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PJBS

ISSN 1028-8880

# Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 12 (5): 451-454, 2009
ISSN 1028-8880


# 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 EPSS 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 causes 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 of 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 beta1 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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tartrate, but there was no difference in hospitalization (Bauman and Talbert, 2004). We studied carvedilol in our center last year that resulted in positive beneficial effect (Rashidighader and Mojtahedzade, 2007). The aim of this study is to evaluate the influence of metoprolol on systolic and diastolic cardiac function in children with heart failure. Given the differences in common causes of heart failure in pediatric and adult age groups and limited relevant studies in children, we were to do this study.

## MATERIALS AND METHODS

This is a double-blind placebo controlled clinical trial study performed on pediatric patients who referred to pediatric clinics' in sari/ Iran in 2007. Thirty patients age ranged (3 months to 10 years old) with mild to moderate CHF due to structural heart disease leading to LV volume overload including VSD, PDA, AI, MR alone or in combination enrolled in the study. The patients set in two groups similar of sex, age, kind of disease and cardiac drugs (except for metoral). The patient group received metoral (dose = 1 mg/kg/day, daily single dose) in addition to other drugs and the control group received placebo made in Mazandaran University, Pharmacology Ward. The study was done on patients with the symptoms of heart failure such as failure to thrive, sweating, recurrent pneumonia, exercise intolerance, despite receiving conventional heart failure drugs such as digoxin±ACE inhibitors±diuretics.

**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 $p<0.05$.

## RESULTS AND DISCUSSION

All 30 patients completed the study, 16 in patients group and 14 in control group. Mean age was 37±32.9. 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 (P), 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 1: Demographic and clinical characteristics of children in both groups (patients and control)

| Variables | Number (%) and SD (control = 14) | Number (%) and SD (patient = 16) | Levene's test for equality (%) |
|---|---|---|---|
| **Sex** | | | |
| Male | 5(35.7%) | 6(37.5%) | 92 |
| Female | 9(64.3%) | 10(62.5%) | |
| Age(month) | 31±35(4-108) | 32.9±37(2-132) | 94 |
| Weight (g) | 10857±6014 (4100-25000) | 10812±5708 (4100-25000) | 98 |
| **Kind of disease** | | | |
| VSD±MR | 7(50%) | 6(37.5%) | 38 |
| PDA±MR | 3(21.4%) | 3(18.8%) | |
| MR±MVP | 1(7.1%) | 2(12.5%) | |
| AI±MR | 1(7.1%) | 1(6.3%) | |
| VSD+AI±MR | 2(14.3%) | 3(18.8%) | |
| VSD+PDA | 0(0%) | 1(6.3%) | |
| **Kind of drug** | | | |
| Digoxin | 2(14.3%) | 2(12.5%) | 43 |
| Dig+ACEI (inhibitor) | 6(42.9%) | 5(31.3%) | |
| Dig+diuretic | 3(21.4%) | 3(18.8%) | |
| Dig+ACEI+ diuretic | 3(21.4%) | 6(37.5%) | |

Table 2: Echocardiographic indices in both group (patient & control) before and after the study

| | Month | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | | 1 | | | 2 | | | 3 | | |
| Variable±SD group | Patient | Control | Patient | Control | p-value | Patient | Control | p-value | Patient | Control | p-value |
| **Systolic function** | | | | | | | | | | | |
| LVEF | 68.20±2.80 | 68.40±2.60 | 69.10±2.60 | 68.80±2.40 | 0.06 | 69.90±2.60 | 69.50±2.30 | 0.040 | 70.75±2.60 | 69.5±2.50 | 0.001 |
| EPSS | 6.20±1.30 | 5.70±0.70 | 5.30±1.30 | 4.90±0.90 | 0.23 | 4.80±1.40 | 4.80±0.70 | 0.020 | 4.20±1.20 | 4.5±0.75 | 0.008 |
| CI | 4.90±0.20 | 3.70±0.20 | 3.90±0.90 | 3.70±0.10 | 0.01 | 3.70±0.13 | 3.70±0.14 | 0.020 | 3.60±0.13 | 3.6±0.14 | 0.030 |
| **Diastolic function** | | | | | | | | | | | |
| E wave | 0.49±0.10 | 0.52±0.10 | 0.50±0.05 | 0.52±0.04 | 0.34 | 0.50±0.04 | 0.50±0.04 | 0.310 | 0.52±0.05 | 0.52±0.05 | 0.170 |
| A wave | 1.06±0.10 | 1.03±0.10 | 1.04±0.06 | 1.02±0.04 | 0.30 | 1.01±0.06 | 1.00±0.03 | 0.300 | 0.96±0.05 | 0.97±0.03 | 0.002 |
| E/A | 2.20±0.40 | 2.00±0.20 | 2.11±0.30 | 1.94±0.20 | 0.14 | 2.01±0.26 | 1.90±0.17 | 0.160 | 1.86±0.23 | 1.88±0.22 | 0.030 |
| Dv/dt of dt | 9.70±1.00 | 9.08±0.90 | 9.05±1.20 | 8.70±1.07 | 0.05 | 8.80±1.20 | 8.49±1.13 | 0.030 | 8.50±1.20 | 8.40±1.00 | 0.001 |
| MPI | 0.33±0.04 | 0.31±0.03 | 0.32±0.04 | 0.30±0.03 | 0.01 | 0.30±0.04 | 0.29±0.02 | 0.002 | 0.28±0.04 | 0.29±0.03 | 0.000 |

The present study showed that metoral 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 (Galie *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 Metprolol 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 axplanation 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 antinflammatory 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 vasopeptidase inhibitors, moxonidine, 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.

## ACKNOWLEDGMENT

The present study was financed by pediatric Department of Booali Sina University Hospital, related to Mazandaran University Medical Science, Sari/ Iran.

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