OBJECTIVE OF INTERVENTIONAL CARDIAC CATHETERIZATION IN INFANTS WEIGHING LESS THAN 2500 GRAMS: A COMPARATIVE STUDY

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ABSTRACT

Objectives: A retrospective study to evaluate the outcome of interventional cardiac catheterization in infants weighing <2500 grams.

Background: The mortality of small weight infants undergoing heart surgery remains high, so cardiac catheterization has been utilized to improve the outcome.

Methods: The study included infants who underwent interventional cardiac catheterization within the first 60 days of life in New Children Cairo University Hospital, Cairo, Egypt from January 2015 to January 2018. The study group included infants < 2500 grams while the comparative group included infants ≥ 2500 grams. Adverse events were classified according to the mechanism and seriousness.

Results: The study group (37 patients) had a mean weight of 2.35 ±0.13 Kg, while the comparative group (164 patients) had a mean weight of 3.54 ±0.71 Kg. The procedures included balloon atrial septostomy, pulmonary balloon valvuloplasty, ducal arteriosus stenting and radiofrequency perforation of pulmonary atresia. The study group showed less success rates as compared with the comparative group (83.8% versus 93.9%, p = 0.04), and higher incidence of overall adverse events (48.6% versus 20.1%, p<0.001) as well as catheterization-related mortality (29.7% versus 4.9%, P<0.001). In the study group, pulmonary balloon valvuloplasty showed the highest incidence of major adverse events while ducal arteriosus stenting had the highest incidence of mortality.

Conclusions: Compared to normal weight infants, interventional cardiac catheterization in small weight infants is associated with lower success and higher morbidity and mortality rates. Pulmonary balloon valvuloplasty and ductal arteriosus stenting have the highest morbidity and mortality, respectively.

INTRODUCTION

Low birth weight (LBW) has a prevalence of around 8% of all births. Among all birth defects, cardiovascular malformations are the most common and result in significant mortality worldwide with a prevalence of around 8-9 per 1000 live births. There is a consistent association between congenital heart diseases (CHD) and low and very low birth weight (<2,500 g and <1,500 g respectively). Many infants with CHD are born prematurely; suggesting that the association of LBW with CHD may be attributed, in part, to prematurity. The mortality risk is higher in LBW infants with CHD as compared to the optimal birth weight infants with CHD. The mortality for LBW infants undergoing surgery for CHD remains high. So, cardiac catheterization has been increasingly utilized to improve the outcome of these risky infants. Few studies involved a sizeable catheterization experience and showed an increased risk of mortality and morbidity in LBW infants. However, some studies reported that such complications were less likely to result in permanent sequelae. The aim of this study is to evaluate the in-hospital outcomes of interventional cardiac catheterization in infants weighing less than 2500g as compared to the infants weighing more than or equal to 2500g.

METHODS

This retrospective study included infants who have undergone interventional cardiac catheterization through the first 60 days of life. Patients were selected from New Children University Hospital, Cairo University, Egypt from January 2015 to January 2018. The study group included infants < 2500 grams while the comparative group included infants ≥ 2500 grams. Adverse events were classified according to the mechanism and seriousness.

The study group (37 patients) had a mean weight of 2.35 ±0.13 Kg, while the comparative group (164 patients) had a mean weight of 3.54 ±0.71 Kg. The procedures included balloon atrial septostomy, pulmonary balloon valvuloplasty, ducal arteriosus stenting and radiofrequency perforation of pulmonary atresia. The study group showed less success rates as compared with the comparative group (83.8% versus 93.9%, p = 0.04), and higher incidence of overall adverse events (48.6% versus 20.1%, p<0.001) as well as catheterization-related mortality (29.7% versus 4.9%, P<0.001). In the study group, pulmonary balloon valvuloplasty showed the highest incidence of major adverse events while ducal arteriosus stenting had the highest incidence of mortality.
January 2015 to January 2018. To study the effect of patients’ weight upon the results, they were divided into two groups: a study group including patients weighing < 2500g and a comparative group with patients weighing ≥ 2500g. Only life-threatening CHD cases that required interventional cardiac catheterization were included.

We excluded babies with associated extra-cardiac congenital anomalies and those with apparent syndromes or genetic disorders to exclude confounding factors that may contribute to the outcome rather than the patient weight. For the same reason, any case with sepsis, coagulopathy or arrhythmia was excluded.

The present study reports in-hospital outcomes. Any event from which injury occurred, potentially or definitely as a consequence of performing the catheterization was collected as an adverse event (AE). These AEs were classified as follows:

**According to the mechanism:**

i. Access-related: Hemothorax / pneumothorax, groin hematoma, pulse loss, bleeding from puncture site or vein thrombosis.

ii. Catheterization-related: arrhythmias, CNS event like seizures and inability to regain conscious level after anaesthesia, or sudden cardiac arrest.

iii. Balloon dilation-related: Balloon rupture, failure to pass through the stenotic lesion, heart block or heart perforation after balloon inflation.

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

**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.

In balloon atrial septostomy, the mean pressure gradient between the left and right atria should be less than 2–4mmHg to be a successful procedure. The radiofrequency perforation of the atretic pulmonary valve and balloon dilatation of critical pulmonary stenosis were considered successful if prostaglandin (PGE) was successfully discontinued with no need for any further interventions to augment the pulmonary flow during the same admission. In PDA stenting, angiography was performed to confirm good position and flow of the stent.

Mortality was counted as catheterization-related if it happened potentially or definitely as a consequence of performing the catheterization i.e. tamponade after rupture right ventricle outflow tract (RVOT). Mortality related to ICU events (e.g. sepsis, ventilator related, etc) was not counted as catheterization-related.

**Statistical methods:**

Numerical data were summarized using means and standard deviations or median and ranges and compared using Mann Whitney U test. Categorical data were summarized as numbers and percentages and compared using chi-square test or fisher exact test, if appropriate. All P values were two sided. P values less than 0.05 were considered significant.

**RESULTS**

A database was created to record the demographic data of the patients (table 1), the procedures done (table 2), the outcome (table 3), and the adverse events (AEs) related to these procedures (table 4).

The study group included 37 patients, while the comparative group included 164 patients. The demographic characteristics are shown in (table 1). None of the patients had any previous cardiac intervention.

Four procedures were performed; balloon atrial septostomy (BAS), pulmonary balloon valvuloplasty (PBV), ductus stenting and radiofrequency perforation of pulmonary atresia (table 2). Other manoeuvres like Aortic valve balloon dilatation and neonatal coarctation stenting have been done only in large babies during the study period, so not included.

The success rate of all the procedures in the study group was 83.8% while it was 93.9% in the comparative group, P = 0.04. The overall incidence of catheter lab related adverse events was significantly higher in the study group (48.6%) than in the comparative group (20.1%), P<0.001 (table 3). This included all cases of access, catheter manipulation, balloon and stent-related adverse events (table 4).

The overall incidence of access related adverse events was significantly higher in the study group being 32.4% while in the comparative group was 9.1%, P <0.001. Groin haematoma happened significantly more in the study group. Other AEs like external bleeding at the access site, deep vein thrombosis and weak dorsalis pedis pulse also were observed more in the study group (table 4).

Similarly, the overall incidence of catheter manipulation related adverse events was higher in the study group being 27% while in the comparative group is 8.5%, P 0.002. Sudden cardiac arrest with asystole had occurred in 4 patients weighing less than 2.5Kg (10.8%), but only one patient from the comparative group. Two of the four patients in the study group died on table. The others resuscitated and recovered. Other AEs like arrhythmias and seizures happened, again, more in the study group (table 4).

The results showed statistically significant difference in the overall incidence of balloon related AEs between the two groups being higher in the study group 13.5% and only 3.7% in the comparative group, P 0.017. Failure to cross the stenotic valve and myocardial perforation occurred more in the study group (table 4).

Moreover, the results showed statistically significant difference in the overall incidence of stent related adverse events between the two groups being higher in the study group 16.2% and only 4.9% in the comparative group, P 0.014. Failure to probe the PDA, stent malposition and stent thrombosis were more in the study group (table 4).

Regarding 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). Five of the eleven mortality cases in the study group were cases of PDA stenting. Those eleven patients had variable courses. Four patients had failed/thrombosed
or malposed stents, three patients had perforated myocardium and hemopericardium, two patients developed right-sided heart failure and cardiogenic shock, and two patients had a massive external haemorrhage. Infants with lesser weights stayed more in the ICU with a mean of 5.2 ± 5.9 days, while the heavier weight infants had lesser duration of stay with a mean of 2.9 ± 3.9 days.

Although statistical analysis for every single procedure was not possible because of the small sample size, some striking results had come up. Patients who underwent PBV showed a statistically significant higher incidence of major adverse events (55.6%) in the study group than in the comparative group (13%), \( P = 0.002 \). Moreover, PDA stenting in small weight infants showed a significantly higher mortality (50% versus 12.5%) than in the comparative groups, \( P = 0.019 \) (table 5).

DISCUSSION

Among all live births, CHDs are quite common, with a prevalence rate of 8-9 per 1000 live births (4). The mortality for LBW infants undergoing surgery for CHD remains high \((9)\). So, interventional cardiac catheterization has been utilized increasingly to enhance the outcome of these risky infants \((9)\).

In our study, 32.4% of the study group had access related complications while the percentage was only 9.1% in the comparative group, \( P < 0.001 \). In a similar study, access site bleeding that required blood transfusion happened in 5% of the study group patients who weighed less than 2500g \((10)\). The increased incidence of thrombotic events, in our study, was consistent with the findings of another prospective cohort study done on 50 neonates who had central venous catheter-related thrombosis and found that LBW was an independent risk factor \((11)\). Another study about venous thromboembolism in CHD patients 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 \((12)\).

As regard catheter manipulation adverse events, they happened in 27% of the study group, buy only 8.5% in the comparative group, \( P = 0.002 \). The increased risk of developing arrhythmias in the smaller group may be argued by the increased traumatic mechanical effect of the catheters and wires in smaller babies with smaller intracardiac rooms for manipulation than in larger ones. Karagoz et al in a similar study reported that 5% of patients weighing less than 2.5kg had supraventricular tachyarrhythmia \((10)\). Similar studies showed incidence of intra-procedural sudden cardiac arrest (asystole) to be 4.3% and 5% \((16,19)\).

The balloon related AEs were higher in the study group 13.5% and only 3.7% in the comparative group, \( P = 0.0017 \). In a study conducted on 12 infants in their first 60 days of age with critical pulmonary stenosis, failure to cross the valve happened in one patient (8.3%) while 2 patients (16.6%) complicated with cardiac perforation, one of them during PBV while the other during radiofrequency perforation of atretic pulmonary valve \((14)\). In a six-year study conducted on low birth weight infants which included 46 infants less than 2.5kg, no cardiac perforation cases were reported \((15)\).

Regarding stent-related AEs, the overall incidence was 16.2% in the study group and 4.9% in the comparative group, \( P = 0.014 \). The patients who got tortuous PDAs were not excluded and that may explain the increased incidence of PDA stenting adverse events. With respect to PDA stenting, a study done on 21 patients with mean weight 3.3kg reported overall complications in 4 patients (19%), malposed/embolised stents in 3 patients and thrombosed stent in 1 patient. However, the failure rate was reported in 4.7% \((15)\).

A study conducted on PDA stenting in 21 infants with the mean body weight 2.9 ± 0.35kg, 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 \((16)\). In another study, on infants with the mean body weight 3.3 ± 0.8kg, the failure rate was reported to be 7.7% \((2/26)\) due to the extreme tortuosity of the ductus \((17)\).

In a large study done on 106 infants with mean weight 2.9kg \((2.5-3.5)\), who had augmentation of the pulmonary flow either by surgical shunt or PDA stenting, one patient (0.94%) developed stent migration \((18)\). Stent thrombosis was reported in 2.7% of our study group and 1.2% of the comparative group, whereas Santoro et al reported in 8.3% patients \((11)\).

Looking at the aforementioned AEs, the overall incidence of catheter laboratory-related AEs was statistically higher in the study group \((48.6\%)\) as compared to the comparative group \((20.1\%)\), \( P < 0.001 \). Many factors were thought to be contributing to these numbers. The increased risk of central venous catheter-related thrombosis in low birth weight babies, not excluding cases with tortuous PDAs, and probably the relatively increased traumatic injury by hardware (catheters/wires) in smaller intracardiac rooms might have been contributing to that outcome. In a multi-center study about small weight as an independent risk factor for adverse events during cardiac catheterization of infants, Backes et al reported the incidence of adverse events being 20% of cases <2kg: 28%, 2.3kg: 25%, 3-5kg: 23%, ≥5kg: 16% \((19)\). In another study comparing the outcome of cardiac catheterization in infants weighing less than 1.5 kg with a larger comparative group, Sutton et al reported that the total complication rate was 56% in patients <1,500 g and 57% in the comparison patients 2000-3000 g \((20)\). Mobley et al, in a six-year-long study conducted on 46 LBW infants, reported that the overall incidence of complications was higher in neonates ≤2.5kg as compared with neonates >2.5kg \((34.8\%\) versus 17.6%) \((16)\).

Mortality rates were also significantly higher in the study group \((29.7\%\) versus 4.9%) than in the comparative group, \( P < 0.001 \). In a multi-center study, Backes et al reported mortality cases 7/57 (12%) in the <2kg group \((19)\). In another study on cardiac catheterization in infants weighing less than 1.5kg, Sutton et al reported that the catheterization related mortality incidence was 5/18 (27.7%) \((20)\). One more study that included infants weighing less than 2500g, reported the rate of mortality after invasive cardiac catheterization to range between 0% and 39% \((10)\).

Although statistical analysis for every single procedure was not possible because of the small sample size, PDA stenting and balloon pulmonary valvuloplasty of critical PS had shown significant differences between the study and comparative groups. The fact that the PDA tortuosity was not addressed as an exclusion criterion for stenting may explain the high mortality in this group of patients. As well, this may explain why Alwi and Mood, in their review about PDA stenting in duct dependent pulmonary blood flow, recommended that PDA stenting should be avoided in infants less than 2.5Kg \((21)\).

Limitations of the study:

Not all procedures were included due to lack of cases in babies less than 2.5kg. The small sample size of the study group made it sometimes not possible to do statistical analysis for each single procedure. Prematurity is an important determinant of the outcome in small neonates, but addressing this point was beyond the scope of the present study.
Conclusion and Recommendations:

Interventional cardiac catheterization in small weight infants is associated with a decreased incidence of success and an increased incidence of morbidity and mortality. Pulmonary balloon valvuloplasty in small weight infants with critical pulmonary stenosis is associated with a higher incidence of major adverse events with no significant increase in risk of mortality. PDA stenting is associated with increased mortality in small weight infants. Suggested strategies to improve the outcome of PDA stenting in small babies may be to let them gain some weight on intravenous prostaglandin infusion, exclude the cases with tortuous PDAs and encourage studies comparing the outcome of surgical versus intervention options in this fragile group of patients.

Ethical declaration:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.
### Table (1): Demographic characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Below 2.5kg</th>
<th>Above 2.5kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 37)</td>
<td>(n = 164)</td>
</tr>
<tr>
<td>Age (days)</td>
<td>Mean ±SD</td>
<td>15.6 ±13.6</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>10 (1 - 60)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male n (%)</td>
<td>20 (54.1)</td>
</tr>
<tr>
<td></td>
<td>Female n (%)</td>
<td>17 (45.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean ±SD</td>
<td>2.35 ±0.13</td>
</tr>
</tbody>
</table>

### Table (2): Different procedures done in the studied patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Below 2.5 kg (n=37)</th>
<th>Above 2.5 kg (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon atrial septostomy</td>
<td>14 37.8</td>
<td>59 36.0</td>
</tr>
<tr>
<td>Pulmonary balloon valvuloplasty</td>
<td>9 24.3</td>
<td>69 42.1</td>
</tr>
<tr>
<td>PDA stent</td>
<td>10 27.0</td>
<td>24 14.6</td>
</tr>
<tr>
<td>Radiofrequency perforation</td>
<td>4 10.8</td>
<td>12 7.3</td>
</tr>
</tbody>
</table>

PDA= patent ductus arteriosus

### Table (3): The overall outcome

<table>
<thead>
<tr>
<th></th>
<th>Below 2.5 kg (n = 37)</th>
<th>Above 2.5 kg (n = 164)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success rate</td>
<td>31 83.8</td>
<td>154 93.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Cath-lab related complications</td>
<td>18 48.6</td>
<td>33 20.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Catheter related mortality</td>
<td>11 29.7</td>
<td>8 4.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Cath-lab = catheter laboratory

*P values less than 0.05 considered significant
Table (5): Detailed statistics for each single procedure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>&lt;2.5 kg</th>
<th>≥2.5 kg</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Balloon atrial Septostomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major complications</td>
<td>2/14</td>
<td>14.3</td>
<td>1/59</td>
</tr>
<tr>
<td>Minor complications</td>
<td>2/14</td>
<td>14.3</td>
<td>5/59</td>
</tr>
<tr>
<td>Catheter related mortality</td>
<td>2/14</td>
<td>14.3</td>
<td>0/59</td>
</tr>
<tr>
<td>Pulmonary balloon valvuloplasty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major complications</td>
<td>5/9</td>
<td>55.6</td>
<td>9/69</td>
</tr>
<tr>
<td>Minor complications</td>
<td>6/9</td>
<td>66.7</td>
<td>7/69</td>
</tr>
<tr>
<td>Catheter related mortality</td>
<td>3/9</td>
<td>33.3</td>
<td>3/69</td>
</tr>
<tr>
<td>Pulmonary radiofrequency perforation</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Major complications</td>
<td>1/4</td>
<td>25.0</td>
<td>4/12</td>
</tr>
<tr>
<td>Minor complications</td>
<td>3/4</td>
<td>75.0</td>
<td>3/12</td>
</tr>
<tr>
<td>Catheter related mortality</td>
<td>1/4</td>
<td>25.0</td>
<td>2/12</td>
</tr>
<tr>
<td>PDA stent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major complications</td>
<td>7/10</td>
<td>70.0</td>
<td>9/24</td>
</tr>
<tr>
<td>Minor complications</td>
<td>6/10</td>
<td>60.0</td>
<td>10/24</td>
</tr>
<tr>
<td>Catheter related mortality</td>
<td>5/10</td>
<td>50.0</td>
<td>3/24</td>
</tr>
</tbody>
</table>

N= number of patients in each single procedure group, PDA= patent ductus arteriosus

*P values less than 0.05 considered significant
REFERENCES