Intravenous Home Inotropic Use is Safe in Pediatric Patients Awaiting Transplantation

Birnbaum et al: Pediatric Home Inotrope Use

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Abstract

Background—Intravenous inotropic therapy can be used to support children awaiting heart transplantation. Although use of this therapy is discouraged in adults due to poor outcomes, its use in children, particularly outpatient, has had limited evaluation. We aimed to evaluate the safety and efficacy of this practice.

Methods and Results—A retrospective analysis of an intent to treat protocol was completed on UNOS status 1A patients discharged on inotropic therapy from 1999 until 2012. Intravenous inotropic therapy was initiated for cardiac symptoms not amenable to oral therapy. Patients who were not status 1A or required more than 1 inotrope were excluded. Efficacy was analyzed by time to first event: transplantation; readmission until transplantation; improvement leading to inotrope withdrawal; or death. Safety included analysis of infection rates, line malfunctions, temporary hospitalization, neurologic events and arrhythmias. 106 patients met inclusion criteria. The mean age was 10.1 ± 6.4 years, 47% of patients had congenital heart disease, and 80% of these patients had single ventricle physiology. In patients without congenital heart disease, 53% had dilated cardiomyopathy. 91% of patients received milrinone. 85% of patients underwent transplantation. 8% of patients successfully weaned from support as outpatients, while 6% died. 50% of patients were readmitted prior to transplantation or weaning from support, of which 64% required only 1 readmission. The majority of readmissions were for heart failure.

Conclusions—Outpatient intravenous inotropic therapy can be safely utilized as a bridge to transplantation in pediatric patients. A minority of patients can discontinue inotropic therapy due to clinical improvement.

Key Words: pediatric, heart transplantation, inotropes, safety
Inotropic therapy in adults with heart failure (HF) is recommended only in patients in acute decompensated heart failure with reduced cardiac output, and discontinuation should be reassessed regularly. Several studies in the adult population have shown this therapy to potentially be harmful to patients with worse outcomes while on inotropic therapy compared to no intravenous inotrope use. The pediatric heart failure population uses this therapy as a bridge to transplantation, in part due to the limited availability of ventricular assist devices (VADs) in children. Although many patients on inotropic therapy are clinically unstable, a subset of this population may safely await transplantation at home. Previous studies have evaluated the use of intravenous inotropic therapy in children in the ambulatory setting (AI). Although these studies contained only a small number of patients, the therapy did appear to be safe and effective. We aimed to better characterize the safety and efficacy of AI in children awaiting heart transplantation.

**Methods**

**Patient Selection:** After receiving Institutional Review Board approval with a waiver of informed consent from Washington University School of Medicine, a retrospective analysis of an intent to treat protocol with AI was completed. Beginning in 1999, we developed a protocol for the discharge of patients on inotropic therapy. Inclusion criteria included patients listed as United Network for Organ Sharing (UNOS) Status 1A, cardiac symptoms that were not amenable to maximum oral heart failure therapies, and were stable in the hospital on single inotrope support for 1 week. Maximal tolerated oral heart failure therapies, including beta blockers and angiotensin converting enzyme inhibitors, were continued on all patients while initiation of inotropic therapy took place. A central venous line was inserted in all patients for inotrope...
infusion. Exclusion criteria were if the patent was not listed as a Status 1A, or were not clinically stable on a single inotrope.

At time of discharge from the hospital, all patients with a chest circumference of at least 66cm without an implantable cardioverter defibrillator (ICD) were fitted for a LifeVest external automatic defibrillator (Zoll Inc., Pittsburgh, PA) and patient and family education were completed. Home healthcare support, including nursing, was available to all patients to assist the patient and their family with medication administration. Home healthcare support was also responsible for dressing changes that were not performed during clinic visits. Patients discharged from the hospital remained local for at least 1 week. Following this period, patients were allowed to return home without geographic restriction, which in some cases was more than 4 hours away by private vehicle. All patients discharged on AI were evaluated every 1-2 weeks in clinic until transplantation. Outpatient evaluation included panel reactive antibodies every 3 months in patients with elevation in their panel reactive antibodies or every 6 months without, a basic metabolic panel and albumin every 4 weeks, telemetry from the LifeVest, pacemaker or (ICD) at each visit, and vital signs including weight at each visit. In patients who did not tolerate high dose oral heart failure therapies at the time of AI initiation, these therapies were maximized while on AI. Weaning of AI was attempted if the patient had achieved high dose oral heart failure therapy and was NYHA functional class I. Patients successfully weaned from inotropic therapy were removed from listing.

*Analysis-Efficacy:* Efficacy of AI was defined based on the outcome following discharge, and included transplantation, permanent readmission to the hospital until transplantation, weaning
from inotropic support and death. The time to each of these outcomes was determined. Patient characteristics evaluated included age at discharge, ventricular physiology (single ventricle vs. two ventricle), etiology of their cardiac disease (congenital /structural vs. cardiomyopathy), inotrope used, gender, previous cardiac surgeries, and presence of other medical diagnoses.

**Analysis-Safety:** Safety of AI was defined based on the readmission rate as well as adverse events that occurred. Adverse events that were analyzed included line infections, exit site infections, other infections, line malfunctions, bleeding, thromboembolic events, arrhythmias, neurologic events and cardiac arrest. Line infections were based on a positive blood culture. Exit site and other infections were diagnosed clinically. Line malfunctions included any problem with the line, including line occlusion or dislodgement. Arrhythmias were determined by interrogation of the LifeVest, pacemaker or ICD for patients with these devices. Escalation of therapy to mechanical ventilatory or circulatory support was also evaluated.

**Statistical Analysis:** Age at listing was reported as mean +/- standard deviation and other categorical clinical characteristics were reported as percentages. Heart transplantation, permanent hospitalization, inotropic discontinuation and death were analyzed as the competing outcomes after listing. Standard Kaplan-Meier analysis was used to estimate the freedom from central line problems and mechanical circulatory/ventilatory support. A competing risk Fine-Gray model was used with proportional hazard regression to determine the risk factors of permanent hospitalization, inotropic discontinuation, and death after taking inotropes. Hazard ratios (HR) with 95% confidence intervals (CI) were reported. A value of P≤0.05 was used to
determine statistical significance. All statistical analyses were performed with SAS 9 software (SAS Institute, Cary, NC).

**Results**

*Patient Population:* From 1999 to 2012 there were 110 total discharges involving 106 total patients listed for orthotopic heart transplantation while on inotropic therapy. Four patients who were discharged initially were able to wean from inotropic medications within the first 4 weeks of discharge and not require re-initiation of inotropic therapy for at least 6 months after weaning. These four patients subsequently required reinitiation of inotropic therapy. Only the second initiation of AI is included in the analysis.

The mean age in our population was 10.1 years (± 6.4 years, range 0.2–26.0 years). 6% of patients were less than 1 year of age, 23% were between 1 and 5 years of age, 23% between 5 and 10 years of age and 49% were greater than 10 years old. 50% of patients were male, and all patients were listed as UNOS status 1A.

47% of patients carried a congenital/structural diagnosis with 80% of those patients having single ventricle physiology. For patients with heart failure from non-structural causes, 53% were from dilated cardiomyopathy, 15% from restrictive cardiomyopathy with reduced cardiac output, 6% from anthracycline toxicity, 6% were from arrhythmias, 6% were from myocarditis, 4% from hypertrophic cardiomyopathy with reduced left ventricular ejection fraction, 4% from left ventricular non-compaction, 4% from repeat transplantation, 2% from trauma and 2% with Becker Muscular Dystrophy. 91% of patients were on milrinone, with the remainder on
dobutamine. 53% of patients had a peripherally inserted central line, 42% had a Broviac catheter, and in 5% of patients the type of line was not specified. A LifeVest was given to 23% of patients, 3% of patients had an ICD in place, 11% had a pacemaker already in place. One patient with a pacemaker was also given a LifeVest. One patient received a Holter monitor while on AI therapy. 63% of patients did not have an ambulatory monitoring of their rhythm due to patient size.

**Efficacy:** Of the 106 patients discharged on AI, the first outcome was transplantation in 71 patients (67%), hospitalization until transplantation in 19 (18%), weaning of intravenous inotropic support in 9 (8%), death in 6 (6%) and 1 patient remains stable on AI awaiting transplantation 432 days following discharge. Thus, 90 patients total (85%) underwent transplantation after discharge home on AI. A cumulative incidence function was used to estimate the incidence in the first year for permanent hospitalization 0.179 (standard error = 0.037), weaning from inotropes 0.085 (0.027), and death 0.057 (0.022).

In patients who underwent transplantation without requiring readmission until transplantation, the median time to transplantation was 42 days (4-323 days). Including patients who required re-hospitalization until transplantation, the median time to transplantation was 47 days (4-323 days).

In patients requiring permanent re-hospitalization, 2-ventricle physiology was a risk factor in comparison to single ventricle physiology (hazard ratio 3.65, 95% confidence interval 1.10-12.11, p=0.035). Age, gender, etiology of heart failure and previous cardiac surgery were not
found to be risk factors (Table 1). Median time to permanent readmission was 38 days (3-113 days). All patients that required readmission until transplantation were readmitted for worsening heart failure. Of these 19 patients, 13 patients were placed on a second inotrope, while 5 had an increase in their inotropic infusion and 1 patient was initiated on nesiritide. A total of 12 patients required mechanical ventilatory support, and an additional 7 patients received a ventricular assist device. Two of these patients required ECMO prior to their ventricular assist device placement. Freedom from mechanical ventilatory and/or circulatory support is shown in Figure 1.

Death occurred in 6 patients (6%) before transplantation following discharge on AI. The median time to death in this group was 40 days (3-82 days). Causes of death included progressive heart failure in 3 patients, and sudden cardiac death, plastic bronchitis and influenza infection in 1 patient each. Two ventricle physiology was found to be protective (hazard ratio 0.113, 95% confidence interval 0.01-0.94, p=0.043, while age, gender, underlying cause of heart disease and previous cardiac surgery were not found to be risk factors (Table 2).

Weaning from AI was attempted in all patients on optimal oral medical therapy, and 9 patients (8%) were able to ultimately wean from AI. The median time to weaning from AI was 32 days (5-198 days). Age, gender, etiology of heart disease, previous cardiac surgery and ventricular physiology did not predict ability to wean from AI (Table 3). In this subgroup of patients, 8 (89%) have remained transplant free at a median follow up of 6.3 years (range 101 days to 12.0 years). The other patient ultimately underwent transplantation after being re-listed without reinitiation of AI therapy at 421 days following initial discharge on AI.
Safety: The safety profile of AI in our cohort was also analyzed. Events that were considered included temporary and permanent hospitalizations, infections both related and unrelated to intravenous access, intravenous line malfunctions, arrhythmias, central nervous system (CNS) events, non-CNS thromboembolic events and clinically significant non-CNS bleeding. Line malfunctions included occlusion requiring thrombolytic therapy, line leaking or the line becoming dislodged. Clinically significant bleeding events were defined as bleeding that required hospital admission. In addition, in patients with a LifeVest, pacemaker or ICD, or ambulatory Holter monitoring, frequency of arrhythmias requiring hospitalization or a change in therapy was also assessed.

Fifty-three patients (50%) were readmitted a total of 83 times following discharge on AI. The frequency of readmissions is shown in Figure 2. Of the patients readmitted, 67% required only 1 readmission, and an additional 22% had 2 readmissions. The median total time of re-hospitalization for all readmissions combined was 12 days (range 1-80 days). For patients who ultimately underwent transplantation, there were 4.8 readmissions per patient year from discharge on AI to transplantation. The majority of readmissions were for worsening heart failure, accounting for 64% of all readmissions (Figure 3). In patients temporarily readmitted for worsening heart failure, intravenous diuretics, increased single inotrope infusion rates, and/or the addition of a second inotrope was used to improve their clinical status. Weaning of the second inotrope and reduction to oral diuretic therapy was completed prior to consideration for discharge following readmission. Other common reasons for readmission included infections (17% of readmissions) and line malfunctions (13% of readmissions).
There were 13 total infections in our patient cohort. Seven (7%) of these were not directly related to the central line. These included one each of herpes zoster, influenza, sinusitis, viral upper respiratory infection, viral gastroenteritis, culture negative endocarditis and pneumonia. There were 5 (5%) line infections and 1 (1%) exit site/skin infection. A total of 8 patients (8%) required antimicrobial therapy for treatment of their infection.

Line malfunctions occurred 11 times in 6 patients (6%). One patient required PICC line replacement 4 times following initial discharge home, meaning the other 5 patients had a total of 7 line malfunctions. The overall freedom from line events, including both malfunctions and infections, is shown in Figure 4.

One patient suffered cardiac arrest immediately upon presentation to our emergency department from home while on AI. She ultimately survived and was able to undergo transplantation. One patient developed ventricular tachycardia resulting in a defibrillation from her LifeVest while hospitalized following readmission. One additional patient suffered a cardiac arrest due to the LifeVest competing with the pacemaker. This patient was a 17 year old with heterotaxy palliated with a Fontan operation. No other clinically significant arrhythmias were detected in our patients with a LifeVest, ICD, pacemaker, or with Holter monitoring or following readmission. Thus only 2 of the 106 patients (2%) had clinically significant arrhythmia while on inotropic therapy.
In our entire cohort, no patients developed a clinically significant CNS event while on AI, while either at home or during re-hospitalization. In addition, there were no clinically significant bleeding events or thromboembolic events in our patient cohort.

Discussion

The most recent ACC/AHA guidelines for adults specify that intravenous inotropic medications are reasonable in patients with stage D HF that is refractory to goal directed medical therapy and who are eligible for and awaiting mechanical circulatory support or cardiac transplantation (Class IIa recommendation)\(^1\). Long-term support is reasonable in select patients with stage D heart failure who are not eligible for mechanical support or transplantation (Class IIb). Long term support is not recommended in patients other than for palliative care, and may be potentially harmful. In addition, their use in patients without severe systolic dysfunction, low blood pressure or impaired perfusion with reduced cardiac output may also be harmful\(^10-12\). One major factor contributing to mortality in adults with heart failure is arrhythmias\(^13,14\), which are potentiated with the use of inotropic medications\(^15-17\).

The use of AI in adults has also been studied\(^1-4,18-20\). Although these studies are smaller, they did show that AI are feasible in the adult population. There is a reduced cost associated with AI compared with continued inpatient inotropic treatment\(^3,18\). However, as with inpatient treatment, mortality in the outpatient setting is substantial\(^19\). In particular, AI may be well suited in the adult population for palliative care in allowing patients to be discharged from the hospital who otherwise could not be, and may potentially reduce re-hospitalizations in this patient population\(^21\).
These limitations have contributed to the increased use of MCS in the adult patient. MCS in adults is used as a bridge to transplantation, bridge to candidacy or as destination therapy (Class IIa recommendation). These devices lead to improved functional status and quality of life in this patient population, and have shown improved outcomes compared to optimal medical therapy. However, MCS is not without complications. Bleeding requiring transfusion both from the pump site and from arteriovenous malformations in the gastrointestinal tract and nasal mucosa is not uncommon. In addition, cerebral hemorrhage causes substantial morbidity and mortality, regardless of the type of MCS device used.

In addition to the risk of bleeding, there is a substantial risk of pump thrombosis. Recently there appears to have been an increase in pump thrombosis events in patients on MCS. There are a variety of reasons for this increase, including changes in anticoagulation management, patient factors, increasing use of MCS in patient populations not included in the original studies, better recognition of potential pump thrombus, changes in surgical technique and minor changes in the hardware itself.

There has been very limited analysis of AI in pediatric patients. In the study by Price and colleagues, seven patients awaiting transplantation were discharged on AI. There was a reduction in the number of emergency department visits and admissions after starting inotropes as compared to before starting inotropes. Six of the seven patients were successfully bridged to transplantation at a median duration of 10 weeks. A total of five complications occurred, all of which involved the indwelling intravenous catheter.
In the other study by Berg et al\textsuperscript{7}, a total of 14 patients with end stage heart failure were discharged home. Six of these patients were listed for transplantation, while the other eight were discharged on AI for palliative care. Of the six discharged while awaiting transplantation, five underwent transplantation, and the final one was still awaiting transplantation. For the entire cohort of 14 patients, there were a total of 26 hospital readmissions, and similar to our study the majority (58\%) were for acute decompensated heart failure. Catheter infections accounted for 15\% of readmissions, which is slightly higher than in our cohort. There were also 6 (23\%) readmissions for infections not directly related to the indwelling catheter.

While adults with heart failure are at high risk for sudden cardiac death\textsuperscript{13,14}, this risk has not been realized in the pediatric population\textsuperscript{32}. This was apparent in our study as well, as only one patient suffered a cardiac arrest that could be attributed to inotropic therapy, and one patient developed ventricular tachycardia while hospitalized. This was terminated with defibrillation by the external defibrillator.

Mechanical circulatory support is now available for children\textsuperscript{33}. Although many of these patients are not eligible for discharge from the hospital, adolescent patients with continuous flow VADs can be discharged while awaiting transplantation. However, such devices can have significant complications, including strokes and thrombus formation\textsuperscript{33,34}. Given the high incidence of neurologic complications with device therapy, the use of AI may continue to find use. This appears to be a significant advantage in our cohort, as no patients on ambulatory inotropic therapy suffered from a significant neurologic complication.
A substantial minority of our patients were also able to wean from inotropic therapy. This has not previously been described in the pediatric population, and there has been only limited evaluation in the adult population\(^35,36\). It is not unexpected that pediatric patients should have a higher likelihood of weaning from inotropic therapy, as previous studies have shown some cardiomyopathies are more likely to improve in the pediatric population than in adults\(^37\). Further investigation is warranted to assess which patients are more likely to wean from inotropic therapy.

Limitations of our study are that it is a single center, retrospective, observational study. No control group was available as all patients stable on a single intravenous inotrope were considered for discharge. The most appropriate control group would be patients on stable inotropic support who remained hospitalized for non-medical (i.e. social) reasons. This patient population does not exist at our institution as all patients listed for transplantation have a thorough social work evaluation, and any concerns are addressed prior to listing for transplantation. Another potential control group would be patients on VADs. These patients are inherently more ill and remain hospitalized until time of transplantation. We also did not evaluate the cost effectiveness of this approach, in part because the study encompassed a relatively long time frame. Seemingly the cost of outpatient therapy should be lower than with inpatient therapy.

Conclusion

In summary, AI therapy as a bridge to cardiac transplantation is practical in pediatric patients. The majority of patients successfully undergo cardiac transplantation with a low incidence of
adverse events, and many patients are able to separate from inotrope dependence. A prospective, randomized, multicenter study should be considered to better delineate which patients are ideal candidates for AI therapy.

Sources of Funding

Statistical support provided with use of internal funds.

Disclosures

None.

References


Table 1. Risk factors for permanent hospitalization after taking inotropes

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<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (%95 Confidence interval)</th>
<th>P value</th>
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<tr>
<td>Age, year</td>
<td>1.03 (0.96 to 1.09)</td>
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<td>Male vs. Female</td>
<td>1.52 (0.62 to 3.73)</td>
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<td>Congenital Heart Disease vs. Acquired</td>
<td>0.77 (0.31 to 1.88)</td>
<td>0.563</td>
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<tr>
<td>With 2 ventricles, %(n)</td>
<td>3.65 (1.10 to 12.11)</td>
<td>0.035</td>
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<td>Surgery related to cardiology, %(n)</td>
<td>0.85 (0.34 to 2.14)</td>
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Table 2. Risk factors for death after taking inotropes

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<td>Age, year</td>
<td>0.906 (0.78 to 1.05)</td>
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<td>Male vs. Female</td>
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<tr>
<td>Congenital Heart Disease vs. Acquired</td>
<td>5.900 (0.71 to 48.79)</td>
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<td>With 2 ventricles, %(n)</td>
<td>0.113 (0.01 to 0.94)</td>
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<tr>
<td>Surgery related to cardiology, %(n)</td>
<td>3.019 (0.35 to 26.07)</td>
<td>0.315</td>
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Table 3. Risk factors for inotropes D/C after taking inotropes

<table>
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<th>P value</th>
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<td>Age, year</td>
<td>.902 (0.77 to 1.05)</td>
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<tr>
<td>Male vs. Female</td>
<td>1.323 (0.36 to 4.86)</td>
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<tr>
<td>Congenital Heart Disease vs. Acquired</td>
<td>0.310 (0.06 to 1.49)</td>
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<td>With 2 ventricles, %(n)</td>
<td>5.095 (0.65 to 40.13)</td>
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<tr>
<td>Surgery related to cardiology, %(n)</td>
<td>0.423 (0.10 to 1.75)</td>
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Figure Legends

Figure 1. Freedom from mechanical support.

Figure 2. Number of readmissions by patient. The majority of patients requiring readmission were readmitted only 1 time prior to transplantation or discontinuation of inotropes.

Figure 3. Causes of readmissions. Most readmissions were for worsening heart failure. Infections, including non-central line related infections were second most common followed by line malfunctions.

Figure 4. Freedom from line problems, defined as line infections or malfunctions requiring medical care, in patients discharge on ambulatory inotropes.
Readmission: 67%

Readmissions:
- 22%
- 9%
- 2%
- 1%

Circulation: Heart Failure
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Worsening Heart Failure 64%
Infection 17%
Line Malfunction 13%
Other 6%
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