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BENEFITS OF PARACETAMOL IN THE CLOSURE OF PATENT DUCTUS ARTERIOSUS: REVIEW ARTICLE.

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Rafael Antonio Barahona Avalos*

*Corresponding Author
ady.barahona11@gmail.com

Celina Rentería Coronel

Renata Michelle Granados Sánchez

Margarita Díaz Torres

Rosy Elena Arias Pérez

Leonardo Esteban Arias Pérez

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ABSTRACT:

OBJECTIVE: To know the role of paracetamol in the pharmacological treatment of persistent ductus arteriosus.

METHODS AND MATERIAL: We collected studies in an independent way, we assessed the methodological quality of the studies and extracted the data, resolving the discrepancies by consensus. The approach was the treatment for the closure of the patent ductus arteriosus, exposing the benefits of paracetamol

RESULTS: Paracetamol shows to be a good measure for the decrease in the incidence of side effects, in addition to this, for the remarkable efficacy in premature babies in unfavorable extremes. Giving a turn for them with benefit in time of evolution and action of it.

CONCLUSION: Paracetamol as a pharmacological alternative in PDA is feasible and with several benefits for the patient.

OBJETIVO: Conocer los beneficios del uso del paracetamol en el tratamiento farmacológico del ductus arterioso persistente.

MÉTODOS Y MATERIALES: Se recopilaron artículos de forma independiente y se valoró la calidad metodológica de los estudios de cada uno de ellos, con el fin de extraer todos los datos que fueran requeridos para resolver las discrepancias por consenso. El enfoque fue el tratamiento para el cierre del ductus arterioso persistente, exponiendo los beneficios del paracetamol en este.

RESULTADOS: El paracetamol muestra ser una alternativa nueva y en aumento para el tratamiento del ductus arterioso persistente. Su uso tiene beneficios significativos en la disminución de la incidencia de efectos secundarios, aunado a esto la notable eficacia en prematuros en extremos desfavorables. Dando un giro para ellos con beneficio en tiempo de evolución y reacción al mismo.

CONCLUSIÓN: El paracetamol como alternativa farmacológica en el PDA resulta factible y con varios beneficios para el paciente.

INTRODUCTION.

The ductus arteriosus is a structure that allows the life of the intrauterine fetus, the same that must be closed after birth in a period no longer than 72 hours, if this does not happen within this period, the neonate will have persistent ductus arteriosus, this occurs in pre-term in 23.5 % and term births in 6 % [9].The existence of a persistent and hemodynamically significant ductus arteriosus has a high morbidity and mortality that affects more than 40 % of preterm infants. [7].

The ductus arteriosus is a musculoskeletal vessel, measuring 5 to 10 mm in diameter, located between the left pulmonary artery and the descending aorta. [10]. During intrauterine circulation most of the expenditure of the right ventricle passes through the ductus arteriosus to the aorta and only a small part reaches the lungs. It usually closes within a few hours of birth (functional closure), and complete obliteration is achieved after three weeks (anatomical closure). At birth, with the onset of respiration, the flow in the pulmonary artery increases significantly, decreasing in turn the pulmonary vascular resistance; at the same time the CA initiates functional closure, influenced in large part by the increase in oxygen saturation and in two to three weeks it is completely obliterated in anatomical form. [11].

"Ductus arteriosus persistent" (DAP) means that the vessel remains open after birth, if it does not close, the blood will pass from the aorta to the pulmonary artery and then to the lungs, causing the heart and lungs to perform more work. [15]. It is a frequent pathology of the premature newborn that complicates its clinical course and increases the risk of other diseases.

Lack of closure of ductus arteriosus due to the presence of factors that interfere with the normal development, such as hypoxemia, decreased ability early to respond to stimuli for closure, that accompanied by respiratory distress respiratory distress syndrome, shorts from left to right and pulmonary congestion, aggravate hypoxemia and lengthen the respiratory process. [11].

Yeh, in 1981, established a scale of cardiovascular dysfunction in premature infants with Patent Ductus Arteriosus, to evaluate the severity of the short circuit consisting of heart rate, heart murmur, peripheral pulses, precordial hyperactivity and the cardiothoracic index, in order to establish that the ductus arteriosus is clinically significant when the score is ≥ 3 points. [12].

The diagnosis of persistent patent ductus arteriosus in the premature must be echocardiographic because the clinical signs are often unreliable and there may be a large ductus arteriosus with large flow passage from left to right in the absence of symptoms.

It is reported that on the 4th day of life the Patent Ductus Arteriosus will persist in 10 % of the children with gestational age between 30 - 37 weeks, in 80 % between 25 - 28 weeks and up to 90 % in the age of 24 weeks. [13].

Ductus arteriosus is frequent in preterm infants, with an incidence of 1: 2,500 - 5,000, and represents 9 - 12% of congenital heart diseases. Various drugs have been used for hemodynamically significant patent ductus arteriosus closure. The first employee for this purpose was indomethacin, with a success rate of 70 % and reopening of 35 %; However, due to its high cost, other options have been sought, such as ibuprofen; but these are not innocuous and are associated with reduced renal, mesenteric and cerebral perfusion, and ibuprofen is associated with hyperbilirubinemia. Recently, the usefulness of paracetamol for this purpose has been demonstrated, without reporting toxicity so far. This study reports the use of oral paracetamol in preterm infants, which has been safe and effective for the closure of hemodynamically significant patent ductus arteriosus.

Up to 50 % of newborns with a birth weight < 1500 g require treatment (either medical or surgical). The administration of traditional treatment has been related to complications because it causes a decrease in cerebral, renal and mesenteric perfusion. Paracetamol could be an alternative whose effectiveness seems proven, but there are also doubts about aspects of its safety.

There are multiple treatment strategies, different paracetamol, both to prevent and close the patent ductus arteriosus. Prevention should be initiated prenatally, usually with the administration of steroids to the mother and continue postnatally avoiding the administration of parenteral fluids, which is a risk factor. There is also the prophylactic indication, the use of this medication and the patient's response depends on factors such as birth weight, the time of treatment initiation and the severity of patent ductus arteriosus, the use of symptomatic persistent ductus arteriosus infection and of the co-morbidities associated with this. Prophylactic indomethacin has a reduction in the incidence of patent ductus arteriosus, although it is associated with severe pulmonary hemorrhage and interventricular grade 3 - 4 hemorrhagic and oliguria, the prophylactic utility is in doubt and exposes a high percentage of neonates to the use of a drug that it may not be indicated and cause different adverse effects. There is also prophylactic treatment with ibuprofen, which reduces the incidence of patent ductus arteriosus but also represents a risk when exposing a large percentage of patients who may not need the medication. (Medrano, C. 2015).

These observations stimulated the authors' interest in answering the following question: what is the efficacy and safety of paracetamol for the closure of the hemodynamically significant ductus arteriosus ?, with the objective of evaluating these parameters. The intention was to confirm that paracetamol is effective and safe for the closure of the duct arteries.

MATERIALS AND METHODS.

The search of the studies on which this review article is based was carried out during a period of three weeks, divided into three phases, the first phase was dedicated to the compilation of studies that made reference to the subject of interest, this was achieved with designating words or sentences of reference, which were divided into two groups, the first encompasses the words or main sentences that give direction to the search on the subject, such as: patent ductus arteriosus and paracetamol or acetaminophen. The first group of reference words were randomly added to the second group of words, which specify some characteristics of the study groups within the articles and approach the investigation towards the treatment and the pathophysiology of persistent ductus arteriosus, the words of the second group were: Treatment, preterm neonates, physiopathology, contraindication of Nonsteroidal Anti Inflammatory Drugs, adverse effects and benefits. During this phase, 30 articles were found that accomplished the objective of exposing the benefits of the use of paracetamol as a treatment for the closure of persistent ductus arteriosus.

The second phase of the investigation was carried out with the aim of generating a filter for the 30 articles on the subject, since the first part was only responsible for selecting articles that fulfilled the topic of the review article. The filter was generated from inclusion criteria and exclusion criteria, which would facilitate the final selection of the 15 articles with the best potential to achieve the objective. Starting with the exclusion criteria, the first criterion is the year of publication, since it is important to eliminate articles that are obsolete in terms of information, in addition paracetamol is considered an innovative treatment for the closure of the ductus, so the publication is determined by the most recent ones and emphasizing in the ones subsequently of the year of 2012. On the other hand, the articles where paracetamol was not the main treatment and it was only mentioned as secondary treatment but not used in the study group, were excluded of the investigation. The inclusion criteria are formed basically the opposite of the exclusion criteria, those that have been published after 2012 and that fulfill the characteristic of using paracetamol as a treatment for the closure of persistent ductus arteriosus in a study group.

The third phase started with 20 articles that met the above criteria, which could be used to gather the necessary information to efficiently expose the subject. Within these 20 studies, 15 were chosen based on the materials and methods used in them, this phase is of great importance since the objective was to expose the benefits of paracetamol in the closure of patent ductus arteriosus, for which it should be included articles that use the same method of study, managing to homogenize the information, otherwise results would be obtained under different circumstances, which could affect the conclusions; Despite the fact that different studies were carried out in different parts of the world and at different times, it was of great interest that the studies carried out were similar in the selection criteria and form of evaluation, although each patient was in diverse conditions, the results obtained in each of them, shows a response pattern similar to the treatment administered. This phase consisted of an extensive analysis of the criteria for patient selection, the material used, the study method and the form of evaluation of results. After analyzing each study and search for the criteria used in the studies that were similar to each other; and in case of not mentioning different or contradictory inclusion criteria and agreeing in most of the exclusion criteria, the study would be accepted for the realization of the review article.

The inclusion criteria to select patients who would receive treatment with paracetamol start with all those patients who have undergone the relevant studies to obtain the definitive diagnosis of persistent ductus arteriosus. The second criteria refers to the range of 30 to 36 weeks of gestation that the preterm infants had, in whom all the studies were focused, due to the higher incidence of the disease within this age range and the greater need for the use of paracetamol, mostly because of the contraindication of other treatments. Another inclusion criterion, which goes hand in hand with the previous one, the maximum weight accepted in this trial was of ≤1,500 grams. The fourth criterion is about the hemodynamic status of the patient with persistent ductus arteriosus, which must have been affected, to standardize the criterion and that it wouldn't be subjective according to the opinion of the attending physician, the classification of Yeh was used with a score greater than 3 points, which tells us that the patient has signs of hemodynamically significant persistent ductus arteriosus. These inclusion criteria eliminated 2 articles which had characteristics of the patients contradictory to most of the other studies, the first one had characteristic that all the included patients had a gestational age at term, from 36 to 41 weeks of gestation. The second article that was

eliminated lacked a confirmatory diagnosis of hemodynamically significant persistent ductus arteriosus in the patients treated with acetaminophen.

Subsequently the same procedure was performed for the exclusion criteria, the first criterion that was presented in all the articles were all those patients with congenital heart disease that needed the presence of persistent ductus arteriosus to maintain blood flow. The following criteria refer to a deteriorated condition of the patient that jeopardizes the survival of the patient and was a contraindication for the treatment of patent ductus arteriosus with paracetamol, such as a life-threatening infection, the presence of necrotising enterocolitis, recent intraventricular hemorrhage of a degree greater than 2, in addition to thrombocytopenia in a range of less than 20,000 mm 2 and serum creatinine greater than 88.4 umol / L, hepatic dysfunction accompanied by hyperbilirubinemia requiring exchange blood transfusion and finally bronchopulmonary dysplasia. After applying these exclusion criteria, 2 articles were eliminated that included patients with life-threatening infections in their studies, while in the rest of the investigations this was a reason to stop the treatment or not even start it.

Within the third phase of study selection, it was considered important to standardize the way in which paracetamol was administered, in order to have more specific and reliable results, since the dose or form of administration could change the patient's response to treatment. The standardized form of administration was a dose of paracetamol of 15 mg / kg every 6 hours, both orally and intravenously. Administered for a minimum of 48 hours, until a positive response was detected in the patient or reaching a maximum of 7 days. To classify if there was a response to the treatment, echocardiographic studies were performed every two days, in case of not obtaining a response within the established time, surgical treatment was chosen. One of the studies defined the administration of the drug in two phases, the first one was a short course of paracetamol in which the medication is administered for 48 hours and the second one or long course of paracetamol in which the medication is administered for 7 days, since these periods of time are within the standard established by the other articles used, it was considered that the study was useful for the data collection. Only 1 study used another dose in the administration of the drug so it was discarded, because as mentioned above, the dose response could be altered, so the patient could have different results and it was consider really important to have reliable results.

Likewise, within the studies there were safety factors of the medicine mentioned, which were used to measure the risk of presenting factors to stop the treatment, in addition to ensuring the patient's welfare, leading to results more specific and reliable, for which it was considered important to standardize which ones would be the safety factors, these were measured every 24 hours and include the production of urine, the bleeding tendencies, especially preventing bleeding from the gastrointestinal tract and interventricular hemorrhages, serum creatinine and bilirubin levels, these factors are related to the exclusion criteria mentioned above, in case that these factors were not detected or under other circumstances in which the patients presented any of the exclusion criteria but within the period of treatment with paracetamol, the study would be stopped to continue with a different approach, reiterating that the criteria are renal failure, necrotising enterocolitis, grade > 2 interventricular hemorrhage, or gastrointestinal bleeding.

Within this third phase it has been mentioned that the intention was to standardize the study methods within the consulted articles, in order to obtain reliable results in patients who were in similar circumstances. Likewise, it was considered of great importance to look for articles in which the way to evaluate the patient's progress was the same, without leaving the results to the subjectivity of the attending physician, this was achieved thanks to the results in the selected articles that were measured according to the range of ductal closure and the safety of the medication, the latter refers to the adverse effects that the patient could present, after the administration of paracetamol and after the closure of the patent ductus arteriosus. The adverse effects were divided into 2 groups, which occurred early, in the first 7 days after the closure of the canal, which include oliguria, interventricular hemorrhage and necrotizing enterocolitis, which had already been mentioned before to stop the treatment, but they are still useful to measure the safety of the medication as long as they appear after having an improvement in the condition. The second group are the late adverse effects, which occur after 7 days with favorable results, these effects include periventricular leukomalacia, necrotising enterocolitis, retinopathy, sepsis and death. In this way it will be possible to create conclusions about the safety of the medication in an equal way in all the studies.

After an exhaustive analysis of the third phase and in a way of summary, 2 articles were eliminated because they contained patients with infections that endangered their lives due to circumstances other than the persistent ductus arteriosus or the treatment. Two other articles were discarded since they had characteristics of contradictory patients. Most of the other studies had the number of weeks of gestation and in the absence of a confirmed diagnosis. Finally, 15 articles were found that met the same or similar characteristics, but more importantly, they did not contradict the selection criteria, the administration of the medication and the safety of the same, which will be used to extract relevant information and results that after an analysis will achieve a discussion of the appropriate topic, seeking to achieve the objective of identifying the benefits of paracetamol as a treatment for the closure of the patent ductus arteriosus.

PHYSIOPATHOLOGY.

Ductus arteriosus (DA) is a vascular structure that connects the proximal descending aorta with the main pulmonary artery near the origin of the left pulmonary branch. It usually closes spontaneously after birth in most full-term infants. [34-35]

Functional closure usually occurs within the first day of the newborn's life. On the other hand, the anatomic closure, where the ductus arteriosus loses the ability to reopen, may not occur until after several weeks after birth.[35] However, up to 60% of preterm newborns weighing <1,500 grams closure of the ductus occurs beyond the first week of life and may have a patent ductus arteriosus, which will become a condition which puts at risk the life of the newborn [33-34]

In the case of term newborns it is usually related to an anatomical defect of the ductus or other parts of the heart, but most cases occur sporadically, and it is important to highlight the role of genetic factors and prenatal infections, As an example of the above, we find Rubella [16-17].

As mentioned before, the incidence of persistent ductus arteriosus in preterm infants is high, increasing according to the decrease in birth weight of neonates, so that in the case of newborns weighing <1000 grams the incidence is even higher [22-23].

Epidemiology.

The incidence is 20% in preterm infants over 32 weeks and 60% in children under 28 weeks. The high incidence in premature babies under 30 weeks, reaching ranges between 4-55%. [36]Functionally, it must occur due to vasoconstriction within the first 48 postnatal hours. The delay in ductal closure is inversely related to gestational age (GA).

How Does The Arteriosus Ductus Compose?

The ductus arteriosus in intrauterine life derives from the sixth aortic arch. From the sixth week of gestation this conduit is responsible for supporting most of the debit of the right ventricle, which

constitutes 60% of the total cardiac output of the fetus, so that while the product is inside the uterus it is of the utmost importance that this structure is available, even though it may subsequently cause damage to the health of the newborn and even death.[33, 36]

The ductus arteriosus histologically has a medium tunic poor in elastic fibers and rich in smooth muscle fibers arranged in a helical shape, which allows it to contract and dilate, which gives it the possibility of supporting the percentage of cardiac output. [36]

How Is It Closed?

In order for the ductus arteriosus to close physiologically, several processes occur, one of which is the high oxygen pressure which produces the ductal closure, while the hypoxemia induces the relaxation of the muscular fibers of the duct, which is why it remains open . [32, 37] Prostaglandins (PGE2) and prostacyclins (PG12) circulating and locally produced, very high in the fetus, induce vasodilation of the ductus. Both processes expose the reason why the ductus arteriosus remains open and is of greater incidence in preterm infants.[35]

The increase in arterial oxygen tension inhibits the calcium channels dependent of potassium of the ductal smooth muscle, increasing the intracellular calcium which conditions the constriction of the ductus arteriosus. [37] After this the levels of prostaglandins PGE2 and prostacyclins PG12 fall abruptly, so that the muscle fibers in the middle layer contract, decreasing the luminal blood flow and creating ischemia of the internal wall, resulting in the definitive closure of the ductus. [Brethauer. 237-240]

Preterm infants have a decrease in the number of muscle fibers, the intrinsic tone of the ductal wall and subendothelial tissue, which will facilitate the failure of the closure of the ductus arteriosus. [36, 37]

There is a sensitivity for high oxygen pressure, much higher in full-term infants. But by the older gestational age, the less sensitivity of the ductus arteriosus to the vasodilatory effects of the prostaglandins PGE2, it is logical to think of the inhibitors of cyclooxygenase as the treatment of choice. [35] However, the efficacy of indomethacin is lower in immature newborns less than 1000 grams, this could be due to the special sensitivity they have to the action of prostaglandins PGE2, as to the vasodilation produced by nitric oxide. Another cause of the persistent opening of the ductus arteriosus is the expression of nitric oxide synthetase since it is higher in immature fetuses; this enzyme would contribute to the persistence of the ductus arteriosus. [Overmeire. 2005. 177-184] of the

Related Factors.

The prenatal administration of steroids seems to exert a protective factor, in the other hand other substances studied are the drugs administered to the mother, such as magnesium sulfate, where there are already recent studies in which it has been associated with greater risk for ductal persistence. being dose-dependent effect. [16,36, 37]

The excessive administration of fluids to the preterm newborn is a predisposing factor, if it exceeds an average of 169 cc / k / day (+/- 20) from the third day of life there is more possibility of ductal persistence, so the administration of Furosemide in the first days of life has been associated with a higher incidence of persistent ductus arteriosus, probably because it induces the release of prostaglandin PGE2, even though it counteracts the excessive administration of fluid. [32, 36]

Finally, protection of the thorax when the child is receiving phototherapy has been shown to be a protective factor since it has been observed with the reduction of the incidence of persistent ductus arteriosus.

Clinical Picture

The most common clinical sign is a systolic ejection murmur, which is better heard in the left infraclavicular region and upper left parasternal border, which often radiates to the dorsum. It may be accompanied by: hyperactive precordium, tachycardia, protruding pulses in the postductal region, polypnea, apnea, hepatomegaly [16, 32]

The chest radiograph may be normal or show cardiomegaly and signs of pulmonary congestion depending on the intensity of the ductal shunt

Adverse Effects With The Persistent Ductus

The symptomatic ductus arteriosus of the asymptomatic differs, because the first one has hemodynamic repercussion, manifests itself with respiratory problems, metabolic acidosis and pulmonary congestion, being the greater risk of complications such as intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), pulmonary disease chronic (PCD) and death. [32, 36, 38]

A large left-right shunt could influence the mechanics of pulmonary function by decreasing the dynamic compliance and leading to an increase in the requirements of respiratory support reason why the ductus arteriosus would facilitate the development of chronic lung disease.

The ductal short circuit decreases the diastolic blood flow and the velocity of diastolic blood flow and the speed of flow to the intestine with the consequent ischemia and increased risk of necrotizing enterocolitis, the same happens at the splanchnic and renal level, facilitating the development of renal failure At a cerebral level the increase in blood flow would facilitate the appearance of the necrotizing hemorrhage. [Laughon. 2007. 498-502]

How Can The Arteriosus Ductus Be Prevented?

It should be initiated in the prenatal stage, with the administration of steroids to the mother and continue postnatally avoiding the excessive administration of parenteral fluids both in maintenance and in boluses.

Prophylactic indomethacin, its use as prophylaxis has benefits such as the reduction of the incidence of symptomatic ductus of the need for surgical closure, severe pulmonary hemorrhage and intraventricular hemorrhage grade III-IV. However, it is not exempt from side effects, prophylaxis with indomethacin does not show any advantages over expectant management with early treatment of symptomatic ductus arteriosus. Prophylaxis with ibuprofen reduces the incidence of symptomatic ductus, but it would expose a large part of neonates to a drug that is not free of side effects, mainly in the kidneys. [16, 37, 38]

DIAGNOSIS:

According to the clinical signs, the patent ductus arteriosus is classified in the following forms: [24,25]

- Asymptomatic (Patent Ductus Arteriosus -A): no heart murmur.
- Symptomatic (Patent Ductus Arteriosus-S): significant heart murmur is heard along with other clinical signs.
- No hemodynamic repercussion (Patent Ductus Arteriosus-SRH): no cardiovascular dysfunction.
- With hemodynamic repercussion: with cardiovascular dysfunction (Patent Ductus Arteriosus-RH)

The clinical signs of Patent Ductus Arteriosus are manifested depending on the clinical picture presented. The classic ones are left subclavicular systolic murmur, hyperactive precordium, pulses that are easily palpated, tachycardia, hypotension or increase in differential pressure, tachypnea, apneas, respiratory deterioration, metabolic acidosis and later pulmonary hemorrhage and heart failure.

The findings of symptomatic patent ductus arteriosus include a characteristic systolic or continuous murmur in the left superior

sternal border, however if the clinical signs are present, the diagnosis is easy, but there may already be a significant compromise in the newborn. [16] Other manifestations that can be found are tachycardia, precordial hyperdynamic and hypotension, worsening of the respiratory state, tachypnea, dyspnea, pulmonary edema, apnea, mechanical ventilation dependence, hepatomegaly, abdominal distension, intolerance to the oral route, oliguria persistent metabolic acidosis, failure to thrive, lethargy, bulging pulses, increased pulse pressure (> 30 mm Hg) or shock.

In the Patent Ductus Arteriosus-RH is a diameter is> 1.5 mm, the ratio pulmonary flow / systemic flow (Qp: Qs) is greater than 1.5 and the diameter is greater than 2.0 mm and the ratio greater than 2 to 1. However, the diagnosis of Patent Ductus Arteriosus in the preterm newborn should not be solely clinical, since many of the signs can actually be seen until after the first week of birth, so that if these are taken into account only the diagnosis could be delayed and the premature newborn would be exposed to a higher frequency of complications of the patent ductus arteriosus.

The most common diagnostic tools for their easy access and high sensitivity are echocardiography, chest x-ray, catheterization or angiocardiography, and circulating level of B-type natriuretic peptide.

Echocardiography

It is currently the gold standard test for the diagnosis and evaluation of Patent Ductus Arteriosus. [7] The confirmation or permeability requires color Doppler, with which it is sought to rule out congenital heart diseases and especially those ductus dependent. The main indication is to be done among the first 24 and 72 hours of life, in symptomatic newborns of 1,500 g or less or less than 28 weeks and newborn that require assisted ventilation.

The ideal echocardiographic projection to diagnose the ductus, the direction of the passage and the diameter of the same is the view in parasternal short axis, where the patent ductus, trunk and pulmonary branches are observed, however, there are other planes from which it is possible to demonstrate it. [3,4] The suprasternal plane targets the Patent Ductus Arteriosus and aortic arch, parasternal plane high left, where the ductus arteriosus easily unfolds between the trunk of the pulmonary artery and the descending aorta, and the intermediate plane (between the parasternal and suprasternal).

The parameters that evaluates are internal diameter of the ductus, direction of the shunt and flow pattern during the cardiac cycle, cardiac function (maximum systolic pressure peak gradient), relation of the left atrium and aorta (LA/Ao) ratio, aortic root and effects on the peripheral circulation. With all these echocardiographic data and assessing the magnitude of the ductus in the patient, the clinical repercussion can be established in case of being hemodynamically significant and needing the indication of its closure. (Table 1) The result in the echocardiogram suggestive of significant ductus arteriosus persistence is internal diameter ≥ 1.6mm, with a left atrial / aortic root ratio equal to or greater than 1.2. It must be requested at all newborns ≤ at 32 weeks or ≤ 1500 grams within the first 24 hours of life and provide daily echocardiographic follow-up according to evolution. For post term newborns of 32-34 weeks it is also recommended to make a more active search of the Patent Ductus Arteriosus the first 72 hours of life.

Table 1. Echocardiographic data that define the magnitude of the Patent Ductus Arteriosus

Echocardiographic findings	Small	Moderate	Large
Diameter of DAP per color Doppler	<1.5 mm	1.5-2mm	> 2mm
LA / Ao	<1.4	1.4-1.6	> 1.6
Fraction of shortening	> 40%	30-40%	<30%

Chest x-ray

Although it is a frequently used study, it must be done to complement the clinical and echocardiographic diagnosis. The radiological findings are related to right ventricular overload, such as cardiomegaly, prominent pulmonary vascular markings, dilation of the left atrium and horizontalization of the left main bronchus, but they are late, also there could appear left ventricular hypertrophy. [16,21,24] The image usually shows variable increased pulmonary vascularity and also increased pulmonary circulation and opacity when there is congestion.

Catheterization or angiocardiography

This technique is reserved for those cases in which echocardiography is not conclusive, when the existence of pulmonary hypertension is suspected or as a pre-intervention phase, during the same procedure. It is performed by venous access to the right cavities and pulmonary artery, from where the ductus is placed (aorta and left ventricle). An oximetry jump greater than 4-5% between the right ventricle and the pulmonary artery indicates that the left-right shunt is significant. The calculation of Qp /Qs can be complex because the pulmonary trunk and branch saturations can be different, as well as the presence of a permeable foramen ovale, with right atrial interatrial short circuit. In cases of pulmonary hypertension, the saturation of the descending aorta is greater than that of the ascending aorta. A small ductus may not be reflected in saturation and pressure measurements. In a moderate ductus, systolic, diastolic and mean pulmonary pressures may be slightly elevated, and systemic diastolic blood pressure is usually low. The mean pressures of the left atrium (measured directly through the foramen ovale or assumed by the pulmonary capillary pressure or left ventricular end-diastolic pressure) are usually slightly elevated. In the large ductus, these data are more striking and in the cases of severe pulmonary hypertension with right-side shunt, we will find the typical data of pulmonary artery mean pressure in supra systemic values. In these cases, the calculation of lung flow is also complex, so functional tests with balloon occlusion or vasodilators are usually done to evaluate pulmonary reactivity and tolerance to ductus closure.

Angiocardiography provides the most useful information about catheterization versus echocardiography. The injection of contrast at the end of the aortic arch-origin of the descending aorta in lateral projection or left anterior oblique demonstrates the ductal anatomy and helps us to perform a classification in morphological types with a practical purpose when planning closure with a device. [17]

Regarding laboratory tests that may indicate the presence of Patent Ductus Arteriosus, the circulating level of B-type natriuretic peptide (BNP) has been shown to have a good sensitivity and specificity to detect Patent Ductus Arteriosus-Hemodynamic Repercussion. [26] As Sanjeev explains, it is a hormone secreted by the ventricles when they are under hemodynamic stress.

TREATMENT

INTRODUCTION.

A persistently patent ductus arteriosus (PDA) has significant clinical consequences in preterm neonates during the recovery period from respiratory distress syndrome. The classic treatment for Persistent Ductus Arteriosus consists of water restriction, IV diuretics and management of congestive heart failure, in addition to pharmacological therapies for closure, such as Nonsteroidal Anti Inflammatory Drugs (NSAIDs). Indomethacin and ibuprofen are COX-inhibitor drugs used for the treatment of hemodynamically significant Patent Ductus Arteriosus. Despite the about 70% success rate, COX-inhibitors are frequently contraindicated in early life and their use has been associated with serious adverse events, such as gastrointestinal perforation, renal failure and bleeding. Paracetamol, an inhibitor of the peroxidase component of prostaglandin-H2 synthase, is commonly used in pediatric age, and has been recently proposed for the treatment of Patent Ductus Arteriosus, because of the benefits and fewer adverse effects.

Arachidonic acid does not exist in free form inside cells, but is normally esterified in membrane phospholipids especially at the C2

position of phosphatidylcholine and phosphotidylinositol. Its release from cellular deposits of lipids depends on the action of acylhydrolases and, in particular, phospholipase A2 and on human platelets by diacylglycerol lipase. It is our purpose to analyze how the biosynthesis of eicosanoids is regulated in a precise way before very diverse stimuli and how their products participate by modifying the inflammatory process.
Cyclooxygenase pathway

The synthesis of prostaglandins occurs gradually by a complex of microsomal enzymes of very wide distribution. In this synthesis route, the first enzyme is prostaglandin endoperoxide, also called cyclo-oxygenase. There are 2 isoforms of the enzyme that are recognized by their initials COX-1, COX-2. The first is expressed in a constitutive form in virtually all cells and has great ubiquity, however, COX 2 does not appear constitutively in the cells. cells, but can be induced by cytokines, growth factors and endotoxins, effect that is blocked by the administration of corticosteroids.

Cyclooxygenases act on arachidonic acid and cause 2 different actions: one that oxygenates and produces a ring structure and forms the cyclic endoperoxide PGG 2 and a peroxidase activity that transforms PGG 2 into PGH 2.

The endoperoxides G and H are chemically unstable, but by enzymatic action they are transformed into various products that include prostaglandins (PGE2, PGD2 and PGF2a or prostacyclin (PGI2) and thromboxane (TXA2).

Almost all tissues can synthesize intermediates and unstable products called cyclic endoperoxides from arachidonic acid once free, however, its biotransformation varies in each tissue and depends on the enzymatic battery that exists in it; For example, lung and spleen can synthesize all the diversity of substances mentioned above, but unlike these 2 organs, platelets only have thromboxane synthetase and lack enzymes to synthesize prostaglandins, so platelets are formed elements of the blood with exclusively aggregant capacity.

PGE 2 is an important mediator of vasodilation and also potentiates the effect of increased vascular permeability.

PGE 2 and PGI 2 lower the threshold of excitation of the afferent ends to the effects of chemical and mechanical stimuli.

COX – 3

COX-3 is transcribed from the *PTGS1* (*COX1*) gene, but the resulting mRNA is spliced differently. In dogs the resulting protein resembles the other two COX enzymes, but in mice and humans it does not, owing to a frame - shift mechanism. This mechanism is due to the fact that the spliced intron has 93 bases in dogs, resulting in the loss of 93:3 = 31 amino acids in the COX-3 sequence, which apparently does not impair its functionality. In humans, the intron is 94 bases long, leading to a protein with a completely different amino acid sequence from those of COX-1 or COX-2. The expressed protein does not show COX activity, and it is unlikely to play a role in prostaglandin-mediated physiological responses.

The sites of COX-3 expression do not appear to fit in well with those sites associated with fever, and the protein should be present within the hypothalamus rather than the cerebral cortex. All these considerations appeared to argue against COX-3 being the site of the antipyretic actions of NSAIDs and COX-2-selective agents. However, the results could be read as showing that paracetamol acts at a different site than the other NSAIDs and that more than one COX isoform contribute to the fever response.

Mechanism of action.

In general, the mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs) is based on the inhibition of the enzyme cyclooxygenase (COX), which converts arachidonic acid into endoperoxides that are transformed into prostaglandins and thromboxanes and are mediators of inflammation. [14] Paracetamol is not a classic non-steroidal anti-inflammatory drugs, it has weak antiplatelet and anti-inflammatory activity, and it exerts analgesic and antipyretic central effects. (Yeh, 1981) Inhibition occurs irreversibly (Acid Acetilsalicilic), competitive (ibuprofen) and non-competitive reversible (paracetamol). As Bardanzellu said, COX has two catalytic zones: cyclooxygenase and peroxidase; non-steroidal anti-inflammatory drugs inhibit the former while paracetamol inhibits peroxidase activity. [13] Inhibition of prostaglandins relaxes smooth muscle and interferes with closure of DAP. (Bardanzellu, 2016) It addresses the constriction of the muscular wall of the Arterial Duct through the hypoxia of the ductal *vasa vasorum* and local angiogenesis, the formation of neointimal tissue and apoptosis. As Yeh said, this together with the recruitment and activation of platelets, leads to obstruction and fibrosis and, as a result, to anatomical ductal closure.

As a physiopathological mechanism, it has been established that the imbalance between the relaxing and constricting factors of the ductal tissue, particularly the concentrations of circulating prostaglandins, leads to a premature constriction *in uterus*.

Prostaglandins are substances from the group of unsaturated fatty acids whose precursor is arachidonic acid. This is transformed by the action of cyclooxygenase in endoperoxides, which finally, and again by enzymatic action, are transformed into prostaglandins. The action of cyclooxygenase is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid, indomethacin and ibuprofen. Prostaglandins have been found in virtually all tissues in mammals. They are not stored, but are synthesized and released as required. Their half-life is very short, and they are inactivated by 90 % in their first step through the lungs. During fetal life, the permeability of the ductus is maintained mainly by the combined action of the relaxing effects on it of the low tension of O2 and of the prostaglandins PGE2, which are synthesized locally. (Cartaya, 2000)

During pregnancy is frequent the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin which is the most potent, diclofenac, ibuprofen, naproxen, nimesulide and finally aspirin which is the least potent. This type of drugs acts by blocking the synthesis of prostaglandins by inhibiting the enzyme cyclooxygenase, which from the substrate arachidonic acid produces the synthesis cascade of prostaglandins: E2, F2, alpha, I2, thromboxane A2 and D2. In pregnancy they should be administered with caution; receive risk classification B.

It has been determined that acetaminophen or paracetamol has antipyretic effects in addition to analgesics, but its mechanism of action is unknown. It is thought to act at the level of the central nervous system, where it inhibits both isoforms of cyclooxygenase (cox 1 and cox 2). It differs from NSAIDs because it does not inhibit cyclooxygenase in peripheral tissues, so it lacks anti-inflammatory effects. Case reports clearly demonstrate the association between paracetamol consumption and transient constriction of the ductus arteriosus. [31] With all the documented evidence, sufficient information is available that supports the recommendation to avoid the use of nonsteroidal anti-inflammatory drugs NSAIDs, including paracetamol and metamizole, in the third trimester of pregnancy, since its use during this period could explain some sudden intrauterine deaths. [29]

Acetaminophen is a metabolite of phenacetin, an analgesic widely used in the past, which, because it is toxic at therapeutic doses and metabolized to paracetamol, is no longer used. Acetaminophen has analgesic and antipyretic properties similar to those of aspirin but has no anti-inflammatory activity, nor does it exert any antiplatelet effect. Paracetamol is used in the treatment of moderate acute and chronic pain, and is considered the analgesic of choice by most of the authors in patients over 50 years. It is also the analgesic of choice

when aspirin is not well tolerated or when contraindicated. (Cartaya, 2000)

Pharmacokinetics: After oral administration, acetaminophen is rapidly and completely absorbed by the digestive tract. The maximum plasma concentrations are reached at 30-60 minutes, although they are not completely related to the maximum analgesic effects. Paracetamol binds to plasma proteins by 25%, about a quarter of the dose experienced in the liver a first-pass metabolism. It is also metabolized in the liver most of the therapeutic dose, producing conjugates glucuronides and sulfates, which are subsequently eliminated in the urine. Between 10 - 15% of the dose undergoes an oxidative metabolism by cytochrome P450 isoenzymes, later being conjugated with cysteine and mercapturic acid. (Amadio, 1984)

After an overdose, in the presence of malnutrition there is a hepatic depletion of glucuronides and sulfates, so paracetamol undergoes oxidative metabolism, which is the most toxic, through the CYP2E1 and CYP1A2 enzymatic system. This metabolite can also occur when paracetamol is administered with drugs that are hepatic inducers. Overdoses of paracetamol or the continuous use of this drug can cause hepatotoxicity and nephropathy, due to an oxidative metabolite that occurs in the liver and, to a lesser extent, in the kidney. This metabolite covalently binds to proteins containing sulfur, causing cell necrosis. The depletion of the reserves of a fluctuation constitutes the beginning of the hepatotoxicity of paracetamol. The elimination half-life of paracetamol is 2 - 4 hours in patients with normal hepatic function, being practically undetectable in the plasma 8 hours after its administration. In patients with hepatic dysfunction the half-life increases substantially, which can lead to the development of hepatic necrosis. [29]

The agents that inhibit CYP2E1 or CYP1A2 enzymatic system may, in principle, reduce the risk of hepatotoxicity by paracetamol when competing with it, reducing the generation of toxic metabolites. Paracetamol is classified within the category B risk in pregnancy, for any of the three quarters. Although there are no data that associate this drug with teratogenic effects, there have been no controlled studies that demonstrate that such an association does not exist. Some isolated publication has associated the use of paracetamol during pregnancy with a lower weight and height of the fetus at birth, however, a prospective study of 48 cases of paracetamol overdose during pregnancy did not highlight any case of directly associated fetal toxicity. To the drug. The Food and Drug Administration considers paracetamol as the drug of choice during pregnancy, as long as its use is strictly necessary. [31]

RESULTS

To achieve the review, a variety of cases were taken into account in which the use of paracetamol for the closure of the patent ductus arteriosus was implemented, which were analyzed through studies and are described below:

Study 1. This first study reports the use of oral paracetamol in preterm infants, which has been safe and effective for the closure of hemodynamically significant patent ductus arteriosus, in which premature patients from 30 to 36 weeks of gestation were included in their first 10 days of life, with hemodynamically significant patent ductus arteriosus. Patients with duct-dependent heart disease, intraventricular hemorrhage, thrombocytopenia, renal failure, hyperbilirubinemia, and necrotizing enterocolitis were excluded. They were divided into 2 groups on the basis of weight, group I less than 1 kg and group II greater than 1 kg, both treated with paracetamol at 15 mg / kg / dose orally every 6 h, with a cumulative total of 60 mg /kg ; 48 h after the first dose, echocardiographic monitoring was performed. In case of demonstrating patency of the ductus arteriosus, a second pharmacological cycle was administered; if the second treatment showed permeability of the ductus, surgical closure was performed. All patients were treated on the first day with total fluids at 70 ml / kg / day, with a daily increase of 10 to 20 ml / kg / day to a maximum of 160 ml / kg / day at the end of the first week of life. 10 patients were included for pharmacological treatment, of which the closure was obtained in 6 patients with the first pharmacological cycle, 4 patients underwent a second cycle, and closure was obtained only in 1 case and the 3 remaining patients were treated with surgery. , with a final success rate of 70%. During the application of the drug, liver function and platelet count were monitored, without observing significant changes. Two patients died, patient 4, due to septic shock, 48 h after the end of the cycle, and patient 8 died due to hypovolemic shock secondary to the surgical event. Mortality was not related to the use of the drug. As in this study, other authors have described that acetaminophen has success rates similar to other drugs. [7]

Study 2. In the study conducted by Ozmert, a success rate of 71.4% with the use of paracetamol. [5]

Study 3. Within this there was an analysis of three cases:
The first was a male patient who was born by emergency caesarean section due to acute fetal distress, weighing 810 gr. At 48 hours the echocardiogram shows a patent ductus arteriosus of 1.5 mm, without criteria of hemodynamic repercussion. It was managed with assisted ventilation and inotropic support. At 9 days he presented clinical deterioration with acute renal failure, signs of congestive heart failure, thrombocytopenia, high digestive bleeding. After contraindications to the use of other drugs, we opted for a pharmacological closure with intravenous acetaminophen at 15 mg / kg one dose every 6 hours. 48 hours after administration, presented clinical improvement with decreased congestive heart failure. It was administered for 3 days, checking the complete closure with an echocardiogram and suspending the treatment.

The second case was a female patient who was born by emergency cesarean at week 29, indicated by total placenta previa. It had a weight of 1,300 gr. After 3 days he presented with signs of congestive heart failure. The echocardiogram showed a patent ductus arteriosus of 3.2 mm, with hemodynamic repercussion. He also presented sepsis, thrombocytopenia and acute renal failure. The pharmacological closure with intravenous acetaminophen was chosen at a dose of 15 mg / kg every 6 hours. Echocardiographic monitoring was maintained every 24 hours. After 72 hours, the size decreased to 2 mm and disappearance of the clinical signs of congestive heart failure. The administration was continued for 5 days, corroborating the total closure and suspending acetaminophen. He had follow-up at one month, and at 3 and 6 months with transthoracic echocardiography, which ruled out the reopening of the ductus arteriosus, without major complications or pulmonary hypertension data. (Tofé, 2017)

Finally, the third case was a male patient, who was born by emergency cesarean at week 32, due to acute fetal distress, weighing 1,670 gr. Echocardiogram at 24 hours showed pulmonary hypertension, 3.7 mm persistent ductus arteriosus. Ventilatory support was given. During his evolution he presented acute renal failure, sepsis and thrombocytopenia. At 5 days of age, the ductus arteriosus was 3.9 mm, with data of hemodynamic repercussion. A pharmacological closure with intravenous acetaminophen was chosen at a dose of 15 mg / kg every 6 hours. He was suspended from therapy on day 7, demonstrating a complete closure with the echocardiogram. Reopening of the ductus arteriosus was ruled out, and cardiac functional normality was confirmed. [7]

Study 4. The use of paracetamol as an alternative for the closure of the patent ductus arteriosus showed significantly lower incidence of bleeding from the gastrointestinal tract and hyperbilirubinemia. [8] In addition to a favorable effect in extreme premature and lower weight, this is due to the circulatory physiology of the almost immature persistent ductus arteriosus, where the expression of COX-3 receptors is higher. (Araújo, 2016)

Study 5. The literature on this study talks about three patients treated with paracetamol, at the doses indicated in the methods, who had contraindications for non-steroidal anti-inflammatory drugs, since they had thrombocytopenia, renal failure, gastrointestinal bleeding and a high surgical risk, so that We chose to use paracetamol, where no toxic effects were reported and a total treatment time was recorded with a range of 3-7 days. [5]

Study 6. Another study in which acetaminophen is administered, with the doses described in the methods, to 80 premature patients with patent ductus arteriosus, closure of the conduit was reported in 65 patients, equivalent to 81.2%, of which 45 showed resolution of the condition with only 1 cycle of treatment, which lasted 3 days. Likewise, recurrence is reported in 5 of them, who are again administered paracetamol at the same dose, resulting in final closure. Only 8 patients reported adverse effects, among which are digestive tract bleeding and hyperbilirubinemia, which were removed from the study. [4]

Study 7. In this case, as Peña said, in order to corroborate the persistence of the hemodynamically significant patent ductus arteriosus using the clinical and echocardiographic criteria included in the Yeh scale, baseline laboratory studies were requested, this before the treatment with paracetamol, the studies included blood count , serum electrolytes, renal function tests, liver function tests, coagulation times, blood culture and transfontanelle ultrasound. In the selected patients, intravenous water restriction of 80 to 120 ml / kg / day was indicated between the third and seventh days of life, after seven days the intravenous therapy was restricted to 130 mL / kg / day. All the included patients received intravenous furosemide only after the fifth day of life, with a dose of 1 mg / kg / every 12 hours, if they did not receive fluids orally. When the oral intake was greater than 100 mL / kg / day, hydrochlorothiazide was prescribed at a dose of 1 mg / kg / 12 hours and spironolactone at a dose of 1 mg / kg / 24 hours. (Peña, 2017)

They were administered intravenous paracetamol Bristol-Myers Squibb bottle with 100 mL ampule with 1 g of paracetamol at a dose of 15 mg / kg / every six hours for three to seven days. All patients received conventional treatment according to the accompanying conditions; In addition, the administration of surfactant, antibiotics, glucose, parenteral solutions, parenteral nutrition and the different modalities of oxygen therapy were included.

When the closure of the ductus arteriosus occurred on the third day of treatment, the administration of paracetamol was discontinued. In cases where the canal was not closed, treatment was continued for up to seven days and, on the eighth day, new laboratory tests, echocardiography and transfontanelle ultrasound were requested. If closure of the ductus arteriosus was not achieved after this time in the patient, paracetamol was suspended and the surgical closure of the duct was used. [27]

Study 8. Ninety patients were studied, of which 67% were male and 33% were female. The gestational age ranged from 30 to 36 weeks with an average of 33 weeks; the average weight was 1 509 grams with intervals of 1,002 to 2 294 grams. The most frequent diagnoses associated with the persistence of the ductus arteriosus were the syndrome of respiratory distress due to surfactant deficit in four patients, equivalent to 44%, pneumonia in 8 patients, 89%, necrotizing enterocolitis in 2 patients, ie 22% and early neonatal sepsis in nine patients, equal to 100%. In the end, the closure of the hemodynamically significant ductus arteriosus, corroborated by echocardiography, was achieved in 89% of the patients. On the other hand liver enzyme concentrations, renal function tests and transfontanel pretreatment and posttreatment ultrasound were normal in all patients. One patient had thrombocytopenia due to Klebsiella sepsis that improved with specific antibiotic treatment. In the study, the frequency of closure of the ductus arteriosus was 89% of the patients compared to the study of Hammerman and Yetka, where they describe a frequency of closure with oral paracetamol of 87.5% and 100% enters the same range. [28]

Study 9. Here we included preterm patients from 30 to 36 weeks of gestation in their first 10 days of life, with hemodynamically significant patent ductus arteriosus, according to some of the following echocardiographic parameters Qp / Qs greater than 1.5 / 1 and / o left / aortic ratio greater than 1.8 in addition to ventilatory support.

They were divided into 2 groups on the basis of weight, group I included patients weighing less than 1 kg and in group II patients weighing more than 1 kg, both groups treated with paracetamol at a dose of 15 mg / kg / dose orally every 6 h with a cumulative total of 60 mg / kg and then, 48 hours after the first dose, echocardiographic monitoring was performed to evaluate the ductus arteriosus. If the patency of the ductus arteriosus was demonstrated, a second pharmacological cycle was administered with the same doses as in the first cycle. If the second treatment showed patency of the ductus arteriosus, it was closed surgically.

The patients of the two groups were treated on the first day with total fluids at 70 ml / kg / day, with a daily increase of 10 20 ml / kg / day up to a maximum limit of 160 ml / kg / day at the end of the first week of life. There were 10 patients who were included for the pharmacological treatment of which 6 were closed in the first cycle, 4 entered the second cycle and 1 was closed and the last 3 patients were treated with surgery since they did not respond to the pharmacological treatment. (Araújo, 2014)

The final rate of closure of the hemodynamically significant patent ductus arteriosus was 70%. In patients with a weight greater than 1 kg, the closure was significantly faster, and the ratio was female 3: 1. The echocardiographic control was performed periodically to evaluate the evolution of the patients, the following data were analyzed:

- Cardiac output in systole, the average was 292.5 with a range of 143-440 mmHg);
- Qp / Qs the average was 2 with a range, 1.1-3.5
- The left atrial / aortic ratio was on average 1.23 and the range was 1-1.8.

During the application of the drug, liver function and platelet count were monitored, without observing significant changes. Two patients died one due to septic shock, at 48 hours after the end of the cycle and the other due to hypovolemic shock secondary to the surgical event. However, mortality was not related to the use of the drug. The pharmacological closure of the ductus arteriosus with acetaminophen is similar to that of other non-steroidal anti-inflammatories, with a percentage of 70%. [30]

Study 10. In this case, as Risco said, intravenous paracetamol was used in infants with extreme low birth weight. In 10 preterm newborns of 27 weeks gestation and weighing 775 g; there was successful closure in all patients, 70% with a single cycle. All had normal pretreatment and post-treatment liver enzyme levels.

Study 11. We analyzed 15 studies and 16 reviews. The standard doses of paracetamol were 15 mg / kg / 6 h. It was found that paracetamol has fewer side effects than the rest of the non-steroidal anti-inflammatories. When used as first-line treatment, a 100% closure rate was achieved and no hepatotoxicity was detected. There was an occurrence of intestinal hemorrhage due to the high osmolality and it appeared to be more effective in men than in women. It was demonstrated that paracetamol is not effective in newborns with postnatal age greater than 2 weeks. The closing rate was 46%. Efficacy increases when it starts in the first week of life. There was hepatotoxicity in two patients. It is concluded that paracetamol is effective in closing the ductus arteriosus, with inconstant transient side effects. It has greater safety in terms of gastrointestinal hemorrhage and hyperbilirubinemia. And there was less efficacy in neonates younger than 28 weeks of gestation. (Bardanzellu, 2017)

CONCLUSIONS

In all the studies that were reviewed with paracetamol as a treatment for hemodynamically significant patent ductus arteriosus closure, an additional benefit was observed to the conventional treatment, which was that in no case was there any adverse effect related to the drug and in general the closing rate in the first cycle was very good, between 75 - 80% of all cases.

It is not possible to reach precise conclusions, but it has shown that paracetamol is effective with few side effects; although it is necessary to continue with long-term studies and larger samples to show this pharmacological effect more clearly, in addition to analyzing possible complications.

According to reports of a possible association between prenatal paracetamol and the onset of autism or autism spectrum disorder in childhood and language delay in girls, long-term follow-up until at least 18 to 24 months of postnatal age should be included in any study of paracetamol in the neonatal population.

Paracetamol for the closure of patent ductus arteriosus completely turns the treatment of this pathology, since paracetamol has a lower cost and is easier to access than conventional treatment, which provides an additional benefit to the health sector and the patients.

Paracetamol does not have adverse events in the short term because the drug performs its action through the non-selective inhibition of cyclooxygenase, the enzyme responsible for prostaglandins, without causing vasoconstriction and reduction of renal, mesenteric and cerebral blood flow.

The PGs product of the action of COX-2 are responsible for: fever, pain and inflammation, those derived from the COX-1 action are gastric protectors and participate in the initiation of platelet aggregation.

The COX are: bifunctional enzymes (cyclooxygenase and peroxidase). Non-steroidal anti-inflammatory drugs (NSAIDs) act by blocking the cyclooxygenase function, which is more active in situations of significant inflammation, high concentrations of peroxides and oxygen (high anti-inflammatory power in systemic diseases). Acetaminophen blocks the peroxidase function, acts at ten times less concentrations of peroxides, hence its effectiveness in hypoxia situations where the cyclooxygenase function is less effective.

Paracetamol has a difference in the inhibition of prostaglandins, since it does not act with the isozyme of the COX 1 Y 2 cyclooxygenase, but it acts on the central nervous system level where it has been seen that an isoform called COX 3 of the whose mechanism of action has not been well defined, since it takes place at the level of the central nervous system and in the endothelium. And the benefits that are given to people for a better treatment is that paracetamol by not interacting with the isoforms of the cyclooxygenase COX 1 and COX 2 is prevented from inhibiting the production of thromboxanes having as a benefit no alteration in platelet aggregation protection of the gastrointestinal mucosa, thus avoiding complications as with classic treatments.

Another aspect that is important to take up again is the lack of availability of traditional drugs for the treatment of persistent ductus arteriosus, such as ibuprofen or indomethacin, which does not exists in all the hospitals in our country. Although ibuprofen is found with greater availability, paracetamol would represent the opening and disposition of a definitive treatment for patients who could have a future full of complications. Paracetamol is a drug that began its use in search of minor adverse effects and its availability in the market, either orally or intravenously. Therefore, it is important to expose the benefits of this drug, in addition to increasing its use, can reach places where the treatment of this condition is still very expensive and unattainable for some patients. In addition to its availability, the course of long-term treatment has shown to have fewer adverse effects than traditional ibuprofen or indomethacin, although its use was doubtful on the assumption that it would increase bilirubin levels, because of the type of metabolism, but after the studies performed it was shown that this is false since it does not represent a greater incidence in this adverse effect, inclusively a decrease in the incidence of other adverse effects was demonstrated.

The use of paracetamol as an alternative for the closure of the patent ductus arteriosus showed significantly lower incidence of bleeding from the gastrointestinal tract and hyperbilirubinemia. In addition to a favorable effect in extreme premature and lower weight, this is due to the circulatory physiology of the almost immature ductus arteriosus, where the expression of COX-3 receptors is higher.

As it is a safety drug easily accessible and tested in newborns, with the properties for the closure of hemodynamically significant patent ductus arteriosus, it is expected that the hospital stay will decrease and with it the associated morbidity.

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