peripheral and mesenteric ischemic effects.

One other reason about infrequent use of VP in newborns is the paucity of data about when to start the medication. In adult studies VP is started if norepinephrine requirement exceeds 0.6 mcg/kg/min [103]. However there is no similar data in neonatal population making it difficult for the physician to take action, although some authors prefer to take the same norepinephrine dose as a limit to start VP, while others prefer higher doses as limit [87, 97].

Conclusion: Both AVP and TP have potential favourable effects in newborns with catecholamine and /or corticosteroid unresponsive shock. The potent vasoconstriction effect necessitates adequate fluid balance before treatment and administration via central venous line. Patients on AVP or TP should be carefully monitored for possible side effects.

There are many unknown issues in the use of these medications in newborn infants. Carefully designed studies are required to answer some of these questions, until then it can be foreseen that use of AVP/TP in newborn population will remain as a rescue or last resort therapy for refractory circulatory failure.

SUMMARY AND CONCLUSION

Historically, neonatology has extensively used therapy or medications that initially look promising, but resulting in suboptimal outcomes or adverse effects over the long term. The physiology of the newborn differs completely from that of paediatric or adult populations - attempting to apply clinical approaches that work well in the older age groups to newborns can create difficulty. Even within the neonatal age group, term and preterm infant populations vary with regards to drug metabolism and responses to treatment. For preterm infants, negative effects on cerebral perfusion are of major concern [104].

Definition of circulatory failure or compromise in neonatology demands further investigation. Current definitions of cardiovascular insufficiency and shock in neonates are based mainly on BP assessment, despite no clear evidence for the “normal BP” for different gestational age groups [105]. The poor correlation between blood pressure and organ blood flow, together with the lack of evidence that treating hypotension improves neurological outcome, impedes the establishment of clear indications for treatment. In spite of this clinicians find it relieving to treat hypotension, presumably because it is an easily obtained physical finding, readily available in neonatal clinical practice and measured continuously without the need of expert input. As a result dopamine has been used most frequently for circulatory support given that it raises blood pressure. Currently, neonatologists prefer to see a reasonable measurement of BP and focus less on the implications that such measurement may have on cerebral or organ perfusion given the underlying pathophysiology. However, the more we learn about cerebral perfusion or organ blood flow, the more we question our current treatment strategies for circulatory failure, which rely on an assessment method that we have conveniently reduced to BP measurement only.

There are new methods for assessment of circulation including cardiac function or tissue oxygenation which may lead to better evidence-based treatment options. Neonatologists should consider using the new methods more often in clinical practice. This may be more labour intensive and more expensive and will for sure represent an intellectual challenge compared to purely looking at BP and starting dopamine; but is a goal worth pursuing in benefit of our neonatal patients. For future studies the use of novel non-invasive biomarkers other than just blood pressure has been discussed elsewhere [106].

The medications reviewed in this article are primarily used by neonatologists for treatment of circulatory failure/hypotension. However, as with other treatment options in neonatology, there are many unknown issues in the use of the reviewed medications in newborns including;

- Which group of patients would benefit most? - What is the right dose for preterm population? - At what stage of circulatory failure should it be started? - If a second/third medication is going to be added when should it be started? Right from the start or after reaching a certain inotrope dose? What is the impact of administering more than one medication at the same time or through the same line? - What are the effects on cerebral, mesenteric blood flow or tissue oxygenation in preterm infants? -What other disadvantages the drug may have especially in preterm infants? Could it have any long term adverse effects with regards to cerebral development?

Unfortunately the current data obtained from the literature review is insufficient to answer these questions. As shown in Table 1 from the year 2000, less than 23 studies have been identified as providing a high level of evidence for the effects of the searched 8 medications – far less than expected. Most of the medications have been assessed with regards to their impact on blood pressure with less emphasis on effects for other components of circulation and organ blood flow. The number of RCTs and systematic reviews are limited even for the treatment of hypotension. Data on long term outcome results are only reported for some of the drugs.

There is an urgent need for well-designed clinical trials for newborns that include long term follow up, specifically for those frequently used medications administered for circulatory support.

CONFLICT OF INTEREST

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Table 1. Levels of evidence (LOE I-IV) for PD effects of most commonly used medications in newborns for circulatory support. (↑: Increase; ↓: Decrease; ↔: No Change).

PD effect	DOB	DA	EPI	HC	LS	MIL	NE	VAS
Blood Pressure	LOE I ↑[13]	LOE I ↑[13]	LOE II ↑[20]	LOE I ↑[52-54]	LOE II ↓[61, 63]	LOE II ↓[63, 68]	LOE IV ↑[23, 80]	LOE I ↑[89]
Heart Rate	LOE II ↑[13, 15]	LOE I ↑[13]	LOE II ↑[20]		LOE II ↓[61, 63]	LOE II ↑[63, 68]	LOE IV ↑[23, 80]	LOE I ↓[89]
Systemic Vascular Resistance	LOE II ↑[12] ↓[16]	LOE II ↑[12]				LOE II ↔[68]		
Pulmonary Flow	LOE II ↑[17]							
Superior Vena Cava Flow	LOE II ↑[15, 17]	LOE II ↔[17]			LOE II ↔[63]	LOE II ↔[63, 68]		
Cardiac Output	LOE II ↑[12, 17]	LOE II ↑[21]			LOE II ↑[62] ↔[63]	LOE II ↔[62, 63, 68]		
Cardiac Functions ¹	LOE II ↔Contractility [16]	LOE II ↔Contractility; ↑LV stress [16]			LOE II ↔ FS and EF, TAPSE [63]	LOE II ↔ FS and EF, TAPSE [63]		
Renal Blood Flow / Urine Output	LOE II ↑[10] ↔[14, 15]	LOE II ↑[10] ↑[28]	LOE II ↔[38]		LOE II ↔[61]			
Mesenteric Artery Flow	LOE II ↑[18]	LOE II ↑[18]						
Cerebral Flow ²	LOE II ↔Doppler/NIRS [15]	LOE II ↑[20] ↔[21]	LOE II ↑[20]		LOE II ↑[63]	LOE II ↑[63]		
Peripheral / Organ Perfusion ³		LOE IV ↔ SDF imaging[23]	LOE IV ↔ SDF imaging[23]		LOE II ↑ HbD-NIRS [63]	LOE II ↔ HbD-NIRS [63]	LOE IV ↔ SDF imaging[23]	
Blood Lactate	LOE II ↔[15]		LOE II ↑[38] LOE IV ↔[23]		LOE II ↓[61, 63]	LOE II ↑[63]		

Used abbreviations are DOB: Dobutamine, DA: Dopamine, EPI: Epinephrine, HC: Hydrocortisone,

LS: Levosimendan, MIL: Milrinone, NE: Norepinephrine, VAS: Vasopressin.

¹ **Cardiac Functions:** In [16] contractility was measured by mean velocity of circumferential fractional shortening versus left ventricular wall stress; while [63] measured shortening/ejection fraction and tricuspid annular plane systolic excursion (TAPSE).

² **Cerebral Flow:** In [15,20] NIRS was used, in [21] Doppler USG was used, in [63] NIRS was used for assessment.

³ **Peripheral/Organ perfusion:** In [23] SDF imaging for measurement of capillary blood flow and density was used, in [63] peripheral NIRS was used for assessment.

Table 2 - Characteristics of included studies investigating the use of dobutamine (DOB).

Reference	Study Type	Level of Evidence	Study Population	Dobutamine infusion dose range
Subhedar <i>et al</i> 2013. [13]	Systematic review	I	Included 5 RCTs (209 patients in total) with neonates born before 37 weeks gestation and less than 28 days of age. No specific definition of hypotension was used.	As in studies [11,18,10,12]
Klarr <i>et al.</i> 1994 [10]	Randomised controlled trial	II	63 neonates (GA \leq 34 weeks) with hypotension and RDS.	5-20 mcg/ kg/min
Greenough <i>et al.</i> 1993 [11]	Randomised controlled trial	II	40 neonates (median GA = 27 weeks) with hypotension	5-15 mcg /kg/min
Roze <i>et al.</i> 1993 [12]	Randomised controlled trial	II	20 neonates (GA \leq 32 weeks) with hypotension	5-20 mcg/ kg/min
Filippi <i>et al.</i> 2007 [14]	Non-blind randomised controlled trial	II	35 neonates with BW <1500grams with hypotension	4-20 mcg/ kg per min
Bravo <i>et al.</i> 2015 [15]	Randomised controlled trial	II	28 neonates (GA \leq 32 weeks) with low superior vena cava flow in the first 24 h of life	5-20 mcg/ kg/min
Osborn <i>et al.</i> 2007 [16]	Randomised controlled trial	II	37 neonates (GA \leq 30 weeks) with low superior vena cava flow in the first 24 h of life	10-20 mcg/ kg/min
Osborn <i>et al.</i> 2002 [17]	Randomised controlled trial	II	42 neonates (GA \leq 30 weeks) with low superior vena cava flow in the first 24 h of life	10-20 mcg/ kg/min

Table 3 - Characteristics of included studies investigating the use of dopamine (DA).

Reference	Study Type	Level of Evidence	Study Population	Dopamine infusion dose range
Subhedar <i>et al.</i> [13]	Systematic review	I	Included 5 RCTs (209 patients in total) with neonates born before 37 weeks gestation and less than 28 days of age. No specific definition of hypotension was used.	As in studies [11,18,10,12]
Greenough <i>et al.</i> 1993 [11]	RCT	II	40 neonates with median GA 27 weeks (range 23-33) randomized to dopamine or dobutamine infusion. Hypotension: systolic BP < 40 mmHg despite receiving a colloid infusion.	5-15 mcg/ kg/min
Hentschel, R. <i>et al.</i> 1995 [18]	RCT	II	20 neonates with GA 25-36 weeks and BW 830 - 2610 g randomized to dopamine or dobutamine infusion. Hypotension: Mean BP < 10th percentile of GA-dependent normal values	10 mcg/kg/min
Klarr <i>et al.</i> 1994 [10]	RCT	II	63 neonates < 34 weeks gestation randomized to dopamine or dobutamine infusion after volume expansion with 20 ml/kg . Hypotension: mean arterial blood pressure <30mm Hg persisting for >30min.	5-20 mcg/ kg/min
Roze <i>et al.</i> 1993 [12]	RCT	II	20 neonates with GA 26 -31 weeks and BW 670 - 1800 g randomized to dopamine or dobutamine infusion. Hypotension: Mean BP < 30 mmHg	5-20 mcg/ kg/min
Pellicer, A. <i>et al.</i> [20] (same study as [38])	RCT	II	59 neonates with BW <1501 g or GA <32 weeks' were randomized to dopamine or epinephrine Hypotension: mean BP < GA in the first 24 hours of life	2.5-10 mcg/ kg/min
Valverde <i>et al.</i> 2006 [38] (same study as [20])	RCT	II	60 neonates of BW<1501g or GA<32 weeks with a, randomized to dopamine or epinephrine Hypotension: mean BP lower than GA in the first 24 hours of life	2.5 -10mcg/ kg/min

Reference	Study Type	Level of Evidence	Study Population	Dopamine infusion dose range
Lundstrom, K. et al. [21]	RCT	II	36 neonates with GA < 33 weeks, with mean BP between 29 and 40 mm were randomised to receive either dopamine, volume expansion with albumin or no treatment. Normotensive preterm neonates	5 mcg/ kg/min
Osborn, D.A. [16]	RCT	II	42 neonates with low SVC flow (<41 mL/kg/min) were randomized to volume and dobutamine versus volume and dopamine.	10-20 mcg/ kg/min
Seri, I. et al [24]	Observational study	IV	20 indomethacin-treated normotensive preterm neonates with patent ductus arteriosus and mean GA 27.2+/-1.5 weeks were treated with dopamine	5 mcg/ kg/min
Bouissou, A. et al. [26]	Prospective observational study	IV	17 neonates with patent ductus arteriosus and systemic hypotension and mean GA 28+/-2 weeks and BW 1030 +/- 400 g. Hypotension: mean BP < GA during the first 2 days after birth, or mean BP < 10th percentile of GA-dependent normal values.	Mean rate 8 +/- 2 mcg/ kg/min
Seri, I. et al. [28]	Prospective observational study	IV	6 neonates with BW< 2500 g and GA<36 weeks were given dopamine for oedema, moderate oliguria, poor peripheral perfusion and/or mild systemic hypotension and matched with controls.	2 mcg/ kg/min
Ishiguro, A. et al. [31]	Prospective observational study	IV	29 neonates with median GA 27.1 (23.8–29.7) weeks and BW (g) 790 (388–1,292) were treated with dopamine Hypotension: mean BP< 10th percentile of GA-dependent normal values	5-20 mcg/ kg/min
Saini, S.S. et al. [25]	Prospective observational study	IV	52 neonates with septic shock (shock group) with mean GA 31.1±2.8 and BW 31.2±2.3 (g) and matched healthy control group. Hypotension: systolic BP or diastolic BP less than fifth percentile for the postmenstrual age	10-20 mcg/ kg/min

Reference	Study Type	Level of Evidence	Study Population	Dopamine infusion dose range
Zhang, J. et al. [22]	Prospective observational study	IV	50 hypotensive preterm neonates in whom cardiac output increased or decreased after dopamine treatment. Hypotension: mean BP < 10th percentile of the normal range, taking account of BW and postnatal age	5-10 mcg/ kg/min
Liet, J.M. et al.[27]	Prospective observational study	IV	14 neonates with GA < 32 weeks (range 24 to 31 weeks), with BW ranging from 480 to 1482 g were treated with dopamine for hypotension after initial volume expansion Hypotension: mean BP \leq 10th percentile of the normal range	5-10 mcg/ kg/min
Seri, I. et al. [30]	Prospective observational study	IV	61 neonates with variable characteristics analysed in different substudies (control-normotensive, hypotensive and oliguric) Hypotension: systolic BP > 15 mm Hg below the predicted normal the time of the studies	2-4 mcg/ kg/min
Lynch, S.K. et al. [29]	Prospective observational study	IV	15 neonates with mean GA 34+/-2 weeks and mean BW 2.43+/-0.6 kg) who had respiratory distress, were normotensive, and had a low urine output (0.9+/-0.1 ml/kg per hour)	0.5-7.5 mcg/ kg/min

Table 4 - Characteristics of included studies investigating the use of epinephrine (EPI).

Reference	Study Type	Level of Evidence	Study Population	Epinephrine infusion dose range
Buijs <i>et al</i> 2014 [23]	Prospective observational cohort study	IV	70 neonates with median BW 3125 grams and GA 38.6 weeks. (28 controls)	0.02-0.22 mcg/ kg/min
Heckmann <i>et al</i> 2002 [40]	Retrospective cohort study	IV	31 neonates with BW 390-1310 grams and GA 23-30 weeks	0.05-2.6 mcg/kg per min
Pellicer <i>et al</i> 2005 [20]	Randomised controlled trial	II	60 neonates with BW <1501grams, GA <32 weeks and <24 hours post-natal age.	0.125-0.5 mcg/kg per min
Phillipos <i>et al</i> 1996 [37]	Randomised controlled trial	II	20 neonates with BW >1750grams and <24 post-natal age.	0.125-0.5 mcg/kg per min
Rai <i>et al</i> 2010 [39]	Case series	IV	20 neonates with BW 1400-3400 grams, GA 30-39 weeks and 20-32 hours post-natal age.	0.3-1.5 mcg/kg per min
Valverde <i>et al</i> 2006 [38]	Randomised controlled trial	II	60 infants with BWs <1501g, GA <32 weeks and <24 hours post-natal age.	0.125-0.5 mcg/kg per min

Table 5 - Characteristics of included studies investigating the use of hydrocortisone (HC).

Reference	Study Type	Level of Evidence	Study Population	Hydrocortisone infusion dose range
Dempsey <i>et al.</i> 2007 [52]	Systematic review	I	Preterm hypotensive newborns 15 studies included	
Higgins <i>et al.</i> 2010 [53]	Meta-analysis	I	7 studies 147 preterm newborn included	
Ibrahim <i>et al.</i> 2011 [54]	Cochrane review	I	4 studies 123 newborns included	

Table 6 - Characteristics of included studies investigating the use of levosimendan (LS).

Reference	Study Type	Level of Evidence	Study Population	Levosimendan infusion dose range
Ricci, <i>et al</i> 2012 [61]	Randomised controlled trial	II	63 neonates (< 30 days of age) undergoing corrective open-heart surgery	0.1 mcg/ kg/min
Lechner <i>et al</i> 2012 [62]	Randomised controlled trial	II	40 infants <1 year of life undergoing corrective open-heart surgery	0.1 mcg/ kg/min
Pellicer <i>et al</i> 2013 [63]	Randomised controlled trial	II	20 neonates (6-34 days of age) undergoing corrective open-heart surgery	0.1-0.2 mcg /kg/min

Table 7 - Characteristics of included studies investigating the use of milrinone (MIL).

Reference	Study Type	Level of Evidence	Study Population	Milrinone infusion dose range
Lechner <i>et al</i> 2012 [62]	Randomised controlled trial	II	40 infants <1 year of life undergoing corrective open-heart surgery	0.5 mcg/ kg/min
Pellicer <i>et al</i> 2013 [63]	Randomised controlled trial	II	20 neonates (6-34 days of age) undergoing corrective open-heart surgery	0.5-1 mcg /kg/min
Paradisis <i>et al</i> 2009 [68]	Randomised controlled trial	II	90 neonates (GA \leq 30 weeks) < 6 hours of age	Loading dose 0.75 mcg /kg/min for 3 hours then maintenance 0.2 mcg/kg/min until 18 hours after birth
Jain <i>et al</i> 2012 [69]	Retrospective cohort study	IV	52 neonates (mean GA 25 weeks) undergoing PDA ligation	0.33 mcg /kg/min for 24 hours

Table 8. Characteristics of included studies investigating the use of norepinephrine (NE).

Reference	Study Type	Level of Evidence	Study Population	Norepinephrine infusion dose range
Buijs <i>et al</i> 2014 [23]	Prospective observational cohort study	IV	28 neonates with CDH with median BW 3125 grams and GA 38.6 weeks. (28 controls)	0.11 mcg/ kg/min (median)
Rowcliff <i>et al</i> 2016 [80]	Retrospective cohort study	IV	48 neonates with BW 390-1310 grams and GA 26-30 weeks, BW 726-1450 grams	0.2-1 mcg/kg per min

Table 9. Characteristics of included studies investigating the use of vasopressin (VAS).

Reference	Study Type	Level of Evidence	Study Population	Vasopressin infusion dose range
Buijs <i>et al.</i> 2014 [23]	Prospective observational cohort study	IV	28 neonates with CDH with median BW 3125 grams and GA 38.6 weeks. (28 controls)	0.11 mcg/ kg/min (median)
Masarwa <i>et al.</i> 2017 [89]	SR-MA-Trial Sequential analysis	I	35 newborns out of 248 children	TP 4-20-mcg/kg/h AVP 0.01-0.04 u/kg/h
Rodriguez-Nunez <i>et al.</i> 2010 [87]			2 term newborn	TP 20mcg/kg Q 6 h AVP 0.01-0.04 u/kg/h
Bidegain <i>et al.</i> 2010 [100]			20 ELBW (23-27 weeks, 400-980 g)	
Matok <i>et al.</i> 2005 [85]			3 term newborns	

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