Influence of Metoprolol on Systolic and Diastolic Function in Children with Heart Failure

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Abstract: The aim of this study was to assess the effect of metoprolol on cardiac function in children with heart failure. This randomized double-blind placebo controlled clinical trial was performed in children with heart failure due to left ventricle volume overload structural heart disease such as VSD, PDA, AI and MR who referred to pediatric cardiology clinics in sari in 2007. The patients divided into case and control groups. All cases were matched as viewpoints of age, sex, weight, kinds of primary disease and cardiac drugs (except for metoprolol). Metoprolol with single daily dose of 1 mg kg⁻¹ and placebo were given to patients in case and control groups respectively. Echocardiography with cardiac indices of systolic and diastolic function was done as baseline and monthly for 3 months in all the patients. Data were analyzed using SPSS software and statistical t-test. Thirty patients (16 cases and 14 controls) were enrolled in the study. CI, MPI and dv/dt (dt) decreased significantly at first month. Significant changes in LVEF and EFSS appeared on the second month and in E wave and E/A appeared on the third month. The results were in favor of systolic and diastolic improvement. Metoprolol caused improvement of cardiac systolic and diastolic function in children with heart failure due to cardiac defect. Therefore, metoprolol is recommended in patients with heart failure in above mentioned diseases that have not been controlled adequately in spite of receiving standard cardiac failure drug therapy such as an inotrope, a diuretic and a vasodilator agent.

Key words: Metoprolol, cardiac systolic, diastolic function, pediatrics

INTRODUCTION

Congestive Heart Failure (CHF) is a clinical syndrome resulted from structural or functional cardiac disorders that decrease ventricular capacity to fill or contract (Hunt et al., 2005). Despite recent advance in pharmacological therapy, it remains a devastating disease with considerable adverse economic impact (Bristow et al., 2003). These facts are the motivation to find the additional proper drugs and effective therapy. Beta blockers block the sympathetic nervous system at the receptor level. There is much evidence that they can have positive outcomes on mortality, morbidity and quality of life in patients with mild to moderate heart failure (and severe in fewer studies). Long term effects on beta blockers include an increase in stroke volume. Cardiac output and exercise intolerance and a decrease in the number of hospitalization, sudden death and other symptoms of disease (Delea et al., 2005; Sauls and Rone, 2005; Reiter, 2004; Adams, 2004; Palazzuoli, 2005). There are several studies examined two main groups of beta blockers including betal selective (such as metoprolol and bisoprolol) and nonselective (such as carvedilol) which blocks not only β1 but also β2 and α1 receptors. They both have beneficial effect in heart failure treatment (Bristow et al., 2003; Cleland, 2004). Given their profound benefit in heart failure, there is a tendency to investigate whether these agents differ in clinical efficacy, so that it is preferred to switch from one to another in patients. Metoprolol prevents the sodium retention in heart failure possibly by blunting of the neurohormonal response. This in turn decreases the symptoms such as pulmonary congestion, peripheral edema and ascites (Wuerzner et al., 2005). Cardiomyocyte death resulting from apoptosis in heart failure has been ascribed to excessive sympathetic nervous system activity, so, it can be controlled by different groups of β blockers (Communal and Colluci, 2005). The COMET (Carvedilol or Metoprolol European Trial) found that carvedilol reduced mortality compared with immediate release metoprolol.

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RESULTS AND DISCUSSION

All 30 patients completed the study, 16 in patients group and 14 in control group. Mean age was 37±3.2. Demographic data of patients and control group with Levene's test for equality were shown in Table 1. Echo quantitative data at baseline and 1, 2 and 3 months of treatment were shown in Table 2.

We observed CI (F), dv/dt of dt (p), MPI (p) improved at one month. EPSS (p), LVEF (p) at 2 months and E (p), E/A (p) at 3 months were added to them, but E wave didn't change significantly. It means that systolic and diastolic function both improve in patients group, some indices earlier than others.

CI and A wave had positive correlation with kind of disease (stratified upon the number of structural disease):

- CI and kind of disease: \( R = 0.47, p = 0.008 \)
- A and kind of disease: \( R = 0.36, p = 0.05 \)

Sex, weight and age didn't have significant correlation with systolic and diastolic function.

E wave, MPI and dv/dt had positive correlation with type of drugs (stratified upon their number, dig = 1, dig+ACEI = 2, dig+ACEI+Diuretic = 3). It means that the more drug, the more number and actually the more severity of heart failure.

- E and drug types: \( R = 0.45, p = 0.012 \)
- MPI and drug types: \( R = 0.42, p = 0.02 \)
- Dv/dt of dt and drug types: \( R = 0.52, p = 0.002 \)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number (%) (control = 14)</th>
<th>Number (%) (patient = 16)</th>
<th>Levene's test for equality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5(35.7%)</td>
<td>6(37.5%)</td>
<td>92</td>
</tr>
<tr>
<td>Female</td>
<td>9(64.3%)</td>
<td>10(62.5%)</td>
<td></td>
</tr>
<tr>
<td>Age(month)</td>
<td>31-35(4-106)</td>
<td>32.9(37-2132)</td>
<td>94</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>1085±56014</td>
<td>1081±5708</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>(4100-25000)</td>
<td>(4100-25000)</td>
<td></td>
</tr>
<tr>
<td>Kind of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD=MR</td>
<td>7(50%)</td>
<td>6(37.5%)</td>
<td>38</td>
</tr>
<tr>
<td>PDA=MR</td>
<td>3(21.4%)</td>
<td>3(18.8%)</td>
<td></td>
</tr>
<tr>
<td>MR+MVP</td>
<td>1(7.1%)</td>
<td>2(12.5%)</td>
<td></td>
</tr>
<tr>
<td>AH=MR</td>
<td>1(7.1%)</td>
<td>1(6.3%)</td>
<td></td>
</tr>
<tr>
<td>VSD=AH+MR</td>
<td>2(14.3%)</td>
<td>3(18.8%)</td>
<td></td>
</tr>
<tr>
<td>VSD=PDA</td>
<td>0(0%)</td>
<td>1(6.3%)</td>
<td></td>
</tr>
<tr>
<td>Kind of drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>2(14.3%)</td>
<td>2(12.5%)</td>
<td>43</td>
</tr>
<tr>
<td>Dig+ACEI (inhibitor)</td>
<td>6(42.9%)</td>
<td>5(31.3%)</td>
<td></td>
</tr>
<tr>
<td>Dig+diuretic</td>
<td>3(21.4%)</td>
<td>3(18.8%)</td>
<td></td>
</tr>
<tr>
<td>Dig+ACEI+diuretic</td>
<td>3(21.4%)</td>
<td>6(37.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Exclusion criteria: bradycardia (in relation to age), cardiomyopathy (LVEF< 50%), PA pressure of more than 60 mmHg (so, that they were referred for surgery).

All patients continued any previous medication sixteen patients were randomized to metoprolol therapy and 14 patients to placebo.

Written informed consents were obtained from the patients' parents.

2D, Color, Doppler echocardiography was performed at baseline and after 1, 2, 3 month of treatment. Echo instrument was vingmed 800. Echo systolic indices including Cardiac Index (CI), E Point Septal Separation (EPSS), Left Ventricular Ejection Fraction(LVEF) and diastolic indices including dv/dt of deceleration, maximal velocity of early diastolic filling (E wave), maximal velocity of late diastolic filling (A wave), the ratio of E and A (E/A) and myocardial performance index (MPI) were determined. PA pressure was evaluated from the tricuspid and pulmonary valve flow velocities.

The data were analyzed by t-test (SPSS software). Pearson and Chi square was used to determine the relation of some variables. Significance level was set at \( p<0.05 \).
The present study showed that metolol caused systolic and diastolic improvement in heart failure in patients with structural heart disease. Gali et al. (1993) showed that enoximone (phosphodiesterase 3 inhibitor) improved hemodynamic in CHF but in most cases doesn’t influence energetic. The addition of metoprolol to enoximone reduces heart rate, CI and myocardial oxygen consumption (Gali et al., 1993). There have been suggestion of potential superiority of carvedilol based on comparison of change in LV function but mechanistic data don’t demonstrate important and unequivocal difference in LV function and hemodynamic between carvedilol and metoprolol. There are two formulation of metoprolol including Extended Release Metoprolol Succinate (ERMS) and Immediate Release Metoprolol Tartrate (IRMT), of which only the former is FDA approved in heart failure, but the later was shown in the MDC (Metoprolol Dilated Cardiomyopathy) trial to significantly improve cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. In fact ERMS caused more sustained β1 blockade than IRMT over 24 h (Bristow et al., 2003). To compare this two there is a study showing more effect of ERMS in reducing mortality and morbidity (Bauman and Talbert, 2004). In this study we used IRMT due to nonavailability of ERMS, however it caused significant improvement of both systolic and diastolic function. Carvedilol was more effective drug compared to metoprolol in two other studies (Cleland, 2004; Al-Hesayen et al., 2005), but in another study it has been reported that carvedilol given in a relatively high β1 receptor blocking dose regimen was superior in mortality reduction to IRMT given in a relatively low β1 receptor blocking dose schedule (Bristow et al., 2003). To explain this superiority it has been reported that carvedilol also increases insulin sensitivity (metoprolol has the opposite effect) and has antioxidant properties improving endothelial dysfunction and preventing apoptosis (Delea et al., 2005). It also decreases microalbuminuria (Hansson, 1998). Terra et al. (2005) showed heart failure patients with Arg 389 Arg genotype and Gly 49 carriers had greater improvements in LV remodeling from betablocker treatment (Terra et al., 2005). This fact can explain individual differences in β blocker responsibility. There are also more explanation for positive effect of β blocker in heart failure which include a decline in apoptosis and sodium retention (Wuerzner et al., 2005; Communal and Colluci, 2005; Al-Hesayen et al., 2005). In another study, mortality of myocardial infarction declined with propranolol, timolol, metoprolol and in the presence of LV dysfunction carvedilol (Reiter, 2004). In a study, metoprolol therapy induced positive filling changes not only in idiopathic cardiomyopathy but also in ischemic cardiomyopathy and advanced CHF. These changes are caused by decreasing of adrenergic toxicity, oxygen consumption and in carvedilol group its properties such as antioxidant and antiinflammatory action, peripheral vascular dilatation and specific drug related metabolic effects leading to reduction of myocardial fibrosis and LV chamber rigidity with elasticity improvement (Palazzuoli et al., 2005). In this study, there is a positive relation between kind of disease and drug with MPI, dv/dt of dt and E wave. This echo indices increase in volume overload. Given in our study kind of disease and drug, stratified based on severity of disease, it's plausible that these echo indices increase in more severe state of heart failure. As CI is cardiac output corrected by body surface area and equal to stroke volume multiplied by heart rate, it's expectable that it increases in more severe heart failure and decreases more by β blockers. In another study, it has been considered diuretic, ACE inhibitors and β blockers as the cornerstone of pharmacologic treatment of CHF. However, a large number of new agents have been developed as add on treatment over the last few years. They include vasopressorase inhibitors, m Cox2 inhibitors, endothelin antagonists, immunomodulating agents, growth hormone, caspase inhibitors, adrenomedullin, erythropoietin and selective aldosterone receptor blocker (eplerenone).
(Van de Wal, 2004). As it is evident in our study, there are no considerable side effects leading to discontinuation of metoprolol in other articles (Galie et al., 1993; Bristow et al., 2003).

Based on our study, it is now clear that the addition of metoprolol to routine medical therapy of heart failure causes more improvement in systolic and diastolic function. Therefore, metoprolol is recommended in patients with heart failure in some structural heart disease with LV volume overload that have not been controlled adequately in spite of receiving standard cardiac failure drug therapy such as an inotrope, a diuretic and a vasodilator agent.

Hopefully lessons learned in this regard will contribute to further progress in evaluation of newer drugs or overall management of heart failure.

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REFERENCES
