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Use of sildenafil in late postoperative period of congenital diaphragmatic hernia

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TO THE EDITOR

Congenital diaphragmatic hernia (CDH) occurs in about 1 in 3,300 live births. It is a congenital defect of the diaphragm with herniation of the abdominal viscera into the thorax. Abnormal pulmonary development leads to hypoplasia and pulmonary hypertension, which are the main determinants of morbidity and mortality for these patients.[1]

Between 2015 and 2019, 83 patients with CDH were admitted to the Neonatal Intensive Care Center-2 (NICC-2) of the Child and Adolescent Institute of the Clinics Hospital of the University of São Paulo School of Medicine (*HCFMUSP*), São Paulo, Brazil. Of these, 42 (50.6%) were discharged from the hospital and enrolled in a specialized follow-up outpatient clinic, in which six patients (14.2%) used sildenafil. The other 36 patients had normal pulmonary pressure and therefore there was no indication for use of sildenafil.

NICC-2, aligned with the most up-to-date guidelines, uses systematized protocols for the CDH approach.[1,2] This protocol is multidisciplinary and begins with the admission of the newborn shortly after birth in the surgical room or obstetric center. It includes resuscitation in the delivery room, transfer to CTIN-2 for monitoring, ventilation assistance, central and arterial venous accesses, drug treatment of pulmonary hypertension, fluid control, comfort measures, and pain reduction.[3]

All these measures aim not only to stabilize the newborn for surgical correction of the congenital defect, but also to allow an adequate recovery in the postoperative period, increasing its survival. Moreover these newborns are referred to a specialized follow-up outpatient clinic.

The main characteristics of the children on sildenafil after hospital discharge were the following: 83.3% were male, 100% were Cesarean born, average birth weight was 3058.3 ± 306.2 grams, mean gestational age was 38.3 ± 1.0 weeks, and in relation to karyotype, three had 46XY, one had mosaicism 46X0/46XY and two families did not agree with the test. As there may be an association of CDH with trisomy, especially 18 and 21, it is recommended to perform fetal karyotype routinely[4].

Regarding the type of CDH, five children (83.3%) had the defect on the left side and all required a prosthetic patch during surgery to repair the diaphragm. Congenital anomalies were found in three (50%) different cases (hypoplasia of the aortic isthmus, ventriculomegaly and hydrocephalus).

Table 1 shows the doses of sildenafil used, as well as the time of use and evolution of pulmonary hypertension measured by echocardiography.[5]

According to "The Canadian Congenital Diaphragmatic Hernia Collaborative"[1], the treatment of pulmonary hypertension in CDH consists in using the following drugs: inhaled nitric oxide - indicated in the treatment of pulmonary hypertension without left ventricular dysfunction, but in the absence of clinical response and/or echocardiography, its use should be discontinued (grade II evidence); milrinone - drug of choice in the treatment of pulmonary hypertension with cardiac dysfunction (grade I evidence); sildenafil - used in pulmonary hypertension refractory to nitric oxide and/or in conjunction with nitric oxide (grade II evidence); prostaglandin E - used to keep the ductus arteriosus patent and reduce the right overload in newborns with pulmonary hypertension and right ventricular failure or in imminent ductus arteriosus closure (grade II evidence).

After the instability phase, the drugs of choice by enteral route for treatment of pulmonary hypertension are sildenafil and bosentan.[6] In our country, sildenafil is chosen over bosentan because of the high costs involved.

After several controversies, sildenafil was released to control neonatal pulmonary hypertension in the following conditions: as adjuvant to inhaled nitric oxide or to facilitate weaning, as primary treatment of persistent pulmonary hypertension of the newborn when nitric oxide is not available or contraindicated and as first option in the chronic treatment of pulmonary hypertension in bronchopulmonary dysplasia and CDH.[7,8,9]

In our sample, 14.2% of the children required sildenafil after hospital discharge (average of 144 days), with doses between 2 and 4 mg/kg. In a similar study, Behrsin et al.[10] reported that 17% used the drug after discharge at a dose of 8 mg/kg/day, with a median of 343 days. This showed a consistency in the dose, but with a much longer period of use of sildenafil, probably due to severities other than pulmonary hypertension. Furthermore, the discontinuation of sildenafil was gradual (0.5 mg/kg/week) in the Australian study,[10] which was not performed in our sample because the drug was discontinued and there was no rebound effect on pulmonary hypertension, showing no need for drug discontinuation. Our protocol does not establish a specific time for the use of sildenafil as it depends on the pulmonary hypertension reversal.

The side effects of sildenafil were categorized into gastrointestinal (diarrhea, dyspepsia), vascular (epistaxis, flushing, headache) and neurological (abnormal vision, hyperactivity, insomnia, myalgia, pyrexia),[2] but such an event was not observed in the medical records regarding the use of sildenafil.

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Table 1. Variable doses of sildenafil used, time of use and evolution of pulmonary hypertension.

Case	Dose of sildenafil (g/kg/dose)	Time of use (days)	Echocardiography PASP at discharge (mmHg)	Echocardiography at sildenafil discontinuation
1	4	71	85	Absence of indirect PH signs*
2	2	124	70	PASP=31 mmHg
3	2	266	73	Absence of indirect PH signs*
4	2	77	65	Absence of indirect PH signs*
5	2	120	58	Absence of indirect PH signs*
6	2	210	60	Absence of indirect PH signs*

PASP = pulmonary artery systolic pressure at hospital discharge. PH = pulmonary hypertension. *Indirect signs of PH on echocardiography = pulmonary artery dilation, changes in pulmonary valve movement and pattern of the flow velocity curve of the right ventricular outflow tract.[5]

In conclusion, the prescription of sildenafil for pulmonary hypertension control was effective and showed no side effects. It is noteworthy that several of these effects are subjective (dyspepsia, headache, hyperactivity, abnormal vision, myalgia, pyrexia) and difficult to evaluate and/or measure in young infants as they may go unnoticed in the follow-up appointment. Thus, in these children should be asked about all the side effects listed above. Moreover, families should be instructed to monitor these side effects and report on them so that appropriate action is taken.

It is worth emphasizing that this is the first Brazilian report describing the outpatient use of sildenafil for treatment of pulmonary hypertension in children with corrected CDH.

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