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ABORDAGEM E TRATAMENTO FARMACOLÓGICO DA PERSISTÊNCIA DO CANAL ARTERIAL

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ARTIGO REVISÃO

RESUMO

O canal arterial (CA) é um vaso importante, responsável por redirecionar o sangue do ventrículo direito para aorta descendente no feto. Com o nascimento, o CA sofre estímulos fisiológicos gerando uma constrição do vaso. Algumas cardiopatias congênitas se dão pela malformação nas estruturas do coração resultando em uma disfunção hemodinâmica cardiovascular, dentre elas a maior ocorrência é da persistência do canal arterial (PCA), onde é a dificuldade do fechamento do canal arterial nos recém nascidos. Este artigo tem por objetivo realizar uma varredura na literatura médica para compreender detalhadamente a fisiopatologia da PCA para o desenvolvimento de estratégias diagnósticas eficazes e abordagens terapêuticas adequadas. Foi realizada uma revisão bibliográfica integrativa, utilizando como motores de busca as bases de dados e definição dos descritores com finalidade de filtrar os dados. Desse modo, a revisão desses artigos mostra uma relação entre a persistência do canal arterial com a idade gestacional, especialmente em idade gestacional inferior a 28 semanas, a prevalência ocorre devido à imaturidade estrutural e funcional do canal arterial que se mantém aberto para suprir a circulação fetal, sendo assim necessário intervenção e condutas eficazes, que deve seguir um protocolo escalonado, capaz de evoluir de tratamento farmacológico até procedimento cirúrgico. Na qual a escolha deve ser compatível com as condições clínicas do paciente para um bom desfecho clínico.

Palavras-chave: Patent ductus arteriosus, Persistent ductus arteriosus, congenital heart disease.

PHARMACOLOGICAL APPROACH AND TREATMENT OF PATENT DUCTUS ARTERIOSUS

ABSTRACT

The ductus arteriosus (CA) is an important vessel responsible for redirecting blood from the right ventricle to the descending aorta in the fetus. At birth, the AC undergoes physiological stimuli, causing the vessel to constrict. Some congenital heart diseases are caused by malformations in the structures of the heart resulting in cardiovascular hemodynamic dysfunction, among them the most common is patent ductus arteriosus (PDA), which is the difficulty in closing the ductus arteriosus in newborns. The aim of this article is to scan the medical literature to gain a detailed understanding of the pathophysiology of PDA in order to develop effective diagnostic strategies and appropriate therapeutic approaches. An integrative literature review was carried out, using databases as search engines and defining descriptors in order to filter the data. Thus, the review of these articles shows a relationship between patent ductus arteriosus and gestational age, especially at gestational ages of less than 28 weeks. The prevalence is due to the structural and functional immaturity of the ductus arteriosus, which remains open to supply the fetal circulation, thus requiring intervention and effective approaches, which should follow a step-by-step protocol, capable of evolving from pharmacological treatment to surgical procedure. The choice must be compatible with the patient's clinical conditions for a good clinical outcome.

Keywords: Quality of life, Satisfaction, Mucus-supported complete denture, Implant-supported complete denture.

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INTRODUCTION

According to the literature, complications from congenital malformations can occur in 1% of newborns (NB) and are considered high risk with high morbidity and mortality (Damasceno et al., 2022). Congenital heart defects are characterized by malformations in the structures of the heart that result in cardiovascular hemodynamic dysfunction and are considered one of the main causes of morbidity and mortality in neonates, with a prevalence of 0.8 to 1% of live births. Of these, patent ductus arteriosus stands out as it afflicts approximately 10% of all congenital heart defects in newborns (Araújo et al., 2020).

Among congenital malformations, the highest occurrence of patent ductus arteriosus (PDA) is related to low gestational ages. In addition, PDA in premature neonates is associated with complications such as chronic lung disease and other negative outcomes. Part of the difficulty in closing the ductus arteriosus in premature babies is related to histological differences, since the ductus arteriosus is thinner and less muscular. In addition, the smooth muscle cells that make up the ductus arteriosus appear to be more reactive to circulating PGE2 and nitric oxide, levels of which are generally high in premature NB due to the presence of systemic inflammatory mediators such as tumor necrosis factor alpha (Capuruço and Mota, 2020; Pugnaloni et al., 2024).

Pediatric cardiology has advanced significantly with the introduction of echocardiography, interventional catheterization and improved surgical techniques. Fetal echocardiography stands out as a major milestone in the ability to detect cardiac malformations early, as it aids diagnosis while still in the intrauterine period. As well as being non-invasive, this procedure is a crucial approach to saving lives (Oliveira et al., 2022).

During the development of the cardiovascular system, the aortic arches - initially placed bilaterally and symmetrically - undergo specific transformations in which the proximal portion of the embryonic sixth aortic arch remains the pulmonary arteries, while the distal portion remains the ductus arteriosus. As a result, only 65% of the blood flowing to the heart is directed to the right ventricle, of which only 13% reaches the pulmonary circulation, which is equivalent to 8% of the blood pumped by both ventricles

(Máximo et al., 2024).

The rest of the blood diverts through the ductus arteriosus (CA), going from right to left to the descending aorta, with ⅓ going to the fetal body and ⅔ to the placenta in search of nutrients (Schmidt et al., 2024). With birth comes functional closure, which still leaves a residual flow in the first few weeks of life, and anatomical closure, which takes place over the first few months and completes the interposition. These transformations should be completed by the eighth week of fetal life (Carvalhais et al., 2023).

In healthy, full-term babies, the closure of the ductus arteriosus occurs in two stages: one functional and the other anatomical. Functional closure takes place in the first 18-24 hours and is mainly achieved by the constriction of smooth muscle cells, secondary to an increase in arterial oxygen content, a drop in prostaglandin concentration and a decrease in blood pressure. Anatomical closure, on the other hand, takes days or weeks to complete because its mechanism is more complex, comprising migration and proliferation of smooth muscle cells, production of extracellular matrix, proliferation of endothelial cells and rupture of internal elastic laminae (Pugnaloni et al, 2024).

Cardiac malformations during pregnancy can be seen through obstetric ultrasound, which is the essential test for suspecting this diagnosis. But after birth, specific diagnostic tests are carried out, such as the little heart test and pulse oximetry, cardiac magnetic resonance imaging and echocardiography. Signs such as cyanosis, heart failure and developmental delay observed on physical examination may indicate a murmur (Conrad and Newberry, 2019).

In order to confirm the diagnosis, the type of congenital heart disease and its severity, imaging tests are extremely important. Echocardiography is essential for visualizing the heart and malformations in real time. However, for a more complex and detailed visualization of the heart, with an assessment of the severity of the malformation, cardiac magnetic resonance imaging is the most suitable, also helping to better plan treatment (Barrera_Colin and Corona, 2024).

The therapeutic approach to PDA can be divided into four main categories: conservative management, pharmacological management, surgical intervention by

ligation and transcatheter surgical repair. Conservative treatment is based on the expectation of spontaneous closure of the ductus arteriosus and is a non-invasive strategy. Its greatest advantage is the absence of adverse effects related to the use of drugs or surgical procedures (Capuruço and Mota, 2020).

Pharmacological intervention consists of administering drugs that act mainly by inhibiting the action of prostaglandins, promoting contraction of the ductus, favoring its closure. Indomethacin has a success rate in closing the ductus arteriosus of between 70% and 85%. However, its use is limited by its strong vasoconstrictive effect, which can cause complications such as renal failure (acute or chronic), oliguria, proteinuria and hyperkalemia (Batista e Lorenzi et al., 2023). Ibuprofen, on the other hand, shows similar efficacy to indomethacin, but with a lower incidence of renal and systemic side effects. Paracetamol has shown a lower incidence of adverse effects compared to other drugs, with satisfactory efficacy in the management of patent ductus arteriosus in premature newborns with a gestational age of more than 25 weeks (Ohlsson et al., 2020).

The third method is surgical correction by ligation, a procedure that is performed through a left lateral thoracotomy, with the placement of a clip to block the flow in the ductus arteriosus. This approach is recommended for patients unable to receive enteral nutrition or when drug therapy has not been successful (Manica et al., 2022).

Finally, the last therapeutic option discussed is the introduction of a device that will block the blood flow between the aorta and the pulmonary artery, promoting the definitive closure of the ductus arteriosus by stimulating the formation of thrombi around the device (Barcroft et al., 2022).

It can be seen that the scope of congenital heart malformations is very broad, and the analysis of post-birth patent ductus arteriosus is no different. In view of this, it is of the utmost importance to understand the pathophysiology of PDA in order to develop effective diagnostic strategies and appropriate therapeutic approaches and the main aspects related to pathophysiology, the most commonly used diagnostic methods, the most viable treatment options and the clinical results obtained, in order to provide a comprehensive perspective on the advances and challenges in the management of this complex condition.

METHODOLOGY

Using the integrative review method, the topic of patent ductus arteriosus was selected. The study was carried out in the following stages: selection of databases and definition of the descriptors used in order to filter the data; elaboration of inclusion and exclusion criteria for articles and selection of studies; organization of the selected items and, finally, presentation and analysis of the data.

The Health Sciences Descriptors (DeCS/MeSH) used were “congenital heart disease” and “patent ductus arteriosus” and “ductus arteriosus”, and the databases selected were the National Library of Medicine (PubMed), Scientific Electronic Library Online (Scielo), Latin American and Caribbean Health Sciences Literature (Lilacs).

The search for papers resulted in 101 articles, of which 82 were excluded because they did not fit the established criteria, 22 were selected by reading the title, then the abstract and, finally, 17 were selected, read in full and included in this review. Articles published between 2019 and 2024 in Portuguese, English and Spanish were included. Only studies that were available in full, had a well-described methodology and were related to the main subject were selected.

Research with a publication date prior to 2017, available only in abstract form, published in journals of low scientific relevance or with unclear methodologies was excluded.

At the end of the selection, the articles were organized according to the year of publication, the name of the journal, the title and the database in which it was found.

The content analysis technique was chosen, following the stages of reading, classification, categorization, analysis and interpretation of the data, which in turn led to the analysis described, and 25 references made up of articles were selected to make up this work.

RESULTADOS E DISCUSSÃO

The research selected 11 studies for the results. The selection criteria were relevance, quality and contemporaneity in order to guarantee robust evidence on the subject.

Chart 1: Summary of the main results highlighted by author/year, database, title and important findings.

Author/Year	**Title**	**Important Findings**
Nascimento et al., 2019	Prevalence of persistence of the arterial canal in newborns in a public hospital	By collecting data from 313 newborns' medical records, we observed the occurrence of a diagnosis of PCA in a sample of newborns hospitalized up to the seventh day of life. There was a higher incidence of PCA in premature infants when gestational age and birth weight were inversely proportional.
Su et al., 2019	Therapeutic strategy of patent ductus arteriosus in extremely preterm infants	He points out that prophylactic treatment of Persistent Ductus Arteriosus can lead to unnecessary interventions, since in most cases spontaneous closure occurs, while if clinical treatment is not sufficient, ligation and transcatheter closure are indicated options. In addition, there is not enough evidence to indicate a universal prophylactic approach. a abordagem precoce e Targeted treatment is suggested for high-risk newborns, especially those under 26 weeks of age, with the help of serial echocardiograms, as these help to identify patients who benefit from early treatment.

Sarmento et al., 2020	Percutaneous patent ductus arteriosus closure: Twelve years of experience	They analyzed 221 patients with an average age of 5.5 years treated with a surgical approach and concluded that the treatment was safe and effective, with only 1.8% of complications.
Cakir e Tayman, 2021	What Should be the First-line Treatment for the Closure of Hemodynamically Significant Patent Ductus Arteriosus in Premature Infants?	He examined 486 premature infants and treatment with paracetamol or ibuprofen in up to 3 courses of treatment reduced 90% of the illnesses.
May et al., 2023	The ductus arteriosus: a review of embryology to intervention	It explains the pathophysiology of the ductus arteriosus and the importance of imaging tests, especially magnetic resonance imaging and computed tomography, in assessing patent ductus arteriosus.
Su et al., 2019	Therapeutic strategy of patent ductus arteriosus in extremely preterm infants	The ductus arteriosus tends to close without treatment in babies born at gestational ages greater than 28 weeks. However, in premature babies there is a high risk of serious bleeding related to the persistence of the ductus arteriosus. Treatment with Ibuprofen, Paracetamol and Indomethacin is successful in 80% of cases.
Sung et al., 2019	Natural evolution of ductus arteriosus with non interventional conservative	Determines the natural course of the condition with non-interventional conservative treatment in 195 preterm births

	management in extremely preterm infants born at 23-28 weeks of gestation	and concluded that the prolonged presence of the clinical condition does not increase the mortality or morbidity rate
Batista e Lorenzi., 2023	Tratamento da Persistência do Canal Arterial: Uma revisão de LIteratura	It addresses the management of patent ductus arteriosus in newborns, with the main therapies being water restriction and diuretics as non-pharmacological measures, and the use of indomethacin, ibuprofen and paracetamol as pharmacological options, so that each approach has different risks and benefits. In refractory cases, surgical ligation and percutaneous closure stand out as effective alternatives. The study suggests individualizing treatment based on the severity of symptoms, highlighting that there is a great need for more comparative studies to define the best therapeutic strategy.
Mendívil et al., 2021	Patent ductus arteriosus in premature babies: Analysis of diagnosis and treatment in a public maternity hospital in Joinville-SC	The study analyzed 151 cases of patent ductus arteriosus (PDA) in premature infants treated at a public maternity hospital in Joinville-SC between 2009 and 2015. The average gestational age was 28 weeks and the average birth weight was 1151.3g. Of the patients, 48.43% received pharmacological treatment

		with ibuprofen or indomethacin, with a success rate of 76.71% in closing the canal, while patients with lower weight, larger canal size (>1.8 mm) and use of furosemide had a greater need for surgery. Indomethacin showed superior efficacy, however, more studies are needed to consolidate these approaches.
Silva, Oliveira e Reis., 2022	Patent ductus arteriosus in premature newborns: an integrative review	It indicates that treatments for PDA closure in premature infants vary between surgical, pharmacological, clinical and conservative methods, depending on the clinical condition and hemodynamic status of the newborn. However, there is no consensus on the ideal protocol, with the choice being influenced by factors such as gestational age and birth weight. It is concluded that the management of PCA is still controversial, and the selection of treatment is based on specific clinical criteria and auxiliary tests.
Meena et al., 2019	Comparison of the efficacy and safety of indomethacin, ibuprofen and paracetamol in closing patent ductus arteriosus in preterm newborns – A randomized clinical trial	A prospective randomized study evaluated ibuprofen, indomethacin, and paracetamol for closure of patent ductus arteriosus (PDA) in preterm neonates (<37 weeks) with hemodynamically significant PDA. Paracetamol was equally effective and had a

		superior safety profile, with no significant changes in blood count or renal and hepatic function. In contrast, indomethacin and ibuprofen increased urea nitrogen and creatinine levels. Paracetamol was thus shown to be a safer option for these patients.

Fonte: Autores, 2024.

Studies indicate a relationship between patent ductus arteriosus and gestational age. In premature births, especially at gestational ages of less than 28 weeks, the prevalence is due to the structural and functional immaturity of the ductus arteriosus, which remains open to supply the fetal circulation (Mendívil et al., 2021). As the closure of this structure after birth can be ineffective in these neonates, the need for intervention and effective conduct arises.

The conservative approach includes clinical monitoring of the patient with pharmacological management and has been advocated as the first line of treatment. With this in mind, some authors have stated that this approach is capable of avoiding significant amounts of surgery. This is important because it reduces the risk associated with surgical procedures in patients who are known to be fragile, such as premature infants (Silva et al., 2022). This format is therefore widely recommended.

Pharmacological treatment with Ibuprofen or Paracetamol has shown equivalent efficacy in promoting closure of the ductus arteriosus, based on studies showing a reduction in the incidence of the disease. Intravenous paracetamol is successful in treating between 52% and 88% of cases, with a reduction in the percentage of efficacy for the oral route due to the immaturity of the gastrointestinal system, in treatments with 15 mg/kg/6h for 2 to 3 days for the oral route and 15 mg/kg/6h for 3 to 5 days for the intravenous route (De Resende et al., 2022). Therefore, although the high rate of closure of the ductus arteriosus shows the importance of these drugs, there are adverse effects that must be taken into account in the treatment.

The pharmacological comparison between Ibuprofen and Paracetamol should be discussed in cases where Ibuprofen is contraindicated. The clash between the drugs

indicates that although the success rate is similar, with a reduction of around 90% in the incidence of the condition. Paracetamol's safety profile may be favorable in patients at risk of renal complications (Meena et al., 2020). Therefore, pharmacological treatment requires a personalized choice for the patient through a holistic vision that respects individual clinical conditions.

On the other hand, the surgical approach is a safe and effective option, particularly in cases where pharmacological treatment has been unsuccessful. Thus, one of the studies indicates that the complication rate of 1.8% suggests a high level of safety in the procedure (Wang et al., 2021). However, the risks of a surgical approach limit its indication as secondary to the conservative approach.

FINAL CONSIDERATIONS

Thus, the review of these articles shows that the treatment of patent ductus arteriosus should follow a staggered protocol, capable of evolving from pharmacological treatment using ibuprofen or paracetamol to surgery in refractory cases. Therefore, the choice should be compatible with the patient's clinical conditions and the resources available, paying attention to associated complications that require early intervention for a good clinical outcome.

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