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by Sari Yunita Sukmawati Noer

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Sari Yunita Sukmawati Noer[1], Mahrus A Rahman[1,*], Budi Utomo[2]

Sari Yunita Sukmawati Noer[1], Mahrus A Rahman[1,*], Budi Utomo[2]

[1]*Pediatrics Department, Faculty of Medicine, Airlangga University, Surabaya, INDONESIA.*

[2]*Faculty of Public Health, Airlangga University, Surabaya, INDONESIA.*

Correspondence

Mahrus A Rahman

Pediatrics Department, Faculty of Medicine Airlangga University, Surabaya, INDONESIA.

Email: mahrus_rahman@yahoo.com

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is one of the complications due to acyanotic congenital heart disease. New treatment approach using natural ingredients from plants has been demonstrated *in vitro* to prevent and improve vascular remodeling in PAH. **Objective:** This study aimed to analyze the effect of pomegranate extract on N-terminal pro brain natriuretic peptide (NT pro BNP) and asymmetric dimethylarginine (ADMA) levels in children with PAH in acyanotic CHD. **Method:** This study is a double-blind, quasi-experimental text with pre-test, post-test, and control group approach to children aged one month to 10 years old in Outpatient Department of Pediatric Cardiology Department/Pediatrics Department RSUD Dr. Soetomo in the period of February-October 2022, alongside met the inclusion criteria. Data were analyzed using Wilcoxon and Mann-Whitney test with 95% CI. **Result:** The study cohort included 15 subjects in the placebo group and 15 subjects in pomegranate extract group. The study was predominantly female (53,3%) with a mean age of each group, i.e., placebo group was 49 months, and pomegranate extract group was 58 months. The mean level of NT pro-BNP in the pomegranate extract group was 29.31 ± 33.55 ng/L (p= 0.008) and its mean ADMA level was 5619 ± 6166 ng/L (p= 0.173). As for the difference of NT pro-BNP and ADMA level changes after the intervention did not show a significant difference (p-0,330; p=0,885, respectively). **Conclusion:** No significant effect towards NT pro-BNP and ADMA levels found with giving pomegranate extract to children with PAH due to acyanotic CHD.

Key words: Congenital heart disease, Pulmonary artery hypertension, Terminal pro brain natriuretic peptide, Asymmetric dimetylarginine, Punica Granatum.

INTRODUCTION

Pulmonary arterial hypertension is children's most common complication of acyanotic congenital heart disease due to pulmonary vascular remodeling.[1] Pulmonary arterial hypertension (PAH) was defined as mean pulmonary artery pressure (mPAP) ≥25mmHg measured by right atrium catheterization at rest. Pulmonary arterial hypertension was reported to be 15-50 cases in every 1000 adults and 2-16 cases in every 1000 childbirths.[2] Various etiologies can cause pulmonary arterial hypertension. According to the United Kingdom National Pulmonary Hypertension Audit, the second most common cause of PAH is congenital heart disease (CHD). Demographic data show an increase in the number of CHD patients in children. The estimated prevalence of CHD was around 6 to 10 per 1,000 live births, and 4-15% of patients with CHD will develop PAH.[3] Despite significant advances in treatment, PAH has a poor prognosis, with an estimated mortality of between 25% - 60% within five years of diagnosis.[4]

The mechanism of PAH caused by acyanotic CHD occurs because of the gap between the ventricles, the atria, and the arteries, which causes an increase in blood flow and pressure in the pulmonary veins, which induces vascular remodeling of the pulmonary artery wall layer, and then cause right ventricular failure and death.[5] In PAH, pulmonary vasculature is damaged, forming reactive oxygen species (ROS). The formation of ROS in PAH was caused by the formation of the enzyme NADPH oxidase, eNOS uncoupling, decreased DDAH activity, and increased stimulation of protein arginine N-methyltransferase (PRMT-1), thereby increasing asymmetric dimethyl-l-arginine (ADMA). ROS have an impact on the loss of endothelial barrier function and induce the activation of proinflammatory cytokines (IL-6, IL-1b, MCP-1, and TNF-a), causing degradation of the extracellular matrix (matrix metalloproteinases) and the release of growth factors (fibroblast growth factor and transforming growth factor). factor-β). It will induce hypertrophy and proliferation of pulmonary vascular smooth muscle cells. In addition, in PAH, there is also a decrease in the vasoactive mediator nitric oxide (NO), prostacyclin, and overexpression of the vasoconstrictor endothelin-1, which results in pulmonary artery vasoconstriction.[6] Until now, therapy based on the pathobiology of PAH is still being developed. Various types of drugs are used in PAH patients to inhibit active pulmonary vasoconstriction and prevent progression by improving pulmonary artery remodeling.[7]

Pomegranate (*Punica granatum L*) is a fruit of the Punicacea family, subfamily Punicoideae

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which is currently widely used, especially for health. Pomegranates have essential compounds that are found in all parts of the fruit. Approximately 50% of the total weight, consists of the skin which is an important source of bioactive compounds such as phenolics, flavonoids, ellagitannins (ETs), proanthocyanidin compounds, minerals and complex polysaccharides.[1] Pomegranate has derivative components in vasculoprotective, reducing oxidative stress and atherogenesis.[8,9] The most crucial phytochemical in pomegranates is punicalagin. Punicalagin has a high antioxidant effect, anti-inflammatory effect, and anti-fibrotic effect.[8,10,11] As an antioxidant, punicalagin reduces oxidative stress and lipid peroxidation, thereby improving endothelial cell function by increasing NO, lowering glucose, and preventing platelet aggregation. Punicalagin acts as an anti-inflammatory by reducing the expression of vascular inflammatory markers thrombospondin, the cytokine TFGP 1, and increasing plasma nitrite and nitrite. In addition, the anti-inflammatory effect of punicalagin is also through its inhibition of NADPH oxidase.[8] According to several studies, the punicalagin content in pomegranate has also been used as a new alternative for inflammatory diseases involving oxidative stress processes such as IBD, rheumatoid arthritis, and atherosclerosis.[12] Punicalagin also has an anti-fibrotic effect by inhibiting the progression of fibrosis in the tunica adventitia of the pulmonary artery in PAH model mice through inhibition of TGF-β1 expression, type I collagen, and an increase in the MMP-1/TIMP-1 ratio.[13]

Various noninvasive methods have been developed to assess the evaluation of PAH therapy. The European Society of Cardiology Guidelines reveals no specific markers currently used in PAH. Until now, NT-proBNP is the only biomarker widely used in clinical trials to determine risk stratification and assess treatment response.[14] NT-proBNP correlates with myocardial dysfunction (right ventricular hypertrophy due to PAH) and provides prognostic information during diagnosis and further management. NT-proBNP has 100% sensitivity and 94% specificity in determining the progression and mortality of PAH.[15] In addition to NT-pro BNP, there are other biomarkers, namely ADMA, a potential biomarker that describes endothelial dysfunction, so it can predict morbidity and mortality in PAH.[16] This article aims to analyze the effect of pomegranate extract on levels of N-terminal pro-brain natriuretic peptide (NT pro-BNP) and Asymmetric dimethylarginine (ADMA) in pulmonary artery hypertension in children with cyanotic congenital heart disease.

MATERIALS AND METHODS

Study design and population

This research is a quasi-experimental double-blind study using a pre-test and post-test control group approach and consecutive sampling methods. This research measured ADMA and NT Pro BNP levels in pulmonary artery hypertension of children with congenital heart disease who receive standard therapy for arterial hypertension pulmonary. Two groups were divided into groups that got administration of pomegranate fruit extract and standard therapy, and the other groups got placebo and standard therapy (control group) for pulmonary hypertension. The study was double-blind because neither the researchers nor the research subjects knew whether the treatment was given pomegranate extract (PE) or a placebo. After all, the pharmaceutical installation carried out the drug administration. The population of this study was all children with pulmonary arterial hypertension caused by acyanotic congenital heart disease who went to the Pediatric Cardiology Outpatient Installation at the Integrated Service Center of RSUD Dr. Soetomo. The sample in this study was children aged one month – 10 years with acyanotic congenital heart disease who developed pulmonary arterial hypertension based on echocardiographic examination and received standard therapy for pulmonary arterial hypertension. The research sample was selected based on predetermined inclusion and exclusion criteria. This study was conducted from February 2022 to October 2022. The sample size was calculated based on Bebchuk and Wittes' research results. The results obtained were 15 people in each test group.

Data retrieval and collection procedures

The primary data are collected based on examination data on mean pulmonary artery pressure, ADMA levels, and NT pro-BNP levels in both groups from February 2022 to October 2022. The materials used in this study were sildenafil and beraprost in powder/capsule form provided by the pharmacy at the outpatient installation at RSUD Dr. Soetomo Surabaya, and pomegranate extract produced by Xi'an Biof Bio-Technology Co., Ltd. (Room 1-1111, High-tech Venture Park, no.69, Jinye Road, Gaoxin District of Xi'an, Republic of China). Pomegranate extract was made in the form of syrup by the pharmacy of Dr. Soetomo Hospital Surabaya, while the placebo was also in the form of syrup in the same form as PE, which was labeled by the pharmacy of Dr. Seotomo Hospital Surabaya. The instruments used in this study were data collection sheets to record the characteristics of the research subjects, echocardiography brand GE model LOGIC P6, and blood collection facilities.

Data analysis

All data were tested for normality distribution using the Kolmogorov-Smirnov test. Changes in ADMA and NT pro-BNP levels before and after treatment in each group were tested using the Wilcoxon statistical test. Differences in changes in levels of NT pro-BNP and ADMA between the treatment group and the control group were tested by the Mann-Whitney test.

Ethical clearance

The research subject must obtain written consent from a parent or guardian. This study also received approval from the Health Research Ethics Committee of RSUD Dr. Soetomo Surabaya no 0353/KEPK/I/2022.

RESULT

In this study, 40 research subjects met the inclusion criteria. Patients with congenital heart disease who experienced PAH and were taken as samples were divided into two groups: the group receiving standard therapy and placebo and the group receiving standard therapy and PE. The division into two groups was done through simple randomization by the pharmacy team of RSUD Dr. Soetomo Surabaya. After randomization, there were 20 patients receiving standard therapy and PE. However, at the end of the observation, 15 patients underwent post-therapy evaluation, four patients were excluded due to spontaneous closing heart defects, and one patient underwent heart defect correction surgery. In the group that received standard therapy and placebo, there were 20 patients, with the number of patients undergoing therapy until the completion of the observation as many as 15. Of the 20 patients in the second group, two experienced heart defect closure, one underwent cardiac defect closure catheterization, and two dropped out because the patient did not come on time to take the drug despite confirmation *via* cellular.

Based on age, in this study, the minimum age was four months, and the maximum age was 120 months, with an average age of 53.90 ± 37.45 months. The median age in the placebo group of this study was 36 months, with an age range of 4-120 months, while the median in the PE group was 60 months, with a range of 5-120 months. The largest age group in this study ranged from >5-10 years, with a percentage of 36.7%.

This study found fewer males (46.7%) than females (53.3%). In this study, all subjects had been diagnosed with PAH in patients with CHD based on echocardiography. Based on the type of acyanotic

CHD defect, there were various variations of acyanotic CHD in the total study subjects. The majority of acyanotic CHD subjects in this study were VSDs of 43.3% with large defect sizes. The PAH assessment was assessed based on measurements of pulmonary artery systolic pressure obtained from continuous waves of tricuspid jet regurgitation in a four-chamber apical view plus pressure in the right atrium (Pra) of 6.7 mm Hg. It was found that the majority of study subjects had severe TR by 50%. The results showed no significant differences in age, sex, type of heart defect, and pulmonary artery pressure in the two test groups before intervention therapy with a p>0.05. It shows that the characteristics of the study subjects in the two test groups were homogeneous, and there were no confounding factors.

ADMA levels in both groups were also tested for normality before intervention was given. In the placebo group, a normality test value of p = 0.046 indicated that the data were not normally distributed. In contrast, the PE group with a p = 0.000 showed that the data was not normally distributed. Then the data were analyzed using a non-parametric test, namely the Mann-Whitney test with a p=0.395 value which stated that there was no significant difference in the ADMA level data in the two test groups.

The NT pro BNP levels in the normality test before the intervention were given, the results in the placebo group obtained a normality test value of p = 0.132, indicating a normal distribution of data, while the PE group with a p = 0.000 showed an abnormal distribution of data. Furthermore, the data were analyzed using a non-parametric test, namely the Mann-Whitney test with a p = 0.468, which stated that there was no significant difference in the data on levels of NT pro-BNP in the two test groups. The results of the normality test can be seen in Table 2.

Table 1: Distribution of the characteristics of the research subjects.

Characteristics	Placebo n (%)	PE n (%)	P-value
Age (months). mean	49.4 ± 40.4	58.4 ± 35.02	0.299[*b]
1-5 months	1(6.7)	1(6.7)	
6-11 months	2(13.3)	1(6.7)	
1-2 year	3(20)	2(13.3)	
>2-5 year	5(33.3)	4(26.7)	
>5–10 year	4(26.7)	7(46.7)	
Gender			1.00[*a]
Boy	7(46.7)	7(46.7)	
Girl	8(53.3)	8(53.3)	
Type of heart defect			0.809[*b]
ASD	5(33.3)	4(26.7)	
VSD	6(40.0)	7(46.7)	
PDA	2(13.3)	2(13.3)	
ASD + VSD	1(6.7)	0(0.0)	
ASD + PDA	0(0.0)	2(13.3)	
VSD + PDA	0(0.0)	0(0.0)	
ASD + VSD + PDA	1(6.7)	0(0.0)	
Size of heart defect			0.87[*a]
Small	2(13.3)	1(6.7)	
Medium	5(33.3)	6(40.4)	
Large	8(53.3)	8(53.3)	
Pulmonal Arterial Hypertension			0.78[*b]
Mild TR	1(6.7)	7(46.7)	
Moderate TR	5(33.3)	2(13.3)	
Severe TR	9(60.0)	6(40.0)	

p[a] = tested using Chi-squared. pb = Mann-Whitney Test. *p-value above 0.05 means no difference between the placebo and PE groups.

Table 2: Normality test in both groups.

Normality Test	Placebo	PE	p
ADMA	0.046	0.000	0.395[*b]
NT pro BNP	0.132	0.000	0.468[*a]

p[a] = Mann-Whitney Test. *p-value above 0.05 shows normally distributed data.

Table 3: Laboratory characteristics in the placebo and PE groups.

Examination (Pre)	Placebo group Median (Min-Max)	Treatment group Median (Min-Max)	p
Hemoglobin	11.9 (10.2-15.3)	10.9 (9-16.2)	0.50[*a]
Leukocytes	11980 (7120-19100)	8590 (370 – 15320)	0.128[*a]
Platelets	348.10[3] (231-497. 10[3])	333.10*3 (165-539.10*3)	0.67[*b]
BUN	11.8 (4-22)	10.3 (6-19)	0.56[*b]
Creatinin	0.53 (0.2-0.53)	0.428 (0.12-1.18)	0.136[*b]

p[a]= tested using Mann-Whitney Test, p[b] = T test, * p-value above 0.05 means that there is no difference between the variables

Table 4: Pro-BNP NT levels in the placebo and PE treatment groups.

Group	Intervention		Mean
Plasebo	Min	16.8	51.23
	Max	119.7	31.37
PE	Min	10.7	62.52
	Max	301.7	29.31

Table 5: ADMA levels in the control and treatment groups.

	Group		Mean
Plasebo	Min	2176	8898
	Max	24694	4841
PE	Min	906	8602
	Max	44918	5619

Table 6: Effect of PE on pro-BNP NT levels in both groups.

Group	Placebo			PE		
	Pre	Post	p	Pre	Post	p
95% CI	51.23±31.63	31.37±19.16	0.037[*a]	62.52±79.11	29.31±33.55	0.0008[*b]

p[a]= tested using paired sample test, p[b]= Wilcoxon Signed Ranks Test, * p-value <0.05 means significant variable based on the statistics.

Table 7: Effect of PE on ADMA levels in both groups.

Group	Placebo			PE		
	Pre	Post	p	Pre	Post	p
95% CI	8998 ± 6389	4841 ± 2899	0.041[*b]	8602 ± 10799	5619 ± 6166	0.173[*b]

p[b]= Wilcoxon Signed Ranks Test, * p-value <0.05 means significant variable based on the statistics.

Table 8: Changes in pro-BNP NT levels between the control group and the PE group.

Group	n	Median (min-max)	p
Placebo	15	-12.57 (-105.19 until 22.23)	0.330[*a]
PE	15	-33.21 (-170 until 61.96)	

p[a]tested using Mann-Whitney Test, * p-value <0.05 means significant variable based on the statistics.

Table 9: Changes in ADMA levels between the control group and the PE group.

Group	n	Median (min-max)	p
Placebo	15	-2082 (-23681 until 4077)	0.885[*a]
PE	15	-2625 (-36367 until 13272)	

p[a]tested using Mann-Whitney Test, * p-value <0.05 means significant variable based on the statistics.

The research subjects underwent routine blood tests and kidney function before receiving treatment in each group, along with the ADMA and NT pro-BNP levels listed in Table 3.

The results of NT pro-BNP measurements in PAH pediatric patients with CHD showed that the average level of NT pro-BNP before intervention was 51.23 ng/L in the placebo group and 62.52 ng/L in the PE group. The highest NT pro BNP value among all subjects before treatment was 301.729 ng/L. The results of NT pro-BNP levels before the intervention can be seen in Table 4.

ADMA measurements in PAH pediatric patients with CHD showed that all study subjects had an average ADMA level before the intervention of 8898 ng/L in the placebo group and 8602 ng/L in the PE treatment group. The highest ADMA value among all subjects before treatment was 44918 ng/L. The average results of ADMA levels before the intervention can be seen in Table 5.

In this study, NT pro-BNP examination was carried out in both the placebo and PE groups before and after the intervention. The mean levels of NT pro-BNP in the PE group post-PE administration were 29.31 ± 33 ng/L, while the average level of NT pro-BNP in the placebo group post administration of placebo was 31.37 ± 19.16 ng/L. Statistically, before and after the intervention showed a significant decrease in NT pro BNP levels in both groups with p = 0.037 (control group) and p = 0.008 (PE group). The results can be seen in Table 6.

In this study, ADMA examination was carried out in both the placebo and the PE groups before and after the intervention. From the results of the ADMA examination, an analysis was carried out. The mean ADMA level in the PE group after the intervention was 5619+ 6166. Meanwhile, the mean ADMA level in the placebo group post-placebo was 4841±2899. The ADMA level in the group before and after the intervention showed a decrease in ADMA levels in both groups. However, statistically, ADMA levels in the group before and after the intervention showed a significant decrease in ADMA levels only in the placebo group with a p-value = 0.041. However, there was no significant difference in ADMA levels after being given intervention for three months in the group receiving PE with a p-value = 0.173. The results of the effect of PE on ADMA levels can be seen in Table 7.

In this study, both placebo and PE groups were tested for normality distribution using the Kolmogorov-Smirnov test. In the change in NT pro-BNP in the placebo group, a significance value of p=0.018 was obtained, meaning that the data was not abnormally distributed, and in the PE group, a significance value of p=0.001 was obtained, which meant that the data had an abnormal distribution. Furthermore, further analysis was carried out with the Mann-Whitney Test to determine the difference in delta levels of NT pro-BNP between the control group and the PE group. Table 8 shows no difference in changes in NT pro-BNP levels before and after supplementation in the control group and the PE group with p=0.330. Meanwhile, Table 9 shows no difference in ADMA levels before and after the intervention in the placebo group and the PE group (p=0.885). Changes in NT pro-BNP and ADMA levels between the control group and the PE group can be seen in Table 8.

DISCUSSION

Pulmonary hypertension (PAH) caused by acyanotic congenital heart disease is a complex condition involving the heart, lungs, and systemic. PAH contributes to morbidity and mortality in the pediatric population. In this study, the mean age of children with PAH due to acyanotic CHD was 49.40 ± 40.44 months in the placebo group and 58.40 ± 35 months in the PE group. The results of this study follow research by Epcacan *et al*, 2019, the average age of children with pulmonary artery hypertension caused by CHD is 4-5 years old.[17] Research at RSUD Dr. Soetomo by Sidqoh 2020 stated that the characteristic distribution of PAH was caused by congenital heart disease at 0-5 years (86.67).[18]

Pulmonary artery hypertension occurs due to CHD secondary to left-to-right shunt. Defects generally cause PAH, namely VSD, ASD, and PDA.[17] Based on the results of the characteristics of the subjects of this study, the most common type of congenital heart disease suffered by research subjects was VSD 43% (13/30), followed sequentially by ASD 30% (9/30), PDA 13.3% (4/30), and combination defect 33.3% (4/30. The most prominent defect size is a significant defect (53.55). Research by Epcacan *et al.*, 2019, VSD is CHD's most common type of defect that causes PAH. However, it is different from research at Dr. Soetomo Hospital by Sidqoh 2020 explained that ASD was the most common cause, 35.56%. In this study, it was found that there were more girls than boys, which is in line with research by Barst 2003 with a comparison of PAH in CHD girls and boys of 1.8:1, and there was no significant difference in younger children compared to older children.[19] On pulmonary artery pressure measurements, most subjects had PAP with a severe TR of 50% (15/30). Studies with character exposure Eristics in children with PAH caused by CHD conducted in Indonesia in 2020 stated that the most common cause of PAH in acyanotic CHD was ASD, primarily found in female patients, with mild PAH of 52%, and large defect size (66%).[20]

In this study, the average level of NT pro-BNP in all study subjects increased before intervention was given. A diagnostic study in Atlanta in 2021 stated that the median NT pro-BNP result was significantly higher in children with PAH. ROC curve analysis shows that NT pro-BNP has a specificity of 87% for the diagnosis of pulmonary artery hypertension.[21] Research by Williams et al. showed that NT pro-BNP correlated with mPAP (r=0.62), PVR (r=0.81), RAP (r=0.53), and cardiac index (r= 0.50), which can describe the hemodynamic condition of the lung and also as a predictor of survival. Sanli *et al,*[22] mention that homocysteine, ADMA, and NO levels in plasma were determined by immunosorbent assay. Homocysteine and ADMA had higher levels in the PAH-CHD group (n = 30) than among CHD patients with left-to-right shunt but no PAH with p<0.001 and healthy control subjects (P<0.001). In addition, a systematic literature review study stated that the use of BNP and NT-proBNP can be used as biomarkers in the diagnosis and stratification of PAH risk and prognosis.[23] A longitudinal cohort study in the Netherlands performed serial measurements in 82 children with PAH, concluding that high levels of NT pro-BNP are associated with higher WHO-FC, higher risk of death, and the need for heart transplantation. NT pro-BNP levels were higher in the non-survivor group than in the survivor group from time to time, with a p-value <0.005.[24]

In this study, there was an increase in ADMA levels in all research subjects. This is in line with a study in Egypt where ADMA levels were found to be significantly higher in patients with pulmonary arterial hypertension compared to only CHD. This increase was positively correlated with increased severity of pulmonary arterial hypertension. Another study by Sanli *et al.* stated that higher levels of ADMA were found at higher pulmonary pressures, and pulmonary vascular resistance was reflected in an increase in right ventricular diameter.[22] Elevated ADMA has been found in children and adolescents who exhibit endothelial dysfunction, including hypertension, hypercholesterolemia, chronic kidney disease, and diabetes mellitus. Measurement of ADMA in the pediatric population must consider heterogeneity, an unavoidable feature in pediatric studies. From birth to adolescence, many physiological changes occur in the body. As much as 20% of ADMA is excreted in the urine, and kidney function differs from birth through adolescence, ADMA levels vary widely in the pediatric population because of the broad age range. These factors affect ADMA levels in the pediatric population requiring further research.[25]

In acyanotic congenital heart disease, there is an increase in blood flow through defects between the atria or between the ventricles causing an increase in pulmonary artery pressure, causing vascular remodeling

and involving endothelial cell dysfunction, abnormal pressure shifts, vascular wall stretching, and imbalance of vasoactive mediators such as prostacyclin, thromboxane (TXA2). ET-1 and endothelin A (ETA). Increased pulmonary vascular resistance in pre-tricuspid lesions results in increased right ventricular volume and right ventricular hypertrophy. In post-tricuspid lesions, high-pressure left-to-right shunt results in left ventricular volume overload and pulmonary circulation. Furthermore, cardiomyocytes in the heart ventricles will release NT pro-BNP and BNP hormones in response to stretching caused by an increase in ventricular blood volume. Research by Sauza states that NT-pro-BNP levels show a high correlation with hemodynamic parameters, such as mean pulmonary artery pressure (MAP) with a p<001 value, right artery pressure (RAP) with P<0.004 and FC class with a p<0. 02.[26] Research by Samantha L. Wronski studied the application of non-invasive tests to assess long-term outcomes and predictions in patients with PAH. This study, using 836 data and 65 journals explaining NT pro-BNP, 6MWD, and FC function as prognostic indicators of measurable outcomes, namely morbidity and mortality which, can be assessed early to determine the course of therapy and improve therapy outcomes.[27]

Pomegranate (*Punica Granatum. L*) is a fruit with high antioxidant content. Pomegranates contain polyphenols, which include ellagitannins, gallotannins, and flavonoids. The main thing is that punicalagin (PG) is the main ellagitannin component isolated/extracted from pomegranate, which has high antioxidant content. Pomegranate extract also has anti-inflammatory and anti-proliferative effects by inhibiting MAPK and endothelin activity, thereby reducing ET-1 levels. According to research by Hashemi in 2010,[28] in a randomized clinical trial (RCT), PE contains antioxidants and improves endothelial function in adolescents with metabolic syndrome, as measured by the assessment of dimensions and dilatation of the basal brachial artery *via* ultrasound. Ganesha also researched the effects of PE as an antioxidant and anti-inflammatory in 2019 by observing the histopathology of rat lung tissue.[29] PE inhibited the increase in the number of cells expressing ET-1. Endothelin-1 *via* ETA and ETB receptors increases intracellular calcium (Ca+) and causes pulmonary artery vasoconstriction. Endothelin A activates PKC and p38-MAPK through Phospholipase C (PLC), which stimulates the proliferation of pulmonary artery smooth muscle cells, with the result being the thickening of the tunica media of pulmonary artery smooth muscle.[30] In this study, the pomegranate extract used was standardized PE containing 40% ellagic acid in powder form. The dose of PE used is 120 mg/kg/day with an ellagic acid content of 48 mg/kg/day. Dosage equivalence based on the conversion table from Luarence and Bacharach 1964. The initial dose was obtained in an *in vitro* study by Hidayat *et al* 2016, and Rahman *et al*, 2018, where male rats were given PE at a dose of 150 mg/kg BW/day.

Research on PE as an alternative therapy in children with PAH caused by CHD with an evaluation of biomarker therapy has not been studied. However, the use of pomegranate *in vitro* until now has been carried out. It has been proven to be an alternative therapy to overcome vascular remodeling in pulmonary blood vessels that occurs in PAH as a complication of CHD. The use of ADMA and NT pro-BNP biomarkers as a non-invasive method for evaluating standard PAH therapy is also being developed in humans. This study showed a statistically significant decrease in NT pro-BNP levels in both intervention groups, with a higher decrease in the PE group (p = 0.008) than in the placebo group (p = 0.037). Decreased levels of NT pro-BNP in the PE group compared to the placebo group should be monitored on clinical hemodynamic parameters and echocardiographic examinations to objectively ascertain the effect of PE in improving vascular remodeling in PAH-CHD.

Furthermore, in this study, an analysis was carried out using the Mann-Whitney test to determine the difference in change of levels of NT pro-BNP pre and post-intervention in the placebo and PE groups. Based on the results of the Mann-Whitney test, it was found that there was no difference in changes in NT pro-BNP levels before and after the intervention in the two groups (p-value = 0.330). In this study, we also added a correlation test between changes in the two biomarkers, namely NT pro-BNP and ADMA, with the Spearman test, and the results obtained that the two biomarkers correlated with p-value = 0.005.

Based on the results of this study, after the intervention, ADMA levels in the two intervention groups experienced a decrease in ADMA levels, with the difference in the decrease in ADMA levels being higher in the placebo group than in the PE group. The decrease in ADMA levels was statistically significant in the placebo group with p=0.041. In the PE group, it was found that ADMA levels decreased after PE administration, but in the statistical test, the decrease in ADMA levels in the PE group was not significant with p-value = 0.173, which means that there was no difference in ADMA levels before and after PE was given. In the final result of measuring ADMA levels in each test group, it was concluded that there were differences in ADMA levels before and after the intervention only in the placebo group. Furthermore, in the two intervention groups, the Mann-Whitney statistical test was also carried out, and it was declared not significant with p-value = 0.885, which means that there were no differences in changes in ADMA levels pre and post-intervention both in the placebo group and the PE group. The results of this study were also complemented by a correlation test with Spearman's test between the two biomarkers after the intervention, with the results that there was a correlation between ADMA and NT pro-BNP levels with a correlation value of p < 0.001. ADMA levels in the PE group before treatment were lower than in the placebo group. According to the literature, lower levels before PE intervention could be due to ADMA being affected by drugs that improve endothelial dysfunction and NO availability, such as ACE inhibitors and phosphodiesterase 5 inhibitors. A study in Egypt evaluated sildenafil therapy in children aged 14-28 months for six months with PAH due to CHD using clinical data, echocardiography, hemodynamic parameters, and ADMA as biomarkers. The study stated that the results of ADMA levels were significantly lower in patients receiving sildenafil compared to the control group.[31] Meanwhile, according to research by Mass R (2005), the administration of ACE inhibitors and ARBs can reduce plasma ADMA levels by 12-20%.[32] In this study, the duration of administration of ACE inhibitors and sildenafil was not previously included in the research data on all study subjects in both groups. So, it is possible to influence ADMA levels before intervention in the PE group. Another thing that might cause differences in ADMA levels before and after the intervention is the administration of sildenafil therapy in the range of 0.5-2 mg/kg BW/time, which was optimized during the study in the placebo group. The decrease in ADMA levels was higher in the placebo group, possibly since subjects received heterogeneous doses of sildenafil and a long duration of administration.

We also evaluated differences in the duration of PE therapy in humans and experimental animals. How many studies in children related to standard therapy for PAH using markers as therapy evaluation require at least six months? Wu *et al*., 2015 studied the effect of supplementing PE orally with a capsule dose of 1000 mg/day for seven days over six months in patients with chronic kidney failure using blood pressure parameters, inflammatory markers, and oxidative stress. This study showed that PE could reduce blood pressure and increase antioxidant activity in haemodialysis patients but PE supplementation does not affect other markers, such as inflammation and oxidative stress.[33] In contrast to research by Faraq, who evaluated the administration of sildenafil therapy in children with PAH caused by CHD and used the ADMA marker as a therapy evaluation. A decrease in ADMA levels occurred after six months of therapy, but in this study, it was unclear

how long the study subjects had PAH. The results of this study stated that high levels of ADMA correlated with increasing the severity of pulmonary artery hypertension.[31] It can be concluded that to get changes in ADMA markers as a therapeutic evaluation requires a minimum of 6 months.

Another study related to the benefits of PE in experimental animals has been conducted by Shao *et al.* According to his research, the effect of PE as a new vasculoprotective was obtained for a minimum duration of 2 weeks. Experimental animal models also affect the exact age that can be representative of the target human age in research. Based on the life span, one human year is equal to 13.67 days in mice. This simple calculation may not find universal relevance in biomedical research because the acceleration of mouse life stages is not uniform to that of humans, but it is crucial to know the age (days) of a mouse model in human years for research purposes. Accurate estimation of the age of experimental animal models with humans is the primary and essential criterion in animal-based research to determine the duration of intervention when applied to humans.[34] From the study of Shao *et al.*, it can be concluded that the administration of PE in humans can provide a minimal vasculoprotective effect within one year.[11]

This study is the first to analyze the effect of pomegranate extract on pulmonary arterial hypertension caused by congenital heart disease using invasive biomarkers as markers for evaluating therapy. An echocardiographic examination determined pulmonary artery pressure measurement with a sensitivity of 89% and a specificity of 76%. One of the biomarkers used in this study is ADMA which has a specificity of 82.8% and a sensitivity of 63-90%, influenced by drugs and several clinical conditions. Not many markers show vascular remodeling markers that can be used and examined in human plasma. And in this study there were differences in the dosage of sildenafil as standard therapy for PAH in the study subjects.

CONCLUSION

This study showed that pediatric patients with PAH caused by acyanotic CHD had increased levels of NT pro-BNP and ADMA. After the intervention, a more significant decrease in NT pro-BNP levels was found in the pomegranate extract group compared to the placebo group. In contrast, a significant decrease was only found in the placebo group for ADMA levels. There was no difference in NT pro-BNP and ADMA levels after intervention in the PE group and the placebo group in children with PAH with acyanotic CHD.

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ABOUT AUTHORS

Dr. Mahrus A. Rahman, dr., Sp.A(K) is a lecturer and staff at the Pediatric Cardiology Department, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. He completed a Bachelor of Medical Doctor at Universitas Airlangga back in 1987. He continued his studies in the Pediatric Department, Faculty of Medicine, Universitas Airlangga, graduating in 1995. After that, he took a fellowship training in Pediatric Cardiology at UN Malaysia in 2001. In 2005, he took a consultant in pediatric cardiology at the Faculty of Medicine, Universitas Indonesia. He earned his doctorate degree in 2016.

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/100

GENERAL COMMENTS

Instructor

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