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Paediatric heart transplantation — the impact of a ventricular assist device on operative outcomes

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Abstract

Background: The use of a ventricular assist device (VAD) is a life-saving option for patients with heart failure refractory to conventional therapy.

Aim: To assess the effect of VAD on outcomes of heart transplantation in children.

Methods: Between October 1988 and June 2009, a consecutive series of 95 children (mean age 8.6 ± 6.7 years, range 5 days–17.9 years) underwent heart transplantation: patients in group 1 (n = 11) received VAD as a bridge to cardiac transplantation (left ventricular VAD in 4, biventricular VAD in 7), and patients in group 2 (n = 84) underwent heart transplantation without previous cardiac support using VAD. The indication for heart transplantation was cardiomyopathy/myocarditis in 66 (69.5%) of children and congenital heart disease in 29 (30.5%) patients.

Results: Congenital heart disease was diagnosed more often in group 2 than in group 1 (p = 0.047). The two groups did not differ significantly with respect to age, weight and parameters of preoperative liver and kidney function (except for aspartate aminotransferase activity, p = 0.020). The mean waiting time for transplantation was 64.2 ± 87.4 days (range 1–443 days) and did not differ between the groups. The mean follow-up was 6.8 ± 5.4 years (range 1 day–17.6 years). Mortality during long-term follow-up was 9.1% (n = 1) in group 1 and 20.2% (n=17) in group 2 (p = 0.632). We found no significant differences in postoperative ventilatory support time (p = 0.773), duration of hospital stay (p = 0.853), and incidence of acute rejection episodes (p = 0.575).

Conclusions: The use of VAD as a bridge to heart transplantation in children with severe heart failure had no negative effect on treatment outcomes.

Key words: ventricular assist device, paediatric heart transplantation

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INTRODUCTION

Heart transplantation (HTx) is an established treatment of severe, resistant heart failure in children [1]. However, the availability of organs in this age group is very limited, and the waiting time before transplantation is much longer compared to adults and continues to increase [2]. Mortality in children waiting for HTx is much larger than in adults [3, 4]. Clinical experience from recent years shows that implantation of a ventricular assist device (VAD) is an effective method to keep the child alive during the waiting time [3, 5–7]. Ventricular assist devices used in children after cardiogenic shock allow return of normal organ function and increase the likelihood of successful HTx [8, 9]. Mechanical cardiac support is, however, associated with a risk of numerous complications including immunisation (due to transfusion of blood and blood products), mediastinal adhesions (due to sternotomy to

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Table 1. Pre- and postoperative parameters in the study group

	Group 1 (n = 11)	Group 2 (n = 84)	P
Preoperative parameters			
Age [years]	9.4 (1.3–17.0)	9.2 (5 days – 17.9)	0.564
Gender			
Males	7	49	
Females	4	35	0.992
Body mass [kg]	27.9 (8.9–69.6)	13.0 (3.3–60.8)	0.108
Cause of heart failure			
Cardiomyopathy/myocarditis	11	55	
Congenital heart disease	0	29	0.047
Creatinine [mg/dL]	0.5 (0.3–2.0)	0.6 (0.3–1.3)	0.633
Urea [mg/dL]	2.5 (18.0–75.0)	30.0 (8.0–162.0)	0.652
Bilirubin [mg/dL]	1.1 (0.4–12.9)	0.8 (0.1–2.1)	0.078
Aspartate aminotransferase [U/L]	39.0 (15.0–156.0)	25.0 (5.0–222.0)	0.020
Alanine aminotransferase [U/L]	17.5 (11.0–270.0)	22.0 (7.0–411.0)	0.825
Transplant waiting time [days]	33 (8–402)	42.5 (1–443)	0.931
Postoperative parameters			
Duration of ventilatory support [days]	3.0 (0.4–20.0)	2.5 (0.4–361)	0.773
Duration of hospital stay [days]	38.5 (23–68)	40 (19–390)	0.853
Acute rejection	1	18	0.575

implant VAD), and thromboembolic complications (anticoagulant treatment) that may affect HTx outcomes.

The aim of this study was to assess the impact of preoperative VAD implantation in children on the outcomes of paediatric HTx.

METHODS

Study group

We analysed retrospectively 95 children who underwent orthotropic HTx from October 1988 to June 2009. The study group included 56 (58.9%) boys and 39 (41.1%) girls aged from 5 days to 17.9 years (mean 8.6 ± 6.7 years). The body mass at the time of HTx ranged from 3.3 to 69.6 kg (mean 21.9 ± 17.1 kg). Indications for HTx included heart failure due to cardiomyopathy/myocarditis in 66 (69.5%) children or congenital heart disease in 29 (30.5%) children (18 of them underwent previous palliative or corrective surgery). Patients were divided into two groups: group 1 consisted of 11 children who required VAD implantation prior to HTx (VAD was used for the first time in March 1995), and group 2 consisted of 84 patients operated without previous mechanical cardiac support. The characteristic of the study group is presented in Table 1.

Types of VAD used

Two types of VAD were used for mechanical cardiac support: the Berlin Heart Excor system in 7 (63.6%) patients (Fig. 1) and the Medos system in 4 (36.4%) patients. The Berlin Heart system (Excor, Berlin Heart AG, Berlin, Germany) consists of a polyurethane ventricle (stroke volume of 10, 25, 30, 50 or 60 mL) with polyurethane valves, silicon cannulae and a motor unit (IKUS 2000) (Figs. 2, 3). Pulsative flow is generated with a pneumatic-electric drive. All blood contact surfaces are covered with heparin (Carmeda process Carmeda, Upplands Väsby, Sweden). The Medos HIA VAD system (Medos Medizintechnik AG, Stolberg, Germany) is also a pulsative, pneumatic system including a pump with a stroke volume of 10–80 mL. This is a non-heparinised system.

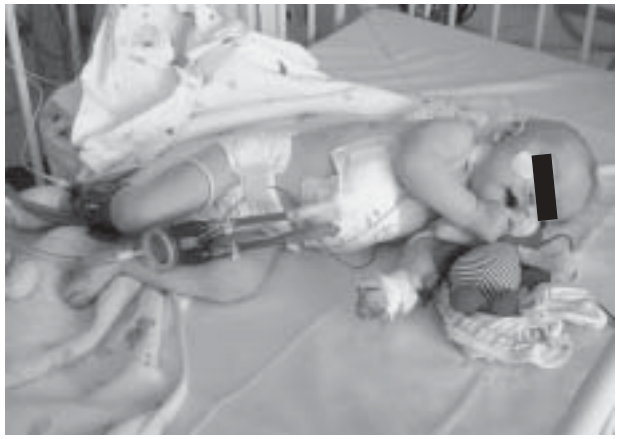

Figure 1. An 8-month infant with an implanted Berlin Heart Excor left ventricular assist device

Implantation technique

A uniform implantation technique of both systems was used in all children [10–12]. The right heart was supported by implantation of a VAD between the right atrium and the pul-

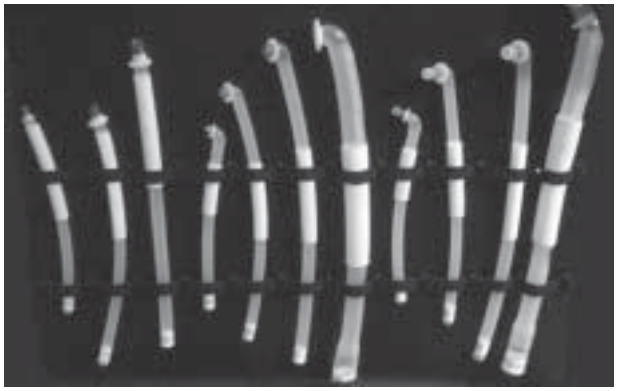

Figure 2. Cannulae of the Berlin Heart Excor system

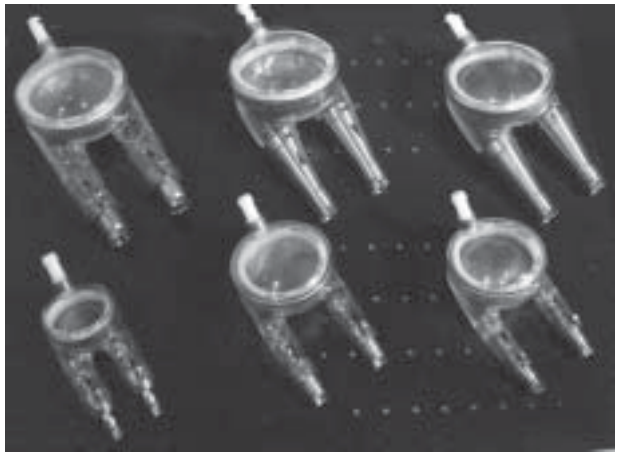

Figure 3. Artificial 10, 25, 30, 50, 60 and 80 mL ventricles available in the Berlin Heart Excor system

monary artery (RVAD), and the left heart was supported by implantation of a VAD between the left ventricle (apex) and the ascending aorta (LVAD). The use of biventricular assist device (BVAD) was necessary in 7 children, while LVAD was sufficient in 4 children. The decision on the extent of ventricular support was made intraoperatively, with initial implantation of LVAD and additional use of RVAD depending on the function of the right ventricle.

At the time of VAD implantation, all patients were in severe, decompensated heart failure that was intractable to medical treatment, with largely reduced peripheral perfusion, metabolic acidosis, the cardiac index below 2 L/min/m^2, venous blood saturation below 40%, and signs of incipient multiorgan failure. Extracorporeal membrane oxygenation (ECMO) was started during resuscitation in one boy 24 hours before VAD implantation. The median duration of mechanical circulatory support was 16.0 days (range 6 days to 15.1 months).

In children below one year of age, anticoagulation with continuous heparin infusion (target APTT 60–80 s) was used. Older children were given heparin for the first few days and subsequently they were switched to oral anticoagulants with target INR of 2.5–3.5. Acetylsalicylic acid was started in all patients after the first week of mechanical circulatory support. Anticoagulation protocol also included antithrombin III substitution if its level was below 70%.

Positive anti-HLA antibody level (patient immunisation) was defined as panel reactive antibodies (PRA) level more than 10%.

Heart was transplanted using the Shumway-Lower method [13]. Initial immunosuppressive treatment consisted of cyclosporine A, azathioprine and steroids (methylprednisolone). Tacrolimus replaced cyclosporine A in 1995, and mofetil mycophenolate replaced azathioprine in 1997. Doses of cyclosporine A, tacrolimus, and mofetil mycophenolate were adjusted to reach target levels of 250–300 ng/mL, 10–15 ng/mL and 2–4 μg/mL, respectively. Azathioprine was given in a daily dose of 0.1–2 mg, aiming for the leukocyte count above 4000/L. Transplant rejection was defined as grade III or higher in cardiac biopsy, and the child presented with heart failure signs or died. Renal failure was defined as the need for renal replacement therapy.

Statistical analysis

We analysed the following parameters: age, gender, body mass, parameters of hepatic and renal function immediately before HTx, cardiac transplant waiting time, complications after VAD implantation, the presence of anti-HLA alloantibodies, duration of ventilatory support following HTx, duration of hospital stay, rejection rate, post-transplantation complications, and survival.

Continuous variables are presented as means and standard deviation, or median and range if the variable was not normally distributed. Categorical variables are presented as percentages. Survival was analysed using the Kaplan-Meier method. The χ^2 test with the Yates correction and the Mann-Whitney U tests were used in the statistical analysis. A p value < 0.05 was considered statistically significant.

RESULTS

The two groups did not differ significantly in regard to indications for HTx ($p = 0.047$). Cardiomyopathy/myocarditis was the indication for HTx in all children in group 1 and in 55 (65.5%) children in group 2, and the remaining patients in group underwent HTx due to a congenital heart disease. Age, body mass and parameters of hepatic and renal function immediately before HTx did not differ significantly between the groups, except for serum aspartate aminotransferase activity ($p = 0.020$). The mean waiting time for transplantation was 64.2 ± 87.4 days (median 34 days, range 1–443 days) and did not differ between the two groups ($p = 0.931$) (Table 1).

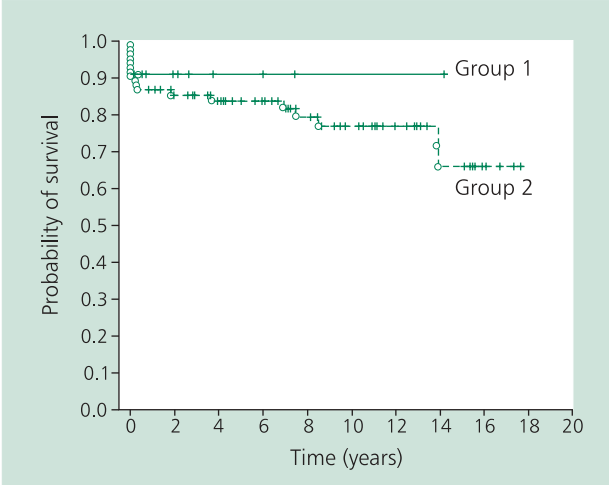

Figure 4. Kaplan-Meier survival curves

The most frequent complication following VAD implantation was bleeding. Reoperation for bleeding was necessary in 5 (45.5%) children. The VAD replacement due to occurrence of a thrombus in the device pump was performed in 3 (27.3%) patients. One (9.1%) child suffered from ischemic stroke and femoral artery embolisation necessitating surgical revision.

The presence of anti-HLA alloantibodies due to immunisation was found in only 3 (3.6%) children in group 2.

Duration of follow-up after HTx was 6.8 ± 5.4 years (range 1 day to 17.6 years). We found no significant differences between the groups in postoperative ventilatory support time ($p = 0.773$), duration of hospital stay ($p = 0.853$), and incidence of acute rejection episodes ($p = 0.575$) (Table 1). Mortality during post-HTx follow-up also did no differ between the two groups and was 9.1% (n = 1) in group 1 and 20.2% (n = 17) in group 2 ($p = 0.632$). Survival curves in the two groups are presented in Figure 4. The cause of death of the single child in group 1 was failure of the transplanted heart. In group 2, 8 (9.5%) children died due to acute transplant rejection, 5 (5.9%) children due to failure of the transplanted heart, one (1.2%) child due to lymphoma, and 3 (3.6%) children died suddenly due to unknown causes.

In group 1, one child required early reoperation due to bleeding. The most common late complications in group 1 included hypertension (n = 3, 27.3%), renal failure (n = 2, 18.2%), and arrhythmia (n = 2, 18.2%).

In group 2, the most common early complication was cardiac tamponade (n = 7, 8.3%). Late complications included renal failure in 16 (19.0%) children (including 1 child treated with kidney transplantation), arrhythmia in 11 (13.1%) children (including 5 children requiring pacemaker insertion), hypertension in 10 (11.9%) children, cytomegaly virus infection in 9 (10.7%) children, and transplant coronary vasculopathy in 4 (4.8%) children (with repeated HTx in 3 of them). In 2 (2.4%) children, a lymphoma with associated Ebstein-Barr virus infection was diagnosed, leading to death of one patient.

DISCUSSION

First commercially available miniaturised VAD (Berlin Heart) for newborns and infants were introduced in the early 1990s [5, 11, 12, 14]. However, the most commonly used approach of mechanical cardiac support in children remains the use of ECMO, which may completely replace cardiac and pulmonary function, may be rapidly started, is relatively inexpensive and easily available, and is an established modality of mechanical cardiac support for a period of up to several weeks [3, 6, 7].

Currently available paediatric VADs have many advantages over ECMO. Mechanical cardiac support with a VAD may be used for a much longer time, requires less intensive anticoagulation, results in less haemolysis, does not require strict continuous surveillance, the patient may be extubated and is not bedridden [3, 6, 7, 9, 14–16]. All these factors contribute to better child comfort and safety during the waiting time for transplantation. Current waiting time for an appropriate donor is much longer than the safe duration of mechanical cardiac support with ECMO [8].

The use of VAD allows significant improvement or even return of normal function of internal organs damaged due to cardiogenic shock, resulting in optimised patient condition before the transplantation. All patients in this study were critically ill at the time of VAD implantation and improved significantly thereafter. Our finding show that nearly all parameters of organ function in children supported with VAD did not differ compared to patients who underwent HTx without prior VAD support. Thus, mechanical cardiac support with VAD allows organ function regeneration.

Our study shows that survival of children treated with HTx who were previously supported with VAD dose not differ compared to HTx patients who did not require such support. These findings have been confirmed by other investigators [8, 9].

Previous cardiac surgery is an important factor in early and late outcomes following HTx [8]. Implantation of VAD requires sternotomy and transfusion of blood and blood products. On the other hand, children waiting for HTx often undergo cardiac surgery due to a congenital heart disease. These patients also require sternotomy and transfusion of blood products. It seems there is no difference in the risk of immunisation and associated rejection risk when patients undergoing VAD implantation or surgery due to congenital heart disease are compared [7, 17]. Our findings also suggest that mechanical cardiac support with VAD does not result in an increased risk of immunisation compared to patient who underwent HTx without prior VAD implantation.

Outcome studies regarding the use of VAD in children showed that survival to transplantation ranges from 76% to 86% [3, 6, 7, 9]. The highest mortality was seen 2 weeks following

VAD implantation [9]. Many authors noted that the use of VAD in children with congenital heart disease was associated with higher mortality and more complications compared to children with cardiomyopathy or myocarditis [7–9, 18]. We could not verify these findings as dilated cardiomyopathy was the indication for HTx in all our patients supported with VAD.

CONCLUSIONS

The use of pneumatic pulsative cardiac support system is a life-saving treatment for children in cardiogenic shock, allowing complete regeneration of organ function prior to HTx. Mortality and complication rates following HTx in children supported with VAD were similar compared to children who did not require such support.

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Transplantacja serca u dzieci — wpływ sztucznych komór serca na wyniki operacyjne

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Streszczenie

Wstęp: Transplantacja serca jest uznaną metodą terapii opornej na leczenie zachowawcze niewydolności serca u dzieci. Dostępność organów w tej grupie wiekowej jest jednak bardzo ograniczona, a czas oczekiwania na dawcę nadal się wydłuża. Wszczepienie sztucznych komór serca jest skutecznym sposobem na utrzymanie dziecka przy życiu w czasie oczekiwania na transplantację. Mechaniczne wspomaganie krążenia wiąże się jednak z ryzykiem licznych powikłań, takich jak: immunizacja, zrosty w śródpiersiu i powikłania zatorowo-zakrzepowe, które mogą istotnie wpływać na wyniki transplantacji.

Cel: Celem pracy była ocena wpływu przedoperacyjnego zastosowania sztucznych komór na wyniki transplantacji serca u dzieci.

Metody: Retrospektywnej analizie poddano 95 dzieci, u których w okresie od października 1988 roku do czerwca 2009 roku wykonano ortotopowe przeszczepienie serca. Wśród badanych było 56 chłopców i 39 dziewczynek, w wieku od 5 dni do 17,9 roku (śr. 8,6 ± 6,7 roku), o masie ciała w chwili transplantacji 3,3–69,6 kg (śr. 21,9 ± 17,1 kg). Wskazaniem do transplantacji była niewydolność serca w przebiegu: kardiomiopatii/zapalenia mięśnia sercowego u 66 (69,5%) dzieci i wrodzonej wady serca u 29 (30,5%) dzieci. Pacjentów podzielono na dwie grupy: grupę 1 stanowiło 11 dzieci, które przed transplantacją serca wymagały wszczepienia sztucznych komór, a grupę 2 — 84 pacjentów bez uprzedniego mechanicznego wspomagania krążenia. W celu mechanicznego wspomagania krążenia stosowano dwa rodzaje sztucznych komór serca: Berlin Heart Excor u 7 (63,6%) i Medos u 4 (36,4%) pacjentów. U wszystkich dzieci stosowano standardową technikę implantacji systemów: prawe serce wspomagano, wszczepiając sztuczną komorę między prawy przedsionek a tętnicę płucną (RVAD); lewe — włączając sztuczną komorę między lewą komorę (koniuszek) a aortę wstępującą (LVAD). Dwukomorowego wspomagania wymagało 7 dzieci, a u 4 wystarczało wspomaganie tylko lewej komory. Mediana czasu mechanicznego wspomagania krążenia wynosiła 16,0 dni (od 6 dni do 15,1 miesięcy).

Wyniki: Struktura obu grup pod względem wskazań do transplantacji serca (kardiomiopatia/zapalenie mięśnia sercowego *v.* wrodzona wada serca) różniła się istotnie (p = 0,047). Wiek, masa ciała i wartości wskaźników wydolności wątroby oraz nerek bezpośrednio przed transplantacją (z wyjątkiem stężenia aminotransferazy asparaginianowej w osoczu, p = 0,020) nie różniły się między grupami. Średni czas oczekiwania na serce wynosił 64,2 ± 87,4 dnia (mediana: 34 dni, 1–443 dni) i nie różnił się w zależności od badanej grupy (p = 0,931). Najczęstszym powikłaniem po wszczepieniu sztucznych komór było krwawienie. Z tego powodu 5 dzieci wymagało reoperacji. Obecność alloprzeciwciał anty-HLA będących wynikiem immunizacji stwierdzono tylko u trojga dzieci z grupy 2. Czas obserwacji pacjentów po transplantacji serca wynosił 6,8 ± 5,4 roku (1 dzień – 17,6 roku). Nie wykazano istotnych różnic między grupami pod względem czasu sztucznej wentylacji po transplantacji (p = 0,773), okresu hospitalizacji (p = 0,853) czy częstości odrzutu przeszczepu (p = 0,575). Śmiertelność po transplantacji w okresie obserwacji nie różniła się między grupami i wynosiła 9,1% (n = 1) w grupie 1 i 20,2% (n = 17) w grupie 2 (p = 0,632).

Wnioski: Zastosowanie pneumatycznie napędzanego, pulsacyjnego systemu wspomagania krążenia przyczynia się do ratowania życia dzieci będących w stanie wstrząsu kardiogennego i umożliwia pełną regenerację wydolności narządów. Śmiertelność i częstość powikłań po transplantacji serca u dzieci, u których wspomagano układ krążenia za pomocą sztucznych komór, jest podobna jak wśród dzieci, u których nie zastosowano wspomagania krążenia.

Słowa kluczowe: sztuczne komory serca, transplantacja serca u dzieci

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