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ORIGINAL ARTICLE

Abdominal surgery in premature infants with patent ductus arteriosus☆

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Patent ductus arteriosus;
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Abstract
Introduction: Patent ductus arteriosus (PDA) is considered a risk factor for necrotising enterocolitis (NEC) and other gastrointestinal complications in preterm infants. The aim of this study is to determine whether there is a higher incidence of abdominal surgery and the associated morbidity and mortality in preterm infants who require treatment due to a significant PDA.
Methods: An observational study was conducted that included preterm infants with <37 weeks of gestational age, and a diagnosis of PDA in the last 10 years. Depending on the treatment received, the patients were divided into 3 groups: medical (A), medical and surgical (B), and no treatment (C). An analysis was performed on the pre- and peri-natal variables, as well as the incidence of gastrointestinal complications (NEC, and need for surgery for this reason), and overall mortality.
Results: The study included a sample of 144 patients, of whom 91 were assigned to group A, 16 to B, and 37 to C. The mean gestational age by groups was 28, 26.7, and 30.1 weeks, respectively. The mean birth weight was 1083.9 g, 909.3 g, and 1471.2 g, respectively. As regards the incidence of NEC, a total of 21, 5, and 5 cases, respectively, were found in each group, with 43%, 60% and 35%, respectively requiring abdominal surgery. Mortality by groups was 12%, 19%, and 3%, respectively.
Conclusion: Patients who required treatment for a significant PDA had a higher incidence of gastrointestinal complications and higher mortality than untreated patients, with no statistically

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significant differences being found. In the group of patients that required treatment, lower gestational age and birth weight, could explain the increase in morbidity and mortality found in these patients.

PALABRAS CLAVE
Persistencia de ductus arterioso;
Enterocolitis necrosante;
Mortalidad neonatal;
Cardiopatía congénita

Cirugía abdominal en prematuros con persistencia de ductus arterioso

Resumen
Introducción: La persistencia de ductus arterioso (PDA), se considera un factor de riesgo para enterocolitis necrosante (ECN) y otras complicaciones digestivas en prematuros. El objetivo del presente trabajo es analizar si existe un mayor riesgo de cirugía abdominal y morbimortalidad asociada en prematuros que precisaron tratamiento debido a una PDA significativa.
Metodología: Estudio observacional, analítico y retrospectivo incluyendo prematuros menores de 37 semanas de gestación, con diagnóstico de PDA en los últimos 10 años. En función del tratamiento recibido, los pacientes fueron divididos en 3 grupos: tratamiento médico (A), tratamiento médico y quirúrgico (B) y sin tratamiento (C). Se analizaron variables pre y perinatales, incidencia de complicaciones digestivas (ECN y necesidad de cirugía por este motivo) y mortalidad global.
Resultados: Se obtuvo una muestra de 144 pacientes: 91 se asignaron al grupo A, 16 al B y 37 al C. La edad gestacional media por grupos fue de 28, 26,7 y 30,1 semanas. El peso medio al nacer fue de 1.083,9, 909,3 y 1471,2 g, respectivamente. En cuanto a la incidencia de ECN, se encontraron un total de 21, 5 y 5 casos en cada grupo, precisando cirugía abdominal un 43, 60 y 35%, respectivamente. La mortalidad por grupos fue del 12, 19 y 3%.
Conclusiones: Los pacientes que precisaron tratamiento por PDA, presentaron una mayor incidencia de complicaciones digestivas y una mayor mortalidad que los pacientes no tratados, sin embargo, no encontramos diferencias estadísticamente significativas. En el grupo de pacientes que requirieron tratamiento, la menor edad gestacional y peso al nacer, podrían explicar el incremento de la morbimortalidad encontrada en estos pacientes.

Introduction

Patent ductus arteriosus (PDA) is a frequent disease in preterm infants, with an incidence that ranges between 40% and 55% in different studies. Depending on the size of the ductus and the volume of the shunt that results from the lack of spontaneous closure of the ductus, patients may develop significant haemodynamic changes, which in most cases manifest as neonatal respiratory distress syndrome.[1–4]

From a pathophysiological standpoint, PDA may lead to the development of significant left-to-right shunt, which increases the risk of complications such as necrotising enterocolitis (NEC), bronchopulmonary dysplasia, intraventricular haemorrhage and death. Several studies have demonstrated that closure of the ductus prior to the development of a haemodynamically significant shunt improves outcomes and increases survival in these patients.[5,6]

When it comes to the management of PDA, most current guidelines support medical management as the first-line treatment, with surgical closure as second-line treatment if medical management is ineffective, the patient has contraindications for medical management or the patient becomes haemodynamically unstable. There are also patients in whom surgical management is considered the first-line treatment, such as preterm newborns delivered before 26 weeks' gestation or with a birth weight of less than 750 g with severe haemodynamic instability and respiratory compromise in whom the probability of successful pharmacological closure is low based on echocardiographic criteria.[7]

In recent years, several studies have analysed the therapeutic profile and adverse effects of the drugs used in the medical management of PDA, most of which belong to the cyclooxygenase (COX) inhibitor family. Indomethacin was the most widely used drug for many years. Ibuprofen started to be used in European neonatal intensive care units from 2005 as an alternative to indomethacin, as the effectiveness and range of adverse effects are similar for both drugs. In Spain, ibuprofen has been used since 2010. Some studies have demonstrated that COX inhibitors, especially indomethacin, may cause vasoconstriction and hypoperfusion in several regions of the circulatory system, including the intestinal vasculature. This additional decrease in mesenteric blood flow could further compromise intestinal perfusion in patients with a haemodynamically significant shunt, increasing the incidence of

gastrointestinal complications such as NEC and isolated intestinal perforations.[8–11]

On the other hand, there have also been studies that did not find evidence of this association. [12–14]

Methods

We conducted a retrospective observational and analytical study where we included all preterm newborns delivered before 37 weeks' gestation and given a diagnosis of PDA between 1997 and 2017. We reviewed the health records of the patients to collect data on various epidemiological and clinical variables.

Based on the treatment received, we divided the patients in 3 groups: medical treatment (A), medical and surgical treatment (B) or no treatment (C). We analysed prenatal and perinatal variables, the incidence of gastrointestinal complications (NEC and need of surgery due to NEC) and overall mortality. In the statistical analysis, we used the chi square or Fisher exact test or the Mann–Whitney *U* test and Kruskal–Wallis test as applicable based on the type of variable. We defined statistical significance as a *P*-value of 0.05 or less in any of the tests.

We defined NEC according to Bell's staging criteria modified by Kliegman and Walsh, by which NEC is classified into 6 stages based on the clinical manifestations and radiographic findings.[15]

The diagnosis of PDA was made by bedside Doppler echocardiography, and the ductus was considered haemodynamically significant based on the classification proposed by McNamara and Sehgal, which takes into account various echocardiographic and clinical criteria to stratify patients according to the severity of haemodynamic instability produced by the ductus.[16]

The management of PDA conformed to the established protocol in the neonatal intensive care unit of our hospital, whereby medical management is the first-line treatment. Medical management included general supportive measures, such as maintenance of adequate oxygenation, fluid restriction and the use of positive end-expiratory pressure (PEEP) and continuous positive airway pressure (CPAP), and the use of vasoactive and diuretic drugs. Pharmacotherapy was used as a second therapeutic step, initiating treatment with intravenous indomethacin at a dose of 0.2 mg/kg followed by 2 additional doses of 0.1–0.25 mg/kg depending on the postnatal age of the patient. The use of ibuprofen started in 2010, with administration of an initial course of 3 doses delivered intravenously by continuous infusion over 30 min at 24-h intervals (initial dose of 10 mg/kg and subsequent doses of 5 mg/kg). In case of failure of the first course or reopening of the ductus, a second course was given 24–48 h after completion of the first course, following the same schedule and dosage. After completion of medical treatment, bedside Doppler echocardiography was used to ascertain whether closure of the ductus had been successful. In cases where medical treatment failed or the patient had contraindications for medical treatment or severe haemodynamic instability, the initial treatment consisted of surgical closure of the PDA with metal clips, which in every case was performed in the neonatal intensive care unit of the hospital by a paediatric cardiovascular surgeon.

Results

We obtained a sample of 144 patients that met the inclusion criteria during the period under study: 91 classified into group A, 16 into group B and 37 into group C.

The mean gestational age in each of these groups was of 28, 26.7 and 30.1 weeks, and the mean birth weight 1083.9, 909.3 and 1471.2 g, respectively.

We collected data on clinical and epidemiological variables from the health records (Table 1). The Apgar score at 1 min, need of prenatal steroid therapy and postnatal surfactant therapy and need of respiratory support were similar in the 3 groups of patients. However, we found that the gestational age and birth weight were significantly greater in the group of patients that did not receive any treatment (group C; $P < .001$).

When it came to the incidence of NEC (Table 2), we found that a total of 21, 5 and 5 patients in groups A, B and C respectively required abdominal surgery, corresponding to 43%, 60% and 35% of that group. However, the statistical analysis did not detect significant differences between the incidence of NEC and need of surgery to treat it found in groups A and B compared to the group of patients that received no treatment ($P = .14$ and $P = .63$, respectively).

The mortality for groups A, B and C was 12%, 19% and 3%. Once again, the statistical analysis did not reveal any significant differences between these 3 groups.

Discussion

Patent ductus arteriosus is a frequent finding in preterm newborns. Depending on the severity of the systemic shunt resulting from PDA, there may be an increased risk of complications and mortality.[1–6]

At present, there is no consensus as to which patients require treatment, the optimal timing of treatment and which type of treatment is most appropriate. However, most current protocols establish that treatment should be given to patients with haemodynamically significant ductus and that medical management should be the first-line treatment, reserving surgery for cases where medical treatment fails.[17,18]

Several studies have analysed the potential adverse effects of COX inhibitors used for treatment of PDA. Works published by different authors, such as Grosfeld et al., Fujii et al., Pezzati et al. and Havranek et al. have found that indomethacin produces vasoconstriction and hypoperfusion in the brain, heart, bowel and kidneys, increasing the risk of potential complications in these regions.[8–11] Other studies have demonstrated that treatment with COX inhibitors is a risk factor for the development of isolated intestinal perforations, especially when used in combination with steroid therapy.[19,20] For this reason, from 2005 most European protocols have introduced the use of ibuprofen, as this drug has a similar mechanism of action as has exhibited a similar effectiveness, but is associated with a lower incidence of adverse events. In addition, given the potential risk of nephrotoxicity associated with ibuprofen, studies are currently underway to assess the efficacy and safety of paracetamol as an alternative drug in the management of these patients.[21,22]

Table 1 Clinical characteristics of patients by treatment received.

	A (medical Tx) $n = 91$	*B* (medical Tx + Sx) $n = 16$	*C* (No Tx) $n = 37$	*P*
Sex				
Male, (%)	45 (49)	6 (38)	15 (41)	.36
Female, (%)	46 (51)	10 (63)	22 (59)	
Gestational age (wk)	27.98 ± 2.6	26.75 ± 1.2	30.19 ± 3.5	.001*
Birth weight (g)	1.083.97 ± 359.7	909.38 ± 285.6	1.471.22 ± 623.7	.001*
Apgar (1 min)	5 ± 1	5 ± 1	6 ± 2	.157
Steroid Tx, (%)	85 (93)	15 (94)	29 (78)	.24
Surfactant Tx, (%)	82 (90)	16 (100)	25 (68)	.35
Respiratory support, (%)	90 (99)	16 (100)	33 (89)	.30
Intraventricular haemorrhage grade III/IV				
Yes, (%)	9 (10)	3 (19)	1 (3)	.279
No, (%)	82 (90)	13 (81)	36 (97)	
Maternal disease				
Yes, (%)	33 (36)	5 (31)	18 (49)	.194
No, (%)	58 (64)	11 (69)	19 (51)	

Sx, surgery; Tx, treatment.
Data expressed as mean ± standard deviation or absolute frequency of patients (%).
* $P < .05$.

Table 2 Gastrointestinal complications and mortality in patients by treatment received.

	A (medical Tx) $n = 91$	*B* (medical Tx + Sx) $n = 16$	*C* (No Tx) $n = 37$	*P*
NEC, (%)	21 (23)	5 (31)	5 (14)	.14
NEC age, (days of life)	17.6 ± 11.4	26.9 ± 8.2	9.8 ± 3.5	.096
Previous feedings, (%)	20 (95)	4 (80)	5 (100)	
Perforation associated with NEC, (%)	6 (29)	3 (60)	1 (20)	.30
Sx for NEC, (%)	9 (43)	3 (60)	2 (40)	.63
Death associated with NEC, (%)	7 (33)	2 (40)	2 (40)	.91
Mortality, (%)	11/91 (12)	3/16 (19)	1/37 (3)	.17

NEC, necrotising enterocolitis; Sx, surgery; Tx, treatment.
Data expressed as mean ± standard deviation or absolute frequency of patients (%).

When it comes to surgical closure of PDA, there is evidence that it may be associated with a higher incidence of complications in both the short and the long term. Early ligation of the ductus is an independent risk factor for the development of bronchopulmonary dysplasia and may increase the risk of other complications such as psychomotor delay, retinopathy of prematurity, vocal cord paralysis and cardiovascular and respiratory instability compared to preterm newborns treated with medical approaches.[23–26] Furthermore, a study published by Mirea et al. found that surgical ligation of PDA in preterm newborns was associated with an increase in morbidity and mortality in analyses that were adjusted for several potential confounders.[27]

In our study, when we analysed the clinical and epidemiological characteristics of the sample we found that the group of patients that did not require any form of treatment had significantly greater gestational ages and birth weights compared to the group of patients that required medical treatment alone or followed by surgery. It is important to take into account that birth weight and prematurity themselves are independent risk factors for the development of various complications and are associated with a higher neonatal mortality.[28] For this reason, studies analyzing comparable groups based on the type of treatment received would be useful in order to eliminate the potential confounding effect of differences in gestational age and birth weight.

As for gastrointestinal morbidity and mortality, we found a higher incidence of NEC, a more frequent need of surgery to treat NEC and a higher overall mortality in the group of patients that received medical or medical and surgical treatment. However, when we performed the statistical analysis, these differences in relation to the group of untreated patients were not statistically significant. These findings disagree with those of previous studies that *evinced* an increased risk of NEC and other gastrointestinal complications in patients treated with indomethacin.[8–11] On the other hand, our results are consistent with those of other, more recent studies that have not found an increased incidence of NEC, other gastrointestinal complications or mortality in patients treated for a haemodynamically significant PDA. O'Donovan et al. analysed a sample of 224 preterm newborns with a diagnosis of PDA with a mean gestational age of 26.2 weeks and a mean birth weight of 870 g.

They divided patients into 3 groups based on the treatment received (medical, surgical and medical-surgical). This study did not find statistically significant differences in the incidence of NEC, need of surgery to treat NEC and overall mortality in the comparison of these 3 groups of patients.[14]

We believe that additional prospective and randomised studies are required with larger samples of patients to determine whether treatment of PDA is associated with a higher incidence of gastrointestinal complications and a greater overall mortality.

Conflicts of interest

The authors have no conflicts of interest to declare.

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