Outcome of interventional cardiac catheterization in infants weighing less than 2500 grams. A comparative study

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Purpose: To evaluate the feasibility, efficacy and safety of interventional cardiac catheterization in infants weighing less than 2500 gm compared to infants weighing more than or equal to 2500 grams.

Methods: This prospective cross sectional study included all patients who underwent interventional cardiac catheterization through the first 60 days of life in the specialized New Children University Hospital (Abu Elreesh), Faculty of medicine, Cairo University during the period from January 2015 till January 2018. The study group included patients less than 2500 grams, while the comparative group included patients weighing ≥ 2500 grams. The demographics, procedures, outcomes and follow-up data were collected. Each adverse event (AE) was classified according to either a single domain of attributability i.e. catheterization, access, stent, balloon or intensive care unit related or the seriousness i.e. major and minor.

Results: The study group included 37 patients with a mean age of 15.6 ±13.6 days and a mean weight of 2.35 ±0.13 Kg, while the comparative group included 164 patients with a mean age of 26.2 ±18.4 day and a mean weight of 3.54 ±0.71 Kg. Four different procedures were included in the study; Balloon atrial septostomy, pulmonary balloon valvuloplasty, PDA stenting and radiofrequency perforation for pulmonary atresia. The overall incidence of complications was higher in neonates <2.5kg compared with neonates ≥2.5 kg (48.6% versus 20.1 %, P<0.001). The overall incidence of catheterization related mortality was also higher in the study group (29.7% {11/37} versus 4.9% {8/164}, in the comparative group, P<0.001). Balloon atrial septostomy recorded the least incidence of adverse events and mortality rates with statistically non-significant different mortality rates between the two groups, 14.3% and 0% in the study and comparative groups respectively. In the other hand, PDA stenting showed the highest incidence of adverse events and mortality rates as major complications occurred in 70% and 37.5% of patients from the study and comparative groups respectively (P value = 0.084), while mortality occurred in 50% and 12.5% of patients from the study and comparative groups respectively which is statistically significant (P value = 0.019). There is no statistically significant difference in incidence of complications between the study and the comparative groups who underwent radiofrequency perforation of atretic pulmonary valve and the mortality rate comparison was not applicable due to the small sample size. However, patients who underwent pulmonary balloon valvuloplasty for critical PS showed statistically significant higher incidence of major (P value =0.002) and minor (P value =<0.001) complications in the study group.

Conclusion: Generally, interventional cardiac catheterization in infants weighing less than 2500 grams is associated with increased incidence of adverse events. Different procedures carry different incidences of adverse events. PDA stent is associated with increased mortality in low birth weight infants while pulmonary balloon valvuloplasty in infants with critical pulmonary stenosis is associated with higher incidence of major complications but no significant increase in mortality rates.

Keywords: Outcomes; complications; pediatric interventional catheterization; low birth weight.
Introduction

Low birth weight (LBW), defined as birth weight less than 2500 g, has a prevalence of around 8% of births (Ades, Johnson et al. 2005). Infants may be of LBW because of prematurity or being small for gestational age (SGA). Among all birth defects, cardiovascular malformations are the most common, and result in significant mortality worldwide (Richards and Garg 2010).

Congenital heart diseases (CHD), among all live births, are quite common, with prevalence to be around 8-9 in every 1000 live births (Botto, Correa et al. 2001, Bjornard, Riehle- Colarusso et al. 2013). One of the most consistent observations among newborns with CHD is being low and very low birth weight infants, i.e. <2,500 g and <1,500 g, respectively. An additional finding is that many infants with CHD are born prematurely, suggesting that the association of low birth weight with CHD may be attributed, in part, to prematurity (Wren, Irving et al. 2012).

The mortality risk is higher in infants who are of LBW and have CHD than infants with CHD who are not of LBW. This is mostly multifactorial, related to the underlying cause of the LBW, associated comorbidities and, technical problems with the small size of the neonate. Management of this group must take into consideration the pathophysiology contributing to the low birth weight, the associated birth defects as well as the small size of the neonate (Ades, Johnson et al. 2005).

The mortality for LBW infants undergoing surgery for CHD remains high (Cheng, Almodovar et al. 2011). So, interventional cardiac catheterization has been utilized increasingly to enhance the outcome of these risky infants (Kobayashi, Sallaam et al. 2013). Technical feasibility, efficacy and safety of cardiac catheterization continue to be a concern because of low infant weight and size. Few large research studies reported their catheterization experience and showed increased risk of mortality and morbidity in LBW infants compared to larger weights (Kobayashi, Sallaam et al. 2013). However, some research studies reported that such complications were less likely to result in permanent sequela (Karagoz, Akin et al. 2015).

Aim of the work

To evaluate the feasibility, efficacy and safety of interventional cardiac catheterization in infants weighing less than 2500 gm compared to infants weighing more than or equal to 2500 grams.

Patients and Methods

That prospective cross sectional study includes all patients who are less than 2500 grams and undergo interventional cardiac catheterization through the first 60 days of life. All patients are previously diagnosed to have congenital heart diseases suitable for percutaneous transcatheter intervention. They are selected from New Children University Hospital (Abu-Elreesh), faculty of medicine, Cairo University during the period from January 2015 till January 2018. A similar group of infants, weighing ≥ 2500 grams, are included as a comparative group.

Inclusion criteria:

• Patient’s age is 60 days or less
• Patient’s weight is less than 2500 grams (the study group) and more than or equal to 2500 grams (the comparative group)
• Urgent life threatening congenital heart disease confirmed by echocardiography
• Known feasibility of the lesion to be cured or palliated by cardiac catheterization

Exclusion criteria:

• Age more than 60 days
• A cardiac lesion, which is not urgent
• Associated extra-cardiac congenital anomalies
• Apparent syndrome or genetic disorders
• Bleeding tendency
• Infection, septicemia or pneumonia
• Arrhythmia

All the studied cases are subjected to thorough clinical examination, two-dimensional and Doppler Echocardiography and laboratory assessment. A database was created and implemented, at the pediatric cardiology department, in the New Children University Hospital (Abu-Elreesh), faculty of medicine, Cairo university, in order to record the demographic data of the patients, procedural characteristics as well as the adverse effects related to cases performed in the catheterization laboratory.

**Collection of Adverse Event Data**

Adverse events are defined as any anticipated or unanticipated event from which injury could occur or actually occurred, potentially or definitely as a consequence of performing the catheterization. Each AE is classified according to either a single domain of attributability i.e. anaesthesia, airway, catheterization, access, stent, dilation or intensive care unit related or the seriousness i.e. major and minor.

**According to the main domain of attributability:**

**I) Adverse events related to catheterization laboratory:**

a) Access-related adverse events (AEs): Hemothorax / pneumothorax, groin hematoma, pulse loss (requiring heparin, bleeding from puncture site that needed blood transfusion or vein thrombosis (confirm with Doppler).

b) General catheterization-related AEs: Supraventricular tachyarrhythmia, ventricular tachycardia, CNS event like seizures and inability to regain conscious level after anaesthesia, low cardiac output status or sudden cardiac arrest.

c) Dilation-related AEs: Balloon rupture, failure to pass through the stenotic lesion, confined vascular tear, heart block or heart perforation.

d) Stent-related AEs: Failure to probe the ductus, stent embolization/malposition, stent fracture or stent thrombosis.

**II) Intensive care unit (ICU) related AEs:**

• Ventilator-related as pneumothorax.
• Procedure-related.
• Renal impairment.
• Infections as sepsis or pneumonia.

**According to seriousness:**

**I) Major complications:** included all events leading to one of the following: a. Death , b. Life-threatening hemodynamic decompensation requiring immediate therapy , c. The need for surgical intervention or d. A significant unanticipated permanent anatomic or functional lesion resulting from the catheterization (e.g., cerebral infarct).
II] Minor complications: all unanticipated events that were transient and resolved with specific treatment e.g., tolerated transient arrhythmic episode and/or hypotension requiring intravenous fluids.

Results

The study group included 37 patients, 20 male (54.1%) and 17 females (45.9%). The age ranged from 1 day to 60 days (median 10 days) with a mean of 15.6 ±13.6 days. Their weights ranged from 2 to 2.49 Kg with a mean of 2.35 ±0.13 Kg. The comparative group included 164 patients, 95 male (57.9%) and 69 females (42.1%). The age ranged from 2 to 60 days (median 23.5 days) with a mean of 26.2 ±18.4 day. Their weights ranged from 2.6 to 5.9 Kg with a mean of 3.54 ±0.71 Kg. Four procedures were performed; Balloon atrial septostomy, pulmonary balloon valvuloplasty, PDA stenting and radiofrequency perforation of pulmonary atresia.

The overall incidence of cath-lab related adverse events was significantly higher in the study group 48.6% and only 20.1% in the comparative group, P<0.001. This included all cases of access, catheter manipulation, balloon and stent related adverse events.

Table 1. Adverse events in the study and comparative groups

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>&lt;2.5 kg (n = 37)</th>
<th>≥2.5 kg (n = 164)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Access related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemothorax / pneumothorax</td>
<td>2</td>
<td>5.4</td>
<td>0</td>
</tr>
<tr>
<td>Groin hematoma</td>
<td>4</td>
<td>10.8</td>
<td>3</td>
</tr>
<tr>
<td>Ext bleeding at access site (needed blood)</td>
<td>2</td>
<td>5.4</td>
<td>4</td>
</tr>
<tr>
<td>Retroperitoneal hematoma</td>
<td>1</td>
<td>2.7</td>
<td>1</td>
</tr>
<tr>
<td>Vein thrombosis</td>
<td>1</td>
<td>2.7</td>
<td>3</td>
</tr>
<tr>
<td>Weak pulse requiring heparin</td>
<td>4</td>
<td>10.8</td>
<td>8</td>
</tr>
<tr>
<td>Overall complications</td>
<td>12</td>
<td>32.4</td>
<td>15</td>
</tr>
<tr>
<td>Access related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachyarrhythmia (SVT)</td>
<td>3</td>
<td>8.1</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>2</td>
<td>5.4</td>
<td>0</td>
</tr>
<tr>
<td>Low cardiac output (needed inotropes)</td>
<td>3</td>
<td>8.1</td>
<td>6</td>
</tr>
<tr>
<td>Cardiac arrest , CPR</td>
<td>4</td>
<td>10.8</td>
<td>1</td>
</tr>
<tr>
<td>DCL</td>
<td>1</td>
<td>2.7</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>3</td>
<td>8.1</td>
<td>3</td>
</tr>
<tr>
<td>Cath manipulation AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall general catheter manipulation complications</td>
<td>10</td>
<td>27.0</td>
<td>14</td>
</tr>
<tr>
<td>Balloon related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed to cross</td>
<td>2</td>
<td>5.4</td>
<td>3</td>
</tr>
<tr>
<td>Perforation/pericadial effusion</td>
<td>3</td>
<td>8.1</td>
<td>3</td>
</tr>
<tr>
<td>Overall Balloon related complications</td>
<td>5</td>
<td>13.5</td>
<td>6</td>
</tr>
<tr>
<td>Stent related AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malposed stent</td>
<td>1</td>
<td>2.7</td>
<td>2</td>
</tr>
<tr>
<td>Thrombosed stent</td>
<td>1</td>
<td>2.7</td>
<td>2</td>
</tr>
<tr>
<td>Fracture</td>
<td>1</td>
<td>2.7</td>
<td>0</td>
</tr>
<tr>
<td>Failed stenting</td>
<td>3</td>
<td>8.1</td>
<td>4</td>
</tr>
<tr>
<td>Overall stent related complications</td>
<td>6</td>
<td>16.2</td>
<td>8</td>
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<tr>
<td>Overall Cath-lab related complications</td>
<td>18</td>
<td>48.6</td>
<td>33</td>
</tr>
</tbody>
</table>
Mortality rates was also significantly higher in the study group 29.7% versus 4.9% in the comparative group, \(P<0.001\). Infants with lighter weights stayed more durations in the ICU with mean 5.2 ±5.9, while the heavier weight infants stayed shorter durations with mean 2.9 ±3.9.

Balloon atrial septostomy recorded the least incidence of adverse events and mortality rates with statistically non-significant different mortality rates between the two groups, 14.3% and 0% in patients in the study and comparative groups respectively. In contrary, PDA stenting showed the highest incidence of adverse events and mortality rates as major complications occurred in 70% and 37.5% of patients from the study and comparative groups respectively (\(P\) value = 0.084), while mortality occurred in 50% and 12.5% of patients from the study and comparative groups respectively which is statistically significant (\(P\) value = 0.019). There was no statistically significant difference between the study and the comparative groups who underwent radiofrequency perforation of atretic pulmonary valve. However, patients who underwent pulmonary balloon valvuloplasty showed statistically significant higher incidence of major (\(P\) value =0.002) and minor (\(P\) value =<0.001) complications in the study group.

**Fig (1): Incidence of major and minor complications and mortality in every single procedure in both the study and comparative groups**

Discussion

Congenital heart diseases (CHD), among all live births, are quite common, with prevalence around 8-9 in every 1000 live births (**Bjornard, Riehle-Colarusso et al. 2013**). The mortality for LBW infants undergoing surgery for CHD remains high (**Cheng, Almodovar et al. 2011**). So, interventional cardiac catheterization has been utilized increasingly to enhance the outcome of these risky infants (**Kobayashi,
Technical feasibility, efficacy and safety of cardiac catheterization continue to be a concern because of low infant weight and size.

In our study, in the study group, 32.4% of the patients had access related complications while the percentage was only 9.1% in the comparative group. These complications included groin hematoma, external bleeding at the access site, vein thrombosis and weak arterial pulse that required heparin. External bleeding at the access site occurred in two cases from the study group (5.4%) and was hemodynamically significant in both as they showed signs of low cardiac output in the form of drowsiness, delayed capillary refill time and hypothermia while the bleeding which occurred in 4 patients from the other group (2.4%) was hemodynamically significant in only 2 cases. Karagoz, Akin et al. (2015), in a similar study had bleeding that required blood transfusion in 5% of the study group patients.

Deep vein thrombosis occurred in only one patient (2.7%) in the study group while occurred in 3 patients (1.8%) from the comparative group. The diagnosis was confirmed in each patient by Doppler and the patients were discharged on subcutaneous low molecular weight heparin. Four patients (10.8%) and eight patients (4.9%) from the study and comparative groups respectively had weak dorsalis pedis pulse after discharge from the catheterization laboratory. Warming the limb, and heparin infusion were done in all cases and all patients improved within hours to days with no long term sequelae. Silvey and Brando (2017) reported that patients undergoing congenital heart cardiac catheterizations develop venous thrombosis with a prevalence ranging from 0 to 27% and femoral artery occlusion between 0.6 and 9.6% with risk factors including younger age and patient size.

Overall incidence of catheter manipulation adverse events was 27% in the study group, however, significantly lower in the comparative group, being only 8.5% (P= 0.002). Three patients in the study group (8.1%) and five in the comparative group (3%) had supraventricular tachycardia attacks that were transient and terminated with only withdrawal of wires and/or catheters except one patient from the study group who needed one dose of adenosine to terminate the attack. Ventricular tachycardia was the other form of tachyarrhythmia that was documented. It occurred in only 2 patients from the study group (5.4%) and no patients from the other group at all. One of those patients had a brief attack that stopped within seconds with no intervention at all. However, the second patient, who had a radiofrequency perforation for pulmonary atresia, developed ventricular tachycardia that received D.C shock before the heart rate became sinus again. Karagoz, Akin et al. (2015) in a similar study reported that 5% of patients weighing less than 2.5 kg had supraventricular tachyarrhythmia.

Sudden cardiac arrest had occurred in 4 patients weighing less than 2.5Kg (10.8%), but only one patient from the other group. From the first group, two patients died on table, one due to PDA spasm during trials to probe the PDA for stenting in a duct dependent pulmonary circulation, while the other one was due to cardiac tamponad during Balloon atrial septostomy. The other two patients were successfully resuscitated and safely discharged to the post-catheterization ICU with successful procedure in one patient (Balloon atrial septostomy) and failed procedure in the other (balloon failed to cross through critically stenotic pulmonary artery). Karagoz, Akin et al. (2015) in a similar study reported sudden cardiac arrest in 5% of patients weighing less than 2.5 kg who were successfully resuscitated. In another study done by Mobley, Stroup et al. (2013), 2 patients (4.3%) were reported to have intra-procedural cardiac arrest that necessitated cardiopulmonary resuscitation.

In the current study, some balloon related adverse events had been encountered. During balloon pulmonary valvuloplasty, failure to cross the stenotic valve occurred in 2 patients form the study group (5.4%) and 3 patients from the comparative group (1.8%). Fedderly, Lloyd et al. (1995) in a study conducted on 12 infants in their first 60 days of age with critical pulmonary stenosis had reported failure to cross the valve in one patient (8.3%). Another complication that was related to balloon procedures was myocardial perforation which occurred in 3 patients (1 Balloon atrial septostomy & 2 PBV) from the study group (8.1%) and 3 patients (all PBV) from the comparative group (1.8%). The 3 patients from the first group were managed urgently with pericardiocentesis, however one of them (septostomy patient) died on
Fedderly, Lloyd et al. (1995) reported 2 patients (16.6%) complicated with cardiac perforation, one of them during PBV while the other during radiofrequency perforation of atretic pulmonary valve. In a six-year study conducted by Mobley, Stroup et al. (2013) on low birth weight infants which included 46 infants less than 2.5 kg, no cardiac perforation cases were reported.

As regard stent related complications in the current study, there were different adverse events. Failure to probe the PDA happened in 3 patients from the study group (8.1%) while in 4 patients (2.4%) from the comparative group. Of the first group, one patient arrested on table secondary to PDA spasm during manipulations and efforts of resuscitation including prostaglandin infusion failed. The 2 other patients form the study group and the whole 4 patients from the comparative group were transferred to the ICU on prostaglandin infusion to be prepared for B-T shunt operation. Hussain, Al-Zharani et al. (2008) conducted a study on PDA stenting on 21 infants with the mean body weight 2.9 +/- 0.35 kg and reported that five patients (23.8%) did not qualify because of a complex tortuous ductus arteriosus or branch pulmonary artery stenosis and two more patients (9.5%) failed to be stented after several trials. In another study, Santoro, Gaio et al. (2008) did a research on infants with the mean body weight 3.3 +/- 0.8 kg and reported failure rate of 7.7% (2/26) due to extreme tortuosity of the ductus. Moreover, Michel-Behnke, Akintuerk et al. (2004) reported failure rate of about 4.7% in a study done on 21 infants, with mean weight 3.3 kg, for PDA stenting.

Another stent related complication in our study, was stent malposition. This was reported in one patient from the first group (2.7%) in whom the stent was malposed across the left pulmonary artery, the patient was transferred to ICU on prostaglandin infusion but died one day later. Two patients from the second group (1.2%) had similar events. In one patient, the stent was malposed in the RPA while in the other patient the stent migrated to the descending aorta and was removed by snare. Both patients were prepared for surgical BT shunt. In a study done on 106 patients with PDA stent with weights 2.9 kg (2.5–3.5), Glatz, Petit et al. (2018) reported that 1 patient (0.94%) developed migrated stent.

One more reported adverse event was stent thrombosis. This was reported in one patient from the first group (2.7%) in whom the stent was thrombosed , in spite of heparin infusion, and the patient died in the ICU two days later. Two patients from the second group (1.2%) had similar events. Both patients were prepared urgently for surgical BT shunt after 3 and 6 days respectively. Santoro, Gaio et al. (2008), in their research on infants with the mean body weight 3.3 +/- 0.8 kg reported stent thrombosis in 8.3% (2/24) who, later, underwent surgical systemic-to-pulmonary artery shunt.

The overall incidence of stent related adverse events showed significant difference between the 2 groups, being 16.2% in the study group and 4.9% in the comparative group (P=0.014). In a PDA stenting study done on 21 patients with mean weight 3.3 kg, Michel-Behnke, Akintuerk et al. (2004) reported overall incidence of complications in 4 patients (19%), three malposed/embolised stents and one thrombosed stent.

In the current study, the overall incidence of catheter laboratory related complications was 48.6% in the study group and 20.1 % in the comparative group (P<0.001). In a multi-center study about low weight as an independent risk factor for adverse events during cardiac catheterization of infants, Backes, Cua et al. (2013) reported incidence of adverse events being 20% of cases (<2 kg: 28%, 2-3 kg: 25%, 3-5 kg: 23%, ≥5 kg: 16%). In another study comparing the outcome of cardiac catheterization in infants weighing less than 1.5 kg with a larger comparative group, Sutton, Lock et al. (2006) reported that the total complication rate was 56% in patients <1,500 g and 57% in the comparison patients 2000-3000 g.

One more six-year study conducted by Mobley, Stroup et al. (2013) on low birth weight infants which included 46 infants less than 2.5 kg, the overall incidence of complications was higher in neonates ≤2.5 kg compared with neonates >2.5 kg (34.8% versus 17.6%).

As regard cardiac catheterization related mortality, the overall incidence was 29.7% in the study group (11/37) and 4.9% % in the comparative group (8/164), (P<0.001). In a multi-center study about
low weight as an independent risk factor for adverse events during cardiac catheterization of infants, 
*Backes, Cua et al. (2013)* reported mortality cases 7/57 (12%) in the <2 kg group. In another study on 
cardiac catheterization in infants weighing less than 1.5 kg, *Sutton, Lock et al. (2006)* reported that the 
catheterization related mortality incidence was 5/18 (27.7%). The rate of mortality after invasive cardiac 
catheterization in infants weighing less than 2500 g has been found to range between 0% and 39% (*Karagoz, 
Akin et al. 2015*).

Balloon atrial septostomy patients had the least incidence of adverse events with no statistically 
significant difference between the two groups. Major complications had occurred in 2/14 patients (14.3%) 
and mortality also was reported in 2/14 patients (14.3%) in the study group. However, in the comparative 
group, only one patient (1.7%) had major complications with no recorded mortality at all.

The pulmonary balloon valvuloplasty group showed less favorable results with statistically 
significant higher incidence of major (P value =0.002) and minor (P value =<0.001) complications in the 
study group. The study group included 9 patients, 5 of whom (55.6%) developed major adverse events 
while 3 patients (33.3%) died secondary to causes related to the catheterization. However, the comparative 
group included 69 cases. Nine patients (13%) had major adverse events while 3 patients (4.3%) died 
secondary to catheterization related causes.

In contrary, PDA stenting shows the highest incidence of adverse events and mortality rates as 
major complications occurred in 70% and 37.5% of patients from the study and comparative groups 
respectively (P value = 0.084), while mortality occurred in 50% and 12.5% of patients from the study and 
comparative groups respectively which is statistically significant (P value = 0.019).

**Conclusion and summary**

In general, interventional cardiac catheterization in low birth weight infants is associated with 
increased incidence of morbidity and mortality. Balloon atrial septostomy is safe and effective procedure 
that can be done in low birth weight. PDA stent is associated with increased mortality in low birth weight 
infants. Pulmonary balloon valvuloplasty, when done in low birth weight infants with critical pulmonary 
stenosis is associated with higher incidence of complications with no significant increase risk of mortality.

**References**

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