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Original Article

Home Milrinone Therapy for Paediatric Advanced Heart Failure Patients: A Canadian Single-Centre Experience

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ABSTRACT

Background: End-stage heart failure (ESHF) is the primary reason for heart transplantation in children with cardiomyopathy. Despite optimizing oral heart failure (HF) medications, some paediatric patients progress to ESHF, necessitating mechanical circulatory support and/or transplantation. Continuous milrinone intravenous support has been used to bridge paediatric patients to transplant. This study aimed to review and report the safety and outcomes of our home milrinone therapy (HMT) programme.

Methods: This single-centre, retrospective cohort study included paediatric patients discharged on HMT between 2001 and 2022. Data were collected from the SickKids HF Database. Outcomes of interest included frequency and indications for rehospitalization, catheter-related complications, and outcomes at the conclusion of therapy.

Results: Thirty-six patients were included, with a median age of 3.6 years and a median weight of 13.1 kg at HMT initiation. HMT was used as a bridge to transplantation (58%) recovery/candidacy (22%), palliative care (17%), and surgical repair (3%). The median duration on HMT was 88 days. Twenty-four patients (67%) were readmitted at least once with a total of 70 admissions, primarily due to central line-related issues (35%) and worsening HF (32%). Among patients discharged as a bridge to transplant, 52% were admitted from home for transplant, whereas 33% required readmission until transplant. No deaths were directly related to HMT.

RÉSUMÉ

Contexte : L'insuffisance cardiaque (IC) terminale est la principale cause des greffes cardiaques chez les enfants atteints de cardiomyopathie. Même si la médication orale pour l'IC a été optimisée, cette affection évolue jusqu'au stade terminal chez certains patients pédiatriques, nécessitant une assistance circulatoire mécanique (ACM) et/ou une greffe. L'assistance continue par administration intraveineuse de milrinone est utilisée comme traitement de transition chez les enfants en attente d'une greffe. Cette étude visait à évaluer l'innocuité et à rendre compte des résultats de notre programme de traitement à domicile par la milrinone.

Méthodologie : Cette étude de cohorte rétrospective monocentrique comprenait des patients pédiatriques ayant reçu leur congé puis traités par la milrinone à leur domicile entre 2001 et 2022. Les données proviennent de la base de données sur l'IC de SickKids. Les critères d'évaluation d'intérêt étaient la fréquence et les indications des réhospitalisations, les complications liées au cathéter et les résultats à la fin du traitement.

Résultats : Trente-six patients ont été inclus, l'âge médian étant de 3,6 ans et le poids médian de 13,1 kg au début du traitement à domicile par la milrinone. Ce traitement a été utilisé comme transition en attendant la greffe (58 %)/le rétablissement/la candidature à la greffe (22 %), comme soin palliatif (17 %) et pour la réparation chirurgicale (3 %). La durée médiane du traitement à domicile par la

End-stage heart failure (HF) is the most common indication for heart transplantation in children with cardiomyopathy.[1] The reported incidence of HF in paediatric patients is 0.97-7.4 per 100,000,[2] of which, approximately 1-2/1000 live births are due to congenital heart defects (CHD) such as complex single ventricle disease or other palliated CHD.[1,3] Despite optimizing oral HF medications, some patients progress to end-stage HF refractory to medical treatment, necessitating the need for mechanical circulatory support (MCS) and/or transplantation. Paediatric patients listed for heart transplantation face the highest waitlist mortality among the solid organ transplant population.[4,5] Although paediatric data are scarce, continuous intravenous (IV) inotropic support has been shown to be a safe and effective method of bridging both adult and paediatric patients to transplant.[6,7] Ambulatory IV inotropes are often used as a bridge to the above treatments or as a

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Conclusions: HMT is a safe and effective method for supporting children with ESHF. This therapy allows children to return to their home environment.

milrinone était de 88 jours. Vingt-quatre (67 %) patients ont été réhospitalisés au moins une fois, pour un total de 70 hospitalisations, principalement en raison de problèmes liés au cathéter veineux central (35 %) et à une aggravation de l'IC (32 %). Parmi les patients ayant reçu leur congé et recevant le traitement en attendant la greffe, 52 % ont été admis à l'hôpital pour recevoir la greffe, alors que 33 % ont dû être réhospitalisés en attendant la greffe. Aucun décès n'a été directement lié au traitement à domicile par la milrinone.

Conclusions : Le traitement à domicile par la milrinone est une méthode sûre et efficace pour soutenir les enfants atteints d'IC terminale. Ce traitement permet aux enfants de retourner dans leur environnement familial.

palliative measure for those who elect against or are not eligible for transplant.[8,9]

Among the various IV inotropes used in advanced HF refractory to guideline-directed medical therapy (GDMT), milrinone has been the most widely used partly given to its vasodilatory properties and lower risk of arrhythmogenic events, compared with other inotropes.[10] In the paediatric population, there is great familiarity with milrinone, as it is widely used in cardiac acute and critical care units and has been shown to prevent low cardiac output syndrome in children after heart surgery.[11] Milrinone is a competitive phosphodiesterase-III inhibitor with both inotrope and vasodilatory properties with minimal chronotropic effects, and thus colloquially referred to as an "inodilator." It decreases the breakdown of cyclic adenosine monophospate in cardiac and smooth muscle cells, increasing calcium influx, and in turn, increasing cardiac contractility and vasodilation in both systemic and pulmonary circulations.[12]

The use of milrinone reduces hospitalization time[13] and costs along with providing a better family experience.[14] In our institution, a home milrinone therapy (HMT) programme has been used in selected patients with the aim of having those patients return to their home or local environment, thereby reducing stress on families and improving quality of life.[13] In this study, we sought to review and report the safety and outcomes of HMT at the largest paediatric programmes taking care of children with advanced HF in Canada.

Methods

Study design and data collection

This was a single-centre, retrospective cohort study including all patients younger than 18 years (2001-2022) discharged from the Hospital for Sick Children (SickKids), Toronto, on HMT. Data were collected from the SickKids Heart Failure Database, which included the primary diagnosis, goal of HMT, dose, concentration and rate of medication delivery, type of vascular access line, reason for rehospitalizations, and end point for HMT (heart transplant, recovery, worsening HF, or death). The study was reviewed by the Institutional Research Ethics Board, and the need for individual consent was waived given that this was a retrospective study using deidentified patient information.

Inclusion criteria

All patients discharged from the Cardiology Ward at SickKids on milrinone between July 2001 and July 2022 were included in this study. Patients were considered for HMT if they had vital signs within their normal or acceptable limits for 48 hours and did not require any modifications to other medications within that time frame. Care providers demonstrated competence in vascular access care. Patients living more than 2 hours away from the hospital found temporary accommodation within that distance.

Outcomes

Outcomes of interest included the frequency and indications for rehospitalization on HMT; catheter-related complications, including line occlusion, infection, and exchange; and clinical outcomes at conclusion of therapy, including transplant, recovery, worsening HF, or death.

Statistical analysis

Categorical data were expressed as percentages and continuous data as median (interquartile range [IQR]). Because of a limited sample size, statistical analyses were not performed, and the study was limited to descriptive data.

Pharmacy/concentration

The concentration of milrinone infusion was set at the minimum rate, which would ensure line patency to avoid volume overload and line blockage. Patients <15 kg started at 3 mL/h and patients >15 kg started at 4 mL/h. The drug concentration was adjusted to the minimum infusion rate to maintain central line patency. Milrinone was supplied by 1 of 2 pharmacies depending on geographic location. One pharmacy provided a 48-hour supply and the other a 24-hour supply.

Results

Thirty-six patients on HMT were identified from the SickKids HF Database during the study period. Sixteen patients (44%) were male, and the median age at HMT initiation was 3.6 years (IQR: 0.9-11.5 years) and the median weight was 13.1 kg (IQR: 8.4-34.1 kg). Twenty patients (56%) had CHD and 16 (44%) had cardiomyopathy. Of the patients discharged on HMT, 21 (58%) were discharged as a bridge to transplantation, 8 (22%) were discharged as a bridge

Table 1. Baseline characteristics of advanced heart failure paediatric population

Characteristic	Median (IQR)	n (%)
Total enrolled		36 (100)
Age (y)	3.6 (0.9-11.5)	
Weight at initiation (kg)	13.1 (8.4-34.1)	
Male sex		16 (44)
Diagnosis		
Congenital heart disease		20 (56)
Cardiomyopathy		16 (44)
Goal of HMT		
Bridge to transplant		21 (58)
Bridge to recovery/candidacy		8 (22)
Palliative care		6 (17)
Bridge to surgical repair		1 (3)

HMT, home milrinone therapy; IQR, interquartile range.

to recovery/candidacy, 6 (17%) were discharged as part of a palliative care goal, and 1 (3%) was discharged as a bridge to eventual surgical repair (Table 1). The median milrinone dose at initiation of HMT was 0.5 mcg/kg/min (IQR: 0.46-0.5 mcg/kg/min), the median infusion rate was 4.0 mL/h (IQR: 3.0-4.0 mL/h), and 35 (97%) patients used a peripherally inserted central catheter as their primary mode of access for milrinone. The remaining patient was placed on milrinone for optimization before cardiac surgery for CHD and was therefore discharged with a peripheral IV for 3 days to spend the holidays at home.

Twenty-four (67%) patients were readmitted to hospital at least once during their time on HMT for a total of 70 readmissions. The median number of readmissions was 2 (IQR: 1-3) with a median duration of 2 days (IQR: 1-6 days), excluding 7 children who remained admitted until outcome. Of the 70 admissions, 17% were discharged on the same day. However, it should be noted that 2 patients with single ventricle physiology accounted for 20 of the readmissions. The most common cause for readmission was central line related (25 admissions, 36%). Of those, 19 were for line exchange, 3 were for instillation of tissue plasminogen activator due to line blockage, and there were 3 line-related infections (Fig. 1). There were 23 readmissions for worsening HF; most required an increase in their milrinone dose and were subsequently discharged, with 7 patients (19%) remaining in hospital until transplant, all of whom received ventricular assist devices (VADs). One patient suffered an out-of-hospital cardiac arrest due to ventricular fibrillation with a background of failing Fontan circulation and a pacemaker. This patient was then found to have a mechanical valve thrombus and underwent mechanical valve replacement. Eleven admissions (16%) were related to other reasons (planned cardiac catheterization, planned surgical intervention, pacemaker reprogramming, gastrostomy tube insertion, seizure, feeding intolerance, and potential heart transplant that was not able to move forward) and 10 (14%) were related to viral illnesses.

The median duration of HMT to outcome was 88 (IQR: 45-200) days. Of the 21 patients discharged as a bridge to heart transplant, 15 received a transplant at the study end point. Eleven of the 21 (52%) patients remained on HMT until transplant, 7 (33%) required readmission due to worsening HF and remained in hospital until transplant, and 3 had recovery of their function and were removed from the active heart transplant waitlist. Regarding the 6 palliative patients, the median survival time was 105 (36-296) days. Three of the 5 patients discharged as a bridge to recovery were transitioned from HMT to GDMT for HF management as outpatients; the other 2 did not recover and were listed for transplant. These patients remained on HMT until the time of transplant. Two of the 3 patients discharged as a bridge to transplant candidacy were listed for heart transplant and admitted from home for transplant; the third patient recovered and was transitioned from HMT to GDMT. The patient discharged as a bridge to cardiac surgery underwent successful operation and weaned from milrinone postoperatively (Table 2).

Discussion

HMT is an established method of supporting some children with end-stage HF who may otherwise be confined to hospital. Over 75% of patients in our HMT cohort were successfully bridged to their initial goal for HMT. Three quarters of the patients required at least 1 readmission to hospital for line-related events or worsening HF and were subsequently discharged on HMT. The use of HMT demonstrated acceptable safety and efficacy in bridging to heart transplantation, recovery, or ongoing palliation. Moreover, there exists the potential for cost saving to the health care system for supporting with HMT vs the cost of several HF hospitalizations and the associated acuity. Care for children with end-stage HF in the ambulatory care setting also allowed for them to return home surrounded by family and resume a lifestyle closer to their normal. This has further implications on growth and development of patients with end-stage HF and minimizes stress caused by prolonged hospitalization on the rest of the family including childcare arrangements and separation from siblings.

Evidence supporting the use of IV inotropic support among the paediatric population is lacking. Despite this, the Canadian Cardiovascular Society Guidelines (2013)[15] and the International Society for Heart and Lung Transplantation Guidelines (2014)[16] endorse the use of IV inotrope support in paediatric patients with refractory HF, despite GDMT, as a bridge to left ventricular unloading, mechanical support device, or heart transplantation. The International Society for Heart and Lung Transplantation Guidelines (2014)[16] has also endorsed the use of inotrope support for palliative therapy.

Focusing on HMT for those with New York Heart Association class III/IV HF in the paediatric population, the body of evidence supporting the use of IV milrinone in an outpatient ambulatory setting in refractory HF paediatric population has been growing over the past decade. Several small-sized studies documented the feasibility of HMT in the paediatric population.[14,17,18] Moreover, Birnbaum et al.[19] reported the safety and efficacy of IV ambulatory milrinone in a cohort of 106 paediatric patients, of whom 67% successfully transitioned to heart transplantation. Several case series reported the success rates of bridge to heart transplantation while on IV inotropes to range from 83% to 86%.[17–19]

A significant number of children (19%) in our cohort eventually required MCS in the form of VAD implantation. Over the past few years, the use of MCS in paediatric HF has

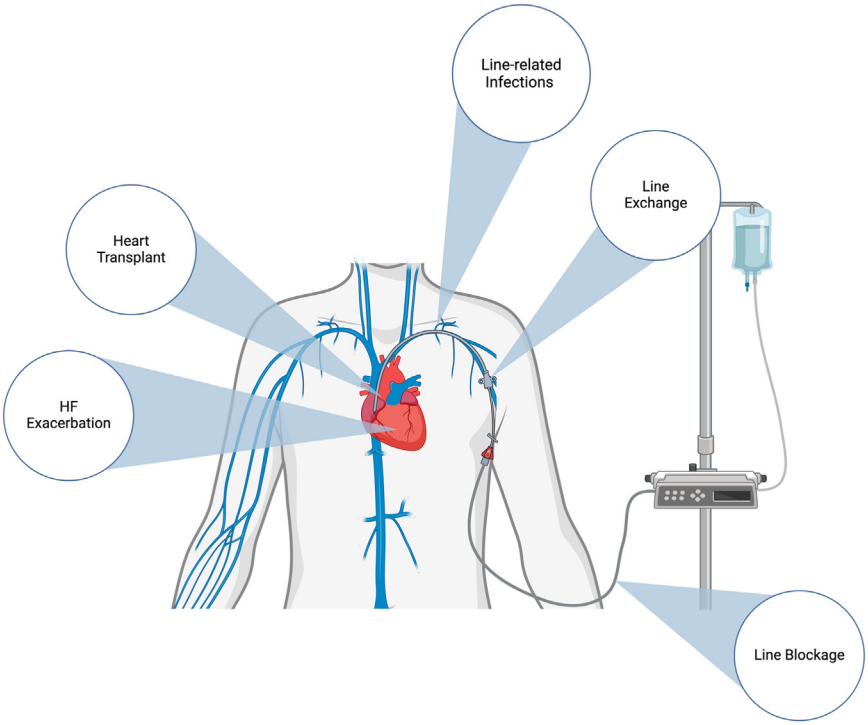

Figure 1. Common causes of admission for patients on home milrinone therapy. Figure created with BioRender.com

been rising, especially in children <25 kg.[20,21] The use of HMT may be especially useful in smaller children to allow growth to a size that permits durable VAD implantation.

Key issues related to milrinone use in the ambulatory setting include infections to central lines, recurrent hospitalizations, dose adjustments in the setting of impaired renal function, and increased risk of arrhythmias and sudden death.[22,23] The likelihood of such risk has been significantly lower in the paediatric population. Our study demonstrates that almost no patients suffered an arrhythmogenic event or sudden cardiac death, in line with previous studies supporting the low incidence of arrhythmogenic-induced sudden cardiac death in the ambulatory IV milrinone cohort.[19,24] Furthermore, reducing duration of hospital stay has a significant impact on child development and reduction of family stress. It allows children to return to school and resume a modified normal lifestyle and gives them the opportunity to interact with other children in their age group. It also has implications on siblings who may have reduced time with the parents and the implications prolonged hospitalizations have on childcare arrangements. This has been shown in similar home-based therapies for other medical conditions.[25] Hansson et al.[26] compared hospital-based vs home-based chemotherapy for children with cancer and showed that the home-based group had significantly improved quality of life and patient-reported physical health.

The notion behind the application of ambulatory inotropes as bridge therapy lies in trying to mitigate longer hospital stay in patients awaiting transplant with the added benefit of allowing for a more convenient approach trying to minimize HF readmission. Despite such efforts, there remains a group of HF paediatric patients more liable to worsening HF despite HMT and GDMT, eventually requiring escalating IV inotropes or mechanical support due to worsening symptoms and hemodynamics. Several reports demonstrated that up to half of the patients on HMT have been readmitted at least once throughout their wait time period,[14,17–19] with HF exacerbation and access-related infections being among the most common causes of readmission.

Table 2. Outcomes of home milrinone therapy

	n (%)	Median (IQR)
Patients readmitted	24 (67)	
Admissions per patient		2 (1-3)
Total admissions	70 (100)	
Central venous line	25 (36)	
Exchange	19	
Blockage	3	
Infections	3	
Heart failure exacerbation	23	
Viral illness	10	
Ventricular fibrillation arrest	1	
Others*	11	
Outcomes at the end of therapy		
Duration to outcome		88 (45-200)
Transplant	15	109 (45-151)
Recovery	7	254 (137-404)
Readmission	7	66 (51-76)
Palliative (death)	6	105 (36-296)
Surgical repair	1	7

IQR, interquartile range.

*Non–home milrinone therapy–related admissions (planned cardiac catheterization, planned surgical intervention, pacemaker reprogramming, gastrostomy tube insertion, seizure, feeding intolerance, and potential heart transplant that was not able to move forward).

Limitations

Several limitations are worth noting. The study was single-centre and included only 36 patients. We are unable to generalize the study conclusions to a larger and different population. We also acknowledge the inherent limitations of a retrospective, observational study design. The study was also not geared towards detailed cost analyses to determine the benefit of HMT over conventional, in-hospital, care.

Conclusions

HMT is a safe and effective method to bridge paediatric patients with advanced HF to heart transplant, recovery, or palliation. There were no deaths directly related to HMT. Although HMT is associated with a high rate of admission, it allows patients to develop in their home environment, attend school, and maintain a somewhat normalized lifestyle.

Ethics Statement

The study was reviewed by the Institutional Research Ethics Board.

Patient Consent

The need for individual consent was waived given that this was a retrospective study using deidentified patient information.

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Disclosures

The authors have no conflicts of interest to disclose.

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