Research, Society and Development, v. 13, n. 1, e14713144910, 2024
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Use of sildenafil for the treatment of neonatal persistent pulmonary hypertension

Uso de sildenafil para tratamento de hipertensão pulmonar persistente neonatal

Uso de sildenafil para el tratamiento de la hypertension pulmonary persistente neonatal

Received: 01/20/2024 | Revised: 01/28/2024 | Accepted: 01/29/2024 | Published: 01/31/2024

José de Ribamar Barroso Jucá Neto
ORCID: https://orcid.org/0000-0003-2750-7621
Centro Universitário Christus, Brazil
E-mail: juca.neto.medicina@gmail.com
Ângela Rocha Mapurunga
ORCID: https://orcid.org/0000-0002-1316-1597
Centro Universitário Christus, Brazil
E-mail: angelamapurunga@gmail.com
Angelica Gomes Belchior
ORCID: https://orcid.org/0009-0009-7713-9071
Centro Universitário Christus, Brazil
E-mail: angelicagomesbelchior@gmail.com
Felipe Rabelo Costa
ORCID: https://orcid.org/0009-0004-4027-1697
Centro Universitário Christus, Brazil
E-mail: frabelocosta14@gmail.com
Vitor Teixeira Boscov
ORCID: https://orcid.org/0009-0005-0573-8324
Centro Universitário Christus, Brazil
E-mail: vitorboscov@gmail.com

Abstract
Introduction: Persistent pulmonary hypertension of the newborn is a neonatal respiratory and vascular pathology with a high mortality rate. Furthermore, its prevalence is 1 to 2 per 1000 live births, accounting for 8%-10% of neonatal deaths. The therapeutic approach involves supporting pulmonary recruitment and pharmacological vasodilation, most notably sildenafil. Methodology: The study is a narrative review of the literature that was carried out from the PUBMED database using the keywords "Persistent Pulmonary Hypertension of the Newborn" and "Sildenafil", with the time filter in the last 30 years (1994- 2023). Discussion: Physiologically, during fetal life, the lungs remain filled with fluids, but immediately after birth, pulmonary vascular resistance decreases drastically, allowing alveolar oxygen tension and ventilation to be possible. However, in the pathogenesis of neonatal persistent pulmonary hypertension, there is an increase in pulmonary vascular resistance and remodeling of the vascular structure after birth, which potentiate this exaggerated vasoconstriction. Therefore, the standard exam for investigating the pathology is echocardiography. Sildenafil is a drug used to treat neonatal persistent pulmonary hypertension, as it enhances better blood flow and better delivery of oxygen to tissues, through its physiopharmacology aimed at vasodilation secondary to inhibition of phosphodiesterase-5. Conclusion: Neonatal persistent pulmonary hypertension is still one of the main neonatal pathologies with high morbidity and mortality in the neonatal population, due to the complexity of presentations and the variation in therapeutic responses to pharmacotherapy.
Keywords: Persistent fetal circulation; Sildenafil citrate; Intensive care units neonatal.

Resumo
Introdução: A hipertensão pulmonar persistente do recém-nascido é uma patologia respiratória e vascular neonatal com alto índice de mortalidade, além disso, sua prevalênica é de 1 a 2 por 1000 nascidos vivos, sendo 8%-10% das mortes neonatais. A abordagem terapêutica envolve suporte de recrutamento pulmonar e vasodilatação farmacológica, em destaque existe o sildenafil. Metodologia: O estudo é uma revisão narrativa da literatura que foi realizada a partir da base de dados PUBMED utilizando as palavras chaves de "*Persistent Pulmonary Hypertension of the Newborn*" e "*Sildenafil*", com o filtro de tempo nos últimos 30 anos (1994-2023). Discussão: Fisiologicamente, durante a vida fetal, os pulmões permanecem preenchidos de fluidos, porém imediatamente após o nascimento, a resistência vascular pulmonar diminui drasticamente, permitindo que a tensão alveolar de oxigênio e a ventilação seja possível. Entretanto, na patogênese da hipertensão pulmonar persistente neonatal ocorre aumento da resistência vascular pulmonar e remodelamento da estrutura vascular após o nascimento, os quais potencializam essa vasoconstricação exagerada, dessa forma o exame padrão de investigação da patologia é a ecocardiografia. O sildenafil é um fármaco utilizado para tratar hipertensão pulmonar persistente neonatal, uma vez que potencializa melhor fluxo sanguíneo e melhor entrega de oxigênio aos tecidos, por meio de sua fisiofarmacologia direcionada na vasodilatação secundária a

inibição da fosfodiesterase-5. Conclusão: A hipertensão pulmonar persistente neonatal ainda configura uma das principais patologias neonatais com elevada morbidade e mortalidade na população neonatal, devido à complexidade de apresentações e à variação de respostas terapêuticas à farmacoterapia.
Palavras-chave: Hipertensão pulmonar persistente do recém-nascido; Citrato de sildenafila; Unidade de terapia intensiva neonatal.

Resumen

Introducción: La hipertensión pulmonar persistente del recién nacido es una patología respiratoria y vascular neonatal con una alta tasa de mortalidad, además su prevalencia es de 1 a 2 por 1000 nacidos vivos, representando entre el 8% y el 10% de las muertes neonatales. El enfoque terapéutico implica apoyar el reclutamiento pulmonar y la vasodilatación farmacológica, en particular sildenafil. Metodología: El estudio es una revisión narrativa de la literatura que se realizó a partir de la base de datos PUBMED utilizando las palabras clave "Hipertensión Pulmonar Persistente del Recién Nacido" y "Sildenafil", con el filtro temporal en los últimos 30 años (1994-2023). Discusión: Fisiológicamente, durante la vida fetal, los pulmones permanecen llenos de líquidos, pero inmediatamente después del nacimiento, la resistencia vascular pulmonar disminuye drásticamente, permitiendo que la tensión alveolar de oxígeno y la ventilación sean posibles. Sin embargo, en la patogénesis de la hipertensión pulmonar persistente neonatal existe un aumento de la resistencia vascular pulmonar y una remodelación de la estructura vascular después del nacimiento, que potencian esta vasoconstricción exagerada, por lo que el examen estándar para investigar la patología es la ecocardiografía. Sildenafil es un fármaco utilizado para tratar la hipertensión pulmonar persistente neonatal, ya que mejora el flujo sanguíneo y el suministro de oxígeno a los tejidos, a través de su fisiofarmacología dirigida a la vasodilatación secundaria a la inhibición de la fosfodiesterasa-5. Conclusión: La hipertensión pulmonar persistente neonatal sigue siendo una de las principales patologías neonatales con alta morbilidad y mortalidad en la población neonatal, debido a la complejidad de las presentaciones y la variación en las respuestas terapéuticas a la farmacoterapia.
Palabras clave: Síndrome de circulación fetal persistente; Citrato de sildenafil; Unidades de cuidado intensivo neonatal.

1. Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a disorder characterized by refractory hypoxemia due to high pulmonary vascular resistance (Simonca & Tulloh, 2017), which leads to a shunt of deoxygenated blood to the right to the left. PPHN has a high mortality rate in newborns (Spillers 2010).

High PVR (pulmonary vascular resistance) and low placental vascular resistance regulate fetal circulation. This condition induces a diversion of pulmonary blood to the circulatory system via the ductus arteriosus and foramen ovale. Low oxygen pressure and decreased endogenous production of vasodilators contribute to maintaining a high PVR in utero (Steinhorn 2016; Perez & Laughon, 2015; Sun et al, 2016).

A few seconds after birth, PVR reduces significantly, which leads to an 8- to 10-fold increase in pulmonary blood flow (Dhillon, 2012) Shear stress in the alveoli coupled with an increase in oxygen tension leads to to a postnatal cascade of pulmonary vasodilation (Samiee-Zafarghandy et al., 2014). This cascade stimulates the nitric oxide and prostacyclin production pathways (Samiee-Zafarghandy et al., 2014). Failure of the postnatal cascade of pulmonary vasodilation reduces perfusion as the heart must pump blood against the high pressure of the pulmonary vasculature, this condition is often a cause of myocardial dysfunction. Hypoxia increases pulmonary vasodilation and acidosis acts as a pulmonary vasoconstrictor. Such a condition leads to a vicious cycle of hypoxia and acidosis, which is a characteristic of PPHN (Shah & Ohlsson 2007).

The diagnosis of PPHN is made when the partial pressure of O2 in oxygenated blood is observed to be less than 55 mmHg with a fraction of inspired oxygen (FiO2) of 1.0, or when a pre-ductal to post-ductal gradient greater than 20 mmHg (Fuloria & Aschner 2017). PPHN affects 1 to 2 per 1000 live births and is responsible for 8% to 10% of neonatal deaths and 25% of neurological morbidities in neonates (Iacovidou et al, 2012; Sanchez Luna et al., 2012; Abman, 2007). PPHN is generally associated with unfavorable outcomes, which may be due to its heterogeneous etiology and limited interventions (Fuloria & Aschner, 2017).

Supportive therapies, pulmonary recruitment, and pharmacological vasodilation are treatments for PPHN, but the main goal is to reduce pulmonary vascular resistance. Three pathways mainly control the contraction and relaxation of pulmonary vascular smooth muscle - nitric oxide, endothelin and prostacyclins - which, in turn, are the targeted targets for the treatment of PPHN (Cruz-Blanquel et al., 2008; Zhang et al., 2020; Luecke & McPherson, 2017).

Soluble guanylate cyclase is activated by inhaled nitric oxide, which leads to an increase in cyclic guanosine monophosphate(cGMP), a secondary messenger that regulates smooth muscle contractility through activation of cGMP-dependent kinases, phosphodiesterases and ion channels, resulting in selective vasodilation and improving perfusion. The effects of nitric oxide are prevented by inhibitors of soluble guanylyl cyclase, a predecessor of cGMP (Oishi et al., 2011; Dani, & Pratesi 2013; Kawaguchi et al., 2013).

From another point of view, sildenafil is an inhibitor of the enzyme phosphodiesterase-5(PDE5). PDEs are enzymes that hydrolyze and inactivate cGMP and cAMP, regulating the concentrations and effects of these chemicals and facilitating the exchange of information between two cyclic nucleotides. PDE5 has a cGMP binding domain that activates its catabolic activity by acting on cGMP, which is an essential messenger for the nitric oxide pathway. Inhibiting PDE5 prevents cGMP from becoming inactive. PDE5 is most prominently expressed in the lungs (Askin, 2006; Cook & Stewart, 2005). If iNO is used for a long time after its withdrawal, rebound PPH is common and sildenafil is useful in reducing the severity of this condition (Oishi et al., 2011; Dani & Pratesi, 2013; Kawaguchi et al., 2013).

From this perspective, the present study aims to gather the existing information in the scientific literature about Neonatal Persistent Pulmonary Hypertension in its definition, identification, pathophysiological and therapeutic understanding through the use of Sildenafil, since there are no protocols that specifically address the disease, causing a gap in scientific technical knowledge.

2. Methodology

This study consists of a narrative literature review (Rother, E.T; 2007; Snyder, H.; 2019) was carried out from the PUBMED database using the keywords “Persistent Pulmonary Hypertension of the Newborn” and “Sildenafil”, with the filter time in the last 30 years (1994-2023) which resulted in 52 articles, of which only 34 were used, and 18 were discarded because they did not have a title or abstract directly related to the key words or had online access restrictions.

3. Results and Discussion

3.1 Pathophysiology

3.1.1 Physiology of Fetal Pulmonary Vascular Regulation

Throughout fetal life, the lungs remain completely full of fluids, and consequently, they are unable to carry out the work of breathing. This work is carried out by the placenta, which is responsible for guaranteeing the essential oxygenation of the blood, which will be directed to the fetal heart and brain to meet the high metabolic demands of the developing fetus. In fetal circulation, all blood that returns to the fetal cardiac system flows preferentially from the right atrium, through the foramen ovale to the left atrium, and is expelled through the left ventricle to be made available for the coronary and cerebral circulation (Verklan, 2006; Storme, et al., 2013; Iijima et al., 2018).

The venous return of blood destined for the brain mixes with the return of coronary venous blood so that this oxygen-poor blood subsequently enters the right ventricle, where most of the right ventricular output is directed through the ductus arteriosus to the placenta through of the descending aorta (Dhillon, 2012; Gien et al., 2016; Panigrahy et al., 2020).

3.1.2 Transition of Pulmonary Circulation in extra-uterine life

From the beginning of extra-uterine life, an orchestrated succession of adaptations of the cardiovascular system is expected to occur to enable a smooth transition from fetal to extra-uterine life. At the end of pregnancy, the pulmonary vessels, through the maturation of pulmonary artery endothelial cells, acquire the ability to respond to vasodilatory stimuli, and when this vasodilation mechanism fails, it leads to PPHN (Latini et al., 2008; Ambalavanan et al., 2016; Samiee-Zafarghandy et al., 2014).

In utero, fetal circulation is controlled by high PVR with low placental resistance, which induces the passage of pulmonary to systemic blood through the foramen ovale and ductus arteriosus. Immediately after birth, PVR decreases exponentially resulting in an eight- to ten-fold increase in pulmonary blood flow. This results from the combined effect of increased alveolar oxygen tension and the onset of ventilation itself, with lung aeration. These mechanisms cause pulmonary vasodilation, which stimulates the production of vasodilators such as NO (nitric oxide) and PG12 (prostaglandin) (Shah et al., 2007).

The postnatal pulmonary vasodilatory cascade begins with high oxygen tension, as well as distension of the air spaces and increased blood flow. Failure to dilate pulmonary vessels mainly results from low oxygen tension, due to the pulmonary vasoconstrictor response to hypoxia (Martinho et al., 2020). These mechanisms prevent the production and, consequently, the release of nitric oxide (NO) and prostacyclin (PGI2), as well as determining high levels of vasoconstrictors. Furthermore, the fluid-filled intrapulmonary space likely contributes to high PVR by creating high extraluminal pressure, which in turn prevents more oxygen from reaching the lungs (Shah et al., 2007).

3.1.3 Pathogenesis of Neonatal Persistent Pulmonary Hypertension

Two main mechanisms may be involved in the pathogenesis of PPHN, causing an increase in PVR in the postnatal period: increased constriction of pulmonary vessels and vascular structural remodeling. However, several other different disorders may be involved in causing both mechanisms and are characteristic of the etiology of PPHN (Latini et al., 2008; Ambalavanan et al., 2016; Samiee-Zafarghandy et al., 2014).

Therefore, the pathogenesis of PPHN depends on several factors, also involving many perinatal risk factors, such as maternal exposures (maternal intake of selective serotonin reuptake inhibitor, type of delivery, maternal asthma). Although the mechanism linking these factors to PPHN is not clear for many of them. However, regardless of causality, these factors demonstrate higher risks for PPHN (Dhillon, 2012; Latini et al., 2008; Panigrahy et al., 2020).

Pulmonary hypertension in the newborn may be primary (idiopathic) or secondary to lung tissue disease (such as surfactant deficiency, meconium aspiration syndrome or alveolar-capillary dysplasia), polycythemia, hypoglycemia, sepsis or maternal ingestion of prostaglandin inhibitors (Storme et al., 2013; Iijima et al., 2018).

Exaggerated vasoconstriction is the result of an imbalance between vasodilatory and vasoconstrictor factors, produced mainly by PAECs (pulmonary artery endothelial cells), which, in turn, stimulates increased contraction of PASMCs (pulmonary artery smooth muscle cells) and, therefore, increased vascular tone. Asphyxia and sepsis are some examples of etiologies that led to an exacerbated increase in pulmonary vessel constriction, either directly, through hypoxia and acidosis, or indirectly, through the release of pulmonary vessel constricting substances, such as TXA2 and leukotrienes (Storme L et al., 2013; Iijima et al., 2018).

The exacerbated proliferation and disturbed development of PASMCs stimulate increased vascular remodeling, which leads to hyperplasia and hypertrophy of the vascular smooth muscle layer leading to pulmonary arteriolar vasoconstriction and increased PVR. This is mainly observed in cases of primary PPHN, such as newborns exposed to chronic intrauterine hypoxia or increased fetal blood pressure (Iijima et al., 2018).

3.2 Sildenafil

Sildenafil is a prototype of the phosphodiesterase 5 (PDE 5) enzyme inhibitor, it produces vasodilation by increasing cyclic guanosinemonophosphate (cGMP) through the inhibition of phosphodiesterase; is a medication used in many cases of severe pulmonary hypertension, allowing better blood flow and oxygen delivery to all organs, especially in places where other treatment approaches are not available, according to a randomized trial of oral sildenafil in babies without access to inhaled nitric oxide demonstrated better survival (6/7) compared to placebo (1/6) (Yaseen et al., 2012).

In a study that compared sildenafil with active controls after the comparison researchers observed a significant reduction in the sildenafil alone group and the trials reported no significant differences in mortality in the sildenafil group versus the active control (65 participants; confidence index 95%) (Fuloria et al., 2017).

Furthermore, another conventional management performed on newborns with persistent pulmonary hypertension with and without the addition of Sildenafil (Sildenafil 13 cases, placebo 11 cases) and showed significant improvement in oxygenation index in the treatment group. Consequently, PaO2 after 72 hours had better efficacy, mean airway pressure and the number of days were reduced in the group that used Sildenafil (Herrera et al., 2010).

Clinically, neonatal pulmonary hypertension demonstrates varying degrees of hypomic respiratory failure and is characterized by labile hypoxemia and a pre-post ductal saturation gradient, which manifests as cyanosis (Mandell et al., 2021; Lakshminrusimha et al., 2016). Hypoxemia is due to intrapulmonary shunting and/or extrapulmonary shunting from right to left through persistent fetal ducts due to increased pulmonary vascular resistance (Kelly et al., 2017; Lakshminrusimha et al., 2017).

The investigational test for diagnosing this pathology is echocardiography, the echocardiographic findings are right ventricular hypertrophy, deviation of the interventricular septum to the left, tricuspid regurgitation and deviation to the left or bidirectional through the patent foramen ovale and the patent ductus arteriosus (Mandell et al., 2021; Kelly et al., 2017; Lakshminrusimha et al., 2016).

Regarding the assessment of the safety of intravenous Sildenafil, a trial carried out in neonates with the pathology and an oxygenation index > 15 (Pedersen et al., 2018). The drug was administered by continuous intravenous infusion with 8 dosage groups for 48 hours up to 7 days, five sites enrolled 36 newborns and 29 of these received inhaled nitric oxide. An improvement was observed in the oxygenation index (28.7 to 19.3) and of the 36 newborns, only one died, according to the experiment (Krishnan, 2010).

In another study, 40 babies with the disease were recorded and were treated with oral Sildenafil. The initial median oxygenation index was 31.95, all neonates received standard therapy with mechanical ventilation, sedation, of the 11 babies, 6 responded positively to Sildenafil while the remaining 5 did not have the same adequate response (Krishnan, 2010).

4. Conclusion

Neonatal Persistent Pulmonary Hypertension is still one of the main pathologies in terms of morbidity and mortality in the full-term neonatal population, due to the complexity of the presentation phenotypes and mainly the variation in the presentation of therapeutic responses to pharmacotherapy with iNO, which despite the wide acceptability of Evidence reported in the scientific literature regarding the effectiveness of the medication still presents significant adverse effects and potential risks. However, there is still a lack of studies that solidly report second line treatment in cases of refractoriness to the use of iNO and its similar products, configuring a context of complexity in the management of this pathology in these situations.

Therefore, more research is needed, especially clinical and randomized trials on the topic of using Sildenafil as a therapy for Neonatal Persistent Pulmonary Hypertension, which aim to statistically analyze the efficacy and therapeutic index, in addition to the most prevalent side effects. , in order to systematically protocol an integrative approach to this pathology.

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