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Original Article

Plasma digoxin levels and ejection fraction in pediatric heart failure

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Abstract

Background Digoxin has long been prescribed in children with heart failure, but its efficacy has not been evaluated. A previous study at the Department of Child Health, Dr. Cipto Mangunkusumo Hospital revealed that plasma digoxin levels, following a maintenance dose of 15 μg/kg/d, were sub-therapeutic. Regarding its narrow margin of safety, the trend is to use digoxin in even lower dose. Thus, the drug's impact on cardiac performance need to be evaluated.

Objective To evaluate whether a lower maintenance dose of digoxin (10 μg/kg/d) is sufficient to achieve a therapeutic level and to assess for possible correlations between plasma digoxin level and left ventricular ejection fraction (LVEF) as well as fractional shortening (LVFS).

Methods A cross-sectional study was conducted on 20 pediatric heart failure patients at the Department of Child Health, Dr. Cipto Mangunkusumo Hospital, Jakarta, from January to May 2012. Plasma digoxin levels were measured by ELISA method after one month or more of treatment; LVEF and LVFS were measured by echocardiography. Correlations between plasma digoxin level and LVEF or LVFS were analyzed by Spearman's correlation test. The LVEF before and after digoxin treatment were compared by paired T-test.

Results Thirteen out of 20 patients had plasma digoxin levels within therapeutic range (0.5-1.5 ng/mL; 95%CI 0.599 to 0.898) and 7 had sub-therapeutic levels (<0.5 ng/mL; 95%CI 0.252 to 0.417). No significant correlations were observed between plasma digoxin level and LVEF (r=-0.085; P=0.722) or LVFS (r=-0.105; P=0.659). There was a significant increase in LVEF before [42.18 (SD 14.15)%] and after digoxin treatment [57.52 (SD 11.09)%], (P < 0.0001).

Conclusion Most patients in this study have plasma digoxin levels within therapeutic range. There are no significant correlations between plasma digoxin level at the time point of measurement and LVEF or LVFS. However, an increase of LVEF is observed in every individual patients following digoxin treatment. **[Paediatr Indones. 2015;55:322-7]**.

Keywords: *digoxin, ejection fraction, fractional shortening, heart failure*

Heart failure is a clinical syndrome characterized by inability of the heart to pump the blood to supply the body's needs, to provide for adequate systemic or pulmonary venous return, or a combination of the two. Heart disease may end with heart failure. To date, there is no valid data concerning the incidence of heart failure in Indonesia. In the United States, it is estimated that 12,000 to 35,000 children under the age of 19 years suffer from heart failure each year due to congenital heart disease and cardiomyopathy.[1] The incidence of heart failure in children in the United Kingdom in 2003 was 0.87 per 100,000 population, most of whom were under 1 year of age, and half were due to dilated cardiomyopathy.[2] About 15-25% of children with structural cardiac abnormalities experience heart failure,[3] and 40% of patients with cardiomyopathy experience severe heart failure that ultimately needs transplantation.[4]

Digoxin is a cardiac glycoside that has been used since 1785,[5] with positive inotropic but negative chronotropic effects,[6] thus making cardiac contractility more efficient. Although the use of digoxin continues

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to decrease due to the emergence of more effective and safer drugs, such as diuretics, ACE-inhibitors, angiotensin receptor blockers, and beta blockers, digoxin is still widely used especially in pediatric or pregnant patients. Digoxin is a drug with a narrow margin of safety. Therapeutic levels of digoxin range from 0.5 to 1.5 ng/mL.[6,7] A dose range of 0.125 - 0.375 mg/kg/d is needed to maintain this therapeutic level.[8] A higher dose is needed for pediatric patients, since the binding of digoxin to its receptor is weaker and there are more receptors in children.[9] Data on the efficacy of digoxin in pediatric patients is limited, however, this drug is still widely used for heart failure, in addition to diuretics and ACE-inhibitors. In 1993, Madiyono conducted a study on 40 patients with rheumatic heart disease and heart failure using a digoxin maintenance dose of 10-15 μg/kg/d. He found that plasma digoxin levels were sub-therapeutic in the majority of patients. However, there was no assessment of therapeutic outcome in his study.[10] Currently, digoxin is used at a dose of 10 μg/kg/d in the Department of Child Health, Dr. Cipto Mangunkusumo Hospital, Jakarta, which is significantly lower than the dose used by Madiyono. Thus, reevaluation of digoxin plasma level, as well as its impact on cardiac performance is needed. We aimed to evaluate plasma digoxin level and its possible correlation with clinical efficacy by measuring LVEF and LVFS.

Methods

This cross-sectional study was conducted on ambulatory patients at the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, between January and May 2012. Children aged ≤18 years who had been diagnosed with heart failure, and had been regularly taking digoxin at least for one month were included in this study. The dose of digoxin used was 10 ug/kg/d. Written informed consent was obtained from parents. The protocol of the study was approved by the Research Ethics Committee of the University of Indonesia Medical School.

A 3-mL venous blood specimen was taken and the plasma was stored at -20^{o} C until plasma digoxin concentrations were examined. Plasma digoxin level was measured by ELISA method by using an *EIA-3268 kit* (Sigma-Aldrich, Indonesia), at the Clinical Pathology Laboratory, Dr. Cipto Mangunkusumo Hospital, Jakarta. Echocardiographic examination was performed on the same day using a *Philips Agilent Sonos 4500*. Left ventricular ejection fraction (EF) and fractional shortening (FS) were calculated according to the following formulas:

$$EF\ (\%) = [(LVEDD\text{-}LVESV)/(LVEDV)] \times 100\%$$
$$FS\ (\%) = [(LVEDD\text{-}LVESD)/(LVEDD)] \times 100\%$$

[Note: LVEDV=left ventricular end diastolic volume, LVESV=left ventricular end systolic volume, LVEDD=left ventricular end diastolic diameter, and LVESD=left ventricular end systolic diameter].

The LVEF at least one month after initiation of digoxin treatment was also compared to LVEF prior to digoxin treatment, with the latter information obtained from patients' medical records.

Sample size was estimated by the formula for correlation coefficient of a single sample group. For obtaining a statistical power of 80% and limit of significance at P value <0.05, a minimum of 30 subjects were needed. However, due to time and budget limitations, only 20 patients were recruited. Correlation between plasma digoxin level and ejection fraction or fractional shortening was analyzed by Spearman's correlation method.

Results

Subjects' characteristics are shown in **Table 1**. There was a nearly equal distribution of male and female subjects. Most of patients were above 5 years of age, and had low body mass index. The predominant cardiac disease in our subjects was dilated cardiomyopathy.

Plasma digoxin levels, LVEF, and LVFS of the patients are depicted in **Table 2**. Overall, the mean levels of the three parameters were within normal limits, although some patients had subnormal values.

There was no correlation between plasma digoxin level and ejection fraction (r=-0.085; P=0.722) nor with fractional shortening (r=-0.105; P=0.659) (**Figure 1A** and **B)**. **Table 3** shows that normal digoxin levels were found in most patients (13/20). In addition, normal LVEF and LVFS (both 14/20) were also observed.

Table 1. Subjects' characteristics according to gender, age, body mass index, and background cardiac disease

Characteristics		(N=20)
Gender, n	Male	9
	Female	11
Age group, n	< 1 yr	3
	1-5 yrs	5
	>5 yrs	12
BMI, n	Low	16
	Normal	4
Background disease, n	Dilated cardiomyopathy	12
	Rheumatic heart disease	3
	Ventricular septal defect	3
	Pulmonary hypertension	1
	Atrial septal defect	1

Table 2. Distribution of plasma digoxin levels, LVEF, and LVFS

Subject number	Digoxin level (ng/mL)	LVEF (%)	LVFS (%)
1	0.8610	64.1	33.9
2	0.2230	60.3	32.2
3	0.7130	44.6	22.3
4	0.5410	70.6	38.8
5	o.4315	51.2	26.0
6	0.5045	59.9	40.0
7	0.6585	45.2	22.9
8	0.4190	62.7	32.7
9	0.6165	65.6	35.8
10	0.5860	68.0	36.5
11	0.6700	68.4	36.5
12	0.2290	0.2	14.0
13	1.1825	58.3	31.3
14	1.2605	41.9	17.0
15	0.9695	60.3	32.1
16	0.3775	42.0	20.4
17	0.3855	66.5	35.7
18	0.5325	57.9	29.0
19	0.6380	60.1	30.0
20	0.2800	72.5	38.5
Mean (SD)	0.6000 (0.28)	57.51 (11.37)	30.28 (7.52)
95%CI	0.46 to 0.73	52.19 to 62.83	26.75 to 33.80

Note: normal range of plasma digoxin level=0.5–1.5 ng/mL; normal LVEF >56%; normal LVFS >28%

In 16 out of 20 patients, echocardiographic data before digoxin treatment could be retrieved. Comparison of this data to the data after at least one month of digoxin administration, revealed significant increases in LVEF [42.18 (SD 14.6)% *vs.* 57.51 (SD 11.37)%, respectively; (P<0.05)] and LVFS [20.67 (SD 8.20) *vs.* 30.28 (SD 7.52)%, respectively; **(Figure 2)**.

Discussion

In this preliminary study, 20 patients aged 0-18 years were recruited. All patients were diagnosed with heart failure and had consumed digoxin for at least one month. Background diseases of the majority of patients were dilated cardiomyopathy (12/20), while rheumatic heart disease and ventricular septal defects each contributed 3/20. Most subjects (18/20) had these three diseases. The minimum one-month period of taking digoxin guaranteed that plasma digoxin levels had reached steady state, and its inotropic effect had stabilized. Digoxin is an old drug, widely used for the treatment of heart failure. Currently, the use of digoxin has been limited due to its narrow therapeutic window. However, since this drug has a good inotropic effect and a simple oral administration, it is still used, especially in the presence of atrial fibrillation or tachycardia. An attempt has been made to reduce its dose in order to avoid toxicity.

The maintenance dose of digoxin used in this study was 10 mg/kg/d, while in the study of Madiyono in 1994, the maintenance dose was 15 μg/kg/d.[10] Interestingly, plasma digoxin level in 13/20 of our subjects reached optimal therapeutic levels ranging from 0.5 – 1.5 ng/mL, and only 7/20 of our subjects had sub-therapeutic levels. In contrast, plasma digoxin levels in Madiyono's study were all sub-therapeutic, despite his use of a higher dose.[10] The reasons for this discrepancy are not clear. However, the difference may be due to the pharmacokinetics of digoxin. Oral digoxin is known to have variable rate of absorption in the presence of food in the stomach. Administration of digoxin with a meal may significantly decrease the absorption rate. In addition, the severity of heart failure affects renal blood flow, thus, affecting digoxin elimination by the kidney. The use of vasodilators, such as ACE-inhibitors, may also alter renal blood flow and increase digoxin elimination,[11] leading to variations in plasma digoxin levels. In addition, digoxin undergoes metabolism by the colonic bacterium, *Eubacterium lentum*.[12] As such, the presence of this bacterium or the

Table 3. Distribution of patients according to normal or sub-therapeutic values of digoxin level, ejection fraction, and fractional shortening

Parameters	n	Mean (SD)	CI 95%
Digoxin level, ng/mL			
Normal	13	0.748 (0.237)	0.645 to 0.853
Sub-therapeutic	7	0.335 (0.089)	0.299 to 0.371
Ejection fraction, %			
Normal	14	63.94 (4.72)	61.21 to 66.67
Low	6	42.51 (6.91)	35.25 to 49.77
Fractional shortening, %			
Normal	14	34.50 (3.41)	32.53 to 36.46
Low	6	20.43 (4.32)	15.88 to 24.94

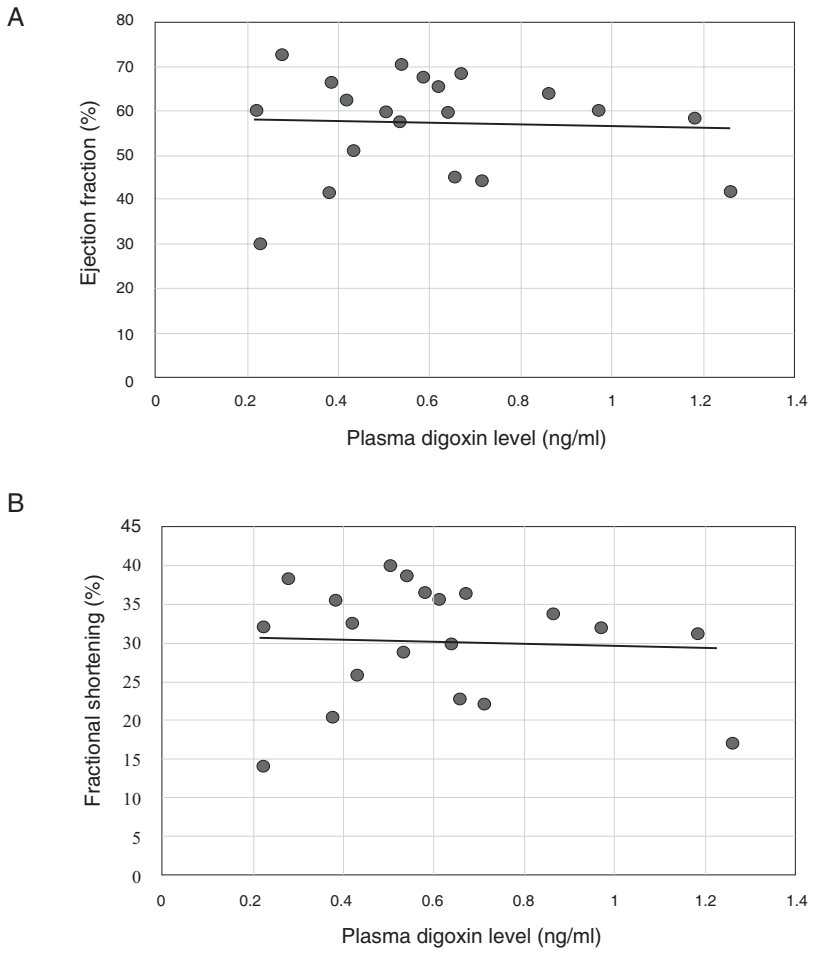

Figure 1. Correlation of plasma digoxin level with ejection fraction (A) and fractional-shortening (B) at the end of observation

use of antibiotics in some patients may have contributed to the bioavailability of digoxin. However, we do not have data on this bacterium in our study subjects.

In this study, 14/20 of patients had normal ejection fraction (56-78%) and fractional shortening (28-44%). However, not all patients with normal digoxin levels

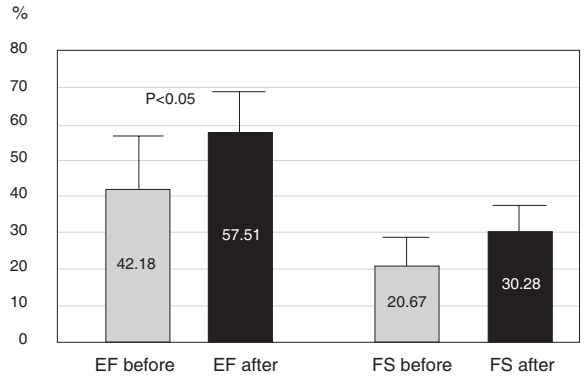

Figure 2. Ejection fraction (EF) and fractional-shortening (FS) before and after treatment with digoxin (n=16)

had normal ejection fraction, and conversely, some patients with low digoxin level had normal ejection fraction. This phenomenon has contributed to the lack of a significant association between plasma digoxin level and ejection fraction, and fractional shortening, as demonstrated in **Figure 1**. This observation suggests that disease severity may have a greater effect on ejection fraction independently of digoxin level. Apart from disease severity, different types of disease entities might have different sensitivities in responding to digoxin treatment. Patients with cardiomyopathy and a primary defect in myocardial contractility would respond less to digoxin than those with valvular heart diseases with apparently intact myocardial function. In our study, 12 out of 20 patients had dilated cardiomyopathy, while three patients had ventricular septal defect and three others had rheumatic heart disease. Thus, most of the response to digoxin was in cardiomyopathy patients with an unimpressive response to digoxin.

When the patients were regrouped according to normal or low plasma digoxin level, no significant differences in ejection fraction or fractional shortening were observed (**Table 3**). However, a separate analysis of patients with cardiomyopathy revealed a positive trend between plasma digoxin level and ejection fraction or fractional shortening. However, due to the small sample size, this correlation was not statistically significant (data not shown).

Sixteen of the subjects had echocardiographic data before digoxin treatment. When these data were compared with data after at least one month of digoxin treatment, significant increases in ejection fraction and fractional shortening were clearly observed (**Figure 2**). Hence, during digoxin treatment, patients experienced an improvement of cardiac performance. This evidence supports the use of digoxin, especially in ambulatory heart failure patients, owing to the ease of its oral administration. Other more widely used inotropic drugs, such as dopamine and dobutamine, must be administered intravenously, therefore, they are only suitable for inpatient settings.

Digoxin is an old drug and its usage is now limited to conditions where optimal treatment with diuretics and ACE-inhibitors is not attainable, or in those with atrial fibrillation or flutter.[13,14] To our knowledge, no other study has directly evaluated the effect of plasma digoxin level on ejection fraction. Several studies have indirectly measured plasma digoxin level and its correlation with hemodynamic and functional class improvement, as well as reduction of mortality.[15-17] Rathore *et al*. assessed for possible correlations between plasma digoxin level and mortality and length of hospital stay in adult patients. However, plasma digoxin level in the study was only used to show that all patients had comparable initial ejection fraction.[15] Further outcomes according to digoxin level were not analyzed. Many large clinical trials have been conducted long ago on adult subjects. Uretsky *et al*. conducted a study on patients with mild to moderate heart failure (EF <35%) and reported a positive improvement of ejection fraction in patients receiving digoxin alone or in combination with captopril.[16] However, another study on patients with heart failure with EF of <45%, showed no significant difference in mortality in patients who had or had not received digoxin. But, there was a significant difference in the incidence of hospitalization.[17]

Packer *et al* reported the effect of digoxin withdrawal in heart failure patients with NYHA class II and III, ejection fraction of 35% or less, under the treatment with digoxin, diuretics, and ACE-inhibitor, and found higher incidence of worsening of heart failure in group withdrawn from digoxin compared to those who continued the digoxin.[18] Ejection fraction is a general proxy of cardiac function improvement. The inotropic effect of a drug may not be the most important factor. We cannot rule out a contribution of diuretics or ACE-inhibitors on the apparently positive effect of digoxin on increased EF. As the diuretic lowers the preload by reducing plasma volume, and ACE-inhibitor

lowers the afterload by inducing peripheral vasodilation, these two treatments consequently improve ejection fraction, and hence, fractional shortening. It is well known that ACE-inhibitors and diuretics comprise the main treatment for heart failure.

In conclusion, a smaller maintenance dose of digoxin is sufficient to reach adequate, therapeutic plasma digoxin levels. Administration of digoxin is associated with significantly increased ejection fraction in all of the patients, however, a significant increase of LVEF in an individual patient was observed.

Conflict of Interest

None declared.

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