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ORIGINAL ARTICLE

Surgical closure of patent ductus arteriosus in extremely low birth weight infants weighing less than 750 grams

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Abstract

Background: Patent ductus arteriosus (PDA) occurs more frequently in premature infants. Depending on the degree of prematurity, these children often have other serious comorbidities that could have a significant impact on surgical outcome.

Aim: This study aimed to evaluate the clinical results of surgical ligation of PDA in extremely low body weight preterm infants with birth weight below 750 g, and to identify risk factors of mortality.

Methods: A total of 31 preterm infants with birth weight below 750 g and significant PDA were operated between 2006 and 2016 through posterolateral thoracotomy (n = 16) or with the use of video-assisted thoracoscopic method (n = 15). Mean weight at the time of surgery was 750.8 ± 104.7 g. The gestational age ranged from 22 to 32 weeks. Data were retrospectively analysed, and prospective 100% follow-up was performed.

Results: In-hospital mortality was 25.8% (n = 8). The type of surgery had no influence on the results. During the follow-up period lasting 5.2 ± 2.5 years, two other patients died. One-year and five-year probability of survival was 77.4% and 74.2%, respectively. The predominant cause of death was acute heart failure. All patients with preoperative renal dysfunction died in the postoperative period. Moreover, Cox regression analysis revealed renal dysfunction as an independent risk factor of early death.

Conclusions: Preterm infants with birth weight less than 750 g and significant PDA are highly challenging patients. Despite the recent advances in perioperative management with neonates, surgery is still associated with a high early mortality rate irrespective of the applied method.

Key words: patent ductus arteriosus, surgical ligation, preterm infants, outcomes

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INTRODUCTION

Prematurity is considered the most potent factor for persistency of the ductus arteriosus. The incidence of patent ductus arteriosus (PDA) in preterm infants born before the 28th week of pregnancy can reach as much as 65% [1, 2]. These infants commonly present reduced weight, which is associated with marked morbidity, and it may have a significant impact on late prognosis. This group of patients can be divided into the following subgroups according to their birth weight: low birth weight (LBW; < 2500 g), very LBW (< 1500 g), and extremely LBW (< 1000 g) infants. Thus, preterm infants with weight less than 750 g are at particular risk of mortality and development of serious complications.

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Currently, diagnosis of haemodynamically significant PDA is not challenging because there is easy and common access to echocardiography, angiography, and other diagnostic tools [3]. There are many available therapeutic options to treat PDA, such as fluid restriction, intravenous administration of cyclo-oxygenase inhibitors and/or diuretics, percutaneous occlusion, or surgical ligation. Although pharmacological treatment and interventional duct ligation are efficient in PDA closure, both are associated with significant adverse events. Recent studies report a higher rate of complications after surgical ligation [2–5] that resulted in the shift from aggressive approach to conservative or pharmacological treatment. However, if they fail and the percutaneous therapy is contraindicated, surgical intervention remains the only solution [6, 7].

The purpose of this study is to present our experience with preterm infants born with birth weight below 750 g, treated surgically for PDA.

Table 1. Demographics and preoperative clinical data

Sex: male/female	12/19
Mean gestational age [weeks]	25.5 ± 1.2
Mean age at the surgery [days]	21.9 ± 9.9
Mean birth weight [g]	697.8 ± 72.9
Mean weight at time of surgery [g]	750.8 ± 104.7
Mean diameter of the ductus [mm]	3.9 ± 1.2
Comorbidity:	
Foetal infection	13 (41.9%)
Anaemia of prematurity	19 (61.3%)
Bronchopulmonary dysplasia	6 (19.4%)
Intraventricular haemorrhage	17 (54.8%)
Renal failure	5 (16.1%)

Data are presented as mean ± standard deviation or number (percentage).

METHODS

Patient population

A retrospective analysis involved 31 preterm infants with symptomatic isolated PDA, who were treated between June 2006 and April 2016. In all patients, PDA satisfied the following criteria of haemodynamic significance: PDA diameter ≥ 2 mm, ratio of the left atrium to the aorta ≥ 1.5, presence of left-to-right shunt, and impaired cardiac performance. All infants were born with birth weight below 750 g, the smallest patient weighed 490 g, and the gestation age ranged from 22 to 32 weeks. Mean weight at the surgery was 750.8 ± 104.7 g. All patients were ventilator-dependent before the surgery. The other demographics and preoperative clinical data are presented in Table 1.

The exclusion criteria were: PDA associated with any other cardiac anomalies that needed to be surgically corrected in a classical way.

Operative technique

After primary pharmacological treatment had failed, infants underwent surgical ligation of isolated PDA. However, two different surgical methods have been applied. Between 2006 and May 2012, 16 children were operated through posterolateral thoracotomy in the third (61%) or fourth (31%) intercostal space. Since June 2012 all infants (n = 15) have been operated by means of video-assisted thoracoscopic surgery (VATS). Emergent conversion to thoracotomy after primary VATS was necessary in two patients. All surgeries were performed in an infant incubator in the operating room. A chest tube was inserted before closing the chest, in patients who presented operative bleeding greater than expected or according to the preferences expressed by the surgeon. Standard echocardiography was performed in the operating room to confirm the complete closure of the duct.

Postoperative period

After surgery, patients were transferred to a paediatric cardiothoracic intensive care unit (ICU) and then 48 h later to a neonatal ICU. Surgical drains were removed the day after the procedure, if not contraindicated. Overall mortality and severe in-hospital adverse events were analysed. After discharge all children underwent systematic clinical and echocardiographic follow-up in the outpatient clinic until October 2016.

Statistical analysis

The continuous variables were checked for normality with the use of the Shapiro-Wilk test. Normally distributed data are expressed as the means ± standard deviations and compared with unpaired t Student test. If they do not meet criteria of normal distribution (e.g. time of weaning from mechanical ventilation), they are presented as median with the range. The categorical variables are expressed as the numbers (n) and percentages (%), and they were analysed with the use of the Yates corrected χ^2 test. Survival curves were calculated by the Kaplan-Meier method, univariate analyses for the identification of prognostic factors were carried out using two separate methods: Breslow's modification of the generalised Wilcoxon statistic and the log-rank test of Mantel-Cox. Cox proportional hazards regression analysis was performed to identify predictors of long-term mortality. Statistical significance was assumed at $p < 0.05$. Statistical analysis was computed with SPSS STATISTICS 24 (IBM, USA).

RESULTS

Surgery

All patients survived operation and were transferred to the ICU. The average operating time defined as 'skin-to-skin' was 37 ± 15 min. Two children qualified for VATS procedures

Table 2. Causes of death

No. of preterm infant	Type of surgery	Sex	Gestational age [weeks]	Age at the surgery [days]	Birth weight [g]	Weight at the surgery [g]	Preoperative state	Survival after the surgery	Cause of death
1	PT	Female	26	24	700	700	HF, RF, AoP, IVH	4 days	Acute cardiopulmonary failure
2	PT	Male	25	13	750	750	NJ, IVH, RD, AoP, PB and CPR	19 h	Respiratory failure, cerebral bleeding
3	PT	Female	24	37	710	850	HF, FI, AoP, RF	3 days	Acute cardiopulmonary failure
4	VATS → PT	Female	24	33	490	810	HF, AoP, IVH, RF	48 h	Acute renal and cardiac dysfunction
5	VATS	Male	24	16	700	700	HF, RD, FI, AoP, IVH, RF	3 days	Acute renal and cardiac dysfunction
6	VATS	Male	26	15	735	700	HF, NJ, FI, RD, IVH	32 h	Massive, cerebral bleeding
7	VATS	Male	26	17	750	820	HF, RD, AoP, FI	139 days	Sudden infant death syndrome
8	VATS	Female	29	14	640	850	HF, RD	18 days	Acute cardiopulmonary failure
9	VATS	Female	25	23	605	750	HF, RD, RF	4 days	Acute renal and cardiac dysfunction
10	VATS	Female	23	50	670	850	HF, RD, FI, AoP, IVH	310 days	Cerebral disorders

AoP — anaemia of prematurity; CPR — cardiopulmonary resuscitation; FI — foetal infection; HF — heart failure; IVH — intraventricular haemorrhage; NJ — neonatal jaundice; PB — preoperative bradycardia; PT — posterolateral thoracotomy; RD — respiratory distress; RF — renal failure; VATS — video-assisted thoracoscopic surgery; VATS → PT — VATS converted to PT

required intraoperative conversion to thoracotomy, one due to the haemodynamic instability and the other due to technical difficulties in ductus visualisation. Nine patients required chest tube insertion, including seven (43.8%) infants after thoracotomy and two (13.3%) patients after VATS.

In-hospital period

In-hospital mortality was 25.8% (n = 8). Three patients died during the first 48 h after the surgery in the paediatric cardiothoracic ICU; two of them died due to massive cerebral bleeding and one patient due to sudden cardiac arrest. Another five children died in the neonatal ICU. Inotropes were already needed preoperatively in all these cases due to myocardial dysfunction and hypotension. Despite intensive heart failure therapy, the haemodynamic instability was unmanageable. The causes of all deaths are outlined in Table 2.

Mean hospitalisation time at the neonatal ICU was 11.4 ± 3.9 weeks. Overall median mechanical ventilator time was 15 days (range 1–45), while among survivors it was 19 days (range 7–45). Comparing the ventilation support time between two surgical accesses, it was slightly shorter in patients after VATS (thoracotomy 25.9 ± 13.0 days vs. VATS 17.7 ± 7.2 days) but this difference did not reach statistical significance ($p = 0.09$). Patients with birth asphyxia required slightly longer mean ventilation support (23.3 days) in comparison to the others (14.7 days; $p = 0.07$). The mean postoperative pleural drainage duration was 22.2 ± 17.6 h. After surgery, blood product transfusion was required in 80.6% of all infants and 77.4% of patients received catecholamine infusion. Routine postoperative echocardiography confirmed complete closure of the duct in all patients and significant reduction of left ventricular end-diastolic diameter from 12.8 ± 1.7 mm to 9.8 ± 2.7 mm after surgery ($p < 0.05$).

The incidence of serious adverse events in the early postoperative period is summarised in Table 3.

Late outcomes

All patients completed a follow-up period lasting 5.2 ± 2.5 years. During the follow-up period two patients died at home 139 days and 310 days after surgery, respec-

Table 3. Incidence of serious complications in the early postoperative period

Chylothorax/pleural effusion	1 (3.2%)
Pneumothorax [treated using chest tube]	3 (9.7%) [1 (3.2%)]
Atelectasis	7 (22.6%)
New occurring arrhythmias	6 (19.4%)

Data are presented as numbers (percentages).

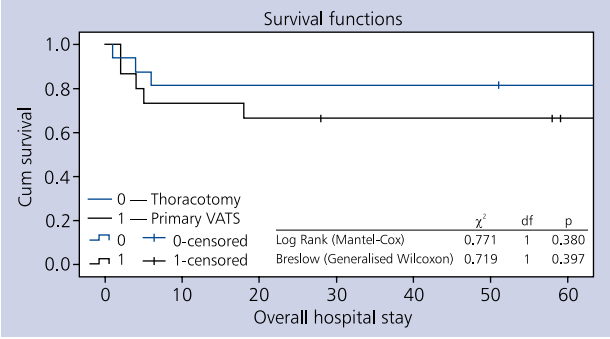

Figure 1. Kaplan-Meier survival curves with respect to method of patent ductus arteriosus closure; VATS — video-assisted thoracoscopic surgery

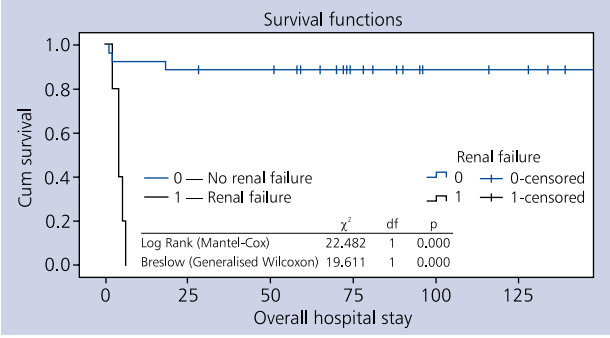

Figure 2. Impact of renal failure early after patent ductus arteriosus closure on survival rate

tively. The overall 12- and 60-month probability of survival was 77.4% and 74.2%, respectively. The type of surgery had no impact on survival (Fig. 1).

All patients included in our study had multiple co-morbidities, but only the association between renal failure and mortality was found to be statistically significant (Fig. 2). In Cox regression analysis, gestational age ($p = 0.791$), PDA diameter ($p = 0.570$), and duration of surgery ($p = 0.934$) were not identified as independent predictors of overall mortality.

Late residual shunt occurred in two children during the follow-up period; however, neither were haemodynamically significant, so they did not require further treatment.

DISCUSSION

Treatment strategy for patent ductus arteriosus in extremely LBW infants is still controversial and still without any consensus on management [8, 9]. Furthermore, recent studies failed to support any significant long-term benefit after invasive treatment. We observe a tendency towards pharmacological or even conservative treatment. Despite new strategies and lack of any guidelines concerning this kind of patients, surgical ligation continues to be widely used and it is an important rescue strategy when other methods fail. Currently, aggressive intervention is reserved only for patients with haemodynamically significant PDA with contraindication for pharmacological treatment or after ineffective therapy [10]. However, the decision on the closure method of PDA should always depends on the preoperative state, ductus size, comorbidities, gestational age, and weight of the infant. Pharmacological treatment fails in up to 40% of cases, and in the others is contraindicated. Additionally, the success rate is markedly lower in extremely LBW infants. Currently, cardiologists and cardiac surgeons are still debating which invasive option is optimal. Percutaneous closure, being minimally invasive, seems to be preferred over other methods. However, catheter-based therapy was shown to be associated with an increase in residual shunt. Moreover, there are some absolute contraindications for catheter closure, such as a large ductal diameter, very small weight of a preterm, infection, unfavourable clinical condition, or calcification of the duct [6, 11]. Our clinical observational study involves only critically ill extremely LBW infants with birth weight less than 750 g. Thus, due to the anatomical conditions and preoperative state, all patients were qualified for surgical ligation.

Preterm infants with birth weight below 750 g are a challenging group of patients. Significant PDA results in haemodynamic instability that eventually leads to further complications such as neonatal respiratory failure, bronchopulmonary dysplasia, asphyxia, anaemia of prematurity, or intraventricular haemorrhage. Our patients were operated at a mean age of 21.9 ± 9.9 days. However, the optimal time for surgery is still debatable. Youn et al. [12] reported no differences between early ligation (≤ 2 weeks of life) and late ligation (≥ 2 weeks of life). The interventional closure should be performed when significant PDA is diagnosed and the conventional therapy is inefficient. Delays to scheduled operations may lead to considerable increase in morbidity, such as necrotising enterocolitis, bronchopulmonary dysplasia, or escalation of the diastolic steal phenomenon [12].

The high mortality rate in these patients is related not only to the underlying cardiovascular pathology but also to complications of prematurity [13]. In our study, the in-hospital death rate of 25.8% was relatively high but was comparable to previous reports analysing the outcomes in extremely LBW infants [12]. Most of the deaths occurred in the first days after the surgery, predominantly due to acute cardiac dysfunction.

Regression analysis revealed that acute renal failure in our group was associated with significantly higher postoperative mortality [14]. In our study, 16.1% children had preoperative renal dysfunction, which was associated with 100% mortality in the postoperative period ($p < 0.001$). Other risk factors of early mortality were previously identified. Higher mortality in preterm infants with large intraventricular haemorrhage (IVH) compared to cases without IVH has been reported [15, 16]. In our series, IVH was diagnosed in 54.8% of patients and two died due to massive cerebral bleeding in the perioperative period. One preterm infant died ten months after PDA ligation due to cerebral dysfunction with history of IVH. However, in our study, the association between IVH and mortality was not statistically significant ($p = 0.757$).

Perioperative mortality and complication rates were similar in both surgical techniques. Therefore, in our opinion, surgery in these patients is associated with high perioperative mortality regardless of the surgical technique applied. We observed a higher overall mortality after VATS ($n = 7$, 46.7% vs. $n = 3$, 18.8%); however, three patients died due to non-cardiac reasons and two of them died after 139 days and 310 days postoperatively at home. On the other hand, children after VATS presented slightly reduced ventilation time after the procedure. Significant PDA in preterm infants is always associated with many multiple organ disorders, and VATS may reduce the trauma of surgery. Burke et al. [11] and Kozlov et al. [17] suggest that the VATS technique is safe and is associated with better results than open surgery in preterm infants, and this technique offers a minimal trauma. We observed no significant differences between these techniques, except for the cosmetic effect. Conversion was necessary in two patients, one of them died due to acute cardiac dysfunction, and the second patient was discharged home after 94 days with a weight of 2450 g. The literature also suggests that rapid conversion to thoracotomy after primary VATS can be performed relatively safely and should not result in an increased early rate of complications [11, 18–20].

In conclusion, preterm infants with birth weight lower than 750 g and significant PDA are highly challenging patients. Surgical intervention is an alternative method, after failed pharmacological treatment. Despite the recent advances in perioperative management with preterm neonates, surgery is still associated with a high early mortality rate, irrespective of the applied method.

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