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Chirurgie du canal artériel chez l'extrême prématuré : étude des morbidités néonatales et du développement à 24 mois d'âge corrigé dans une unité de réanimation néonatale française

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Thèse

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Présentée et soutenue par

Géraldine PONCELET née le 30 janvier 1986 à Caen

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**CHIRURGIE DU CANAL ARTERIEL CHEZ L'EXTREME PREMATURE :
ETUDE PROSPECTIVE DESCRIPTIVE DES MORBIDITES NEONATALES
ET DU DEVELOPPEMENT A 24 MOIS D'AGE CORRIGE DANS UNE
UNITE FRANCAISE DE REANIMATION NEONATALE**

**PATENT DUCTUS ARTERIOSUS AND SURGERY IN EXTREME PREMATURE: A PROSPECTIVE DESCRIPTIVE STUDY
OF NEONATAL MORBIDITIES AND OUTCOMES AT 24 MONTHS CORRECTED AGE IN A FRENCH NICU**

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RESUME

Introduction : Le canal artériel persistant (CAP) chez l'extrême prématuré, son traitement et les conséquences à court et moyen terme, ont été largement étudiés mais restent controversés. Nous avons évalué leur morbi-mortalité néonatale et leur développement neurologique selon la présence d'un CAP et sa stratégie thérapeutique.

Matériels et méthodes : Dans cette étude prospective, ont été inclus tous les prématurés nés entre 23 et 26 semaines d'âge gestationnel (AG) en 2010 et pris en charge en réanimation au CHU de Bordeaux. Le diagnostic et le traitement du CAP étaient réalisés selon le protocole du service. Nous avons comparé les caractéristiques de la population, la mortalité et les morbidités, selon la présence ou non d'un CAP, de son traitement curatif ou conservateur, médical ou chirurgical.

Résultats : 70 patients d'un terme médian de 25 semaines d'AG [24 ; 25] et poids médian de 845g [751 ; 917] ont été inclus sur 12 mois. 82.9% présentaient un CAP, sans facteur de risque anténatal significatif. Le taux médian de dysplasie broncho-pulmonaire (DBP) sévère était significativement plus élevé chez les prématurés avec un CAP (20.7% versus 0%, $p=0.0002$) et qui ont subi une chirurgie (58.8% vs 9%, $p=0.002$), particulièrement quand celle-ci était précoce. Nous notons une tendance à plus de séquelles en présence d'un CAP (47% vs 28%, $p=0.05$) mais un risque plus faible de décès et/ou séquelles neurologiques en cas de chirurgie (24% vs 54%, $p=0.05$). Il n'y avait pas de différence significative entre les différents traitements concernant le taux d'entérocolite ulcéro-nécrosante (ECUN), d'hémorragie intra-ventriculaire (HIV), de rétinopathie oblitérante du prématuré (ROP), de mortalité et de séquelles globales.

Conclusions : Chez l'extrême prématuré, la morbidité néonatale et les séquelles semblent augmenter en présence d'un CAP. La morbidité respiratoire augmente de façon significative en cas de ligature chirurgicale, à l'inverse du risque de décès et/ou séquelles neurologiques. Ces résultats ne nous permettent pas de conclure sur un lien de cause à effet et seront à confronter à des études ultérieures.

MOTS-CLEFS : canal artériel persistant ; extrême prématuré ; ligature chirurgicale ; dysplasie broncho-pulmonaire ; séquelle neurologique

SUMMARY

Introduction: Patent ductus arteriosus (PDA) in extreme premature, its therapies and short and long-term outcomes, have been widely studied but remain controversial. We evaluated neonatal mortality, morbidities and neurodevelopment in this population, according to the presence of PDA and its therapeutic strategy.

Methods: We included in this prospective study all preterm infants born between 23 and 26 weeks of gestation (WG) and hospitalized in neonatal intensive care unit (NICU) in Bordeaux hospital in 2010. PDA diagnosis and management were realized according to the unit's protocol. We compared baseline characteristics, mortality and morbidities, depending on the presence of PDA, its conservative or curative approach, by medical or surgical treatment.

Results: 70 patients with a median birth term of 25 WG [24; 25] and a median birth weight of 845g [751; 917] were enrolled in 12 months. 82.9% had a persistent PDA, without significant antenatal risk factor. The median rate of severe bronchopulmonary dysplasia (BPD) was significantly higher in premature with PDA (20.7% versus 0%, $p=0.0002$) and when it was treated by surgery (58.8% vs 9%, $p=0.002$), particularly when it was early. We noted a trend toward more sequels in PDA population (47% vs 28%, $p=0.05$) but a lower risk of dying and/or neurodevelopmental impairment (NDI) when PDA was surgically managed (24% vs 54%, $p=0.05$). There was no significant difference between the therapeutic strategies concerning rates of necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), mortality and global sequelae.

Conclusions: Neonatal morbidities and sequelae seem to increase in the presence of a PDA in extreme premature. Respiratory morbidity significantly increases in case of surgical ligation, conversely the risk of death and/or NDI. These results do not allow us to conclude a causal link and should be confronted with further studies.

KEY WORDS: patent ductus arteriosus ; extreme premature ; surgical ligation ; bronchopulmonary dysplasia ; neurodevelopmental impairment

ABBREVIATIONS:

BPD	bronchopulmonary dysplasia
BW	birth weight
COX	cyclo-oxygenase
DA	ductus arteriosus
ELBW	extremely low birth weight
IVH	intraventricular hemorrhage
LA/Ao	left atrial to aortic ratio
NDI	neurodevelopmental impairment
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
PDA	patent ductus arteriosus
PVLM	periventricular leukomalacia
ROP	retinopathy of prematurity
WGA	weeks of gestational age

INTRODUCTION

Patent ductus arteriosus (PDA) is a frequent problem in preterm infants, especially in extremely low birth weight (ELBW) (up to 80% in those with birth weight < 800g) (1) and extremely premature ones (Its incidence is evaluated at 65% of premature < 28 weeks of gestational age (WGA) in the EPICURE cohort in the United Kingdom) (2).

PDA is commonly associated with the development of neonatal co-morbidities, such as necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) or retinopathy of prematurity (ROP) (3,4), and an increase mortality in preterm infants (5). But there is no evidence that PDA is the cause of these morbidities, and their long-term consequences are unclear.

Optimal therapy for PDA remains controversial. A recent European study showed a wide variation among neonatal intensive care units (NICUs) and countries regarding the drugs type, the administration route, the number of cures, the prophylactic use and the surgery time, and that no general guidelines are followed (6). Even if medical and surgical interventions are widely used to close PDA, emerging evidence suggests that these treatments may be detrimental, raising doubts about their utilization. Indeed many large review and meta-analysis noted side effects of medical treatment with Cyclo-Oxygenase (COX) inhibitors for PDA (3,4,7,8), and others the impact of surgery (9,10) regarding neonatal mortality and major morbidities. Recently, more and more studies have examined impact of a PDA or its therapies on long-term neurodevelopment (11). These studies combined with the fact that spontaneous permanent closure of the DA in the first week of life can occur in more than 30% of ELBW (34% in the first week of life in the study by Koch) (1) raise the idea of therapeutic abstention for PDA in many preterm. In a recent review, Benitz even wondered if the time has not come to accept the null hypothesis : treatments that close PDA in preterm infants do not improve long-term outcomes (12). Despite all these doubts , about 60 to 70% of preterm infants < 28 WGA receive medical or surgical therapy for PDA (3,11).

In our NICU in Bordeaux, we adopt an early curative approach, with medical treatment generally begun during the first 72h of life, and a surgical ligation of PDA generally made during the first three weeks of life, if failure of the medical management or contraindication to it.

With more and more studies raising doubt about PDA treatment, we aimed to evaluate the short- and long-term outcomes of the extreme premature hospitalized in our unit, depending on PDA and the different therapeutic approaches we use.

Therefore the purpose of this study was to observe the relation between PDA and its therapies, particularly surgical therapy, and the mortality and the short-term (NEC, BPD, IVH, and ROP) and long-term (neurodevelopment, respiratory and hemodynamically consequences at 24 months corrected age) morbidities of the extreme preterm neonates hospitalized in our unit during one year, and to then compare our results with literature data. We studied secondary these same outcomes in two subgroups: early surgery before three weeks of life (< day 21) and delayed surgery after three weeks of life (> day 21).

We thought this study could help us determine if our therapeutic attitude for PDA is good enough to ensure survival without severe morbidities, representing the ultimate goal of neonatal medical care.

METHODS

1. Patients

We conducted a prospective cohort study including preterm infants born between 23 and 26 weeks of gestation and hospitalized in our level III neonatal intensive care unit in Bordeaux University Hospital between January first and December 31st 2010 .

All patients included have survived the initial neonatal resuscitation, were supported in our NICU in Bordeaux, and were planned to be followed-up to 24 months corrected age.

The exclusion criteria were a birth term lower than 23 WG, imprecise birth term and death during initial neonatal resuscitation.

Parents of all the patients in our unit were informed about this study, but no written consent was obtained. Parental written consent was deemed unnecessary by our local ethical committee, as this was an observational study with no intervention on patient care, and collected data were anonymized.

2. Management of PDA

This was a descriptive study with no intervention so PDA diagnosis and treatment was managed according to our unit standard protocol: a bedside echocardiography is performed by local intensivist or neonatologist between 12 and 72 hours of life in all lower than 26 WG premature babies to evaluate PDA. Only echocardiographic criteria, regardless of our patient's clinical status, are considered to decide if and when to initiate PDA treatment. In that we are following the

recommendations which state that echocardiography with Doppler scanning flow studies is required to diagnose a hemodynamically significant PDA, because precision and accuracy of clinical and radiological signs of a PDA are unsatisfactory (13).

We use the three most important criteria of hemodynamic significance in French NICUs (14) and widely described in the literature(3,15,16) : DA diameter \geq 1.5mm, rich end diastolic flow in the left pulmonary artery measured by color Doppler $>$ 0.20m/sec, and the left atrial to aortic (LA/Ao) ratio \geq 1.4. If a large ductus is present combined with one of the two other criteria, the PDA is for us hemodynamically significant and there is an indication to treat PDA, in the absence of congenital heart disease or pulmonary hypertension. We also use secondary criteria such as the flow pattern in the DA, reverse-flow on the anterior cerebral artery and on the descending aorta, and high cerebral artery resistance index. We use these secondary criteria if we have only one of the three primary criteria to assess PDA hemodynamical significance..

The objective of our protocol is a very early curative treatment, regarding medical and surgical therapy. If there is a hemodynamically significant PDA on echo in the absence of contraindication, we use a first course of Ibuprofen (PEDEA) with 10mg/kg on day 1 and 5mg/kg on days 2 and 3. We perform an echocardiographic control between 12 and 24 hours after the third dose of Ibuprofen. If there is a persistent hemodynamic significant PDA and still no contraindication, we initiate a second identical course of Ibuprofen. If PDA is still considered hemodynamically significant on echo after two courses of Ibuprofen, we discuss a surgical therapy for clinically symptomatic patients or conservative approach for the others. If there is medical treatment contraindication, we discuss a primary surgery.

We consider as contraindications to medical treatment, such as most of French NICUs (14) : pulmonary hypertension, ductus-dependent cardiopathy, IVH grade 2 or worse, severe bleeding, severe sepsis, NEC or digestive complications, oliguria $<$ 1mL/kg/h, renal failure and thrombocytopenia $<$ 100,000/mm³.

3. Data collection and statistical analysis

Demographic data, clinical information, data about PDA and its therapies, as well as outcomes, were prospectively collected as anonymized data via an electronic Case Report Form (eCRF) created with SPIP 2.0 software (under GNU/GPL license). The eCRF was hosted by our unit website, with a protected access only available to the study investigators.

We compared the patients in our cohort by dividing them in sub-populations. We first compared infants with and without any significant PDA. Then we compared those who received no curative treatment for PDA and those who were treated, either by medical therapy or surgical ligation. Finally we compared those who received only medical therapy and those who were surgically treated.

We compared these sub-populations regarding baseline characteristics (antenatal and postnatal) and short-term outcomes. These included mortality, NEC, moderate BPD defined as use of oxygen > 0.21 at 28 days of life, severe BPD defined as use of oxygen > 0.21 at 36 weeks' corrected age, IVH stage 1 or greater and periventricular leukomalacia, ROP grade 1 or most. We also compared them according to their long-term outcomes: we evaluated the clinical status of our population at 24-months corrected age, looking at neurodevelopmental impairment (NDI), such as cerebral palsy, motor or sensory disorders, or cognitive delay, and cardio or respiratory impairment such as asthma for example.

We checked every eCRF for inconsistency before converting them into Excel© (Microsoft) files. Results are expressed as median (interquartile range) and number "n" (percentages). Data were analyzed with Student t-Test. A *p*-value of < 0.05 was considered significant. All statistics were done using Excel© (Microsoft, Seattle, WA) and R (GNU/GPL license) softwares.

RESULTS

1. Demographic and descriptive characteristics

A total of 70 premature babies born between 23 and 26 WGA were enrolled in this study, whereas 4 patients were excluded for imprecise birth term. The median birth term was 25 WG [24; 25], with a median birth weight of 845g [751; 817]. Antenatal and immediate postnatal characteristics of our population are described in Tables 1.1, 1.2 and 1.3.

Antenatal risk factors were not significantly different between patients with PDA and those without, except regarding the birthplace (patients without PDA were statistically more inborn) (Table 1.1).

Looking at antenatal characteristics based on PDA treatment, we observed that patients with untreated PDA were significantly of a lesser birth weight (median weight: 660g), with more intra-uterine restriction of growth (58% of them) and maternal vascular abnormalities during pregnancy (53% of them) than patients for whose PDA was treated (Table 1.2).

Table 1.1. Demographic characteristics of population

Demographic characteristics	Significant PDA (n=58)	No significant PDA (n=12)	<i>p-value</i>
Gestational age (weeks)	25 [24;25]	25 [23;27]	0.85
Birth weight (g)	845 [751;917]	790 [530;875]	0.22
Sex			0.91
Male	30 (51.7%)	6 (50%)	
Female	28 (48.3%)	6 (50%)	
Birth weight < 10th percentile	17 (29.3%)	3 (25%)	0.78
Antenatal glucocorticoid	47 (67%)	9 (75%)	0.28
Mother's age (year)	29 (25;33)	29 (23;32)	0.75
Preeclampsia/eclampsia/HELLP	12 (20.7%)	2 (17%)	0.75
Premature rupture of membranes	16 (27.6%)	4 (33%)	0.71
Chorioamnionitis	12 (20.7%)	6 (50%)	0.08
Placenta previa	1 (1.7%)	0 (0%)	0.32
Hematoma retro placental	3 (5.2%)	1 (8%)	0.72
Caesarean	46 (79.3%)	6 (50%)	0.08
Surfactant (total dose mg/kg)	300 [200;400]	300 [200;300]	0.71
Caffeine	42 (72.4%)	7 (58%)	0.39
Birthplace			
Inborn	43 (74.1%)	12 (100%)	0.0003
Out born	12 (20.7%)	0 (100%)	

**Data are presented as n (%) or median [interquartile]*

PDA: patent ductus arteriosus

Table 1.2. Demographic characteristics according to PDA curative treatment or not

Demographic characteristics	Treated PDA (n=39)	Untreated PDA (n=19)	<i>p-value</i>
Gestational age (weeks)	25 [24;25]	24 [24;25]	0.41
Birth weight (g)	860 [825;982]	660 [585;850]	0.02
Sex			
Male	17 (44%)	13 (68%)	0.07
Female	22 (56%)	6 (31%)	
Birth weight < 10th percentile	6 (15%)	11 (58%)	0.003
Antenatal glucocorticoid	31 (79%)	16 (84%)	0.69
Mother's age (year)	28 (25;32)	30 (26-33)	0.42
Preeclampsia/eclampsia/HELLP	3 (7%)	9 (53%)	0.004
Premature rupture of membranes	13 (33%)	3 (17%)	0.13
Chorioamnionitis	9 (23%)	3 (17%)	0.51
Placenta previa	0 (0%)	1 (19%)	0.33
Hematoma retro placental	2 (5%)	1 (19%)	0.98
Caesarean	28 (72%)	18 (95%)	0.01
Surfactant (total dose mg/kg)	300 [200 ;400]	300 [250;400]	0.36
Caffeine	35 (90%)	7 (37%)	0.0002
Birthplace			
Inborn	31 (79%)	15 (79%)	0.70
Out born	8 (20%)	4 (21%)	

*Data are presented as n (%) or median [interquartile]

PDA: patent ductus arteriosus

Table 1.3. Demographic characteristics of population depending on PDA treatment

Demographic characteristics	PDA-medical closure (n=22)	PDA-surgical closure (n=17)	<i>p-value</i>
Gestational age (weeks)	25 [24;25]	24 [24;25]	0.78
Birth weight (g)	905 [832;1025]	850 [760;910]	0.10
Sex			
Male	10 (45%)	7 (41.2%)	0.79
Female	12 (54%)	10 (58.8%)	
Birth weight < 10th percentile	4 (18%)	2 (11.8%)	0.58
Antenatal glucocorticoid	17 (77%)	14 (82%)	0.60
Mother's age (year)	30 [25;35]	29	0.30
Preeclampsia/eclampsia/HELLP	1 (4%)	2 (11.8%)	0.44
Premature rupture of membranes	6 (27%)	7 (41.2%)	0.38
Chorioamnionitis	5 (23%)	4 (23.5%)	0.95
Placenta previa	0 (0%)	0 (0%)	NR
Hematoma retro placental	2 (9%)	0 (0%)	0.16
Caesarean	15 (68%)	13 (76.5%)	0.57
Surfactant	200 [200-300]	300 [300-400]	0.01
Caffeine	19 (86%)	16 (94.1%)	0.42
Birthplace			
Inborn	17 (77%)	14 (82.4%)	0.70
Out born	5 (23%)	3 (17.6%)	

**Data are presented as n (%) or median [interquartile]*

PDA: patent ductus arteriosus

Finally there was only one statistically significant difference on baselines characteristics between patients only medically treated and those surgically treated: the surfactant total dose was significantly higher in PDA surgery group (400 mg/kg) than in Ibuprofen group (300 mg/kg) (Table 1.3).

2. PDA diagnosis and its therapies

Fifty-eight patients (82.9%) had a PDA. The spontaneous DA closure rate among our population was 17% (12 patients).

The median age of echocardiographic PDA diagnosis was 2 days after birth. The echocardiographic criteria showed a median DA diameter of 1.7mm, a median rich end diastolic flow in the left pulmonary artery at 0.30m/sec, a median LA/Ao ratio of 1.14, and a median cerebral artery resistance index of 0.88.

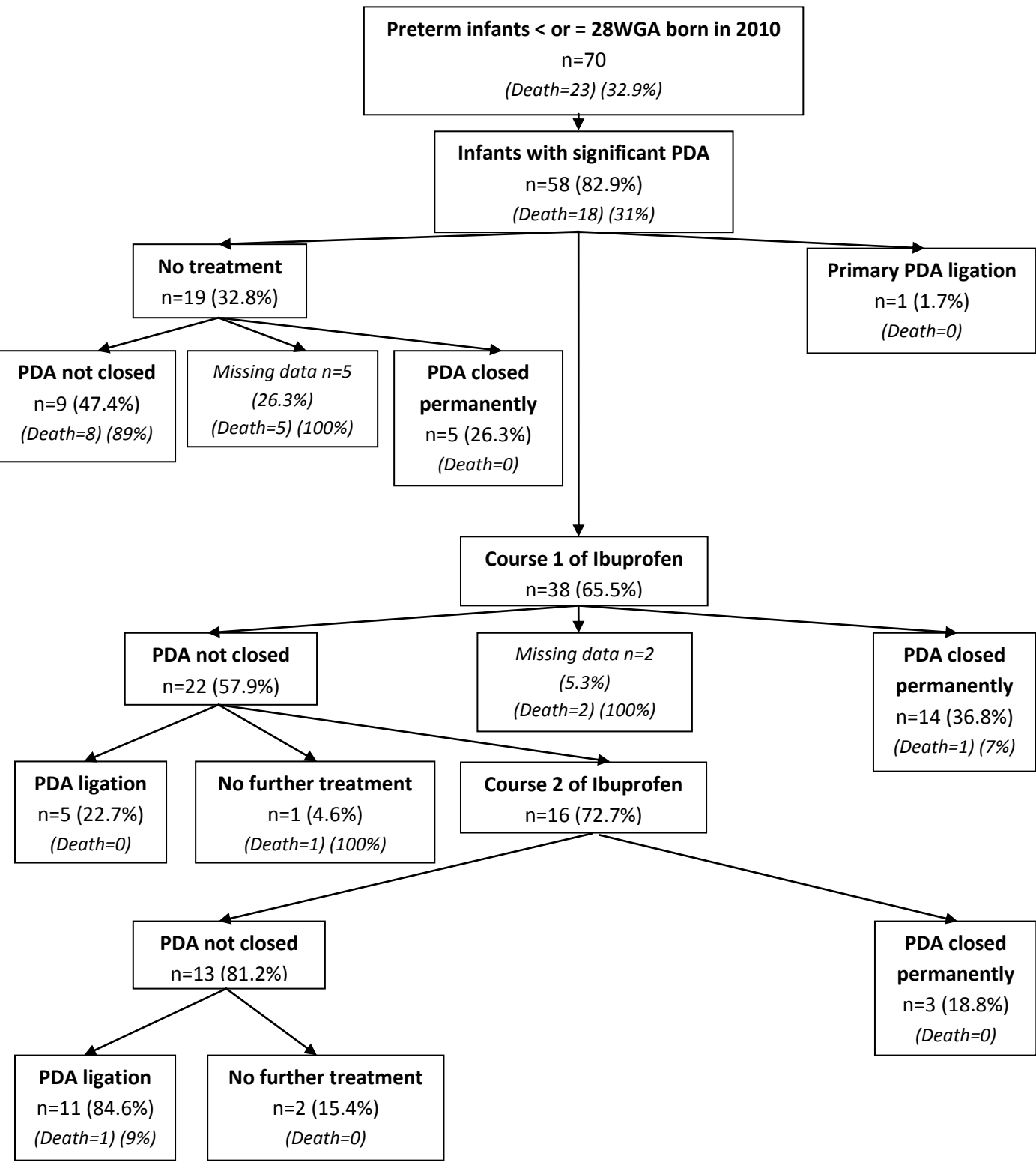
The way we managed PDA in our studied population is summarized on the diagram in figure 1 (Fig.1). Thirty-nine neonates with PDA received a curative treatment (67.2%): the vast majority had a first course of Ibuprofen (97.4%), while only one had a primary surgery (2.6%).

The first course of Ibuprofen was begun at the median age of 2 days of life. The closure rate after one course was 37%. 72% of first course failure underwent a second course of Ibuprofen, which begun at the median age of 4.5 days of life. The closure rate after the second course was 19%, for an overall closure rate of medical treatment of 45%. 42 % (n=21) of PDA who received Ibuprofen in first line remained significant: among them 76% underwent a surgical treatment (31% after one course and 69% after two courses of Ibuprofen), 14% died, and 10% (2 patients) remained open at hospital discharge.

Among curative management, 22 patients received Ibuprofen only (56.4%) and 16 had Ibuprofen followed by a surgical ligation (41%). The overall surgical ligation rate for the population of 58 infants with PDA was 29.3% with only 1.7% of primary surgery. The median age of surgery was at 17 days of life [12; 29], with 65% before three weeks of life and 35% after day 21 of life.

One third of subjects with significant PDA (33%) benefited from a conservative approach including supportive treatment only. 14 of these patients (74%) died. The five remaining patients (26%) survived with a spontaneous closure of their PDA, which gives us a closure rate for untreated PDA of 9%.

Figure 1. PDA management



PDA : patent ductus arteriosus ; WGA : weeks of gestational age

Mortality and morbidities

We observed in our population of extreme premature babies an overall mortality at 32.9%, with no differences between neonates with PDA and those without

Half the deaths of our patients were caused by a multi-organ failure (48%) including septic shock (one third of multi-organ failure). Then came neurological causes (22%) such as IVH grade IV, periventricular leukomalacia and severe hydrocephalus; pulmonary causes (22%) such as refractory pulmonary arterial hypertension, refractory hypoxemia and pulmonary hemorrhage; and finally digestive causes (8%), one NEC and one rotavirus infection.

Among the patients with PDA, those who were not treated had a significant higher mortality rate (68%) than those who were treated (13%), either medically or surgically. There was no difference in mortality rate between medical treatment and surgery.

Neonatal mortality and short-term morbidities depending on PDA and its therapies are described in Table 2.1, 2.2 and 2.3, and outcomes at 24-months corrected age are presented in Table 3.1, 3.2 and 3.3.

Preterm with PDA had a significantly longer duration of mechanical ventilation and higher severe BPD rate than those with no PDA. They also presented more NEC and a longer duration of parenteral nutrition (Table 2.1). There were no significant differences in those two subpopulations regarding ROP and HIV rates. There also was a trend for more sequelae in the PDA population ($p=0.05$) (Table 3.1).

Patients with PDA who didn't receive a curative treatment (either medical or surgical) had significantly less short-term morbidities than patients who received a curative treatment (Table 2.2): shorter duration of invasive and noninvasive ventilation, shorter duration of parenteral nutrition, lower rates of BPD (moderate and severe) and sepsis. But they had more severe IVH (grade 3) and foremost a much higher mortality rate. And the rate of sequelae among the survivors was not different between those two subpopulations (Table 3.2).

Among the patients with PDA who received a curative treatment, patients who underwent surgery had longer duration of invasive ventilation and parenteral nutrition, and higher rates of BPD (moderate and severe), IVH grade 2 and sepsis than patients who only had medical treatment (Fig 2 and Table 2.3). There were no differences regarding NEC, ROP, long-term sequelae and death in the two groups, but using combined criteria there was less death and NDI in the surgery group ($p=0.05$) (Table 3.3 and Fig 3). There was no statistically significant difference between early surgery (before

Table 2.1. Neonatal morbidities and mortality of population

Neonatal morbidities	Significant PDA (n=58)	No significant PDA (n=12)	p-value
Invasive ventilation (days)	10 [2;30]	2.5 [1;8]	0.04
HFV/HFO (days)	1 [0;4]	0 [0;0]	< 0.0005
Non invasive ventilation (days)	23 [0;32]	17.5 (0;22.5)	0.14
BPD day 28	38 (65.5%)	5 (42%)	0.64
BPD 36 WGA	12 (20.7%)	0 (0%)	0.0002
Post-natal steroid	13 (22.4%)	2 (17%)	0.69
Sepsis	34 (58.6%)	5 (42%)	0.31
NEC	8 (13.8%)	0 (0%)	0.004
Parenteral nutrition days	41 [32;58]	24 [17;30]	< 0.05
IVH			
None	34 (58.6%)	9 (75%)	0.30
Grade 1	9 (15.5%)	1 (8%)	0.52
Grade 2	5 (8.6%)	1 (8%)	0.97
Grade 3	5 (8.6%)	0 (0%)	0.30
Grade 4	3 (5.2%)	0 (0%)	0.43
PVLm	2 (3.4%)	1 (8%)	0.45
ROP			
None	25 (43.1%)	3 (25%)	0.25
Grade 1	6 (10.3%)	1 (8%)	0.84
Grade 2	2 (3.4%)	2 (17%)	0.07
Grade 3	4 (6.9%)	0 (0%)	0.36
Other	1 (1.7%)	1 (8%)	0.22
Missing data	20 (34.5%)	5 (42%)	0.64
Death	18 (31%)	5 (42%)	0.52
Age of death (days)	5.5 [2;15]	2 [0;2]	0.31

*Data are presented as n (%) or median [interquartile]

BPD: bronchopulmonary dysplasia; HFV: high frequency ventilation; HFO: high frequency oscillation; IVH: intra-ventricular hemorrhage; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; PVLm: periventricular leukomalacia; ROP: retinopathy of prematurity; WGA: weeks of gestational age

Table 2.2. Neonatal morbidities and mortality according to PDA treatment or not

Neonatal morbidities	Treated PDA (n=39)	Untreated PDA (n=19)	p-value
Invasive ventilation (days)	14 [4;35]	3 [1,5;7,5]	0.0001
HFV/HFO (days)	2 [0;8.5]	0 [0;1]	0.001
Non invasive ventilation (days)	27 [16.5;35]	0 [0;26]	0.0001
BPD day 28	31 (79%)	7 (37%)	0.07
BPD 36 WGA	12 (30%)	0	0.0001
Post-natal steroid	13 (33%)	0	< 0.0001
Sepsis	27 (70%)	7 (37%)	0.02
NEC	7 (18%)	1 (5%)	0.12
Parenteral nutrition days	51 [37;58]	29 [25;33]	0.002
IVH			
None	22 (56%)	12 (63%)	0.63
Grade 1	7 (18%)	2 (10%)	0.47
Grade 2	5 (13%)	0 (0%)	0.11
Grade 3	1 (3%)	4 (21%)	0.02
Grade 4	2 (5%)	1 (6%)	0.60
PVL	2 (5%)	0 (0%)	0.32
ROP			
None	21 (54%)	4 (21%)	0.02
Grade 1	6 (15%)	0	0.07
Grade 2	2 (5%)	0	0.32
Grade 3	4 (10%)	0	0.15
Other	0 (0%)	1 (5%)	0.15
Missing data	6 (15%)	14 (74%)	< 0.0001
Death	5 (13%)	13 (68%)	0.0001
Age of death (days)	10 [6;21]	4 [3;14]	0.39

*Data are presented as n (%) or median [interquartile]

BPD: bronchopulmonary dysplasia; HFV: high frequency ventilation; HFO: high frequency oscillation; IVH: intra-ventricular hemorrhage; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity; WGA: weeks of gestational age

Table 2.3. Neonatal morbidities and mortality depending on PDA treatment

Neonatal morbidities	PDA medical closure (n=22)	PDA surgical closure (n=17)	p-value
Invasive ventilation (days)	7.5 [1;11]	34 [2;30]	< 0.0001
HFV/HFO (days)	0 [0;3.5]	8 [0;4]	0.05
Non invasive ventilation (days)	26.5 [17;35]	27 [1;33]	0.57
BPD day 28	14 (64%)	17 (100%)	0.04
BPD 36 WGA	2 (9%)	10 (58.8%)	0.002
Post-natal steroid	2 (9%)	11 (64.7%)	0.0002
Sepsis	12 (54%)	15 (88.2%)	0.02
NEC	5 (23%)	2 (11.8%)	0.37
Parenteral nutrition days	37 (26;49)	58 (53;65)	0.006
IVH			
None	14 (64%)	8 (47.1%)	0.16
Grade 1	4 (18%)	3 (17.6%)	0.48
Grade 2	1 (4%)	4 (23.5%)	0.04
Grade 3	1 (4%)	0 (0%)	0.19
Grade 4	1 (4%)	1 (5.9%)	0.43
PVLM	1 (4%)	1 (5.9%)	0.43
ROP			
None	13 (59%)	8 (47.1%)	0.23
Grade 1	3 (14%)	3 (17.6%)	0.37
Grade 2	1 (4%)	1 (5.9%)	0.43
Grade 3	1 (4%)	3 (17.6%)	0.43
Missing data	4 (18%)	2 (11.8%)	0.13
Death	4 (18%)	1 (5.9%)	0.23
Age of death (days)	8 (5;13)	61	NR

**Data are presented as n (%) or median [interquartile]*

BPD: bronchopulmonary dysplasia; HFV: high frequency ventilation; HFO: high frequency oscillation; IVH: intra-ventricular hemorrhage; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; PVLM: periventricular leukomalacia; ROP: retinopathy of prematurity; WGA: weeks of gestational age

Table 3.1. Outcomes at 24-months corrected age

Outcomes at 24-months corrected age	Significant PDA (n=58)	No significant PDA (n=12)	<i>p-value</i>
Sequelae	19/40 (47%)	2/7 (28%)	0.05
Neurodevelopmental	13/40 (32%)	1/7 (14%)	0.17
Respiratory	5/40 (12%)	1/7 (14%)	0.45
Cardiovascular	1/40 (2%)	0/7 (0%)	0.34
Missing data	6/40 (15%)	0/7 (0%)	0.14
Death or neuro sequelae	31/58 (53%)	6/12 (50%)	0.83

**Data are presented as n (%) or median [interquartile range]*

PDA: patent ductus arteriosus

Table 3.2. Outcomes at 24-months corrected age according to PDA treatment or not

Outcomes at 24-months corrected age	Treated PDA (n=39)	Untreated PDA (n=19)	<i>p</i>-value
Sequelae among survivors	17/34 (50%)	2/6 (33%)	0.46
Neurodevelopmental	11/34 (32%)	2/6 (33%)	0.96
Respiratory	5/34 (15%)	0/6 (0%)	0.33
Cardiovascular	1/34 (3%)	0/6 (0%)	0.68
Missing data	6/34 (18%)	0/6 (0%)	0.28
Death or neuro sequelae	16/39 (41%)	15/19 (79%)	0.006

**Data are presented as n (%) or median [interquartile]*

PDA: patent ductus arteriosus

Table 3.3. Outcomes at 24-months corrected age depending on PDA treatment

Outcomes at 24-months corrected age	PDA medical closure (n=22)	PDA surgical closure (n=17)	p-value
Sequelae among survivors	11/18 (50%)	6/16 (37%)	0.23
Neurodevelopmental	8/18 (36%)	3/16 (19%)	0.12
Respiratory	2/18 (9%)	3/16 (19%)	0.20
Cardiovascular	1/18 (4%)	0/16 (0%)	0.20
Missing data	0/18 (0%)	6/16 (37%)	0.0005
Death and neuro sequelae	12/22 (54%)	4 /17 (24%)	0.05

**Data are presented as n (%) or median [interquartile]*

PDA: patent ductus arteriosus

21 days of life) and late surgery (after 21 days of life), apart from a higher rate of NEC with late surgery.

Figure 2. Mortality and morbidities according to PDA and its therapies

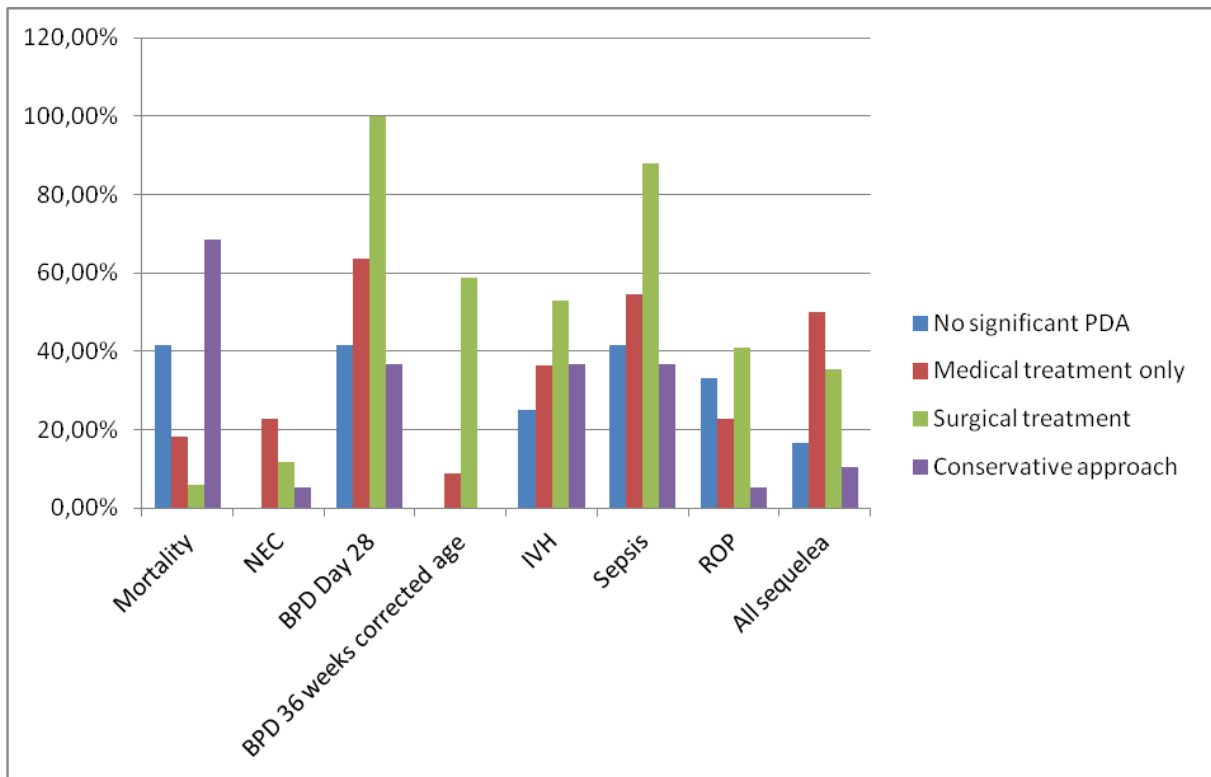
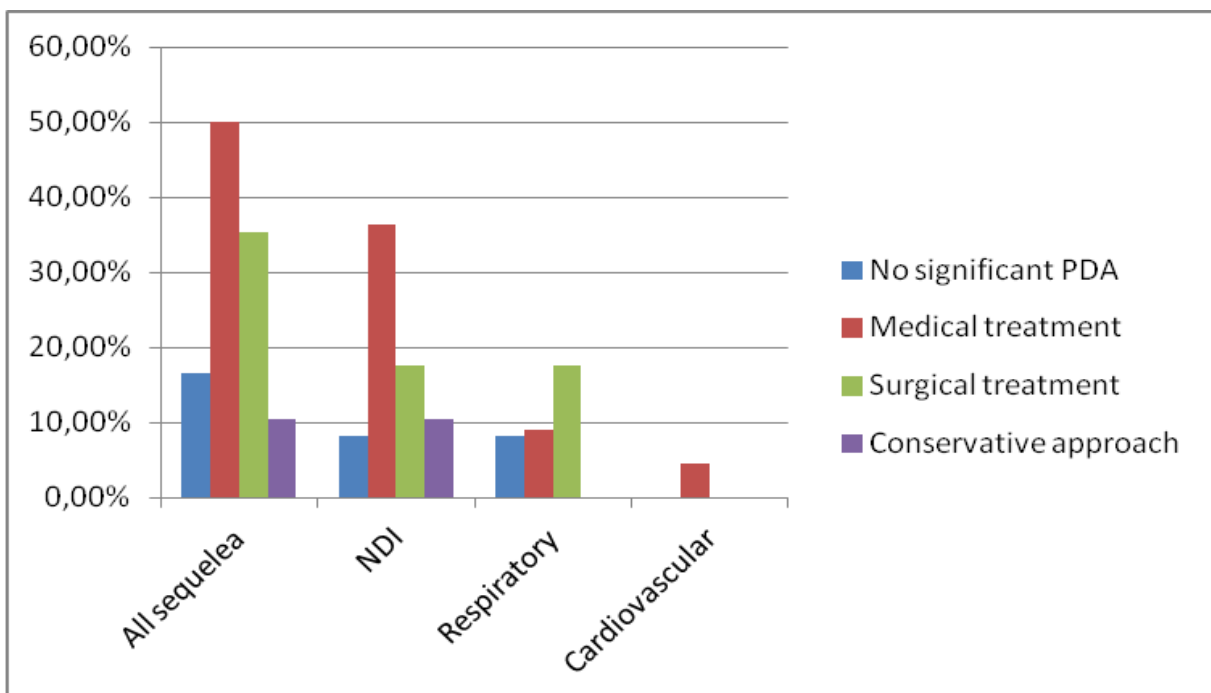


Figure 3. Outcomes at 24-months corrected age according to PDA and its therapies



We identified among the NDI, alone or in combination, 8 delayed psychomotor development (including delayed walking acquisition), 4 behavioral disorders (including one severe disorder and aggressiveness), 3 language delays, and finally 1 neuro-sensory disorder (abnormal vision). All respiratory diseases were infantile asthma (6 in our premature population). We found only one cardio-hemodynamically problem at 24-months corrected age: a persistent ductus arteriosus, with a systolic murmur, for which a definitive ligation is actually discussed.

DISCUSSION

The incidence of patent ductus arteriosus rises to 83% in our ELBW population, whose median gestational age and birth weight are particularly low (25 WGA and 845g). Many studies described a prevalence of PDA increasing with decreasing GA (< 28 WGA) and birth weight (<800g) (1,14,17). Immaturity seems to be the main risk factor to the presence of PDA.

We do not mark any perinatal risk factor to the presence of PDA, including exposition to antenatal steroids (67% in PDA group versus 75% in no PDA group, $p=0.28$), mother hypertensive disease (20.7% vs 17%, $p=0.75$) or Hyaline Membrane Disease (needs surfactant is equivalent between the two populations). These variables have already been associated with the occurrence of PDA (1) and some have been directly and significantly causative in studies in 1980s' decade (17–20). More recently, division of neonatology of Taiwan found that smaller GA, lower BW, lower Apgar score at 5 minutes, more severe respiratory distress syndrome, greater use of surfactant, and lower hemoglobin after birth place VLBW infants at greater risk of PDA (21). From our study, it is uncertain that we can define precisely infants at highest risk of persistent DA.

In our population of 70 preterm infants, 58 had a significant PDA and 12 did not have, with 5 death. We obtained only 7 patients alive without significant PDA. Due to a too small number, we are not able to meaningfully discuss the results of population with versus without significant PDA. We can still say that our preterm with PDA present a greater respiratory and digestive gravity, and a trend toward more sequelae, than others without PDA.

We can also compare premature with PDA according to their PDA's therapy (conservative approach, medical or surgical management and its time).

First of all, our PDA diagnosis and therapeutic approach are similar to French and European NICUs practices (6,14). Curative treatment is currently favored for significant PDA, more than a conservative

approach. Indeed, 98% of European NICUs treat a significant PDA (6), and we have almost 70% of curative management in our population. Majority of significant PDA are treated medically by non-steroids anti-inflammatory drugs, while few of them are operated in first line (only 2.2% of European NICU use surgery by first intention) (6). Despite the same indications of surgical treatment, we observe a high variability as to the date of surgery. Our protocol is certainly more interventionist, because we never administer a third course of Ibuprofen, preferring an earlier surgical ligation of PDA when medical therapy fails (22% of surgery after failure of the first course of Ibuprofen versus 5% of European NICUs, 85% after failure of the second course versus 45%) (6). Moreover, our surgery date is earlier than majority of European NICUs (in our unit, 65% of surgery during the first three weeks of life versus 27%) (6). Despite numerous studies, there is still no consensus concerning surgical therapy of PDA, even within the European community. Concerning the therapeutic abstention, we cannot significantly discuss our results because almost 70% of these subjects died, maybe before PDA diagnosis or initiation of treatment. These patients were certainly more serious. On the contrary, the few survivors have significantly less morbidities and sequelae, because they were definitely less severe.

Then, we studied short and long-term outcomes in our extreme premature population, according to their PDA management. We find that sepsis rate, intensity and duration of mechanical ventilation, moderate and severe BPD rates, and duration of parenteral nutrition are significantly higher when PDA is surgically ligated than medically or conservatively managed. Otherwise, there is no difference regarding IVH and ROP rates between Ibuprofen and ligation, but ROP grade > 3 tends to increase in surgery group. These findings are in accordance to most of the recent studies in 2000s and a large meta-analysis in 2014, which show there is a high risk of severe BPD and ROP grade > 3 in PDA surgery groups (9,10,22–24). This reflects on pathophysiological a persistent shunt through PDA and its surgical ligation significantly increase duration of mechanical ventilation and promotes development of BPD (25–27) and finally chronic lung disease and respiratory long-term sequelae. According to Chorne in 2007, BPD is the only co-morbidity with significantly association with PDA surgery, regardless gestational age or other perinatal risk factors (28). On the contrary, Chock shows in a recent study that only lower gestational age, and not PDA treatment, was associated with the adverse outcome of BPD (29). Similarly, ROP seems to depend more significantly on gestational age and other neonatal risk factors than on presence of PDA or its therapy (28,30). Neurodevelopmental impairment (NDI) tends to be less frequent in our surgery group than in medical, which seems to contradict some data from the literature (23,24). However, two recent studies differ on the relationship between PDA surgery and long-term NDI, because Chorne again find no significantly

association, while Kabra determines that PDA surgery is a significant risk factor of neurosensory impairment and cognitive delay at 18-months corrected age (24,28). Furthermore, pathophysiological theories about brain damage and surgery also differ (31–33). It seems difficult to establish a causal link between PDA, its therapy and long-term NDI. It probably depends on both of immaturity, multiple therapeutic and their potential complication, including operative and anesthetic risks.

Moreover, we noted these results especially when surgery was early. Infants have more likely severe BPD (82% when surgery was before day 21 of life versus 17% after day 21), severe ROP (54% versus 17%) and impairments at 24-months corrected age (36% versus 0%). In fact, premature operated late present fewer short and long-term morbidities than those operated precociously, in agreement with literature data (24,34,35). On the other hand, they are exposed to a higher risk of NEC (33% versus 0%) and mortality (17% versus 0%) when operated after three weeks of life. It also seems well established that PDA is the most significant risk factor of NEC, due to the decrease in splanchnic blood flow (26,36,37), with an overall incidence in VLBW infants of about 12% (38). While most studies do not find a significant difference of NEC incidence between medical and surgical PDA therapies (9,23,38), others demonstrate like us that there is a certain digestive benefit with early PDA surgery (34,39,40). Similarly, mortality rate is higher on presence of PDA (5,28) and PDA surgery does not seem to be a significant risk factor of mortality (9,10,23,24,27,41). Thus, Weisz describes in a recent meta-analysis that, compared with medical treatment, surgical ligation was associated with a reduction in mortality (22). We also have a lower mortality rate in PDA ligation group (5.8% vs 18% in medical therapy group).

Under all these results, it clearly appears a strong association between PDA surgery and short and long-term outcomes, especially when it is performed precociously (before day 21 of life). The main question is whether there is a real causal link between PDA surgical treatment and these morbidities. Indeed, we describe here a premature population with extremely low WGA and BW, particularly immature, multi-pathological and vulnerable. So these outcomes are probably depending on other perinatal factors too, as demonstrated by Chorne with his adjusted analysis for perinatal/neonatal variables (28). Furthermore, we can ask if our respiratory and digestive morbidities are related to presence of PDA or its surgical ligation. However, we must now ask ourselves about our interventionist management of PDA, in order to reduce mortality and morbidity rates as much as possible. As cited in recent studies, should not we select our PDA therapy according to their degree of immaturity and their PDA characteristics? Benitz also offers a therapeutic abstention for preterm infants with a birth weight > 1000g, whose PDA spontaneous closure is expected, and defer PDA

treatment as much as possible for ELBW, in order to reduce the exposure to secondary effects (12,42). In the same vein, others suggest a conservative strategy, which consists of an early medical treatment with COX inhibitors, then a conservative approach, offering a surgery as late as possible, if there is a cardiopulmonary failure due to a persistent PDA (35). On contrary, a recent Korean study shows that early and primary surgical ligation of PDA can be a better choice for VLBW < 1500g with PDA > 2mm (which have 67% absence of response to medical treatment) and can reduce mortality and morbidity including BPD) (41).

To clearly answer all these unresolved questions regarding PDA, it would be necessary to realize other studies, especially one comparing PDA surgery versus placebo. We will also be waiting with great interest for the ongoing French prospective, multi-centric, randomized and controlled trial (TRIOCAPI) comparing early Ibuprofen versus placebo (43).

However, our study presented some limitations; the main was the small size of our cohort, compared to many U.S. studies of thousands of babies. It remains only a descriptive study and it was difficult to compare significant and relevant some subgroups of unequal size. Then, we have not achieved adjusted analyzes for perinatal or neonatal factors. It might be possible to find significantly more powerful results and real causal links independently of other variables. Despite the unit's protocol, there might be differences among the clinicians concerning ultrasound PDA diagnosis, which remains operator dependent, and therefore the decision to treat PDA. Finally, there was probably an information bias due to records sometimes incorrectly filled; this could cause a lot of missing data.

CONCLUSION

In our extreme premature cohort, neonatal respiratory and digestive morbidities, and global adverse outcomes at 24 months corrected age, are more frequent when they have a significant PDA. Compared with a medical treatment, bronchopulmonary dysplasia rate is particularly higher when PDA is surgically ligated. Inversely, PDA surgery is associated with a lower risk of death and/or neurodevelopmental impairment. There is no evidence that PDA and its therapies are the causes of these short and long-term consequences. Further studies comparing medical treatment and surgery versus placebo could help us to determine the best PDA therapeutic approach, to obtain survival without severe morbidities in those infants.

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LE SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.