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Clinical question

Management of Pediatric Emergencies: Current Evidence from Cochrane/ other Systematic Reviews

Clinical Question : Which agent/s for CCF?

Rashmi Ranjan Das, Kamaldeep Arora

Abstract

Although digoxin has played a major role in the therapy of congestive heart failure, its narrow therapeutic index, limited published data on efficacy in children, and the widespread availability of newer drugs like Angiotensin Converting Enzyme inhibitors, has made clinicians questioning the role of digoxin in the present day management of heart failure in children. In this article we have tried to focus on the literature available on the use of these two agents either alone or in combination with other agents and have tried to come up with practical recommendations that are specific to a particular physiologic state.

Key words: Cardiac failure; Cardiac glycosides; Digoxin; ACE inhibitor.

Case scenario

You have been called to manage a 5-month old infant who presented to the emergency department with history of interrupted feeding, sweating over forehead, recurrent pneumonia, and growth failure. On examination, the infant appears listless with respiratory distress and sweating over forehead; his vitals - HR 180/min, RR 60/min, BP 64/36 mmHg, SpO2 94%, and CFT = 4 sec; has cool peripheries; bounding peripheral and central pulses; systemic examination – grade 4 pansystolic murmur, mild chest retractions, fine crepitations over both the lung fields, and liver enlarged 4cm below right costal margin.

After initial stabilization and decongestive measures (diuretics), his vitals are - HR 160/min, RR 52/min, BP 64/40mmHg, and CFT = 3 sec; no crepitations on auscultation, liver 2cm below right costal margin

Now that the infant has improved and there is an underlying cardiac lesion, you are required to start an agent alone or in addition to diuretics to improve his cardiac performance. The questions that come to your mind at this point would be

1. Does this child require a cardiac glycoside or vasodilator or both?
2. If yes, which agent should I start with - Digoxin or ACE inhibitor?
3. What is the current consensus on the use of either of these agents ?
4. Are there any guidelines for the management of congestive cardiac failure with regard to use of vasodilators?

You decide to review the available literature for providing the best therapeutic approach for this child.

INTRODUCTION

In children, the main causes of congestive cardiac failure (CCF) include congenital heart diseases and cardiomyopathies. For a long time there has been a controversy regarding use of digoxin in infants with heart failure secondary to large left-to-right shunts.[1–4] On the other hand, vasodilator therapy in a similar condition has shown to be beneficial in improving the ventricular performance as well as circulatory congestion, depending on baseline hemodynamics.[5,6] Studies have clearly demonstrated that vascular tone plays a critical role, and manipulation of the tone affects hemodynamics in large ventricular septal

Author's Affiliations: Department of Pediatrics, All India Institute of Medical Sciences, New Delhi.

Reprints Requests: Rashmi Ranjan Das, Senior Research Associate, Department of Pediatrics, AIIMS, New Delhi.

Email: rrdas05@gmail.com

defects (VSD's). Digoxin's inability to substantially influence morbidity and mortality in adults eliminates any ethical mandate for its use. As a result, without parallel trials, it would also not be unethical to prescribe Digoxin for the treatment of persistent symptoms after the administration of drugs that do reduce the risk of death and hospitalization (e.g., ACE inhibitors).[7] Based on adult data which support use of ACE inhibitors as first line drugs and digoxin to be used only if symptoms persist the WHO Essential Medicines List for children (EMLc 2007) has included ACE inhibitor as additional treatment option for children. However the evidence supporting or refuting the use of ACE inhibitor or comparing the two is scarce in children. In the light of this, we decided to review the evidence available on the use of these two drugs in children and suggest possible therapeutic options based on the underlying physiology.

ACE inhibitor/ Digoxin

Evidence

There is no published literature comparing the efficacy and safety of ACE inhibitors versus digoxin in pediatric population. There is only one Cochrane systematic reviews on digoxin for heart failure in adult participants. However there are several small uncontrolled studies examining the acute hemodynamic effects of digoxin in children with cardiac failure due to large left-to-right shunts and several observational studies on the efficacy and safety of ACE inhibitors in children. Therefore we shall discuss the literature available on these two drugs individually and try to reach a consensus regarding the same. Digoxin

Till date, there is only one Cochrane review on the use of digoxin in heart failure - by Hood et al. [8]

The objectives of the review were (a) to examine the effectiveness of digitalis glycosides in treating heart failure (HF) in patients with normal sinus rhythm, (b) to examine the effect of digitalis in patients taking diuretics and ACE inhibitors, patients with varying severity and duration of disease; patients with prior exposure to digitalis versus no prior exposure; and patients with "HF due to systolic dysfunction" versus "HF with preserved ejection fraction."

METHODOLOGY

Included were randomized placebo-controlled trials of adult patients of >18 years age of either sex with symptomatic HF who were studied for seven weeks or more. Excluded were trials in which the prevalence of atrial fibrillation was >2%, or in which any arrhythmia that might compromise cardiac function or any potentially reversible cause of HF such as acute ischemic heart disease or myocarditis was present. The focus of this review was on mortality, hospitalization, and clinical status.

RESULTS

Thirteen randomized controlled trials mostly comprising adult patients were included. The data showed no evidence of a difference in mortality between treatment and control groups, but that digitalis therapy is associated with a lower rate of hospitalization and of clinical deterioration, slight increase in risk of arrhythmic deaths. There is no equivalent systematic review looking at the role of digoxin in pediatric cardiac failure and the significance of the conclusions of the Cochrane review for children is unclear, especially given the differing etiology.

CONCLUSION

The author concluded that digitalis may have a useful role in the treatment of patients with cardiac failure who are in normal sinus rhythm. New trials are needed to elucidate the importance of digitalis dosage, and its usefulness in the era of beta-blockers and ACE

inhibitors shown to be effective in treating cardiac failure.

Other systematic reviews

No other systemic reviews were found in children either on individual agents (digoxin or ACE inhibitor) or comparing digoxin versus ACE inhibitor as the first line agent. However, small uncontrolled studies examining the acute hemodynamic effects of digoxin in children with cardiac failure due to large left-to-right shunts showed conflicting results (Table 1).[2-4] There are no data on the efficacy of digoxin in heart failure in children with LV systolic dysfunction or valvular regurgitations and no data on long-term survival in any of these studies. Despite the lack of data in children, digoxin continues to be used by most clinicians in the management of pediatric heart failure due to various causes which includes - widespread availability, low cost, and continued confidence in the usefulness of the drug based on long years' of experience.

Table 1: Studies on use of digoxin in pediatric age group

Year	Author	Subjects	N	Methods	Results	Conclusion
1983	Berman et al [2]	Infants (mean age, 2.7 months) with a VSD	21	Prospective study, used digoxin alone.	Only 6 patients had an inotropic response, but the drug was of clinical benefit to 12 infants (including these 6).	Not all infants benefit from digoxin. Furthermore, in some subjects clinical improvement occurs in the absence of a measurable inotropic response.
1991	Kimbal et al [3]	Infants with symptoms of congestive heart failure due to a VSD	19	Prospective study to determine if digoxin increases "contractility" when added to diuretic therapy; and improves symptoms.	Digoxin + diuretics: contractility index was significantly greater than in control subjects (P = 0.04). Diuretics alone (after discontinuation of digoxin): contractility index was no longer different.	Contractility index was significantly greater than in control subjects. However, neither diuretic alone or in combination with digoxin improved symptoms significantly.
1999	Seguchi et al[4]	Infants with large VSD from 2 to 12 months age.	41	Prospective study to clarify how digitalis changes Rs and Rp and intracardiac hemodynamics in infants with large VSD.	Left atrial or PAWP decreased in patients with lower baseline Rs, whereas it was elevated in patients with higher baseline Rs. The change in Qp was positively correlated with baseline Rs and Rp (p = 0.001). The change in the Qp/Qs ratio, accordingly, was positively correlated to baseline Rs and Rp (p = 0.001).	In a large VSD, intravenous digitalis may act adversely by increasing pulmonary blood flow, with an elevation in PAWP in infants with a rather severe condition, but it is beneficial in less severe cases.

PAWP-pulmonary artery wedge pressure, Rs- systemic vascular resistance, Rp- pulmonary vascular resistance, Qp-pulmonary blood flow, Qs-systemic blood flow.

ACE inhibitors

Till date, there is no Cochrane review on the use of ACE inhibitors in heart failure.

There are several randomized trials on the use of ACE inhibitors for the management of cardiac failure in adults that consistently shows reduction of symptoms, morbidity and mortality.[9,10] But there are no similar trials in children with cardiac failure. Several small observational studies have proven the efficacy and safety of these drugs and in children, the ACE inhibitors which have been most studied are captopril and enalapril. The key studies on the use of ACE Inhibitors in children with cardiac failure are summarized in Table 2.[6,11-19] In common with experiences in adults, a number of children treated with ACE inhibitors experienced deterioration in renal function and hypotension. On the basis of the available data, a recent review of use in pediatric practice concluded that myocardial dysfunction should be treated with ACE inhibitors, mild moderate valvular insufficiency is effectively treated with ACE inhibitors and large left to right shunts should be surgically treated, unless surgery is not appropriate, when an ACE inhibitor should be used.[20]

Table 2: Studies on use of ACE inhibitors in pediatric age group

Year	Author	Subjects	N	Methods	Key findings and comments
1988	Shaw et al[11]	Age: infants. Underlying Left-to-right shunt and HF	20	Prospective study	Clinical improvement in most patients, four developed renal failure or hypotension. Improvements in weight gain and respiration rate reported.
1989	Frenneaux et al[12]	Age: 4 days to 12wks. Underlying VSD and HF	6	Prospective study	Clinical improvements in all patients, improvements in body weight and feeding
1990	Stern et al[13]	Age: 4wks to 15yrs. Underlying DCM	12	Prospective study	Improvements in haemodynamic effects.
1991	Eronen et al[14]	Age: 1.8yrs to 11.2yrs. Underlying CM and HF	8	Prospective study	Persistent clinical improvement after one year, with decreased heart size reported.
1991	Bengur et al[15]	Age: 3months to 18yrs. Underlying CM (congestive & restrictive)	16	Prospective study	May benefit children with congestive CM and probably should not be used in children with restrictive CM (cause acute hypotension).
1992	Sluysmans et al[16]	Age: infants. Underlying VSD and HF	8	Prospective study	Clinically effective and well tolerated in all patients
1992	Webster et al[17]	Age: 6months to 15yrs. Underlying intra-cardiac shunts	26	Prospective study	May benefit HF associated with large VSDs and normal or mildly elevated pulmonary resistance. There were no adverse effects
1993	Lewis et al[6]	Age at treatment: 3.6 +/- 0.6 years. Underlying DCM	27	Prospective study	Significantly improved survival over first two years, trend towards this continued thereafter.
1994	Leversha et al[18]	Age: 9days to 17.2yrs. Underlying LV dysfunction with HF	63	Prospective study	58% of patients improved, 30% had no improvement and 12% had side-effects. Three patients died with cardiac/renal failure.
2000	Mori et al[19]	Age: 3months to 16yrs. Underlying MR/AR with LV volume overload	24	Prospective study	Long-term treatment is effective in reducing not only LV volume overload but also LV hypertrophy in children with LV volume overload.

CM - cardiomyopathy, DCM - dilated cardiomyopathy, HF - heart failure, MR-mitral regurgitation, AR-aortic regurgitation, LV-left ventricle.

Having reviewed the limited evidence available on the two agents the following recommendations can be made:

1. In most cases of heart failure, digoxin can be combined with a diuretic and an ACE inhibitor.
2. Digoxin is the first choice if heart failure is associated with tachyarrhythmias such as supraventricular tachycardia (SVT), atrial flutter and atrial fibrillation (AF).
3. Role of digoxin in heart failure secondary to left-to-right shunt lesions, where systolic function of the myocardium is preserved, is not well defined.
4. ACE inhibitors are the first choice if there is heart failure due to ventricular dysfunction (e.g., idiopathic dilated cardiomyopathies), valvular regurgitation and secondary to large left to right shunts, if the systemic vascular resistance is elevated at the baseline.
5. Avoid using ACE inhibitors in acute decompensated heart failure.

Applying evidence to practice:

Both digoxin and ACE inhibitors are useful for CHF in the index case. But as the child is having underlying VSD causing heart failure, he should be started on ACE inhibitor and monitored to see the effect of therapy and for any worsening of symptoms. If the symptoms are uncontrolled, digoxin can be added to both diuretic and ACE inhibitor.

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Table 3: Class of recommendation of digoxin and ACE inhibitors in heart failure[21]

Drug	Preserved systolic function Left-to-right shunt	MR/AR	Ventricular dysfunction	Pressure overload	Right Ventricular dysfunction
Digoxin	IIa	IIa	I (symptomatic)	III	IIa
ACE inhibitor	IIa	I	I	III	I

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