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ORIGINAL ARTICLE

Evaluation by N-terminal Prohormone of Brain Natriuretic Peptide Concentrations and Ross Scoring of the Efficacy of Digoxin in the Treatment of Heart Failure Secondary to Congenital Heart Disease With Left-to-Right Shunts

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Abstract This study aimed to evaluate the effectiveness of digoxin in children with heart failure secondary to left-to-right shunt lesions and normal left ventricular systolic function. The study registered 37 such patients (ages 10 days to 24 months, groups 1 and 2) and used 20 healthy children as a control group (group 3). Left ventricular systolic function, as assessed by conventional echocardiography, was normal in all the subjects. Congestive heart failure was diagnosed by clinical evaluation and modified Ross scoring. Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentrations and complete blood counts were assessed in all the children. Group 1 was treated with digoxin, enalapril, and furosemide and group 2 with enalapril and furosemide. Approximately 1 month after starting treatment, the patients were reevaluated by physical and echocardiographic examinations, modified Ross scoring, plasma NT-proBNP concentrations, and complete blood counts. The pre- and posttreatment Ross scores of group 1 ($p = 0.377$) and group 2 ($p = 0.616$) did not differ significantly. The NT-proBNP values in both groups decreased after treatment ($p = 0.0001$). The pre- and posttreatment NT-proBNP values did not differ significantly in group 1 ($p = 0.094$)) and group 2 ($p = 0.372$). The pretreatment NT-proBNP values in groups 1 and 2 ($p = 0.0001$) were significantly higher than in the control group ($p = 0.003$). A smaller difference was observed between posttreatment NT-proBNP values in group 1 and the control group ($p = 0.045$). We found no significant difference between the posttreatment NT-proBNP values of group 2 and those of the control group ($p = 0.271$). The study showed that both treatments currently used to treat heart failure secondary to congenital heart disease with left-to-right shunts and preserved left ventricular systolic function are effective and do not differ significantly. Thus, digoxin does not provide any extra benefit in the treatment of such patients.

Keywords Children · Congenital heart disease · Digoxin · Heart failure · Left-to-right shunt

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Heart failure (HF) in congenital heart diseases with left-to-right shunts is a serious problem encountered in early infancy or later depending on the size of the shunt. It is a significant cause of morbidity and mortality in children with congenital heart disease [1, 2].

The main line of treatment for patients who experience HF due to congenital heart disease with left-to-right shunts has been closure of the defects by surgical or other invasive methods. However, if medical treatment succeeds in controlling heart failure in early childhood, surgical or

interventional methods can be postponed or even eliminated altogether [3–5].

The modified Ross score, developed to quantify HF in infancy and early childhood, is based on the patient's clinical signs. This currently is the most commonly preferred method for staging HF in children. The Canadian Cardiovascular Society considers this the main method for scoring such HF [6, 7].

In cardiology, B-type natriuretic peptide (BNP) and the N-terminal segment of this hormone (NT-proBNP) are significant biomarkers. A polypeptide, BNP is released from the ventricles at ventricular volume and pressure loading [8, 9]. In clinical practice, NT-BNP is widely used in the diagnosis and follow-up evaluation of congestive HF as well as in assessing the response to treatment [10–14]. A significant correlation exists between heart failure scores and concentrations of NT-proBNP in pediatric patients [15, 16].

Most information about drugs used to treat HF in children is based on data obtained in adults. However, both the physiopathology of the underlying heart disease and the pharmacokinetics of the drugs usually differ between children and adults [17]. Digital glycosides, diuretics, and angiotensin-converting enzyme (ACE) inhibitors are commonly used to treat HF at all ages [1, 2, 5, 18]. However, digoxin does not have a definitely proven role in HF secondary to cardiac defects with left-to-right shunts in children. No randomized control studies have explored the use of digoxin with these patients. Conversely, small, uncontrolled studies involving children who have cardiac defects with large left-to-right shunts have produced contradictory results [19–22].

Prospective and randomized studies involving children would provide the most reliable information about the treatment of children with HF. We have found no published studies comparing digoxin–enalapril–furosemide and enalapril–furosemide therapies for treating HF secondary to cardiac defects with left-to-right shunts in children.

The current study aimed to use Ross scores and NT-proBNP concentrations to evaluate the efficacy of two drug combinations (digoxin–enalapril–furosemide and enalapril–furosemide) used for children with HF secondary to left-to-right shunt lesions and normal left ventricular systolic function.

Patients and Methods

This study was conducted in the Pediatric Cardiology Department of Inonu University Medical School between 2010 and 2011. The parents of all the participating infants were informed about the study, and their written consent was obtained. In accordance with the Helsinki Declaration, the Ethics Committee of the Medical School approved the study before it began.

Study Population

The study registered 48 pediatric patients (ages 10 days to 24 months) who had a diagnosis of congestive HF secondary to congenital heart disease with left-to-right shunts. The patients in group 1 ($n = 25$) were treated with digoxin, enalapril, and furosemide for HF, and those in group 2 ($n = 23$) were administered enalapril and furosemide. A control group (group 3) consisted of 20 healthy children with innocent heart murmurs. Physical examination of the infants in this group showed no pathologic signs, and their echocardiographic examinations exhibited no cardiac pathology. The patients' relevant clinical variables and laboratory data were recorded on forms.

The exclusion criteria ruled out patients with infections during the previous month or at the initial examination; patients with clinical or historical evidence of noncardiac systemic chronic disease; patients who had digoxin, enalapril, or furosemide treatment administered recently or during the study; and patients whose parents refused to allow their participation. Because NT-proBNP concentrations are characteristically high in premature infants and small neonates [23, 24], neonates with a birth age <10 days and premature neonates also were excluded from the study.

Diagnoses of congestive heart failure secondary to congenital heart disease with left-to-right shunts were based on clinical evaluation, modified Ross scoring, and echocardiographic examination.

Clinical Evaluation

The relevant clinical history of all the patients in the study was recorded in detail, as were the findings of their systemic and cardiac examinations, all performed by the same practitioner. Pre- and posttreatment age, weight, heart rate, and oxygen saturation also were recorded by the same pediatrics polyclinic nurse.

The patients were evaluated clinically before and after treatment using the Ross classification for infants with left-to-right shunts [25] as modified by Reithmann et al. [26]. Sweating, respiratory rate and mode, heart rate, and liver size were evaluated, and the infants were assigned scores of 0, 1, or 2 for each of these variables. Their modified Ross scores then were calculated by adding the individual scores for each variable. Echocardiographic data, NT-proBNP concentrations, and the ultimate group for each patient were not known when the modified Ross scores were assessed.

After the patients' parents had been informed about congestive HF secondary to congenital heart disease with

left-to-right shunts and had given their informed consent, the patients were alternately assigned to one of the following two drug combinations. The patients in group 1 received oral digoxin 0.035 mg/kg/day (loading dose and 2 maintenance doses), oral enalapril 0.2 mg/kg/day in divided doses, and oral furosemide 1 mg/kg/day in divided doses. The patients in group 2 received oral enalapril 0.2 mg/kg/day in divided doses and oral furosemide 1 mg/kg/day in divided doses.

The patients were reevaluated approximately 1 month after starting treatment by physical and echocardiographic examinations, modified Ross scoring, plasma NT-proBNP concentrations, and complete blood counts. Follow-up evaluations were performed 3 to 6 weeks later.

Laboratory Analyses

Analysis Methods. Venous blood samples of 3 mL were collected into heparinized tubes to measure NT-proBNP concentrations. After collection, the blood samples were centrifuged at 3,500 rpm to separate the serum, which then was stored in Eppendorf tubes at −70 °C. Serum concentrations of NT-proBNP were measured by a chemiluminescent immunometric assay (IMMULITE 2000 NT-proBNP; Siemens, Erlangen, Germany) and expressed as picograms per milliliter (pg/mL).

Routine blood samples were collected to rule out anemia and infection. Venous blood samples of 2 mL were taken between 08.00 and 10.00 for whole blood counts. The samples were put into tubes containing ethylenediaminetetraacetic acid and analyzed on the same day by a Coulter LH780 Hematology Analyzer (Beckman Coulter, Fullerton, CA, USA).

Echocardiographic Assessment. Standard two-dimensional, M-mode, color and Doppler echocardiographic studies were conducted by the same pediatric cardiologist using a Vivid Pro 7 echocardiography device (GE, Vingmed Ultrasond, Horten, Norway) before and after treatment of the patients and once in the control group. Echocardiograms were obtained with the patient in the standard precordial positions according to the American Society of Echocardiography recommendations [27].

Statistical Analysis

Quantitative data were evaluated by the Shapiro–Wilk test to determine whether they had a normal distribution. Quantitative data with normal distributions are presented as mean ± standard deviation (SD) and those without normal distributions as median (minimum–maximum) values. Qualitative data are presented as numbers and percentages.

Student's paired t test was used to assess changes in the study groups, whereas one-way analysis of variance (ANOVA) and least significant difference methods were used for comparisons between groups. The relations between the variables were tested by Pearson's correlation analysis. The level of statistical significance was set at a p value lower than 0.05.

Results

Four patients were excluded from the study because of intercurrent acute renal failure, sepsis, metabolic disease, and persistent lung infection. A further four patients who did not attend for follow-up evaluation also were excluded from the study. Three patients with no evidence of clinical improvement at follow-up evaluation also were excluded and directed to surgery. Thus, altogether, 11 of 48 patients were excluded, leaving 37 patients to complete the study.

Patients' age, sex, body weight, heart rate, and hemoglobin values are shown by group in Table 1, types of cardiac defects in Table 2, and Ross scoring and NT-proBNP values in Table 3. The NT-proBNP concentrations did not differ significantly between female and male patients ($p = 0.467$). The pretreatment NT-proBNP concentrations were high in both patient groups and decreased significantly after treatment ($p < 0.0001$ for both groups). The pre- and posttreatment NT-proBNP values did not differ in group 1 ($p = 0.372$) or group 2 ($p = 0.094$). The pretreatment NT-proBNP values in both groups 1 and 2 ($p = 0.0001$) differed significantly from those in the control group ($p = 0.003$). The posttreatment NT-proBNP values in group 1 still differed from those in the control group, but to a smaller extent ($p = 0.045$). No significant difference was found between the posttreatment NT-proBNP values of group 2 and those of the control group ($p = 0.271$).

Discussion

Either the digoxin–enalapril–furosemide or the enalapril–furosemide combination is commonly used to treat HF secondary to congenital heart disease with left-to-right shunts [1, 2, 5, 18]. For many of the drugs used to treat HF in children, the only available data are from studies with adults. However, the etiology, pathophysiology, and physiologic consequences of heart failure in children are characteristically quite different from those in adults. Left ventricular dysfunction is the primary abnormality that causes heart failure in adults. However, intracardiac left-to-right shunts or obstructive lesions usually cause HF in children, whose left ventricular function typically is normal [17].

Table 1 Clinical characteristics of groups

	Group 1 ($n = 19$)	Group 2 ($n = 18$)	Group 3 ($n = 20$)	p (G1–G2)	p (G1–G3)	p (G2–G3)
Sex: n (%)						
Female	6 (31.6)	10 (55.6)	9 (45.0)	NS	NS	NS
Male	13 (68.4)	8 (44.4)	11 (55.0)	NS	NS	NS
Age (months)						
Pretreatment	3.7 ± 4.4	3.4 ± 3.5	5 ± 3.7	NS	NS	NS
Posttreatment	5.4 ± 5	4.5 ± 3.5		NS		
Weight (kg)						
Pretreatment	4.29 ± 1.94	4.47 ± 1.24	6.68 ± 2.01	NS	0.0001	0.0001
Posttreatment	4.82 ± 2.20	5.01 ± 1.27		NS		
p (pre–post)	0.0001	0.0001				
Heart rate (bpm)						
Pretreatment	160.1 ± 9.1	160.2 ± 10.6	124.9 ± 13.7	NS	0.0001	0.0001
Posttreatment	141.5 ± 11.7	140.6 ± 12.3		NS		
p (pre–post)	0.0001	0.0001				
Respiratory rate (breaths/min)						
Pretreatment	64.17 ± 8.19	61.28 ± 4.99	42.6 ± 4.42	NS	0.0001	0.0001
Posttreatment	46.06 ± 6.20	46.83 ± 4.46		NS		
p (pre–post)	0.0001	0.0001				
Liver size						
Pretreatment	2.06 ± 1.03	2.06 ± 0.73		NS		
Posttreatment	0.64 ± 0.64	1.14 ± 0.7		NS		
p (pre–post)	0.0001	0.0001				
Hemoglobin						
Pretreatment	12.7 ± 2.16	11.8 ± 1.86	13 ± 2.58	NS	NS	NS
Posttreatment	11.6 ± 1.4	11 ± 1.4		NS		
p (pre–post)	0.0001	0.001				

G1 group 1, *G2* group 2, *G3* group 3, *pre* pretreatment, *post* posttreatment, *NS* not statistically significant

Table 2 Types of cardiac defects in patients

Cardiac defect	Group 1 ($n = 19$) n (%)	Group 2 ($n = 18$) n (%)
ASD	1 (5.2)	1 (5.5)
VSD	7 (36.8)	8 (44.4)
PDA	1 (5.2)	3 (16.6)
AVSD	1 (5.2)	1 (5.5)
Complex	9 (47.3)	5 (27.7)
Total	19 (100)	18 (100)

ASD atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *AVSD* atrioventricular septal defect

Digoxin, the most commonly used cardiac glycoside for HF, is preferred because of its easy accessibility, low cost, and long history of use. Although digoxin is important in the treatment of children with arrhythmias, no consensus exists its use to treat heart failure associated with left-to-right shunts [5, 18, 28].

Only a few studies have investigated digoxin therapy for treating HF associated with left-to-right shunts in children, with some supporting it and others opposing it. Thus, the efficacy of digoxin for such children is debatable [19, 20, 22].

Despite the scarcity of information regarding the use of digoxin for children, many clinicians use this drug to treat childhood HF of various causes. Therefore, we considered it reasonable to investigate the scientific basis for such digoxin usage. A search of published reports failed to identify any studies that used clinical signs and NT-proBNP concentrations to compare digoxin–enalapril–furosemide and enalapril–furosemide for the treatment of pediatric HF.

Age and NT-proBNP Concentrations

Studies of pediatric subjects indicate that NT-proBNP concentrations are high at birth and remain high for the first days of life, after which they start to decrease, stabilizing on the fifth postnatal day [16, 23, 24, 29]. In the control group, we found no statistically significant relationship

Table 3 Ross scoring and NT-ProBNP values of groups

	Group 1 ($n = 19$)	Group 2 ($n = 18$)	Group 3 ($n = 20$)	p (G1–G2)	p (G1–G3)	p (G2–G3)
NT-ProBNP levels (pg/ml)						
Pretreatment	13962 ± 12025	9323 ± 9166	386 ± 234	NS	0.0001	0.003
Posttreatment	3850 ± 8550	2290 ± 3263		NS	0.045	NS
p (pre–post)	0.0001	0.0001				
Modified Ross scoring						
Pretreatment	8.4 ± 1.4	8.1 ± 1.1		NS		
Posttreatment	2.8 ± 0.8	3 ± 0.7		NS		
p (pre–post)	0.0001	0.0001				

G1 group 1, *G2* group 2, *G3* group 3, *pre* pretreatment, *post* posttreatment, *NS* not statistically significant

between age and NT-proBNP concentrations ($p = 0.256$), consistent with published reports. As expected, the BNP values in the control group were within the normal range [8, 24].

Sex and NT-proBNP Concentrations

Previous studies have failed to establish any correlation between plasma NT-proBNP concentrations and the sex of infants and young children [24, 30]. Consistent with this, our study identified no statistically significant correlation between sex and NT-proBNP concentrations in the control group ($p = 0.467$).

Heart Rates

We found no statistically significant differences in pretreatment heart rates between groups 1 and 2 ($p > 0.05$). After treatment, the heart rates decreased to a similar extent in both groups. However, when we compared both the pre- and posttreatment heart rates of each patient group with those of the control group, we did find a statistically significant difference ($p = 0.0001$). Groups 1 and 2 did not differ statistically in terms of individual pre- and posttreatment heart rates.

One of digoxin's known effects is reduction of the heart rate. However, the data obtained in this study indicate that the two drug combinations have a similar effect on heart rate. Thus, in terms of decreased heart rate, the addition of digoxin to the treatment regimen of group 1 conferred no advantage over the enalapril–furosemide alone received by group 2.

Hemoglobin Concentrations

It is well known that anemia causes increased NT-proBNP concentrations. Thus, a negative correlation exists between hemoglobin and NT-proBNP values [31, 32]. We found no difference between pre- and posttreatment hemoglobin concentrations in groups 1 and 2. However, posttreatment hemoglobin values decreased in both groups. These decreases may have correlated with the patients' increased body mass indexes.

Modified Ross Scores and NT-proBNP Concentrations

Because studies involving children with congestive HF have reported a positive correlation between Ross scores and NT-proBNP concentrations, NT-proBNP may be useful for monitoring the efficacy of treatment for patients with HF [15, 16, 33]. Koch et al. [9] found higher BNP concentrations in children with left-to-right shunt lesions than in those who had congenital heart disease without symptoms of HF and identified a positive correlation between BNP concentration and shunt volume. Zhang et al. [34] assigned 71 children with congenital heart disease to groups with and without congestive HF and measured their BNP scores and NT-proBNP concentrations. They found higher BNP and NT-proBNP values in both groups than in a control group and identified a further increase in these variables in the group with congestive HF.

As expected, our study demonstrated that the patients' modified Ross scores had decreased after treatment. Hence, we found these scores to be a reliable method for assessing HF. However, we noted some clinical problems in the course of Ross scoring. For instance, the parents failed to provide reliable answers to the questions regarding sweating and tachypnea. Such factors may reduce the accuracy of Ross scoring.

Similar to previous studies, our study showed that NT-proBNP concentrations in infants with HF secondary to congenital heart disease with left-to-right shunts are higher than in a healthy control group and that NT-proBNP concentrations decrease in parallel with clinical improvement after treatment. The very high NT-proBNP concentrations at the beginning of the study decreased markedly after treatment but remained higher than those of the control group. We attribute these findings to the fact that the

patients' HF was of cardiac origin. Both patient groups, whether receiving digoxin–enalapril–furosemide or enalapril–furosemide, had similar declines in NT-proBNP concentrations and Ross scores. Thus, as some other authors have suggested, digoxin does not make any extra contribution to the treatment of HF in patients with left-to-right shunts because these patients have no systolic dysfunction [17, 21]. Our study provides reliable data in support of this proposition.

We found no significant differences between the two drug combinations in terms of clinical improvement as quantified by Ross scores ($p = 0.616$). However, the posttreatment Ross scores of the patient groups were still higher than those of the control group ($p = 0.0001$). This did not surprise us because we did not expect that medical treatment alone would lead to sufficient improvement in the cardiac function of patients with congenital heart disease to make them equivalent to a healthy group.

In conclusion, our study showed that both treatments currently used to treat HF secondary to congenital heart disease with left-to-right shunts are effective and that there no significant difference exists between them. We found no significant difference in decreases of NT-proBNP concentrations between the group receiving digoxin–enalapril–furosemide and the group administered enalapril–furosemide ($p = 0.372$). Thus, we concluded that digoxin does not provide any extra benefit in the treatment of HF that develops secondary to congenital heart disease with left-to-right shunts. However, we believe that comparative studies with larger case series and longer follow-up periods may provide illuminating data in this area.

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