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Indicators of surgical treatment of patent ductus arteriosus in preterm neonates in the first week of life

Indicadores para o tratamento cirúrgico na persistência do ducto arterial em neonatos prematuros na primeira semana de vida

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Abstract

Objective: To identify clinical and echocardiographic indicators of the necessity for early surgical closure of patent ductus arteriosus in preterm neonates.

Methods: The prospective study was conducted at the Neonatal Unit of Hospital Municipal Odilon Behrens between 2006 and 2010. The study population comprised 115 preterm neonates diagnosed with patent ductus arteriosus in the first week after birth, of whom 55 (group S) were submitted to clinical and/or surgical closure and 60 (group NS) received non-surgical treatment. The parameters analyzed were birth weight, diameter of the ductus arteriosus (DAD), left atrial-to-aortic root diameter ratio (LA:Ao), the quotient of DAD² and birth weight (mm²/kg), and ductal shunting.

Results: The study population comprised 58 males and 57 females. The average birth weight of group S (924 ± 224.3 g) was significantly ($P=0.049$) lower than that of group NS (1012.3 ± 242.8 g). The probability of the preterm neonates being submitted to surgical closure was 62.1% ($P=0.006$) when the DAD²/birth weight index was > 5 mm²/kg, 72.2% ($P=0.001$)

when the LA:Ao ratio was > 1.5, and 61.2% when ductal shunting was high ($P=0.025$).

Conclusion: The parameters DAD²/birth weight index > 5 mm²/kg, LA:Ao ratio > 1.5 and high ductal shunting were statistically significant indicators ($P<0.05$) of the need for surgical closure of patent ductus arteriosus in low birth weight preterm neonates. Moreover, when an LA:Ao ratio > 1.5 was associated with the occurrence of shock, the probability of surgical closure increased to 78.4%.

Descriptors: Ductus arteriosus, patent. Echocardiography. Infant, premature, diseases.

Resumo

Objetivo: Identificar parâmetros clínicos e ecocardiográficos para a indicação do tratamento cirúrgico precoce da persistência do ducto arterial.

Métodos: Esse estudo prospectivo foi conduzido na Unidade Neonatal do Hospital Municipal Odilon Behrens entre 2006

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Abbreviations, acronyms & symbols

| | |
|-------|---|
| DA | Ductus arteriosus |
| DAD | Diameter of the ductus arteriosus |
| LA:Ao | Left atrial-to-aortic root diameter ratio |
| PDA | Patent ductus arteriosus |
| ROC | Receiver operating characteristic |

e 2010. A população estudada compreendeu 115 neonatos prematuros diagnosticados com persistência do ducto arterial na primeira semana após o nascimento, dos quais 55 (grupo S) foram submetidos ao tratamento clínico e ou cirúrgico e 60 (grupo NS) ao tratamento clínico. Os parâmetros analisados foram peso ao nascer, diâmetro do ducto arterial (DAD), relação diâmetro do átrio esquerdo pelo diâmetro da aorta (AE/Ao), índice DAD2/peso ao nascer e fluxo no ducto.

Resultados: O estudo abrangeu 58 pacientes do sexo masculino e 57 do feminino. O peso médio ao nascer do grupo S ($924 \pm 224,3$ g) foi significativamente ($P=0,049$) menor do que do grupo NS ($1012,3 \pm 242,8$ g). A probabilidade dos neonatos prematuros serem submetidos à cirurgia foi 62,1% ($P=0,006$) quando o índice DAD2/peso ao nascer era > 5 mm²/kg, 72,2% ($P=0,001$) quando a razão LA:Ao era $> 1,5$ e 61,2% ($P=0,025$) quando o fluxo no ducto era alto.

Conclusão: Os parâmetros DAD²/peso ao nascer > 5 mm²/kg, razão LA:Ao $> 1,5$ e alto fluxo no ducto foram preditores estatisticamente significativos ($P<0,05$) da necessidade de fechamento cirúrgico da persistência do ducto arterial em neonatos prematuros com baixo peso ao nascer. Adicionalmente, quando a razão LA:Ao $> 1,5$ estava associada ao choque, a probabilidade de tratamento cirúrgico aumentou para 78,4%.

Descritores: Permeabilidade do canal arterial. Ecocardiografia. Doenças do prematuro.

INTRODUCTION

Patent ductus arteriosus (PDA) is a congenital heart problem that affects some neonates in which the ductus arteriosus, the blood vessel connecting the descending aorta and the pulmonary artery, fails to close after birth. Although the disorder can affect full-term infants, it is significantly more prevalent in preterm babies. The PDA in preterm neonates has been associated with increased morbidity and mortality if left uncorrected [1-3].

Correction of PDA in preterm neonates can be achieved via surgical methods (open surgery, video laparoscopy or endovascular approaches) or via clinical therapy [4-6]. The treatment of choice is the administration of nonsteroidal anti-inflammatory drugs (such as indomethacin and ibuprofen) that inhibit the prostaglandins known to keep the ductus arteriosus (DA) open [1]. In cases where clinical treatment fails, the DA can be closed by surgical ligation. However, while early closure of the DA improves the long-term cardiorespiratory functions of infants [2], the ideal time of application of the surgical procedure in preterm neonates remains somewhat controversial [3].

Although premature surgical closure of DA has received considerable attention in recent years, no definitive criteria of indication of this procedure have been established. The surgical indications most frequently applied appear to be related to the presence of heart anomalies (increased DA diameter and enlarged left atrium) and clinical signs such as shock, high parasternal systolic murmur and hyperdynamic

precordium [7-9]. Considering that early surgical intervention can reduce morbidity and mortality among preterm neonates, it is of the utmost importance to recognize the signs and symptoms that support a surgical approach. Within this context, the aim of the present study was to identify the clinical and echocardiographic parameters that indicate the need for early surgical closure of PDA in preterm neonates who have been found unresponsive to, or unsuitable to receive, appropriate medication.

METHODS

Details of the project were submitted to and approved by the Ethical Research Committee of the Hospital Municipal Odilon Behrens (CAAE 0012.0.216.000-06; FR99402; protocol no. 82/2006). The aims and objectives of the study were explained to the parents or legal guardians of the infants, and written informed consent was obtained prior to the commencement of the study. All procedures were conducted according to the ethical principles of research as embodied in the Declaration of Helsinki.

The prospective study was conducted at the Neonatal Unit of the Hospital Municipal Odilon Behrens between 2006 and 2010. Clinical and echocardiographic data of 215 preterm neonates (gestational age ≤ 30 weeks) were analyzed and those diagnosed with PDA, according to the echocardiogram acquired on the 3rd or 4th day after birth, were selected for possible inclusion in the study. Neonates presenting congenital cardiovascular pathologies other than

PDA (as determined by echocardiography using a Toshiba Nemio 30 ultrasound instrument) and infants who died during the first week after birth were excluded from the study. The final study population comprised 115 infants, all of whom received clinical treatment except for those who presented contraindications for ibuprofen therapy or PDA-induced shock. Sixty of the infants responded to the non-surgical treatment (group NS), while 55 were submitted to surgery for the correction of PDA (group S). The treatment with ibuprofen consisted of intravenous perfusion of three doses at 24 h intervals: 1st dose 10 mg/kg, 2nd and 3rd doses 5 mg/kg. The surgical technique applied to the S group involved left posterior thoracotomy in the third or fourth intercostal space via the triangle of auscultation, followed by extra pleural dissection of the DA and ligation with titanium clips under general anaesthesia [9,10].

The data assessed for all patients included birth weight, gestational age, clinical and echocardiographic signs of PDA in the first week after birth, treatment received to correct the defect (surgical or non-surgical), diameter of the DA (DAD), left atrial-to-aortic root diameter ratio (LA:Ao), the quotient of DAD² and birth weight (mm²/kg), and ductal shunting. Shunting was evaluated on the parasternal short axis by color Doppler from the pattern and magnitude of shunt of the arterial canal in the direction of the pulmonary artery, and classified as: low (flow from the pulmonary branch up to the distal portion of the pulmonary artery), moderate (flow up to the mid-third of the pulmonary artery), and high (flow up to the proximal portion of the pulmonary artery and reaching the pulmonary valve). The diameter of the arterial canal was measured by two-dimensional echocardiography at the level of the pulmonary vein ostium.

Univariate analyzes of the clinical and echocardiographic data and their association with surgical closure was established using χ^2 and Student t tests. Multivariate logistic regression analysis was performed in order to evaluate cross influences between the variables. Results were considered statistically significant at 5% probability ($P < 0.05$). A receiver operating characteristic (ROC) curve was constructed for each of the variables in order to determine those that constituted good

predictors for the outcome of interest (surgical indication). According to the ROC curves, the cut off points for the DAD²/birth weight index was 5 mm²/kg and that for the LA:Ao ratio was 1.5.

RESULTS

Of the 215 preterm neonates initially screened, 115 (53.5%) were diagnosed with PDA by echocardiography and included in the study. While the numbers of males (58/115; 50.4%) and females (57/115; 49.6%) in the study population were similar, the percentage of males submitted to surgical intervention (31/58; 53.4%) was higher than that of females (24/57; 42.1%), although the difference was not statistically significant ($P = 0.223$).

The mean gestational ages of the preterm neonates in groups S and NS were 27.1 and 27.7 weeks, respectively, while the average birth weight of group S was significantly ($P = 0.049$) lower than that of group NS (Table 1). Of the neonates presenting low birth weight in the total study population, more than half (57.7%) were in group S but, according to the ROC curve, birth weight was not a good predictor ($P = 0.107$) of surgical closure. There was no significant difference ($P = 0.155$) between the surgical and non-surgical groups regarding DAD, however, the two groups were significantly ($P = 0.010$) different with respect to the index DAD²/birth weight (Table 1).

According to the percentage distributions shown in Table 2, preterm neonates with DAD²/birth weight index above 5 mm²/kg presented a 62.1% ($P = 0.006$) probability of being submitted to surgical closure of PDA. Elevated probabilities of receiving surgical treatment for the correction of PDA were also associated with preterm neonates presenting LA:Ao ratios above 1.5 (72.2 % probability; $P = 0.001$) or exhibiting high ductal shunting (61.2%; $P = 0.025$). Mortality was not directly associated ($P = 0.151$) with surgical closure, however, since the deaths of seven children from group S and of 13 children from group NS were caused by other factors including sepsis, complex congenital malformations and cerebral ventricular hemorrhage.

Table 1. Main characteristics of the preterm neonates diagnosed with patent ductus arteriosus submitted to surgical (group S) or non-surgical (group NS) treatment of the defect.

| Variable | Group S (n = 55) | | | Group NS (n = 60) | | | P value* |
|--|------------------|---------|----------------------------|-------------------|---------|----------------------------|----------|
| | Minimum | Maximum | Mean \pm SD ^a | Minimum | Maximum | Mean \pm SD ^a | |
| Birth weight (g) | 520 | 1550 | 924.0 \pm 224.3 | 520 | 1540 | 1012.3 \pm 242.8 | 0.049 |
| Diameter of ductus arteriosus (DAD; mm) | 1.2 | 3.8 | 2.2 \pm 0.5 | 0.9 | 3.2 | 2.0 \pm 0.7 | 0.155 |
| DAD ² /birth weight (mm ² /kg) | 1.6 | 16.0 | 5.8 \pm 2.5 | 0.8 | 11.9 | 4.5 \pm 2.6 | 0.010 |

*Differences are statistically significant at $P < 0.05$ (Student t test), ^a Standard deviation

Table 2. Association between the indication for surgical closure of patent ductus arteriosus in a population of preterm neonates (N = 115) and the variables quotient of diameter of ductus arteriosus (DAD)² and birth weight, left atrial-to-aortic root diameter ratio (LA:Ao), ductal shunting and mortality.

| Variable | Group S ^a (%) | Group NS ^b (%) | P value* |
|--|--------------------------|---------------------------|----------|
| DAD ² /birth weight (n = 111) | | | 0.006 |
| ≤ 5 mm ² /kg | 35.8 | 64.2 | |
| > 5 mm ² /kg | 62.1 | 37.9 | |
| LA: Ao ratio (n = 110) | | | 0.001 |
| ≤ 1.5 | 39.2 | 60.8 | |
| > 1.5 | 72.2 | 27.8 | |
| Ductal shunting ^c (n = 104) | | | 0.025 |
| Low | 44.4 | 55.6 | |
| Moderate | 28.6 | 71.4 | |
| High | 61.5 | 38.5 | |
| Mortality (n = 111) | | | 0.151 |
| Yes | 12.7 | 23.2 | |
| No | 87.3 | 76.8 | |

^a Group submitted to surgical treatment, ^b Group submitted to non-surgical treatment, ^c Ductal shunt was classified as low, moderate and high depending on the flow up to the proximal third, mid and distal third of the pulmonary artery, respectively. * Associations between the variables and indication for surgical closure of PDA are statistically significant at $P < 0.05$ (χ^2 test)

Table 3. Multivariate logistic regression analysis (complete model) of the predictors of surgical closure among preterm neonates with patent ductus arteriosus (N = 115)

| Factor | Estimated value | P value |
|---|-----------------|---------------|
| Occurrence of shock | 0.8705 | 0.1403 |
| Drug therapy | - 1.7907 | 0.2474 |
| Administration of ibuprofen | 0.9665 | 0.5367 |
| Birth weight | -0.5099 | 0.3899 |
| Gestational age | - 0.6106 | 0.2579 |
| DAD ² /kg ^a (mm ² /kg) | 0.3211 | 0.6405 |
| LA:Ao ratio ^b | 1.2918 | 0.0315 |
| Ductal shunting | 1.3257 | 0.0370 |
| DA diameter | - 0.7888 | 0.3207 |

^a Quotient of diameter of ductus arteriosus (DAD)² and birth weight,

^b Left atrial-to-aortic root diameter ratio (LA:Ao)

Table 4. Probability of surgical closure in preterm neonates with patent ductus arteriosus considering the combined factors left atrial-to-aortic root diameter ratio (LA:Ao) and occurrence of shock

| LA:Ao ratio | Shock | Probability of surgical intervention (%) |
|-------------------|-------|--|
| Normal (≤ 1.5) | No | 23.4 |
| Normal (≤ 1.5) | Yes | 48.5 |
| Increased (> 1.5) | No | 54.2 |
| Increased (> 1.5) | Yes | 78.4 |

Multivariate logistic regression analysis of the predictors of surgical closure in 115 preterm neonates with PDA revealed that the variables LA:Ao ratio and ductal shunting were significant predictors of surgical closure ($P=0.0315$ and $P=0.0370$, respectively; Table 3). Moreover, the probability of surgical closure increased to 78.4% when the markers LA:Ao > 1.5 and shock were associated (Table 4).

DISCUSSION

In the present study, 47.8% (55/115) of the preterm neonates diagnosed with PDA required surgical closure. The necessity for surgical intervention is decided mainly on clinical and echocardiographic assessment, but this decision

is not always straightforward, particularly in the case of borderline patients. The consideration of various parameters has been proposed in the selection of preterm neonates requiring early surgical correction of PDA in order to prevent future heart problems and to ensure better chances of survival. Tschuppert et al. [1] indicated that a DAD²/birth weight index > 9 mm²/kg and a LA:Ao ratio > 1.5 represented good predictors of the need for surgery. The cut-off points obtained in the present study agree partially with the earlier proposals in that the suggested LA:Ao ratio cut-off was similar (> 1.5) but that for the DAD²/birth weight index was much smaller (> 5 mm²/kg). Furthermore, our results indicated that high ductal shunting is a relevant prognostic marker for surgical closure. According to Chiruvolu et al. [7], high left-to-right

shunting is very aggressive to preterm neonates because it induces pulmonary hypertension, pulmonary congestion and enlargement of heart chambers. A hemodynamically significant degree of ductal shunting may be a decisive factor in the choice of a surgical approach.

The sample size employed in the present study was larger than that reported in earlier studies, and this improved the precision of the statistical analysis of parameters. Thus, the results obtained herein may be considered appropriate for the construction a checklist to serve as a guideline for pediatricians and cardiologists when arriving at decisions regarding surgical closure of PDA. Obviously, meticulous medical assessment on a case by case basis, coupled with sound and prudent judgment, must always prevail in decision making. However, it is important to stress that, while the short- and long-term benefits of PDA closure have been demonstrated by numerous studies [1-3,7,8], delays in the treatment of PDA may lead to severe consequences for the neonate.

CONCLUSION

The parameters DAD²/birth weight index > 5 mm²/kg and LA:Ao ratio > 1.5 along with high ductal shunting are statistically significant indicators ($P<0.05$) of the need for surgical closure of PDA in low birth weight preterm neonates during the first week of life. The probability of surgical intervention when any of these factors are present is greater than 60%. Moreover, when the LA:Ao ratio > 1.5 is associated with the occurrence of shock, the probability of surgical closure increases to 78.4%.

Author's roles & responsibilities

| | |
|------|--------------------------------|
| RB | Main author |
| CLG | Coauthor, statistical analysis |
| FDRA | Performed the echocardiograms |
| KNB | Performed the echocardiograms |
| LDGA | Conducted the data collection |
| PHNC | Conducted the data collection |
| FDC | Coauthor |

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