www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2014;3(2):e030221
doi: 10.7363/030221
Received: 2014 Aug 26; accepted: 2014 Sept 09; published online: 2014 Oct 08

Original article

PDA management in preterm infants: keep your hands off the ductus!

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Proceedings

Proceedings of the 10th International Workshop on Neonatology · Cagliari (Italy) · October 22nd-25th, 2014
The last ten years, the next ten years in Neonatology
Guest Editors: Vassilios Fanos, Michele Mussap, Gavino Faa, Apostolos Papageorgiou

Abstract

The current management of a patent ductus arteriosus (PDA) in preterm infants is fundamentally aimed at the closure of ductus through the cyclooxygenase (Cox)-inhibitors or surgical ligation in case of failure. Although the role of surgical approach to morbidity and mortality remains unclear, measures avoiding it appear entirely justified.

During the last two years, 8 newborns were admitted to our intensive care unit for surgical ligation of a hemodynamic significant PDA, after a two ineffective Cox-inhibitor courses. The mean gestational age was 26 5/7 weeks (24 6/7 - 28 3/7 w.), the mean birth weight 1,000 g (800-1,300 g) and the mean age at admission 20 days (9-29 d.) at a mean post-conceptional age (PCA) of 29 3/7 weeks (27 5/7 - 31 5/7 w.). We have submitted these newborns to an approach consisting in a continuous monitoring of cerebral and renal oxygenations, time-scheduled ultrasound controls, monitoring of blood pressure and of urine output and continuous aEEG registration. All were treated with dopamine infusion. Under dopamine, ranging from 5 to 10 µg/kg/min, the stabilization criteria (see text) were reached in 7/8 infants. Afterwards a new cycle of Cox-inhibitors has been tried with the result of closing the ductus in 4/8 and obtaining a flow closing pattern in other three. None of the seven infants has shown in the following weeks a reapparence of ductal reopening signs. In this way we avoided the surgical intervention in 7/8 newborns.

An attempt with Cox-inhibitors (ibuprofen) has also been proved in the single newborn who didn't reach the stabilization but resulted ineffective. This newborn has been submitted to surgical ligation immediately thereafter.

Moreover, the clinical conditions observed in all the newborns at admission testify that the duration of the exposure to left-to-right shunt is a crucial factor of the organ damage. This aspect is often not considered, waiting for the Cox-inhibitor effects.

The contribution of the aEEG recordings is, in this context, considerable, having shown a background pattern of burst suppression in four subjects and a discontinuous pattern not in line with reached PCA in other three.

On the basis of these results we think that the therapy of PDA in preterm infants must be mainly aimed at the containment of the ductal shunt and of its effects on pulmonary and systemic flow.

In this way the objective of the ductal closure stops to be primary, being possible, under conditions of hemodynamic stability, waiting during the first week of life for the physiologic events of closure or resorting in selected cases to the Cox-inhibitors or to the surgical intervention.

This limited experience requires more consistent proofs of effectiveness, while the impact of this approach on the outcomes needs to be evaluated.

Keywords

Hemodynamic significant patent ductus arteriosus, surgical ligation of ductus, cerebral and renal hemoglobin saturation, cerebral and renal oxygen extraction fraction in hsPDA, effects of dopamine, aEEG registration in hsPDA.

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How to cite

Giliberti P, De Leonibus C, Chello G, Magri D, Giordano L, De Vivo M, Santantonio A, Giliberti P. PDA management in preterm infants: keep your hands off the ductus! J Pediatr Neonat Individual Med. 2014;3(2):e030221. doi: 10.7363/030221.

Introduction

The most followed management of the patent ductus arteriosus (PDA) in preterm infants fundamentally consists in pharmacological closing attempts through the use of cyclooxygenase (Cox)-inhibitors (indomethacin, ibuprofen and more recently paracetamol) [1-3], completed by a supportive therapy [4-7].

Risk factors, as the low gestational age, the intrauterine inflammation, the missed antenatal steroid prophylaxis and the severity of respiratory distress can limit the effectiveness of Cox-inhibitors and prevent the ductal closing in a consistent number of cases [8, 9].

According to studies of small dimensions, showing a ductal closure in at least 40% of the subjects treated again with Cox-inhibitors [10-12], a second attempt seems advisable.

A persistent patency after two unsuccesful courses is considered an indication for surgical intervention.

Unfortunately, many risks are associated with this procedure, consisting acutely in a post-ligation syndrome, due to an impaired left ventricular (LV) performance, caused by a sudden fall of pulmonary venous return and a rise in LV afterload [13, 14]. In addition, the improving of pulmonary compliance can contribute to the decline of LV output, if the risk of lung overdistention is not avoided [15].

Other surgical complications are pneumothorax, chylotorax, laryngeal and frenic nerve injury, intraoperative bleeding, intraventricular hemorrage, bronchopulmonary dysplasia and ultimately death, although the incidence of these events is valued to be very low [16, 17].

As far as the brain injury is concerned, the question whether the surgical intervention could add further risks of neurosensorial damage, is largely justified.

In one trial, 53% of surgical treated infants showed a neurosensorial impairment at 18 months of life vs 34% of the subjects who needed only a medical treatment [18]. However, the association between brain injury and surgical procedure is very difficult to be estabilished since the intervention can contribute to the damage with its complications or simply select the infants at higher risk.

In the light of these considerations, the question arises if alternative possibilities of treatment exist prior to consider the surgical intervention.

We report on the results obtained in 8 preterm infants transferred to our neonatal intensive care unit (NICU) during the last two years with the indication of surgical ligation of a PDA after two courses of Cox-inhibitors.

Methods

In addition to continous monitoring of $tcSO_2$, HR, RR, blood pressure and temperature with the

IntelliVue MP70 (Philips), all newborns admitted to our NICU were submitted to an aEEG recording (CFM Olympic Brainz Monitor [NATUS]) and to a monitoring of cerebral and renal oxygenation by NIRS (Somanetics 5100 Invos™ [Covidien]), during the first 72 hours and for longer time, if necessary.

The EEG signal was recorded from bilateral frontoparietal hydrogel electrodes, corresponding to C3-C4 and P3-P4 of the international EEG 10-20 classification.

The cerebral and renal oxygenations were measured according to modalities just described in a previous paper [19].

The blood pressure was non-invasively measured every hour in the first two hours after the admission and every 4 hours thereafter. During the dopamine treatment (starting, dosing change), the blood pressure was assessed every hour in the first three hours and every 4 hours thereafter.

Moreover, ultrasound examinations of heart and brain were readily available and were repeated every 6-12 hours, if needed.

All data were presented as mean ± Standard Deviation (SD). Differences in continuous variables were examined for paired samples by Repeated Measures ANOVA. P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS® program (Statistical Package for Social Science®), version 20.0 software for Windows (SPSS, Chicago, IL, USA).

Results

During the last two years, 8 newborns were admitted to our intensive care unit for surgical ligation of a PDA after a two ineffective Cox-inhibitor courses. The mean gestational age was 26 5/7 weeks (24 6/7 - 28 3/7 w.), the mean birth weight 1,000 g (800-1,300 g.) and the mean age at admission 20 days (9-29 d.) at a mean post-conceptional age (PCA) of 29 3/7 w. (27 5/7 - 31 5/7 w.). 6/8 (75%) newborns were in assisted ventilation and 2/8 (25%) under a continuous positive pressure (CPAP). At admission, all newborns showed the clinical findings of a hemodynamic significant PDA (hsPDA): prominent LV impulse, 2-3/6 continuous murmur in the left infraclavicular region and upper left sternal border and bounding pulses. The urine output, assessed during the first 6 hours, was in all cases ≤ 1.0 ml/kg/h. The mean blood pressure values during the first two hours were 28.6 ± 2.1 mmHg.

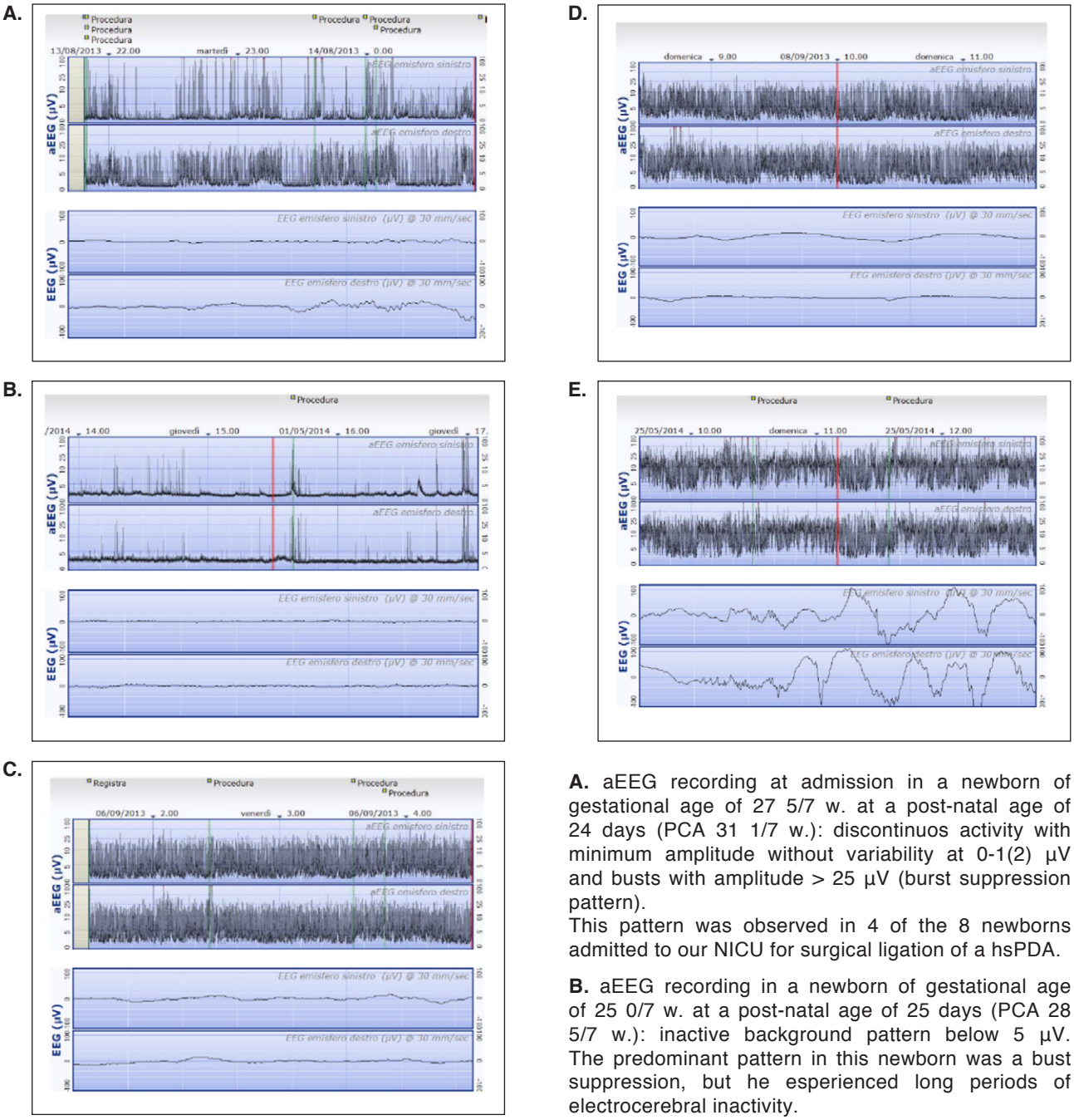
The ultrasound examinations showed the patency of the ductus with an internal diameter of 3.5 ± 0.95 mm, an echocardiographic left atrial/aortic root (LA/Ao) ratio of 1.6 ± 0.16 and an abnormal cerebral blood flow. The diastolic flow in the anterior cerebral artery was retrograde in five and decreased or absent in the other three. The mean resistence index (R.I.) resulted 0.90 ± 0.06 (n.v. 0.55-0.80). A parieto-occipital periventricular leukomalacia in one case, a dilation of the lateral ventricles in three and an old germinal matrix hemorrhage in two were noted.

The mean cerebral saturation (cSO_2), during the first two hours of monitoring, was 62.8 ± 2.3% (n.v. 77.7 ± 7.9 [20]) with an extraction fraction (cFTOE) of 33 ± 3 (n.v. 25 ± 10), while the mean renal saturation (rSO_2) resulted in 46.2 ± 8.4% (n.v. 86.7 ± 7.6) with an extraction fraction (rFTOE) of 50.1 ± 9.2 (n.v. 11 ± 5).

In 4/8 newborns the initial aEEG recording showed a burst suppression with low burst density, but in one the aEEG pattern appeared for long periods inactive. In other three, it was mainly discontinuous but immature compared to the reached PCA. In only one case, the pattern was entirely compatible with the subject's age (**Fig. 1**).

All newborns received a supportive therapy, consisting in fluid restriction (110-130 ml/kg/d), in the maintenance of a hematocrit > 35% (5/8 subjects needed one or more red cell transfusions) and in the avoidance of loop diuretics. It must be underlined that all the eight newborns had been treated with furosemide previously. An enteral feeding was restored only after the hemodynamic stabilization and, thereafter progressively increased. All the newborns received a treatment with dopamine [21] starting at 5 μg/kg/min. The dose of dopamine was increased every 3-6 hours up to 10 μg/kg/min according to the results in order to get a $cSO_2 \geq 70\%$, a cFTOE ≤ 25, a $rSO_2 \geq 80\%$, a rFTOE ≤ 15, a diastolic and a mean blood pressure > 25 and > 30 mm Hg respectively, a R.I. in anterior cerebral artery ≤ 0.80 and a urine output > 1 ml/kg/h. The achievement of these values was considered proof of a reached hemodynamic stabilization. In addition, during the dopamine treatment the internal ductal diameter and the ratio LA/Ao have been systematically measured.

The trend of cSO_2, cFTOE, rSO_2 and rFTOE during the first 48 hours of treatment with dopamine is shown in **Fig. 2**. In 7/8 infants the values progressively inproved, reaching the target with 5 μg/kg/min of dopamine in two, with 7.5 μg/kg/min in



A. aEEG recording at admission in a newborn of gestational age of 27 5/7 w. at a post-natal age of 24 days (PCA 31 1/7 w.): discontinuos activity with minimum amplitude without variability at 0-1(2) µV and busts with amplitude > 25 µV (burst suppression pattern).
This pattern was observed in 4 of the 8 newborns admitted to our NICU for surgical ligation of a hsPDA.

B. aEEG recording in a newborn of gestational age of 25 0/7 w. at a post-natal age of 25 days (PCA 28 5/7 w.): inactive background pattern below 5 µV. The predominant pattern in this newborn was a bust suppression, but he esperienced long periods of electrocerebral inactivity.

C. aEEG recording at admission in a newborn of gestational age of 26 6/7 w. at a post-natal age of 19 days (PCA 29 4/7 w.): discontiuous activity with variable minimum amplitude mainly below 5 µV and maximum amplitude > 10 µV. This pattern was observed in 3 of the 8 newborns. It appears not in line with the reached PCA (see **D** for comparison).

D. aEEG recording in a normal newborn of gestational age of 30 0/7 w.: discontinuous patterm with significant amounts of continuous activity (minimum amplitude > 5 µV and maximum amplitude > 10 µV.). Cyclical pattern suggestive of crude sleep-wake cycling can be seen.

E. aEEG recording at admission in a newborn of gestational age of 28 1/7 w. at a post-natal age of 9 days (PCA 29 3/7 w.): discontinuous pattern with periods of continuous activity. Crude sleep-wake cycling are noted. The pattern is compatible with the reached PCA.

Figure 1. aEEG recording in the 8 newborns admitted for surgical ligation of a hsPDA: at admission 4/8 showed a burst suppression with low burst density (**A**), but in one the aEEG pattern appeared inactive for long periods (**B**). In other three, it was mainly discontinuous but immature compared to the reached PCA (**C, D**). In only one case, the pattern was entirely compatible with the subject's age (**E**). These patterns of electrocerebral activity are the expression of the cerebral hypoperfusion, caused by the ductal steal and its duration. It is not a case that the only newborn with a normal pattern for age (**E**), was the youngest and presumably submitted for briefer time to the effects of a consistent left to right shunt. PCA: post-conceptional age; NICU: neonatal intensive care unit; hsPDA: hemodynamic significant patent ductus arteriosus.

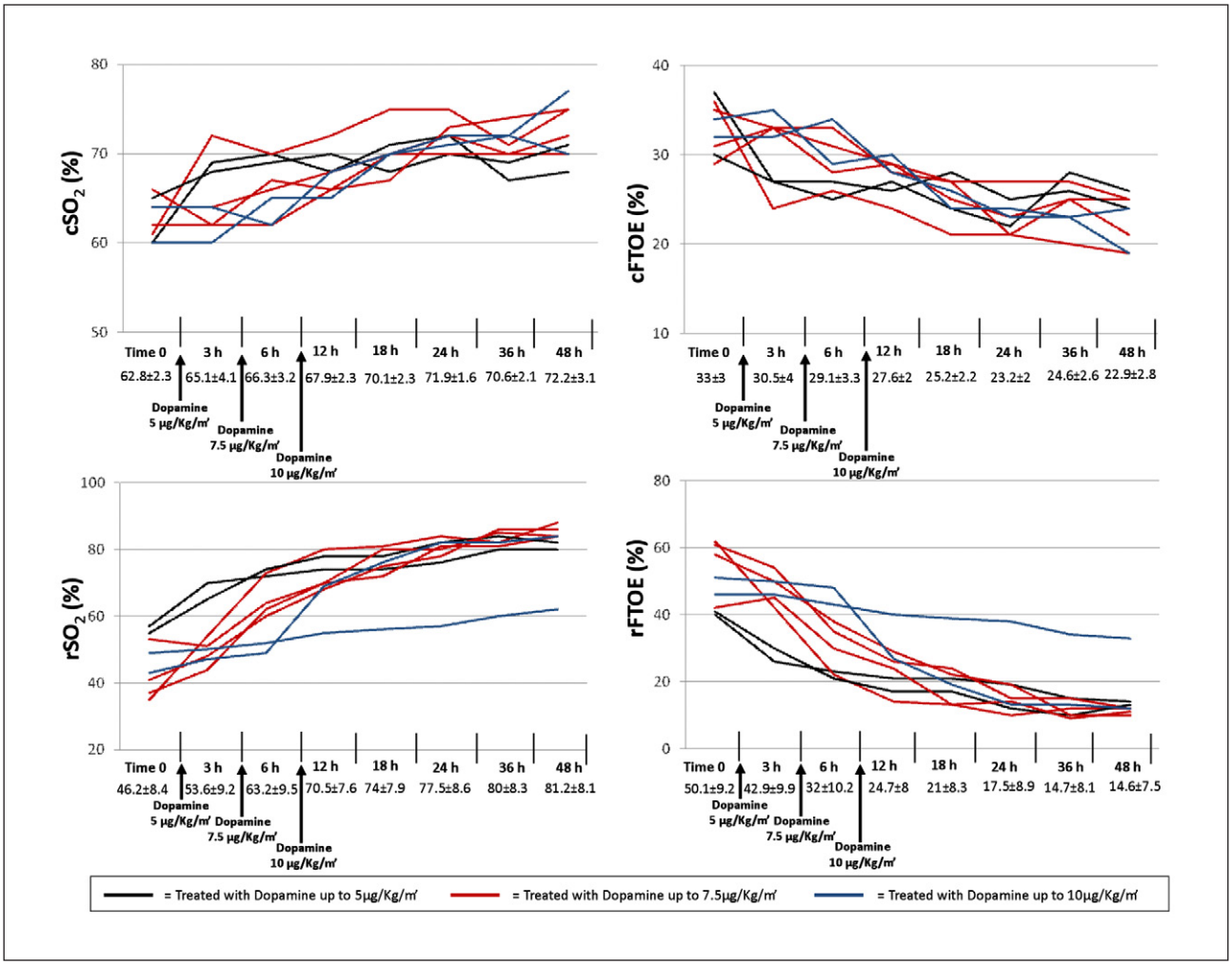


Figure 2. Trend of cerebral saturation (cSO_2), cerebral fractional tissue oxygen extraction (cFTOE), renal saturation (rSO_2) and renal fractional tissue oxygen extraction (rFTOE) during the first 48 hours of treatment with dopamine: 7/8 newborns reached the target values ($cSO_2 \geq 70\%$, a cFTOE ≤ 25 , a $rSO_2 \geq 80\%$, a rFTOE ≤ 15), two with 5 µg/kg/min, four with 7.5 µg/kg/min and one with 10 µg/kg/min. Only in one case, treated up to 10 µg/kg/min, the target values of rSO_2 and rFTOE were never obtained. This newborn who failed a trial with ibuprofen resulted to be affected by a *C. parapsilosis* sepsis. He was the only one submitted to surgical ligation.

other four and with 10 µg/kg/min in one. Only in one case, treated up to 10 µg/kg/min, the target values of rSO_2 and rFTOE were never obtained. This newborn resulted to be affected by a *C. parapsilosis* sepsis.

As shown in **Fig. 3**, a R.I. in anterior cerebral artery ≤ 0.80 was observed in 6-24 h of dopamine treatment in 7/8 newborns, showing a normalization of cerebral blood flow. Only in the single newborn who didn't normalize the rSO_2, the R.I. resulted constantly > 0.80 (0.81-0.90).

Under dopamine, the mean blood pressure progressively increased from values of 28.6 ± 2.1 mmHg to 39.3 ± 4.6 at 6 hours and to 39.9 ± 2.7 at 24 hours of treatment. These values, once reached, have not changed anymore (**Fig. 4**).

The urine output, resulted < 1 ml/kg/h at admission, has progressively increased up to mean values of 2.8 ± 0.5 ml/kg/h, reached in 24 h in all the eight newborns during the treatment with dopamine.

The time scheduled monitoring of ductal dimensions has not shown any change during dopamine administration, while a meaningful reduction of the LA/Ao ratio ($p = 0.043$) appeared (**Tab. 1**).

In the 7/8 subjects satisfying the hemodynamic stabilization criteria, a new cycle of ibuprofen has been tried with the result of closing the ductus in 4/8 and obtaining a flow closing pattern in other two. In the newborn with ductal internal diameter of 5 mm the ibuprofen caused a reduction to 2.5 mm. but a following attempt after 48 h with paracetamol (60 mg/kg/die, p.o., 4x for 7 days) conducted to a flow closing pattern. None of the seven infants has

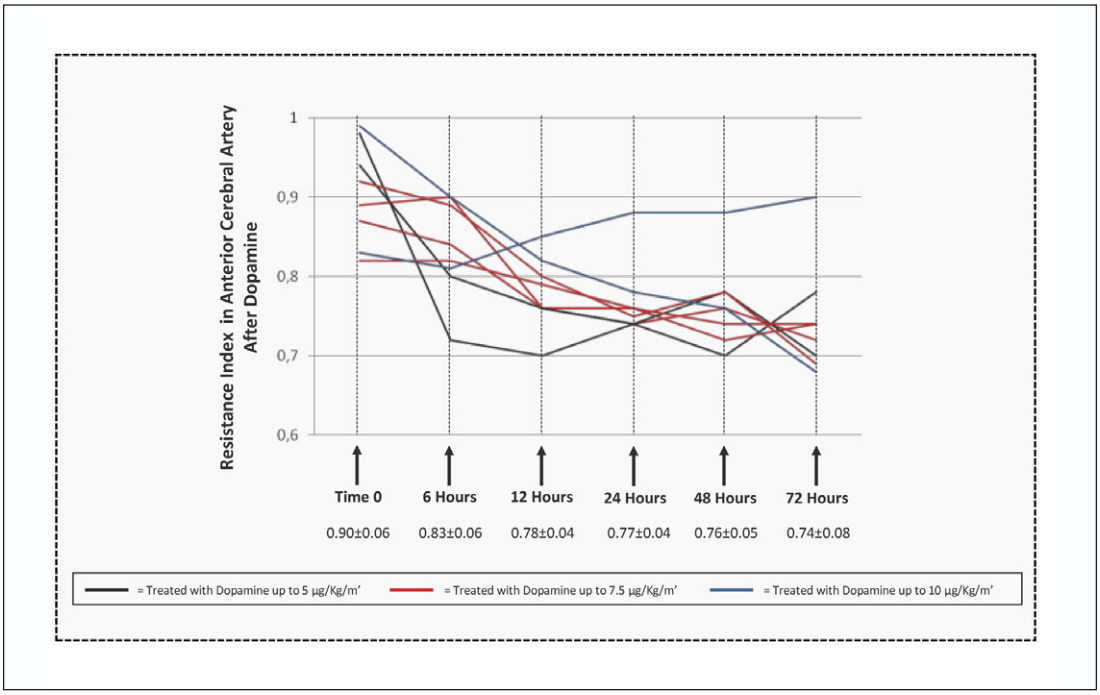


Figure 3. Trend of the resistence index (R.I.) in anterior cerebral artery during the dopamine treatment : a R.I. ≤ 0.80, showing a normalization of cerebral blood flow, was observed in two newborn at 6 h of treatment with 5 µg/kg/min, in other 4 at 12 h with 7.5 µg/kg/min and in one, treated up to 10 µg/kg/min, at 24 h. Only in the single newborn who didn't normalize the renal saturation (rSO_2) and renal fractional tissue oxygen extraction (rFTOE), the R.I. resulted constantly > 0.80 (0.81-0.90).

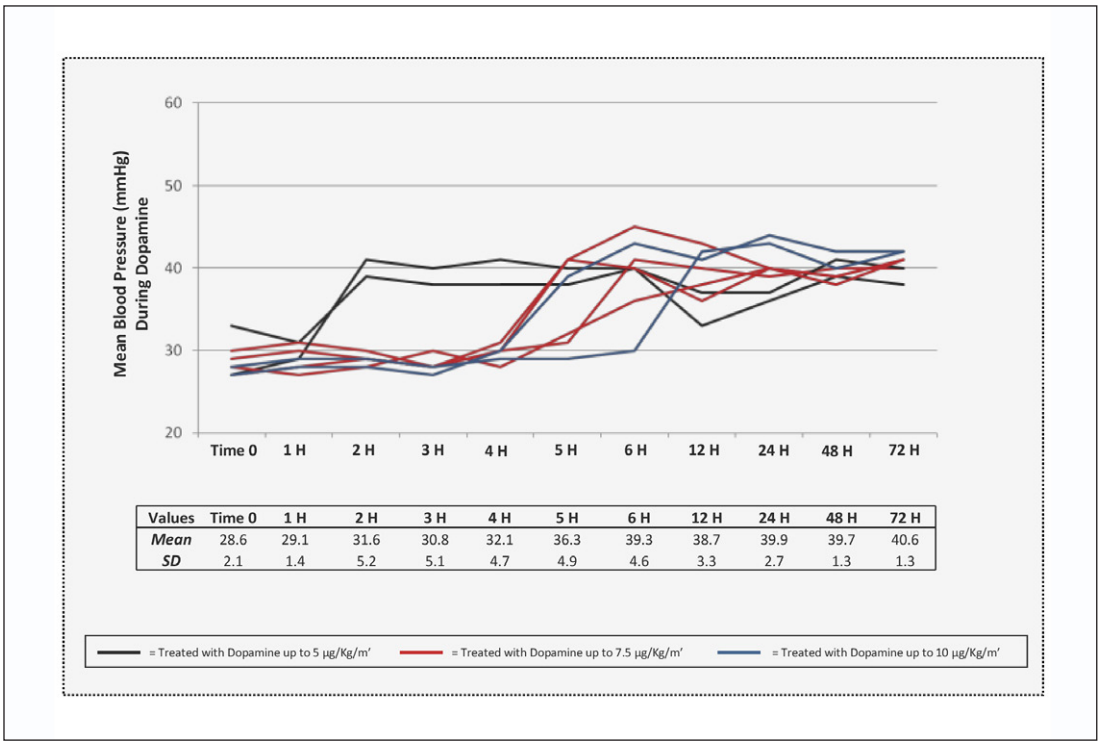


Figure 4. Trend of the mean blood pressure during the dopamine treatment: the mean blood pressure progressively increased from values of 28.6 ± 2.1 mmHg to 39.3 ± 4.6 at 6 hours and to 39.9 ± 2.7 at 24 hours of treatment. These values, once reached, have not changed anymore. This trend confirms that the dopamine effect on the arterial pressure occurs at ~ 2 hours after the attainment of the effective dose [21]. Also the newborn who has not reached normal values of renal saturation (rSO_2) anf renal fractional tissue oxygen extraction (rFTOE) and of the resistence index (R.I.) in anterior cerebral artery has normalized the mean blood pressure with a dopamine dose of 10 µg/kg/min. A confirmation that the measure of the arterial pressure is not sufficient if the target is the control of the organ perfusion [22].

Table 1. Modifications of internal ductal diameter (**A**) and of the left atrial/aortic root (LA/Ao) ratio (**B**) during the dopamine treatment. **A.** The ductal diameter does not change during the 72 hours after dopamine starting. **B.** Instead, the LA/Ao ratio, of 1.6 ± 0.16 before the treatment, progressively decreases to reach values of 1.29 ± 0.28 (p = 0.043). These changes can be considered the expression of the containment of left-to-right shunt through the ductus induced by dopamine [21], but the ratio alone has poor specificity and sensitivity and the limited number of subjects studied prevents any considerations.

A.

Diameter modifications of ductus arteriosus during dopamine						
Patient	**Time 0**	**6 h**	**12 h**	**24 h**	**48 h**	**72 h**
1	3.3 mm	3.0 mm	2.8 mm	2.6 mm	2.8 mm	3.0 mm
2	3.0 mm	2.8 mm	3.0 mm	3.2 mm	3.0 mm	2.6 mm
3	4.1 mm	4.4 mm	3.8 mm	4.0 mm	3.5 mm	3.8 mm
4	3.7 mm	3.6 mm	3.7 mm	3.6 mm	3.7 mm	3.6 mm
5	4.2 mm	4.0 mm	4.0 mm	3.9 mm	4.0 mm	3.9 mm
6	3.5 mm	3.2 mm	3.0 mm	3.2 mm	3.0 mm	3.3 mm
7	5.0 mm	5.0 mm	5.0 mm	5.0 mm	5.0 mm	5.0 mm
8	1.8 mm	1.8 mm	2.0 mm	2.1 mm	2.5 mm	2.1 mm
Mean	3.575	3.475	3.4125	3.45	3.4375	3.4125
SD	0.946799	1.002497	0.910945	0.894427	0.801672	0.88711

P value = NS (not significant) > 0.05.

B.

Modifications of left atrial/aortic root (LA/Ao) ratio during dopamine						
Patient	**Time 0**	**6 h**	**12 h**	**24 h**	**48 h**	**72 h**
1	1.4	1.45	1.5	1.2	1.0	0.92
2	1.6	1.5	1.3	1.1	1.2	1.1
3	1.7	1.8	1.7	1.2	0.9	1.2
4	1.5	1.4	1.3	1.3	0.98	1.0
5	1.8	1.7	1.6	1.4	1.3	1.3
6	1.4	1.4	1.6	1.8	1.4	1.5
7	1.8	1.8	2.0	1.8	1.8	1.6
8	1.6	1.6	1.8	1.5	1.6	1.7
Mean	1.6	1.58125	1.6	1.4125	1.2725	1.29
SD	0.160357	0.168899	0.239046	0.26959	0.317659	0.286257

P value = 0.043.

shown in the following weeks a reapparence of ductal reopening signs.

An attempt with Cox-inhibitors (ibuprofen) has also been tried in the single newborn who didn't reach the stabilitazion, but it was ineffective. This newborn has been submitted to surgical ligation immediately thereafter.

Discussion

Although it is extremely difficult to establish the weight of the surgical ligation on the brief and long term outcomes observed in the newborns with an hsPDA, the adoption of measures to avoid it appears entirely justified. On the basis of the results obtained in our NICU with an approach of containment of the systemic-pulmonary ductal shunt in a population of newborns ≤ 32 weeks of gestational age with a PDA [19] during the first week of life, we treated all the 8 newborns with dopamine and followed them with continuous monitoring of cerebral and renal oxygenations, time-scheduled ultrasound controls, monitoring of blood pressure and of urine output and continuous aEEG registration. In 7/8 subjects, the criteria of hemodynamic stabilization were reached and in these a new attempt with Cox-inhibitors was able to induce the ductal closure in 4/8 cases and a flow closing pattern in the other 3. The single neonate who didn't reached the stabilization criteria was submitted to the surgical ligation immediately after an ineffective cycle of ibuprofen. He resulted to be also affected by a *C. parapsilosis* sepsis and the role of infection on this negative outcome cannot be underestimated.

This experience seems to show that the surgical intervention is not unavoidable even under the extreme conditions of our eight infants, as long as measures of containment of the systemic-pulmonary shunt control the lung overcirculation and the systemic hypoperfusion. It appears, therefore, reasonable to try normalizing the hemodynamic conditions and to make, under these conditions, another attempt of pharmacological closure. A winning approach in seven of our eight newborns. In the case of no effects of the measures, as observed only in one newborn, the surgical intervention is unavoidable.

Moreover, the clinical conditions observed in all the newborns at admission testify the importance of the exposure of the organism to ductal steal. In other terms, the duration of the exposure to left-to-right shunt appears to be a crucial factor of the organ damage. An aspect that is often not considered, waiting for the effects of Cox-inhibitors.

The contribution of the aEEG recordings is, in this context, considerable, having shown a background pattern of burst suppression in four subjects and a discontinuous pattern not in line with reached PCA in other three. It is not a case that the only newborn with a normal background pattern for age, was the youngest and presumably submitted for briefer time to the effects of a consistent left-to-right shunt.

On the basis of these results and of others referred elsewhere [19], we think that the therapy of PDA in preterm infants must be mainly aimed at the containment of the ductal shunt and of its effects on pulmonary and systemic flow.

This aim can be reached with dopamine administration in a program of continuous surveillance of regional oxygenations, cardiac and cerebral ecographic signs, blood pressure and diuresis.

In this way, the objective of the ductal closure stops to be primary, being possible, under conditions of hemodynamic stability, waiting during the first week of life for the physiologic events of closure or resorting in selected cases to the Cox-inhibitors or to the surgical intervention.

This limited experience requires more consistent proofs of effectiveness, while the impact of this approach on the outcomes needs to be evaluated.

In every case, using this approach of hemodynamic stabilitation with dopamine and a supportive therapy, only 1 of the 8 newborns admitted with the indication for surgical ligation of an hsPDA has landed to the surgical intervention.

A result that drives us to tell the surgeon: keep your hands off the ductus!

Declaration of interest

The Authors declare that there is no conflict of interest.

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