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CONTENTS

THE QUALITY OF ANTIBIOTIC USE AMONG PATIENTS FROM INTERNAL MEDICINE AND SURGICAL SERVICE

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ABSTRACT

It is well-known that hospitals are health facility with the widely use of antibiotics. It is about 13-37% from the total hospitalized patients in developed countries use antibiotic, even in developing countries can reach 30-80%. There is identified correlation between antibiotic use and the development of bacterial resistance. Even though the resistance cannot be eliminated, but its development can be suppressed by the increasing of prudent use of antibiotics. The aim of this study was to determine the quality of antibiotic use on internal medicine and surgical patients in Aisiyah Hospital Bojonegoro. The study was a prospective cross sectional observational analytical study of among patients of internal and surgical who received antibiotic therapy in the period of August - September 2017. The total 50 samples were collected in this study which consists of 33 internal medicine and 17 surgical patients. From 50 samples, there were 16 types of antibiotics with the total use of 81 of antibiotic use. As the result, in internal medicine patients there were 22 (40%) of appropriate use of antibiotics, 4 (7.27%) of inappropriate use and 29 (52.73%) use of antibiotics without indication. In surgical patients, there were 12 (46.15%) of appropriate use of antibiotics, 2 (7.69%) of inappropriate use and 12 (46.15%) use of antibiotics without indication. This study showed that more than 50% of antibiotic use were inappropriate, and mainly antibiotic with no indication, among patients hospitalized in Aisyiyah Hospital Bojonegoro.

***Keywords**: ASA; qualitative antibiotic use; prudent; infection*

ABSTRAK

Rumah sakit merupakan sarana kesehatan yang banyak menggunakan antibiotik. Sekitar 13-37% dari total pasien rawat inap di negara maju menggunakan antibiotik, bahkan di negara berkembang bisa mencapai 30-80%. Ada korelasi yang teridentifikasi antara penggunaan antibiotik dan perkembangan resistensi bakteri. Meskipun resistensi tidak dapat dihilangkan, namun perkembangannya dapat ditekan dengan peningkatan penggunaan antibiotik. Tujuan penelitian ini adalah untuk mengetahui kualitas penggunaan antibiotik pada pasien penyakit dalam dan bedah di RS Aisiyah Bojonegoro. Penelitian ini merupakan penelitian analitik observasional prospektif cross sectional pada pasien internal dan bedah yang mendapat terapi antibiotik pada periode Agustus - September 2017. Jumlah sampel yang dikumpulkan dalam penelitian ini sebanyak 50 orang yang terdiri dari 33 penyakit dalam dan 17 pasien bedah. Dari 50 sampel didapatkan 16 jenis antibiotik dengan total penggunaan 81 antibiotik. Hasilnya, pada pasien penyakit dalam terdapat 22 (40%) penggunaan antibiotik yang tepat, 4 (7,27%) penggunaan yang tidak tepat dan 29 (52,73%) penggunaan antibiotik tanpa indikasi. Pada pasien bedah, terdapat 12 (46,15%) penggunaan antibiotik yang tepat, 2 (7,69%) penggunaan yang tidak tepat dan 12 (46,15%) penggunaan antibiotik tanpa indikasi. Penelitian ini menunjukkan bahwa lebih dari 50% penggunaan antibiotik tidak tepat, terutama antibiotik tanpa indikasi, pada pasien yang dirawat di RS Aisyiyah Bojonegoro.

***Kata kunci**: penggunaan antibiotik kualitatif; bijaksana; infeksi*

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INTRODUCTION

Infectious diseases are among the top ten diseases in Indonesia. The non-prudent use of antibiotics will impact the high risk resistance development of bacteria. Hospitals are health facility with the widely use of antibiotics (WHO 2012, Ministry of Health 2011). There is a correlation between antibiotic usages with bacterial resistance development which cause nosocomial infection. The resistance cannot be eliminated but its development can be suppressed by the increasing the prudent use of antibiotics. Resistance has a broad impact such as increasing the risk of morbidity, mortality, and cost (Ministry of Health 2011).

Prudent use of antibiotic rare referred from several criteria such as right indication, right patient, right drug, appropriate dose regimen andalert for drug side effects (Reksoprawiro 2009). Other terminology indicates that the prudent use of antibiotics is the use of antibiotics which suitable with infectious agents, dose regimens, optimal duration of therapy, minimum side effects, and minimum bacterial resistance effects (Gyssens 2017, Hadi et al 2008, Permenkes 2015). This study was conducted in Aisyiyah Hospital Bojonegoro. This study focuses on the analysis of the antibiotic use, measure by Gyssens method.

MATERIALS AND METHODS

This study was a prospective cross sectional observational analytical study which conducted in Aisyiyah Hospital Bojonegoro during the period of August to September 2017. The respondents were the patient hospitalized in internal medicine and surgical that received antibiotic therapy. The total 50 samples were included in this study which consists of 33 internal medicine patients and 17 surgical patients.

Observations were conducted on clinical conditions, medical records and medication records of the patients. Then, data were collected and extracted on the data record form (CRF) which included patients' demographic data (name, sex, age), clinical data and patients' laboratory data (date of get in/get out, diagnosis, WBC, temperature, pulse, complication of other co morbidities in patients) and antibiotic therapy given (date of administration, type, dose, route, interval and duration of antibiotics). In addition to the forms of data collection sheets, there is also a form used to conduct an analysis of the use of antibiotic therapy. Analysis of antibiotic therapy use was performed for all antibiotics which used during the treatment and synchronized with the we diagnosis in the medical record status. Criteria of antibiotics use assessment are using Gyssens method.

RESULTS

From 50 total samples were obtained 33 samples of internal medicine patients consisting of 16 (48.5%) male patients and 17 (51.5%) female patients, with the insured patients status who without insurance were 23 (69.7%) patients, it was more than patients with BPJS insurance were 10 (30.3%) patients. The age majority between 18-65 years old as many as 28 (84.8%) patients. Whereas from 17 respondents of surgery patients there were 10 (58.8%) male patients and 7 (41.2%) female, with the insured patients' status who without insurance were 13 (76.5%) patients more than patients who use BPJS insurance were 4 (23.5%) patients, with age mainly between 18-65 years old counted 15 (88.2%) patients.

Clinical data and laboratory data profiles were presented in the table 1. The clinical data such as: temperature, heart rate and respiratory rate. Meanwhile, laboratory data that observed were white blood cell and erythrocyte sedimentation rate (ESR). Only 31 respondents from all samples were conducted respiratory check in medical record and 17 samples were checked the ESR.

Table 1. Clinical data and laboratory data characteristics on internal medicine and surgical patients in the period of study

Checking Type	Frequency (n = 50)	Percentage
Temperature		
• ≤ 35	0	0%
• 36-38˚C	46	92%
• > 38˚	4	8%
Heart rate		
• 60 – 90	19	38%
• > 90	31	62%
Respiration (RR)* (n = 31)		
• ≤ 20	24	48%
• > 20	7	14%
• No Data	19	38%
WBC		
• < 4000/mm^3	0	0%
• 4000 – 12000/mm^3	28	56%
• > 12000/mm^3	22	44%
Erythrocyte Sedimentation Rate ** (n = 19)		
• Normal (male 0 – 15 mm/hour and female 0 – 20 mm/hour)	2	4%
• Abnormal (male > 15 mm/hour and female > 20 mm/hour)	17	34%
• No Data	31	62%

Table 2. The result of quality analysis on antibiotic use for internal medicine and surgical patients with Gyssens method

Category		Ward/Health Service		
		Internal Medicine	Surgical	Total Use
VI	Incomplete data/cannot be evaluated	-	-	-
V	No indication of antibiotic use	29	12	41
IV	There are another antibiotic which is more effective/less toxic/less expensive/narrower spectrum	3	-	3
III	Antibiotic therapy duration is long/too short	1	2	3
II	Antibiotic use is in inappropriate dose/administration interval/administration route	-	-	0
I*	Antibiotic use in inappropriate time	-	-	0
0	Antibiotic use in appropriate	22	12	34
Total		55	26	81

Note: Category I: for prophylaxis, was excluded in this study

Among 50 samples, the total 16 types of antibiotic were used, which were total of 81 antibiotic were used (one patients can use of more than 1 antibiotic). The quality of antibiotic use in internal medicine patients were 29 (52.73%) of antibiotic use without indication (criteria V), 3 (5.45%) of inappropriate efficacy of antibiotic use/there were less toxic/less expensive/narrower spectrum (category IV), 1 (1.82%) of long duration of antibiotic use/short duration (category III), and 22 (40%) of appropriate antibiotic use (criteria 0). Meanwhile, in surgical patients, it were obtained 12 (46.15%) of antibiotic use without indication (criteria V), 2 (7.69%) of long duration of antibiotic use/short duration (category III) and 12 (46.15%) of appropriate antibiotic use (criteria 0) (Table 2).

From 16 antibiotic types that used in these patients, the highest appropriate use criteria was metronidazole in 9 (11.11%) and antibiotic with the highest inappropriate indication administration criteria was ceftriaxone in 17 (20.98%). In the internal medicine patients, antibiotic with the highest appropriate use criteria was metronidazole in 4 (18.18%) and antibiotic with the highest inappropriate indication administration criteria was ceftriaxone in 11 (37.93%) (Table 3).

Similarly, in the surgical patients, antibiotic with the highest appropriate use criteria was metronidazole in 4 (33.33%) and antibiotic with the highest inappropriate indication administration criteria was ceftriaxone in 6 (50%) (Table 4).

Table 3. The distribution of the quality of antibiotic use (Gyssens criteria) among patient internal medicine in Aisyiyah Hospital Bojonegoro

Antibiotic Type	Gyssens Flow							Total
	VI	V	IV*	III*	II*	I	0	
Amikacin		1						1 (1.82%)
Gentamicin								0 (0%)
Ciprofloxacin		4		1			3	8 (14.55%)
Levofloxacin		1						1 (1.82%)
Meropenem		1	2					3 (5.45%)
Cefuroxime		1						1 (1.82%)
Cefixime		2						2 (3.64%)
Cefotaxime								0 (0%)
Ceftizoxime		3						3 (5.45%)
Cebactam							1	1 (1.82%)
Ceftriaxone		11	1				4	16 (29.09%)
Cefepime		5					4	9 (16.36%)
Metronidazole							4	4 (7.27%)
Rifampicin							2	2 (3.64%)
Ethambutol							2	2 (3.64%)
Isoniazid							2	2 (3.64%)
Total	0	29 (52.73%)	3 (5.45%)	1 (1.82%)	0	0	22 (40%)	55 (100%)

Table 4. The distribution of the quality of antibiotic use (Gyssens criteria) among patient surgical in Aisyiyah Hospital Bojonegoro

Antibiotic Type	Gyssens Flow							Total
	VI	V	IV	III	II	I	0	
Amikacin		1					1	2 (7.69%)
Gentamicin		1						1 (3.85%)
Ciprofloxacin								0 (0%)
Levofloxacin							1	1 (3.85%)
Meropenem								0 (0%)
Cefuroxime								0 (0%)
Cefixime								0 (0%)
Cefotaxime		1					1	2 (7.69%)
Ceftizoxime		1						1 (3.85%)
Cebactam								0 (0%)
Ceftriaxone		6		2			3	11 (42.31%)
Cefepime		1					2	3 (11.54%)
Metronidazole		1					4	5 (19.23%)
Rifampicin								0 (0%)
Ethambutol								0 (0%)
Isoniazid								0 (0%)
Total	0	12 (46.15%)	0	2 (7.69%)	0	0	12 (46.15%)	26 (100%)

Note: Category IV was included IV[a,b,c,d]; category III was included III[a,b]; category II was included II[a,b,c]

DISCUSSION

The study indicated 16 antibiotic types with total antibiotic use in all respondents is 81 times of antibiotic use. The antibiotic use in internal medicine patients was 55 (68%), while the rest 26 (32%) was in surgical patients. Qualitative analysis on antibiotic use by using Gyssens method was confirmed with reviewers (microbiologist and physician in infection specialist). Analysis result then were grouped in 4 categories: appropriate antibiotic use (category 0), inappropriate antibiotic use (category II-IV), without indication antibiotic use (category V) and incomplete data (category VI). From all analysis results of antibiotic use, it indicated that appropriate antibiotic use was 34 (41.97%), inappropriate antibiotic use was 6 (7.41%) and without indication antibiotic use was 41 (50.62%) (Table 2).

Analysis in the internal medicine patients (Table 2) obtained 22 (40%) of appropriate antibiotic use, 4 (7.27%) of inappropriate antibiotic use and 29 (52.73%) of without indication antibiotic use. Analysis in the surgical patients (Table 3) obtained 12 (46.15%) of appropriate antibiotic use, 2 (7.69%) of inappropriate antibiotic use and 12 (46.15%) of without indication antibiotic use. It showed that the antibiotic use with no indication took place in the highest prevalence.

There were similar with the study AMRIN, the year 2000-2004 (Hadi et al 2008). AMRIN study showed that antibiotic use without indication was 55-80% in RSUD Dr Soetomo, while, 20-53% in RSUP Dr Kariadi (Hadi et al 2005). This study showed that 42% cases of antibiotic use was with no indication, 15% cases was inappropriate antibiotic use and 21% cases was appropriate antibiotic use. Analysis result on internal medicine department showed 19% of the case was antibiotic use without indication in RSUD Dr. Soetomo, on the contrary in RSUP Dr. Kariadi was 47% cases. Analysis result on surgery department known 47% use without indication in RSUD Dr. Soetomo, while in RSUP Dr. Kariadi were 45% cases (Hadi et al 2008).

The high prevalence of antibiotic use with no indication (50.62%) in this study showed that higher than the previous studies. Moreover, the case of antibiotic use no indication in internal medicine patients (in this study) was 50.2% whereas it was higher 31.2% compared to the percentage of antibiotic use with no indication in internal medicine patients medicine of RSUD Dr Soetomo (Hadi et al 2008).

Even antimicrobial resistance control program (ARCP) has been strated since 10 years ago, it was still identify the higher use of antibiotic with no indication. It would

be the program was not reach the district hospital. The efforts to prevent antibiotic resistance are prudent use of antibiotics and preventing the spread of resistant bacteria (Hadi et al 2006). The inter-professional collaboration including clinical microbiology, clinical pharmacy, pharmacy and therapeutic committee, and infection control committee, were needed for optimal program of ARCP (Hadi et al 2013).

A pharmacist should have an active role in selecting antibiotics administration for the patients. Pharmacist should also be a partner for the clinician (doctor) and willingly to provide consultations regarding the use of antibiotics (Hadi et al 2013). Policy to use antibiotics wisely is essential for the control of antibiotics resistance. The policy is generally characterized by restriction of antibiotics use for certain indications and within a certain time limit. It may be contained in antibiotics use guidelines in a hospital (Hadi et al 2006). Antibiotics use guidelines are not available in Aisyiyah Hospital Bojonegoro yet, generally the administration of antibiotics in hospitals wass based on clinical consideration of each physician who gives the treatment.

Up till now, there is no facility of microbiology laboratory in Aisyiyah Hospital Bojonegoro, whereas clinical microbiology has a role of providing services and consultation of microbiology and infection management (Hadi et al 2013). This situation to becomes handicap to determine the right type of antibiotic for each of the patient who has the infection. Additionally, there is no data related to antibiogram in this hospital which lead to no consideration for selecting the empirical antibiotics.

The results of quality analysis of antibiotic use in this study encourage the preparation and implementation of antibiotic use guidelines. The prudent use of antibiotic aims to optimize therapeutic effects, minimize the risk of resistant bacteria occurrence and maintain the value of the existence of antibiotic classes, where the application requires a restriction policy of antibiotic use.

CONCLUSION

From the result of quality analysis on antibiotic use for internal medicine patients, it obtained 29 antibiotic uses (52.73%) was without indication (criteria V), on the contrary, for surgical patients obtained 12 antibiotic uses (46.15%) was without indication (criteria V). This study will be based for the further intervention for improving the quality of antibiotic use in in Aisyiyah Hospital Bojonegoro.

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EFFECT OF ATORVASTATIN IN LIPID PROFILE CHANGES AND INFLAMMATION MARKER ON DIABETES PATIENT WITH DYSLIPIDEMIA

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ABSTRACT

Diabetes is one of the risk factors for cardiovascular disease (CVD). Diabetics patients have 2 to 4 times increased risk of cardiovascular disease compared with non-diabetics. TNF-alpha is a proinflammatory cytokine that can be used to determine the risk of atherosclerosis complications triggered by inflammation in diabetes. Statins are a class of HMG CoA reductase inhibitors that inhibit cholesterol biosynthesis and have pleioropic effects that inhibit the release of inflammatory cytokines like TNF-alpha and stabilize atherosclerotic plaques. This study aims to determine the effect of atorvastatin 20 mg/day for 30 days in reducing the lipid profile and TNF-alpha inflammatory markers in patients with diabetes dyslipidemia. Diabetes patient with dyslipidemia who included the inclusion criteria in this observational prospective cohorts studies treated with atorvastatin for 30 days (n = 19). The efficacy of statin therapy was measured by lipid profiles (LDL, TG, HDL, and total cholesterol) and TNF-alpha. The results of the study showed that atorvastatin decreased 40.55% of LDL levels, 15.34% of TG levels, and 30.70% oftotal cholesterol levels which statistically significant (P <0.05). As for HDL, there is an increase of 6.06% but statistically non-significant (P >0.05). TNF-alpha levels increased by 11.30% which statistically non-significant (P >0.05). The use of atorvastatin 20 mg for 30 days gave reduction in LDL, TG, and total cholesterol and increased in HDL. Atorvastatin does not have a reducing effect on TNF-alpha. There was no correlation between lipid profile changes with TNF-alpha changes.

***Keywords**: atorvastatin; lipid; TNF-alpha; diabetes; dyslipidemia*

ABSTRAK

Pasien diabetes memiliki 2 sampai 4 kali peningkatan risiko penyakit kardiovaskular dibandingkan dengan non diabetes. Untuk mengetahui risiko terhadap adanya penyakit kardiovaskular dapat dilakukan pemeriksaan petanda inflamasi TNF-alpha yang merupakan sitokin proinflamasi yang dapat memicu terjadinya aterosklerosis. Statin merupakan golongan HMG CoA reductase inhibitor yang menghambat biosintesi kolesterol dan memiliki efek pleioropik sehingga menghambat pengeluaran sitokin inflamasi seperti TNF-alpha dan menstabilisasi plak aterosklerosis. Pada penelitian ini bertujuan untuk mengetahu pengaruh atorvastatin 20 mg/hari selama 30 hari dalam menurunkan profil lipid dan petanda inflamasi TNF-alpha pada pasien diabetes dislipidemia. Pasien DM tipe 2 dengan dislipidemia yang memenuhi kriteria inklusi dilakukan studi observasional prospektif kohort dan mendapat atorvastatin selama 30 hari (n=19). Efektivitas terapi statin diukur melalui pemeriksaan profil lipid (LDL, TG, HDL, dan kolesterol total) dan petanda inflamasi TNF-alpha. Hasil penelitian didapatkan pada terapi atorvastatin terjadi penurunan untuk LDL sebesar 40,55%, TG 15,34%, dan kolesterol total 30,70% yang signifikan secara statistik (P <0,05). Sedangkan untuk HDL, terjadi peningkatan sebesar 6,06% yang tidak signifikan secara statistik (P >0,05). Untuk nilai TNF-alpha terjadi peningkatan sebesar 11,30% yang tidak signifikan secara statistik(P >0,05). Dari penelitian ini disimpulkan bahwa pemakaian atorvastatin 20 mg selama 30 hari memberikan penurunan terhadap LDL, TG, dan kolesterol total dan terhadap HDL terjadi kenaikan. Atorvastatin tidak memberikan efek penurunan terhadap TNF-alpha. Tidak ada korelasi antara perubahan profil lipid dengan perubahan TNF-alpha.

***Kata kunci**: atorvastatin; lipid; TNF-alpha; diabetes; dislipidemia*

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases with characteristics by hyperglycemia that occurs due to abnormalities of insulin secretion, insulin action or both (PERKENI 2015). Based on the results of basic health research in 2013, diabetes is one of the risk factors for cardiovascular disease (CVD) (Ministry of Health 2013). Diabetic patients have 2 to 4 times increased risk of stroke and cardiovascular disease compared with nondiabetes (Powers 2015). Dyslipidemia in diabetic patients occurs because of insulin resistance that causes lipid disorders. Lipid profiles in patients with type 2 diabetes are usually characterized by hypertriglyceridemia, decreased HDL, and elevated LDL (Wu & Parhofer 2014).

American Diabetes Association (ADA) recommend the target of LDL level in high-risk diabetic patients with cardiovascular risk factors less then 70 mg/dl. If this target can not be achieved, another alternative is chosen by lowering LDL 30% -50% of initial value. In high-risk patients with cardiovascular risk factors, high-intensity statin was used as therapy for more significant LDL reduction (ADA 2017).

One of the therapy used to lower LDL is atorvastatin. Atorvastatin classified as moderate intensity at 10-20 mg doses and high intensity at 40-80 mg doses (ADA 2017). In addition, statins have anti-inflammatory, antithrombotic properties, and the ability to stabilize atherosclerotic plaques (Davignon 2004). Statins can decrease the expression and function of molecules on the surface of leukocytes by inhibiting migration and chemotaxis from neutrophils to the endothelium thereby inhibiting the release of proinflammatory cytokines TNF-alpha (Stancu & Sima 2001). TNF-alpha is a proaterogenic cytokine produced by several cells involved in the process of atherosclerosis including macrophages, endothelial cells and smooth muscle cells (Tousoulis et al 2016).

Atorvastatin has a half-life of 14 hours and has an active metabolite with potent equivalent to its parent compound to inhibit HMG-CoA reductase. The longer actions of atorvastatin providing a greater reduction in cholesterol synthesis (Schachter 2005). This study was conducted to determine the efficacy of atorvastatin 20 mg to decrease the basic lipid profile in the form of total cholesterol, triglycerides, HDL and LDL and TNF-alpha inflammatory markers in DM patients with dyslipidemia. This study was conducted for 30 days according to the maximum effect of cholesterol and triglyceride reduction in 2-4 weeks of therapy (American Society of Health System Pharmacist 2011, Lacy et al 2016).

MATERIALS AND METHODS

This study is a prospective observational study of cohorts. Patients with type 2 diabetes with dyslipidemia in the Internal Medicine Polyclinic of Haji Hospital, Surabaya during November 2017 - January 2018 who included into the inclusion criteria were patients aged > 21-75 years, lipid profiles of LDL > 100 mg/dL, TG> 150 mg/dL, did not receive statin therapy 7 days earlier and had signed informed consent. Exclusion criteria from this study were patients with increased liver function tests, patients with severe chronic kidney disease to renal failure, patients receiving anti-inflammatory medication, patients with infectious disease, inflammation, malignancy, and autoimmune disease. Examination of LDL, TG, total cholesterol, HDL were performed at General Hajj Hospital Laboratory. TNF-alpha examination using ELISA (Biolegend®) methodology was performed at the Infection Specialized Hospital Surabaya. Paired t-test and Wilcoxon test were used to determine differences in lipid, IL6 and TNF-alpha profiles before and after treatment using. The correlation between lipid profile and inflammatory markers TNF-alpha before and after therapy analyse with Pearson correlation test. The result of statistical test is significant if p <0,05 with confidence interval equal to 95%.

RESULTS

A total of 19 patients who met the inclusion criteria were used as the subjects of the study. Patient demographic data can be seen in table 1. Research subjects consisted of 13 women (68.42%) and 6 men (31.58%), with mainly in 46-59 years group (57.89%) and based on BMI 57.89% in 18,5-24,9 kg/m2 group. The comorbid disease are hypertension 10 patients (52.63%) and uric acid 7 patients (31.58%).

Table 1. Early characteristics of diabetes dyslipidemic patients

Characteristics of Patients		N	Persentage (%)	Average ± SD
Gender	Men	6	31.58	-
	Woman	13	68.42	
Age Range (years old)	26 - 45	1	5.26	57.32 ± 7.94
	46 – 59	11	57.89	
	60 - 74	7	36.84	
BMI (kg/m^2)	18.5 – 24.9	11	57.89	25.44 ± 3.65
	25 – 29.9	7	36.84	
	>30	2	10.53	
Comorbid	Hypertension	10	52.63	-
	Uric acid	7	31.58	

There was a reduction of LDL level with mean value of pre 163.47 ± 28.77 mg/dL and post 97.89 ± 29.71 mg/dL, reduction of TG with mean value of pre 161.89 ± 76.12 mg/dL and post 132.21 ± 75.48 mg/dL, and cholesterol total with mean value of pre 232.84 ± 43.19 mg/dL and post 161.89 ± 44.73 mg/dL. There was significantly decreased in LDL, TG, and total cholesterol (P <0.05), whereas an increase in HDL with a mean value of pre 49.00 ± 10.75 mg/dL and post 51.11 ± 9.28 mg/dL did not increase significantly (P >0.05). Results of TNF-alpha with mean values of pre 9.89 ± 3.86 pg/mL and post 161.89 ± 44.73 pg/dL.

Table 2. Effect of atorvastatin on lipid profile and inflammatory marker TNF-alpha on diabetes patients with dyslipidemia for 30 days

Parameter	Pre	Post	Average Difference	% Changes	Significance
LDL (mg/dL)	163.47 ± 28.77	97.89 ± 29.71	65.58	40.12	0.00[a]
TG (mg/dL)	161.89 ± 76.12	132.21 ± 75.48	29.68	15.34	0.026[a]
HDL (mg/dL)	49 ± 10.75	51.11 ± 9.28	2.11	6.06	0.25[b]
Total Cholesterol (mg/dL)	232.84 ± 43.19	161.89 ± 44.73	70.95	30.47	0.00[a]
TNF-alpha (pg/mL)	9.89 ± 3.86	11.01 ± 4.42	0.79	7.09	0.49[a]

Table 3. Lipid profile based on NCEP ATP III

Parameter	Category	Pre Therapy		Post Therapy	
		Total	%	Total	%
Total Cholesterol	Desirable (<200 mg/dL)	3	15.79	18	94.74
	Borderline high (200-239 mg/dL)	10	52.63	-	-
	High (≥240 mg/dL)	6	31.58	1	5.26
LDL	Optimal (<100 mg/dL)	-	-	11	57.89
	Near optimal (100-129 mg/dL)	-	-	7	36.84
	Borderline high (130-159 mg/dL)	10	52.63	-	-
	High (160-189 mg/dL)	7	36.84	-	-
	Very high (>190 mg/dL)	2	10.53	-	-
TG	Normal (<150 mg/dL)	7	36.84	14	73.68
	Borderline high (150-199 mg/dL)	9	47.37	3	15.79
	High (200-499 mg/dL)	3	15.79	2	10.53
	Very high (≥500 mg/dL)	-	-	-	-
HDL	<40 mg/dL	4	21.05	1	5.26
	41-59 mg/dL	11	57.89	14	73.68
	≥60 mg/dL	4	21.05	4	21.05
Total (n)		19 patients			

Table 4. Results of correlation test of TNF-alpha changes to lipid profile changes in diabetes dyslipidemic patients

Parameter		Correlation coefficient (r)	Significance (p)
TNF-alpha	LDL	-0.353	0.139
	TG	0.130	0.597
	HDL	-0.233	0.336
	Total Cholesterol	0.032	0.896

The results of the correlation analysis showed no correlation between the lipid profile and TNF-alpha (P >0.05).

DISCUSSION

uring the three months of the study period, 20 patients included the inclusion criteria with 1 patient dropped out. Demographic data show the age of diabetics is the most common in 46-59 years as 57.89% (Table 1). From epidemiological study, patients with diabetes are most commonly by the productive age of between 40-60 years in developing countries (Shaw et al 2010). It was found that hypertension was the most common comorbidity in 52.63% research subject, followed by 31.58% of uric acid (Table 2). Hypertension is twice more common in diabetic patients as compared to non-diabetics. Hypertension in diabetics has a persistent BP value of >=140/90 mmHg. In the EUROASPIRE IV survey only 54% of diabetic patients achieved BP levels of less than 140/90 mmHg (Grossman & Grossman 2017).

Insulin resistance accompanied by increase free fatty acid into the liver play an important role in increasing the incidence of diabetes dyslipidemia, characterized by high TG concentrations, low HDL concentrations, and high small dense LDL concentrations (Chehade et al 2013). American diabetic association (ADA) and PERKENI recommended that the target lipid profile for patients with diabetes is LDL <100 mg/dl (2.60 mmol/l), HDL <40 mg/dl (1.02 mmol/L, and TG <150 mg/dl (1.7 mmol/l) (ADA 2017, PERKENI 2015).

The NCEP-ATP III Guideline has classified lipid profile based on each levels. Based on guideline, LDL levels are divided into five groups. There is optimal (<100 mg/dL); near optimal (100 - 129 mg/dL); borderline high (130 - 159 mg/dL); high (160 - 189 mg/dL); and very high (>=190 mg/dL). TG levels divided into four groups. There is normal (<150mg/dL); borderline high (150 - 199 mg/dL); high (200 - 499 mg/dL) and very high (>=500 mg/dL) (NCEP-ATP III 2002).

Patients who met the inclusion criteria were measured on the lipid profile before treatment as baseline values. The results of lipid profile from 19 patients showed that for total cholesterol (Table 2) the mean value of pre 232.84 ± 43.19 mg/dL and post 161.89 ± 44.73 mg/dL decreased by 30.70%. For baseline total cholesterol levels (Table 2) were distributed mainly in borderline high (200-239 mg/dl) as 52.63%, high (? 240 mg/dL) as 31.58%.

In the LDL results (Table 2), the mean value of pre 163.47 ± 28.77 mg/dL and post 97.89 ± 29.71 mg/dL decreased by 40.55%. For baseline values of patients (Table 3) mostly in the high borderline range (130-159 mg/dl) as 52.63%, high (160-189 mg/dl) as 36.84%. In diabetic patients there is an increase small dense LDL which more atherogenic that causes risk factor for cardiovascular disease (NCEP-ATP III 2002). For the TG value (Table 2), the mean value of pre 161.89 ± 76.12 mg/dL and post 132.21 ± 75.48 mg/dL decreased by 15.34%. Baseline values of patients (Table 3) mostly located in borderline high (150-199 mg/dL) as 47.37%. For the HDL value (Table 2), the mean value of pre 49.00 ± 10.75 mg/dL and post 51.11 ± 9.25 mg/dL increased by 6.06%. Baseline values of patients (Table 3) <40 mg/dl as 21.05% and >=60 mg/dL as 21.05%.

After 30 days of atorvastatin therapy, there was a change of total cholesterol; desirable range (<200 mg/dL) as 94.74%. In the results of LDL, the most patients were found in the optimal range (<100 mg/dL) as 57.89% and near optimal (100-129 mg/dL) as 36.84%. For the TG value, the most patients were in the normal range (<150 mg/dL) as 68.42%, but there were still patients in the borderline high range (150-199 mg/dL) as 10.53% and high (200-499 mg/dL) as 10.53%. For the HDL values, there are still patients with range <40 mg/dL as 5.26%. Based on the change of lipid profile, statistical analysis used a paired t-test for the data before and after therapy with a significant decrease in LDL, TG, and total cholesterol (P <0.05), but no significant increase in HDL value (P >0.05).

Based on previous study, ATGOAL showed a decrease in LDL-C targeted at week 4 for low, medium, high-risk patients (n = 1049/1246) with percentage of patients achieving LDL-C target of 91.9% , 87.6%, and 79.2% for each category with a total of 84.2% of patients achieving LDL-C target and did not require dose titration (McKenney et al 2005). The Thai ATGOAl study also showed that 81.6% of patients and 87.1% of atorvastatin therapy (n = 240) had achieved LDL targets at week 2 and 4 (Deerochanawong et al 2007).

Atorvastatin also have pleiotropic effects by inhibiting isoprenoid intermediates such as FPP and GGPP causing obstacles to isoprenyl GTPases such as Ras, Rho, and Rac leading to an inactivated Ras and Rho accumulation in the cytoplasm, where Rac causes an increase in NADPH oxidation causing an increase in ROS (Zhou & Liao 2010). ROS increases the translocation of NF-kB p65 subunits by transcribing the pro-inflammatory genes MCP-1, Selectin, VCAM-1, and ICAM-1. This event facilitates monocyte adhesion to endothelial vascular, rolling, and diapedeses in sub-endothel. TNF-a secretions of active macrophages will maintain an increase in adhesion molecules by increasing NF-kB signaling in the endothelium and

promoting smooth muscle cell growth and proliferation leading to atherosclerosis. Therefore, atorvastatin 20 mg for 30 days is expected to provide pleiotropic effect by inhibiting the release of inflammatory cytokines TNF-alpha to prevent atherosclerosis (Paneni et al 2013).

In this study, the mean values of pre TNF-alpha 9.89 ± 3.86 pg/dL and post 11.01 ± 4.42 pg/dL increased by 11.30% which statistically non-significant (P >0.05). In the previous study, TNF-alpha values obtained in normal patients were 4.46 ± 1.42 pg/dL (Goyal et al 2012). Another study showed TNF-alpha levels were 9.28 (7.56-11.40) pg/dL (n = 15) and 10.02 (5.16-14.69) pg/dL (n = 14) in diabetic patients with dyslipidemia (Bellia et al 2010).

Patients who did not achieved fasting glucose and post prandial glucose levels as intended may cause hyperglycaemia. This condition may increase the proportion of FFA that activates TLR resulting in translocation of NF-kB which produced inflammatory cytokines such as TNF-alpha. Increased TNF-alpha may cause a decrease in IRS-1 leading to insulin resistance (Paneni et al 2013).

In obese patients, increased insulin resistance commonly associated with the increased amount of visceral adipose tissue. Abdominal fat tissue has a large lipolysis rate and insulin resistance, resulting in increased free fatty acid production. High free fatty acids will transport to the liver and converted to VLDL and will increase insulin insensitivity. Abdominal fat tissue also triggers an increase in the production of several inflammatory mediators such as TNF-alpha. Inflammatory mediators also contribute to increased peripheral tissue insulin resistance (Triplitt and Reasner 2011).

CONCLUSION

The results of this study showed that therapy of atorvastatin 20 mg for 30 days reduced LDL, TG, total cholesterol values and increased HDL and TNF-alpha values. There was no correlation between changes in lipid profile values (LDL, TG, total cholesterol, HDL) with TNF-alpha value.

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EFFECT OF ATORVASTATIN IN LIPID PROFILE CHANGES AND INFLAMMATION MARKER ON DIABETES PATIENT WITH DYSLIPIDEMIA

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ABSTRACT

Thyroid cancer is one of the commonest cancer, while the incidence of occult thyroid cancer is only 0.05%. The completion total thyroidectomy as one of treatments choice for thyroid cancer which initially diagnosed preoperatively as benign thyroid mass, has remained controversial. This study aimed to understand the effectiveness of completion total thyroidectomy after partial thyroidectomy by analyzing the proportion of malignant contralateral thyroid tissue, post operative complications, and recurrence of cancer. This retrospective study collected medical record data in 2011 and 2016. The samples were 16 patients consisting of 15 females and 1 male. There was no significant difference on contralateral thyroid tissue malignancy proportion between completion total thyroidectomy and without total thyroidectomy (P = 0.375). It was found that 3 surgical complications (50%) of 6 patients with completion total thyroidectomy and 3 complications (30%) of 10 patients without completion total thyroidectomy. The complications were temporary injury of recurrent laryngeal nerve (P = 0.511), seroma (P = 0.375), and hypoparathyroidism (P = 0.375). No recurrence event after 4 years follow up amount both groups. In conclusion, there is no advantage in completion total thyroidectomy analized from proportion of malignant contralateral thyroid tissue, post operative complication, and recurrence in 4 years-follow up.

***Keywords**: occult thyroid cancer; partial thyroidectomy; completion total thyroidectomy*

ABSTRAK

Kanker tiroid merupakan keganasan kelenjar endokrin yang paling sering ditemukan, tetapi insiden kanker tiroid tersembunyi (occult) yang tampak secara klinis hanya sekitar 0,05%. Tiroidektomi total completion sebagai terapi standart masih kontroversial, dan belum ada konsensus untuk pasien yang dioperasi dengan tumor jinak tiroid dan didiagnosis kanker setelah operasi. Tujuan penelitian ini adalah untuk mengetahui efektifitas tiroidektomi total completion dengan riwayat tiroidektomi parsial dilihat dari proporsi keganasan jaringan tiroid kontralateral,komplikasi post operasi, dan proporsi rekurensi kanker. Penelitian ini adalah penelitian retrospektif menggunakan rekam medis pada periode 2011-2016. Total terdapat 16 kasus yang terdiri atas 15 pasien perempuan dan 1 laki-laki. Penelitian ini menghasilkan bahwa tidak didapatkan perbedaan pada proporsi keganasan jaringan tiroid kontralateral antara tiroidektomi total completion maupun tanpa total completion (P = 0,375). Komplikasi post operasi tiroidektomi total completion dijumpai pada 3 kasus (50%) dari 6 pasien, sedangkan pasien tanpa tiroidektomi total completion 3 kasus (30%) dari 10 pasien. Jenis komplikasi adalah cedera nervus laringeus rekuren sementara (P = 0,511), seroma (P = 0,375) dan hipoparatiroid (P = 0,375). Tidak didapatkan rekurensi kanker kontralateral dalam follow up selama 4 tahun pada kedua grup. Sebagai kesimpulan, tidak didapatkan manfaat tindakan tiroidektomi total completion dalam hal proporsi keganasan jaringan tiroid kontralateral, komplikasi post operasi, maupun rekurensi kanker tiroid tersembunyi selama follow up 4 tahun.

***Kata kunci**: kanker tiroid tersembunyi; tiroidektomi parsial; tiroidektomi total completion*

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INTRODUCTION

Thyroid cancer is the most common malignancy of endocrine gland and the incidence is increasing in some areas. Based on pathology data in Indonesia, thyroid cancer is ranked as the 9th most common cancer. However, the incidence of clinically apparent occult thyroid cancer is only about 0.05%. The incidence in Europe is about 1.75 per 100,000 population (0.00175%) in males and 6.38 (0.00638%) in females. Only about 1-2% of occult thyroid cancers alter clinically during life. Incidents around the world ranged from 3 to 4 per 100,000 population with the most incidents in Iceland and Hawaii (15 per 100,000). The small number of occult thyroid cancers incidence has led to prolonged debate on the management of the patients' therapy (Ganly et al 2009, Manuaba 2010).

Total completion thyroidectomy is an important step in the treatment of thyroid cancer patients, because not all patients receive total thyroidectomy as a standard operation in thyroid cancer. Difficult perioperative procedure in diagnosing cancer leads to the implementation of completion procedure that should have been avoided (Makay et al 2006).

The management of occult thyroid cancer therapy is still in debate. Several studies have demonstrated the advantages of total completion thyroidectomy, such as increasing clinical response to radioactive iodine, ability to accurately monitor thyroglobulin, and removing synchronous tumors in the contralateral lobe. However, this procedure is also at risk for complications, because the number of post completion complication is higher. In terms of cancer recurrence, there is no difference between partial thyroidectomy compared to total thyroidectomy in occult thyroid cancer (Kupferman et al 2002). Currently, there are no data on occult thyroid cancer and the results of the therapy in Indonesia. This study was expected to provide information about profile, complication, proportion of malignancy of contralateral thyroid tissue and occult thyroid cancer recurrence.

MATERIALS AND METHODS

This study was a retrospective study by evaluating medical records of occult thyroid cancer patients who underwent total completion thyroidectomy surgery or no total completion thyroidectomy in terms of postoperative complication, proportion of malignancy of the contralateral thyroid tissue, and proportion of contralateral tumor recurrences. The samples were taken from all patients with history of benign clinical thyroid tumor/occult thyroid cancer post partial thyroidectomy surgery with malignancy from 2011 to September 2016 at Dr. Soetomo Academic Hospital, Surabaya.

RESULTS

A total of 16 patients underwent strumal surgery with anatomical pathology results of thyroid cancer with a cancer size less than or equal to 1 cm called occult thyroid cancer. The most sexes in this study were females as many as 15 patients (93.75%), while male was 1 patient (6.25%). The patients' ages in this study were from 19 years to 64 years. The largest group was in the age range of 41-50 year and the average age of 45 years. Based on AMES for prognostic factors by using age < 50 years as benchmark, there were 11 patients (68.75%) less than or the same as 50 years old and 5 patients (31.25%) were over 50 years. Based on strumal type, the most common struma was multinodosa type in 9 patients (56.25%), uninodosa in 6 patients (37.5%) and diffuse in 1 patient (6.25%). Based on toxicity, the most was non-toxic struma type in 14 patients (87.5%) and toxic in 2 patients (12.5%). The sizes of the struma were between 3 cm to 11 cm with an average size of 6.7 cm.

The types of surgery were subtotal lobectomy in 3 patients (18.75%), total lobectomy in 2 patients (12.5%), isthmulobectomy 4 patients (25%) and subtotal thyroidectomy in 7 patients (43%). Post-operative pathology outcome of occult thyroid cancer showed that the most common type of cancer was papillary cancer in 15 patients (93.75%) and follicular in 1 patient (6.25%), whereas medullary and anaplastic thyroid cancers were not found. In the papillary type, there is no subtype of sclerosing and 1 follicular type with minimally invasive form.

Table 1. Distribution of preoperative diagnosis, type of surgery and pathology results of occult thyroid cancer

Variables	total completion thyroidectomy	without total completion	Total (%)
Strumal type			
Multinodosa	2	7	9 (56.25%)
Uninodosa	3	3	6 (37.5%)
Diffuse	1	0	1 (6.25%)
Size (average (cm))	3.9	6.8	6.7
Toxicity			
Toxic	2	0	2 (12.5%)
Non-toxic	4	10	14 (87.5%)
Type of operation			
Subtotal lobectomy	0	3	3 (18.75%)
Total lobectomy	1	1	2 (12.5%)
Isthmulobectomy	3	1	4 (25%)
Subtotal thyroidectomy	2	5	7 (43.75%)
Type of pathology			
Papillary	5	10	15 (93.75%)
Follicular	1	0	1 (6.25%)
Medullar	0	0	0
Anaplastic	0	0	0
Size (average (cm))	0.8	0.7	0.73
Total cancer			
1	5	9	14 (87.5%)
>1	1	1	2(12.5%)
Extrathyroidal extension			
Yes	4	1	5(31.25%)
No	2	9	11(68.75%)
AMES			
High risk	5	4	9(56.25%)
Low risk	1	6	7 (43.75)

The size of occult thyroid cancer was averagely of 7mm. The unifocal type were 14 cases and multifocal 2 cases. In 9 cases of struma multinodosa, there were 7 unifocal cases and 2 multifocal cases. Based on AMES score, the scores that affected the risk of cancer recurrence were age and extension of cancer. A total of 9 patients had a high risk consisting of 4 patients without total completion thyroidectomy and 5 patients with total completion thyroidectomy. Based on the size of cancer and metastasis, all patients were at low risk.

Postoperative complications were found in 3 (30%) of 10 patients undergoing partial thyroidectomy with temporary recurrent laryngeal nerve injury. In 6 patients performed total completion thyroidectomy surgery postoperative complication was found in 3 patients (50%), such as seroma, hypoparatiroid and temporary recurrent laryngeal nerve injury. There were no differences in complications in patients either with completion or without completion, either on recurrent laryngeal nerve injury ($p = 0.511$), hypoparathyroid ($p = 0.375$) and seroma ($p = 0.375$).

Table 2. Postoperative complications

Types of complication	Partial thyroidectomy (n=16)	Total completion thyroidectomy (n=6)
Recurrent n. laringeus injury	3	1
Hypoparathyroid	0	1
Seroma	0	1

The proportion of malignancy was obtained from pathologic surgery after total completion thyroidectomy and evaluation 6-12 months after thyroid surgery. One patient had positive residual tumor after total completion thyroidectomy and no new cancers were found in patients not undergoing total completion thyroidectomy. The results showed no significant difference between the proportion of malignancy of contralateral thyroid tissue, either in total completion thyroidectomy or without total completion ($p = 0.375$).

Table 3. Pathology of contralateral thyroid

Types of operation		With Cancer	Without cancer
Completion Thyroidectomy (n=6)	Total	1	5
Without Completion Thyroidectomy (n=10)	Total	0	10

Evaluation of cancer recurrence could be performed in 10 patients, consisting of 3 patients with total completion thyroidectomy and 7 patients without total completion thyroidectomy. From 4 years evaluation, there was no recurrence of cancer, either in total completion thyroidectomy or not. Six of 16 patients could not be evaluated because the surgery was performed less than 4 years before and not routinely visited the doctor's office.

DISCUSSION

In this study, most occult thyroid cancers were found in women (93.75%, n: 15) with an age range of 19-64 years, and are often found between 41-50 years. The findings were consistent with the literature that thyroid cancer in women occurred 2-4 times more often than in men, often found in the age of the fourth or fifth decade, and rarely found in children to adults (Schlumberger 2004). The study of Roti et al also found that the percentage in women was about 85% and men 15%. The average age at diagnosis was between 41-55 years (Roti et al 2008).

The occult thyroid cancers were often found in well-differentiated cancers. The histologic type of partial thyroidectomy results was papillary type (93.75%, n: 15) and only 1 patient (6.25%) with follicular type. This result was almost identical to the histologic distribution of well differentiated thyroid cancers in general, where papillary strains were often found to be about 80% and follicular about 5-10% (Figge 2006). From the results of Roti et al's study, the percentage of papillary thyroid microcarsinomas ranged from 65 to 99% of cases. Of the follicular thyroid cancers found, about 0.3-23.6%, 11% of the follicular type was diameter < 1 cm (Roti et al 2008).

Postoperative complications were obtained in 3 (18.75%) of 16 patients who performed partial thyroidectomy with temporary recurrent laryngeal nerve injury. Complications were obtained on subtotal thyroidectomy, istmulobectomy of more than 5 cm in size and TOETVA (Trans Oral Endoscopic Thyroidectomy Vestibular Approach) subtotal lobectomy, which was a new endoscopic technique in Dr. Soetomo. Laryngeal nerve injury temporarily recovered within 6-9 months after surgery. In 6 patients performed thyroidectomy total completion, postoperative complications were obtained as many as 3 patients (50%), such as hypoparathyroid, sera and temporary recurrent laryngeal nerve injury.

Hypoparathyroid complication was treated with calcium supplementation. In seroma, we performed sterile aspiration of the fluid and recovered within 16 days after surgery. Recurrent laryngeal nerve injury was temporary and resolved within 2 months after surgery. Fujimoto (2005) revealed that in patients with low-risk papillary thyroid cancer, hemyiroidectomy has advantage to reduce the risk of hypoparathyroid complications and recurrent laryngeal nerve injuries was primarily performed by surgeons with low operating experience. Post-operative euthyroid conditions did not require hormone replacement therapy for life.

In the case of contralateral pathologic malignancy, 1 patient showed cancer pathology after total completion thyroidectomy. The distance between the first operation with the second was less than 1 month. The type of pathology was similar to that of the previous partial and multifocal thyroidectomy, but there was no difference in the proportion of malignancy of the contralateral thyroid tissue (P = 0.375). Residual malignancy of tumor tissue should be noted during surgery especially in multifocal type. Turanli et al's study of 97 cases of occult thyroid cancer was after total completion thyroidectomy showed that in multifocal tumors malignancy most likely occurred in the residual thyroid (P = 0.02; relative risk 4.9; 95% confidence interval). However, malignant detection of residual thyroid tissue had no effect on disease free survival (P = 0.39) (Turanli et al 2011).

Of 10 cases that could not be followed up for 4 years, there was no cancer recurrence. This result was probable, because there were no presence of sclerosing papillar types and minimally invasive follicular type. Schroder et al's study (1984) showed that 32 cases of papillary thyroid malformations had a good prognosis in a mean follow-up of 7 years and only 2 cases with metastases to lymph nodes were obtained with occult sclerosing carcinoma (Schroder et al 1984).

Papillary cccult thyroid cancer in small size, less than 1 cm, not showing local invasion of the thyroid capsule, had no association with lymph node metastases commonly found at a young age, especially unifocal and of 5 mm in size. Treatment was sufficient with lobectomy without the need for total completion by providing additional hormone suppression therapy and regular monitoring (Kaplan et al 2012). Delbridge et al's study (2002) showed minimally invasive follicular thyroid cancer less than 5% so total completion thyroidectomy and iodine ablation that were not required.

Routine follow up is necessary for the evaluation of cancer recurrence. Patients with high recurrence risk need to be closely monitored. The management of total thyroidectomy surgery is aimed at reducing the risk of recurrence of cancer, because thyroid cancer tends to be multifocal and bilateral. Whereas, in patients with low risk, ie tumor size less than 1 cm, unifocal and intralobar, lobectomy is allowed to be performed (Schlumberger 2004). ATA recommends total completion thyroidectomy in all patients with thyroid cancer except for small one (< 1cm), intrathyroid, without enlarged lymph nodes, and low risk (recommendation B) (Cooper et al 2006).

CONCLUSION

There is no advantage in completion total thyroidectomy analyzed from proportion of malignant contralateral thyroid tissue, post-operative complication and recurrence occult thyroid cancer in 4 years-follow up.

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NEUROMUSCULAR TAPING INCREASES MUSCLE STRENGTH, FLEXIBILITY, AND SHORTEN THE 100 METER SPRINTER TRAVEL TIME

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ABSTRACT

Sprint or short distance run is one of the most prestigious athletic numbers. The runner is called sprinter. NMT is an application technique that uses elastic adhesive tape that provides enhanced muscle functional ability and nervous system stimulation. The purpose of this study was to determine the influence of neuromuscular taping on muscle strength, muscle flexibility and travel time of 100 meter sprinter. This study used pre test-post test method control group design with total sample of 13 people with age range of 15-19 years. This study conducted on 4-5 August 2016 at GOR Gresik. Group 1 received 2 treatments. In the first treatment, before receiving NMT, muscle strength, muscle flexibility, and running time for 100 meter were measured. In the second treatment, the measurement were repeated after receiving NMT. Treatment group 2 as control group received no NMT and subjected to the measurement of muscle strength, muscle flexibility, and running time of 100 meters. The results showed that gastrocnemius muscle strength was increased by 11.38 ± 7.83 kg, P = 0.000, P = 0.003 (dorsiflexion), P = 0.013 (plantarflexion) with mean improvement 3.46 ± 4.27 degrees, and shortening of travel time with p value = 0.001. In group 2, the gastrocnemius muscle strength was found to have a mean decrease of 2.12 ± 2.43 kg, P = 0.009, flexibility P = 1.000 (dorsiflexion), P = 0.165 (plantarflexion) with an average increase of 0.77 ± 1.88 degrees, and the running time extension had a P of 0.001. Providing NMT to the sprinter gives better results in increased muscle strength, muscle flexibility and shortening travel time.

***Keywords**: neuromuscular taping (NMT); sprinter; performance*

ABSTRAK

Lari sprint atau lari jarak pendek adalah salah satu nomor dalam atletik yang paling bergengsi, pelarinya disebut Sprinter. NMT adalah tehnik aplikasi yang menggunakan elastic adhesif tape yang memberikan kemampuan peningkatan fungsional otot, dan stimulasi sistem saraf. Tujuan penelitian ini, untuk mengetahui pengaruh neuromuscular taping terhadap kekuatan otot, fleksibilitas otot dan waktu tempuh sprinter adalah 100 meter. Penelitian ini menggunakan metode pre test-post test with control grup design dengan total sampel berjumlah 13 orang dengan rentang usia atlet 15-19 tahun, pada tanggal 4-5 Agustus 2016 di GOR Gresik. Metode 1 kelompok dengan 2 perlakuan yaitu perlakuan I sebelum pemberian NMT dilakukan pengukuran kekuatan otot, fleksibilitas otot, dan waktu tempuh berlari 100 meter dan sesudah pemberian NMT dilakukan pengukuran kembali, perlakuan 2 sebagai kelompok kontrol dilakukan tanpa pemberian NMT dilakukan pengukuran kekuatan otot, fleksibilitas otot, dan waktu tempuh berlari 100 meter. Hasil penelitian menunjukkan pada perlakuan 1 kekuatan otot gastrocnemius dengan peningkatan rerata 11,38 ± 7,83 kg, P = 0,000, fleksibilitas nilai P = 0,003 (dorsiflexion), P = 0,013 (plantarflexion) dengan peningkatan rerata 3,46 ± 4,27 derajat, dan pemendekan waktu tempuh dengan nilai P = 0,001, pada perlakuan 2 kekuatan otot gastrocnemius dengan penurunan rerata 2,12 ± 2,43 kg, nilai P = 0,009, fleksibilitas nilai P = 1,000 (dorsiflexion), P = 0,165 (plantarflexion) dengan peningkatan rerata 0,77 ± 1,88 derajat, dan waktu tempuh terjadi perpanjangan waktu dengan nilai P = 0,001. Pemberian NMT pada sprinter memberikan hasil yang lebih baik dalam peningkatan kekuatan otot, fleksibilitas otot dan memperpendek waktu tempuh.

***Kata kunci**: neuromuscular taping (NMT); sprinter; performa*

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INTRODUCTION

The history of taping therapy started from the development of bandaging techniques originating from Greece and Roman times. During the last 30 years, there arose the development of bandaging techniques that used non elastic and elastic techniques in different methods with the same concept. Not until 1970, the new techniques emerging that is used in sports is the use of elastic adhesive tape with various pull levels. In 2003, an Australian acupuncturist David Blow developed a neuromuscular taping technique of decompression and compression which is another type of taping and bandaging, called Neuromuscular Taping Concept (NMT). Neuro Muscular Taping (NMT) Concept is a biomechanical handling methodology using compression and decompression stimulation which has benefits on the musculoskletal, vascular, lymphatic, and human nervous system (Blow 2012). NMT's study after its introduction in 2003 until now is more on rehabilitation cases in both sports and clinical cases, while research on improving sports performance has not been widely available.

Running is one of the numbers in athletics competed; the distance varies, and one of the most anticipated and most prestigious sprints or short-range runs. Sprint is running at full speed along the distance that must be traveled to a predetermined distance. The runner can also be called sprinter. When viewed from the stages of the run, sprint consists of reactions and drives, acceleration, transition, speed maximum, maintenance speed and finish. It is all kind of run from start to finish and completed with maximum speed (Suharno 1993). Physical components required in short range run are durability, strength, speed, explosive power, flexibility, reaction time balance, agility, precision and reaction. Speed (movement) is the ability to perform a recurring activity that is the same and continuous in the shortest time (Nala 2011). Speed is a highly difficult physical ability. The increased exclusive training results only increased by 10%. It means that to increase the best time record 100 meters run within 10 seconds or more than 10 seconds, it takes hard training. A speed depends on several factors that influence strength, reaction time and flexibility (Harsono 1988).

NMT (Neuromuscular Taping) is an application technique that uses adhesive elastic adhesive tape attached to the skin, resulting in a local therapeutic effect and directly affecting the reflex pathway with good results. The use of NMT will provide enhanced muscle functional ability by stimulating the response of the nervous system through biochemical, emotional, and energy stimulation mechanisms to achieve desired results. The installation of NMT is combined with movement activation in the taping area so as to stimulate some skin receptors and underlying tissue. The stimulation of these receptors will send exteroceptive and proprioceptive stimulation that will be sent to the central nervous system (Blow 2012). The mechanism of stimulation is obtained through mechanoreseptor and thermoreceptor obtained from changes in pressure, temperature, and movement (long-short) muscles carried through type 1a, 1b, II, and IV nerve fibers (Hall & Guyton 2011). Giving NMT is expected to improve the functional ability of muscles both from strength and flexibility to increase the speed and shorten the travel time of 100 meter sprint athletes, both in training programs and competitions.

MATERIALS AND METHODS

This study was field experiment using pretest and posttest with control group design. This study used 1 group method with 2 treatments. Treatment 1 was done before neuromuscular taping which consisted of muscle strength measurement, muscle flexibility, and travel time run 100 meter and after giving neuromuscular taping measured muscle strength, muscle flexibility, and travel time 100 meter. Meanwhile, treatment 2 as a control group performed without neuromuscular taping performed muscle strength measurements, muscle flexibility, and travel time ran 100 meters. The subjects of the study were 100 meter sprinter athletes amounted to 13 people with the age of 15-19 years. The tape application was cut by the length measured from the gastrocnemius insertio on the heel (os calcaneus) to the length of the popliteal fossa margin. After cutting the length of the tape was made a model piece 'Y' with the base base or branching on the branching of the gastrocnemius muscle, the position at which the ankle was mounted in the dorsiflexion position 150.

Figure 1. NMT application on gastrocnemius muscle

RESULTS

In the test results of pretest and posttest differences on the treatment 1 and 2 obtained some following results.

Table 1. Treatment 1 (experiments)

Variable	Average± SD	
	Pre	Post
Strngth (kg)	55±24,90	66,39±24,23
Dorsofleksi (^{0})	20±6,12	23,46±4,27
Plantar fleksi (^{0})	55,38±7,49	58,85±5,46
Travel time (second)	14,22±1,70	14,03±1,76

Variable	Average±SD	p value
Strength of Gastrocnemius Muscle (kg)	11,38±7,83	0,000
Dorsofleksi Flexibility (^{0})		0,003
Plantarfleksi Flexibility (^{0})	3,46±4,27	0,013
Travel Time (second)		0,001

Notes: Significant when alpha was <0.05

The results of statistical tests on gastrocnemius muscle strength and plantarflexion flexibility used paired t test, because the two variables were normal data distribution, while the flexibility of dorsiflexion and the time of data distribution was not normal. Based on the results of data on gastrocnemius muscle strength, dorsiflexion flexibility, and plantarflexion flexibility increased, while in time occurred shortening time between pre and post treatment, whereas in the p value obtained in all variables both gastrocnemius muscle strength, flexibility dorsiflexion, plantarflexion and travel time had found a significant difference.

Table 2. Treatment 2 (control)

Variable	Average ± SD	
	Pre	Post
Strength (kg)	47,27 ± 21,52	45,15 ± 19,91
Dorsofleksi (^{0})	20 ± 6,12	20 ± 6,12
Plantarfleksi (^{0})	55 ± 7,64	55,77 ± 7,60
Travel Time (second)	14,19 ± 1,67	14,42 ± 1,76

Variable	Average±SD	p value
Strength of Gastrocnemius Muscle (kg)	2,12±2,43	0,009
Dorsofleksi Flexibility (0)	0,77±1,88	1,000
Plantarfleksi Flexibility (0)		0,165
Travel Time (second)		0,001

Notes: Significant when alpha was <0.05

The results of statistical tests on gastrocnemius muscle strength and plantarflexion flexibility using paired t test, because the two variables were normal data distribution, while the flexibility of dorsiflexion and the time of data distribution was not normal. In the strength of the gastrocnemius muscle, there was a decrease in strength with p value which indicated that there was a significant difference. In the flexibility of dorsiflexion, there was no difference, and there was a slight degree increase with the value of p which showed no significant difference on the flexibility of plantarflexion. Meanwhile, on the travel time, there was an elongation of travel time with p values which indicated significant differences.

Table 3. Test of treatment differentials 1 and 2 based on pre and post differences (delta)

Variable	Mean	SD
Strngth_Control	-2,1154	2,43374
Dorso_Control	,0000	,00000
Plantar_Control	,7692	1,87767
Travel time_Control	,2277	,13405
Strengh_Eksperiment	11,3846	7,83463
Dorso_Eksperiment	3,4615	2,40192
Plantar_Eksperiment	3,4615	4,27425
Travel time_Eksperiment	-,1892	,20267

Variable Δ	P value
Strength	0,000
Dorsofleksi	0,000
Plantarfleksi	0,067
Travel time	0,000

Notes: Significant when alpha was <0.05

Based on different test results (delta) treatments 1 and 2 using Mann Whitney test on gastrocnemius muscle strength, dorsiflexion flexibility and travel time, there was a significant difference, whereas there was no significant difference between treatment 1 and 2 in plantar flection flexibility

DISCUSSION

The results of this study showed that muscle strength in treatment 2 (control) had decreased by 2.12 kg, whereas in flexibility dorso flexion and plantar flexion tended to remain, and travel time had increased by difference 0.23 seconds slower. The decrease in gastrocnemius muscle strength was due to muscle fatigue, high intensity exercise would require an increased energy consumption. Energy consumption was generated from aerobic capacity in cells, and the magnitude of ATP usage was broken down from anaerobic metabolic processes. Anaerobic metabolism would break down glycogen that could produce the intracellular concentration of hydrogen (IH +), and lactate ions, so that heavy exercise could decrease PH, and increase lactate concentration in the body (Taylor & Groeller 2008). In a 100 meter athlete the metabolism used predominantly used energies from ATP-PC. The use of this energy had a highly short duration due to the activity with high intensity, so it would produce high lactic acid (Foss et al 1998). In treatment 1 (experiment), the increase of gastrocnemius muscle strength with difference of 11.38 kg, flexibility of dorsiflexion occurred an improvement with difference

3.4600, plantar flexion flexibility increased by difference 3.4700, while travel time had decreased by 0.19 second difference, describes faster travel time. This showed a significant effect with NMT administration, whereas when compared with the difference (delta) of treatment 1 and 2 only the plantar flection flexibility indicated a non-significant result.

NMT administration provided an enhanced muscle functional ability, stimulation of exteroseptive and proprioceptive neural systems. Exteroseptive stimulation in NMT would effect the reduction of blood stagnant and lymphatic fluid, improved local microcirculation, and absorption of edema by removing the skin that could cause the interstitial tissue space beneath it to be wider, increasing circulation and fluid absorption, so that subcutaneous pressure could be reduced, while proprioceptive stimulation was stimuli originating from muscles, tendons, aponeuroses, joint capsules, ligaments, and the stimulation of a condition of contraction or stretching. Both of these stimuli in both the exteroeptive and proprioceptive would provide stimulation to the central nervous system through the sensory nerve fibers, then would impulse the motor's response to the muscles, so that the response became better.

The NMT technique produced eccentric effects on the muscles that would increase elasticity and muscle length. When combined with the pull on the broad area of the skin , it would increase the extension/muscle length, fascia tissue, and skin, whereas there was no significant difference in plantar flexion flexibility due to the installation of NMT with decompression techniques that could have an eccentric effect on the gastrocnemius muscle, so that it tend to only increase the flexibility of dorsiflexion, whereas in plantar flection, it only gave a better motor response effect than without NMT (Blow 2012).

CONCLUSION

The provision of NMT (Neuromuscular Taping) has given better results than without using NMT on 100 meter sprinter athletes.

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CORRELATION OF CELL PROLIFERATION WITH CERVICAL LYMPHOID NODE STATUS IN NASOPHARYNGEAL CARCINOMA PATIENTS

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ABSTRACT

Several studies showed that the index of nasopharyngeal carcinoma (NPC) cell growth could be used to assess the carcinogenesis interaction factor, development and prognosis of NPC. Cell proliferation index could always be assessed with Ki-67 protein expression test. This research was conducted to study the correlation between cell proliferation index with cervical lymphoid node status in NPC in clinical manifestation to asses the progressivity and prognosis on NPC patients. This study used cross sectional design. Biopsy tissue specimen were acquired from 35 NPC patients clinically divided into four criteria of cervical lymphoid node status (N0, N1, N2 and N3). Expression of Ki-67 protein was acquired by immunohistochemistry test using monoclonal rabbit antibody anti-human Ki-67 clone 901-325-091911 (Biocare Medical, LCC. 4040 Pike Line, CA 94520 USA). The measurement of Ki-67 protein was conducted by pathology consultant. Spearman statistic test was performed to asses the correlation between Ki-67 protein expression and cervical lymphoid node status. The statistical significance was defined as p<0.05. Positive expression of Ki-67 protein was found in 33 patients; 4 patients with N0 (11.43%), 5 patients with N1 (14.29%), 9 patients with N2 (25.71%), and 15 patients with N3. Negative expression of Ki-67 protein was found in 2 patients with N0 (5.71%). The Spearman test resulted at p=0.0001 with correlation coefficient of 0.758. The correlation between Ki-67 protein expression with cervical lymphoid node resulted in a significant correlation (p<0.05). In conclusion, cell proliferation index has correlation with cervical lymphoid node status in NPC patients.

***Keywords**: nasopharyngeal carcinoma (NPC); cell proliferation index; Ki-67 protein expression; cervical lymphoid node status*

ABSTRAK

Beberapa penelitian menunjukkan indeks proliferasi sel pada penderita karsinoma nasofaring (KNF) dapat digunakan untuk menilai faktor interaksi karsinogenesis, perkembangan dan prognosis KNF. Indeks proliferasi sel dapat dinilai dengan ekspresi protein Ki-67. Penelitian dilakukan untuk mengetahui hubungan antara indeks proliferasi sel dengan status kelenjar getah bening (KGB) KNF untuk menilai progresivitas dan prognosis penderita KNF. Penelitian ini menggunakan desain cross sectional. Spesimen jaringan biopsi diperoleh dari 35 penderita KNF, secara klinis dibagi menjadi empat kriteria status KGB (N0, N1, N2 dan N3). Ekspresi protein Ki-67 diperoleh dengan uji imunohistokimia menggunakan antibodi rabbit monoklonal anti-human klon Ki-67 901-325-091911 (Biocare Medical, LCC 4040 Pike Line, CA 94520 USA). Penilaian protein Ki-67 dilakukan oleh konsultan patologi anatomi. Uji statistik spearman digunakan untuk menilai korelasi antara ekspresi protein Ki-67 dan status KGB. Signifikansi statistik ditentukan sebagai p <0,05. Ekspresi positif protein Ki-67 pada 33 pasien; 4 pasien dengan N0 (11,43%), 5 pasien dengan N1 (14,29%), 9 pasien dengan N2 (25,71%) dan 15 pasien dengan N3. Ekspresi negatif protein Ki-67 pada 2 pasien dengan N0 (5,71%). Uji Spearman menghasilkan p = 0,0001 dengan koefisien korelasi 0,758. Korelasi antara ekspresi protein Ki-67 dengan status KGB menghasilkan korelasi yang signifikan (p<0,05). Sebagai simpulan, indeks proliferasi sel berhubungan dengan status KGB pada penderita KGB.

***Kata kunci**: karsinoma nasofaring; indeks proliferasi sel; ekspresi protein Ki-67; status KGB servikal*

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INTRODUCTION

The general prognosis of nasopharyngeal carcinoma (NPC) is currently based on the assessment of clinical stadium by assessing primary tumor (T), cervical metastatic nodule (N) and widespread metastasis (M). Nasopharyngeal carcinoma patients with equal clinical stadium, but different prognosis are still frequently found. This shows that the TNM evaluation still unable to provide the accurate prediction to the prognosis of NPC. According to this issue, the development to molecular biomarker in NPC is required to be done to evaluate malignancy progressment that can help clinicians in performing interventional treatment in NPC patients and increase prognostic prediction (Li et al 2008).

One of the biomedical indicator that can be used to evaluate progressivity and prognosis of NPC is by measuring the cell proliferation index (Taweevisit et al 2010). Researches were conducted to analyze the correlation between the enlargement of cervical lymphoid node and cell proliferation index to determine the prognosis of NPC patients (Lin 2010, Taweevisit 2007).

Cell proliferation comprises of cell division and cell growth. The cell cycle is underlying the mechanism and regulation of cell proliferation. The proliferation activity of a cell can be determined by counting the mitotic index, proliferating cell nuclear antigen (PCNA) and expression of Ki-67 protein. Inspection of Ki-67 protein expression was recommended because it was being expressed along the cell cycle except during G0 phase (Eccles 2011, Kresno 2012).

Zhuxin and Shaofeng in 2002 conducted a research on the correlation between cell proliferation index and cervical lymphoid node status in NPC patients acquiring a significant result and can be used as a prognostic indicator for NPC patients (Zhuxin & Shaofeng 2013). Shi et al (2005) and Liu et al (2007) conducted the same research and acquired the same result (Liu et al 2008, Shi et al 2005). By contrast, a study which was conducted by Taweevisit et al 2010 in Thailand, acquired a non-significant correlation between cell proliferation index and cervical lymphoid node status in NPC patients (Taweevisit et al 2010). Likewise, Ozel et al in 2004 in Turky also conducted the same research with non-significant result. The differences in result show that there is still an uncertainty in the correlation between cell proliferation index and cervical lymphoid node status in NPC patients (Ozel et al 2004).

High cell proliferation index correlates with bad prognosis. High cell proliferation index shows progesivity of cancer cell growth which in turn has invasive nature and tendency to be metastatic. The evaluation of proliferation index can be used as concideration for interventional therapy and evaluate growth or reduction in tumor mass after chemotherapy and radiotherapy to evaluate respond to the therapy (Taweevisit et al 2010, Lin 2010, Piris & Mihm 2007, Aswarin 2014, Le & Lu 2010, Harahap 2009).

Some malignancies such as limphoma, breast cancer, endometrium cancer, prostate cancer, gastric cancer, NPC and other use cell proliferation index can be utilized to evaluate progressivity and prognostic. Based on the explanation above, there is a need to conduct a study in terms of finding the correlation between cell proliferation index and cervical lymphoid node status that hopefully can be useful to estimate the progressivity and prognosis of NPC patients and used as consideration material to provide intervention therapy to NPC patients.

MATERIALS AND METHODS

This study was an analytical observational research with cross sectional approach. This study was to evaluate the cell proliferation index in NPC patients, to evaluate and to explain the correlation between cell proliferation index with cervical lymphoid node status in NC patients. The study was conducted in Otorhinolaryngology-Oncology OPD Dr. Soetomo Academic Hospital Surabaya from April 2014 until December 2014 with the NPC patients who came to be treated (Medical Records Data in 2014).

The inclusion criteria of this study were NPC patients which had not receive definitive therapies, namely radiotherapy and chemotherapy. The NPC patients without enlargement of cervical lymphoid node were described as N0. Meanwhile, NPC patients with cervical lymphoidnode enlargement were described as N1, N2 and N3.

The exclusion criteria of this study were patients who did not have histopathological sample in the form of paraffin block from nasopharyng biopsy materials that had enough tumor tissue (4 micron in thickness) to be cell proliferation tested. The variables of this research are independent and dependent variable. The independent variable of this research is the cell proliferation index, while the dependent variable of this research is cervical lymphoid node status.

The inspection of cervical lymphoid node status was conducted and gathering a large number of patient samples for each criteria of cervical lymphoid node (N0, N1, N2 and N3) as can be seen in Table 1.

Table 1. Cervical lymphoid node criteria

Stadium	Description
N_0	No enlargement of cervical lymphoid node
N_1	If there is an enlargement of unilateral cervical lymphoid node, ≤ 6 cm, above supraclavicular fossa, and/or unilateral or bilateral, retrofaringlymphoid node ≤ 6 cm, with large size
N_2	If there is an enlargement of bilateral cervical lymphoid node, ≤ 6 cm at the biggest size, above supraclavicular fossa
N_3	If enlargement of cervical lymphoid node> 6 cm, and/or heading toward supraclavicular fossa is present

The selection of nasopharyng tissue from NPC patients and assessment of cell proliferation index by looking at Ki-67 protein expression was performed with immunohistochemistry technique using rabbit antihuman monoclonal antibody Clone 901-325-091911 (Biocare Medical, LCC 4040 Pike Line, CA 94520 USA), then assessment was done toward the expression of Ki-67 protein by anatomical pathologist consultant in the anatomical pathology installation of Dr. Soetomo Academic Hospital Surabaya. Cell proliferation index was counted by looking at the number of cells which express Ki-67 monoclonal antibody which then marked by a brown coloured nucleus. The assessment of Ki-67 protein expression was done by determining hot spot areas using microscope with 100 times magnification. The chosen hot-spot areas then manually counted the expression of Ki-67 which was coloured brown in the nucleus when observed with microscope using 400 times magnification, then presentation of cells which positively expressed Ki-67 protein was measured (Taweevisit 2007). Expression of Ki-67 protein was differentiated into 5 assessment scores as seen in Table 2.

Table 2. Ki-67 protein expression levels score

Score	Annotation
Negative	Brown granules in the nucleus occur in less than (<) 10 % from all field of view with 400 times magnification.
Positif 1	Brown granules in the nucleus occur in between 10 % and 25 % from all field of view with 400 times magnification.
Positive 2	Brown granules in the nucleus occur in between 26 % and 50 % from all field of view with 400 times magnification.
Positive 3	Brown granules in the nucleus occur in between 51 % and 75 % from all field of view with 400 times magnification.
Positive 4	Brown granules in the nucleus occur in more than 75 % from all field of view with 400 times magnification.

Source: Taweevisit et al (2010), Taweevisit (2007), Shi et al (2005), Ozel et al (2004)

Acquired data was analyzed statistically. Spearman statistic test was used to determine correlation between cell proliferation indexes with cervical lymphoid node status in NPC patients. Significant level (alpha) = 0.05.

RESULTS

There were 35 gathered samples that fulfill the criteria from NPC patients. Distribution data of NPC patients were found based on cervical lymphoid node status and Ki-67 protein expression.

Table 3. Distribution of cervical lymphoid node status

Cervical Lymphoid Node Status	N	%
N_0	6	17.14
N_1	5	14.29
N_2	9	25.71
N_3	15	42.86
Total	35	100.00

Table 3 showed that there were 6 patients without cervical lymphoid node enlargement (17.14%) and 29 patients with enlargement (82.86%). Patients with N3 cervical lymphoid node status were the most abundant which were 15 patients (42.86%) followed by N2 with 9 patients (25.71%).

Table 4. Ki-67 protein expression distribution

Ki-67 protein expression	N	%
Negative	2	5.71
Positive 1	10	28.57
Positive 2	13	37.14
Positive 3	5	14.29
Positive 4	5	14.29
Total	35	100.00

Table 4 showed distribution of cell proliferation index by evaluating Ki-67 protein expression, negative value were found in 2 patients (5.71%) and positive in 33 patients (94.29%). The positive value with the largest amount is positive 2 at 13 NPC patients (37.14%)

followed by positive 1 at 10 NPC patients (28.57%) and positive 2 and 3, each at 5 patients (14.29%).

Table 5. Ki-67 protein expression test result based on cervical lymphoid node status (N0, N1, N2, N3)

Ki-67 score	N_0	N_1	N_2	N_3	Total	%	Result
Negative	2	0	0	0	2	5.71	p=0.0001
Positive 1	4	3	2	1	10	28.57	r=0.758
Positive 2	0	2	6	5	13	37.14	
Positive 3	0	0	1	4	5	14.29	
Positive 4	0	0	0	5	5	14.29	
Total	6	5	9	15	35	100.00	

*P <0.05 (significance)
r (correlation coefficient) = 0.758 (75.8%)

Table 5 showed test result of Ki-67 protein expression in NPC with cervical lymphoid node status of N0, negative results were found in 2 NPC patients and positive 1 results were found in 4 NPC patients. In NPC patients with N1 cervical lymphoid node status, positive 1 result was found in 3 patients and positive 2 result in 2 patients. In NPC patients with N2 cervical lymphoid node status, positive 1 results were founded in 2 patients, positive 2 in 6 patients and positive 3 in 1 patients. In NPC patients with N3 cervical lymphoid node status, positive 1 result was found in 1 patient, positive 2 in 5 patients and positive 3 in 4 patients. Negative value of Ki-67 protein expression was found in 2 patients (5.71%) of all samples from NPC patients with cervical lymphoid node status of N0. Expression of Ki-67 protein with positive value was found in 33 samples (94.29%) of all samples. Expression of Ki-67 protein with positive value was found in 4 patients with N0 (11.43%), 5 patients with N1 (14.29%), 9 patients with N2 (25.71%), 15 patients with N3 status (42.86%).

The Spearman test resulted in P value of 0,0001 and r (correlation coefficient) value of 0.758. The data above showed that there was a significant correlation between expression of Ki-67 protein and cervical lymphoid node (N0, N1, N2 and N3) and a strong correlation with correlation coefficient which was at 0.758 (75.8%) was acquired.

Results from cell proliferation index checking by assessing the expression of Ki-67 using immunohistochemistry technique in NPC tissue were identified with a smear of dark brown colour in the nucleus. Observation and analysis of Ki-67 protein expression by pathologist consultant was done using binocular microscope with 400 times magnification. Results of immunohistochemistry painting were shown in Figure 1 as follow.

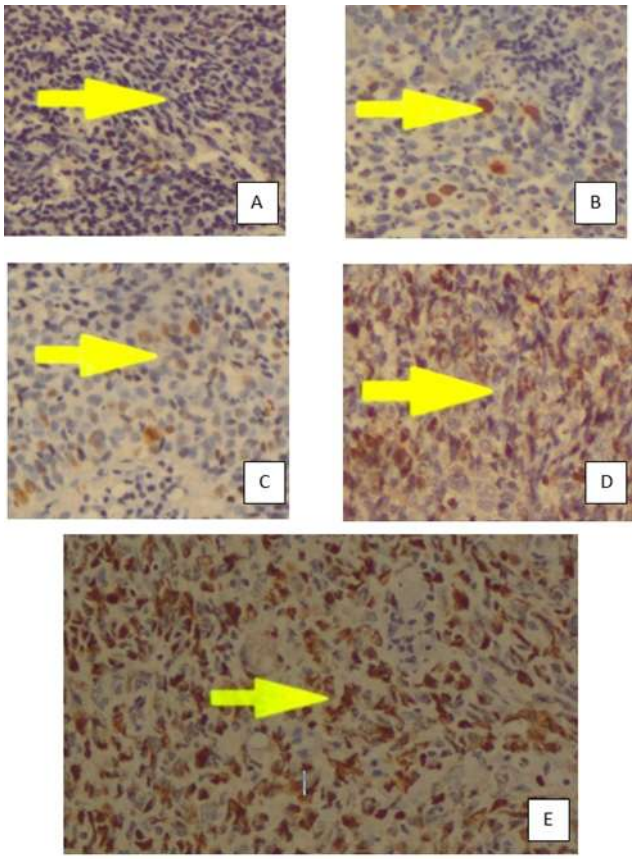

Figure 1. Ki-67 protein painting result in NPC tissue with immunohistochemistry technique, positive expression in the nucleus as brown colored tumor

Notes:
(A) Negative expression of Ki-67 (<10%)
(B) Positive 1 expression of Ki-67 (10-25%)
(C) Positive 2 expression of Ki-67 (26-50%)
(D) Positive 3 expression of Ki-67 (51-75%)
(E) Positive 4 expression of Ki-67 (>75%).

In negative expression of Ki-67, brown smearing in the tumor cell nucleus was not found; yellow arrow show brown smearing in the tumor cell nucleus (400x magnification).

DISCUSSION

This research was performed to analyze the correlation between cell proliferation index assessed from Ki-67 protein expression with cervical lymphoid node status to evaluate cancer cell progressivity and hoped to become alternative to pinpoint therapeutical intervention, progressivity and prognosis of NPC patients. This research only took data from Ki-67 expression checking result to be analyzed statistically without analyzing other factors.

Data of NPC patient distribution based on cervical lymphoid node status was gathered from this research and showed in Table 3. The most abundant cervical lymphoid node status are N3 at 15 patients (42.86%), followed by N2 with 9 patients (25.71%). The distribution of NPC patients based on cell proliferation index by evaluating Ki-67 protein expression were shown in Table 4. Ki-67 protein expression with negative results were acquired from 2 patients (5.71%) and positive in 33 patients (94.29%). Expression of Ki-67 protein with positive results were acquired from 4 patients with N0 (11.43%), 5 patients with N1 (14.29%), 9 patients with N2 (25.71%), 15 patients with N3 (42.86%).

The correlation between cell proliferation index and cervical lymphoid node is shown in Table 5. It shows the Ki-67 protein expression checking result correlated with cervical lymphoid node. The data from the results of the research shows elevation of Ki-67 protein expression followed by cervical lymphoid node enlargement. The data was then analyzed statistically to assess the correlation between cell proliferation index and cervical lymphoid node status using Spearman's test with the following result: P value at 0.0001 and r value (correlation coefficient) at 0.758. The correlation of ki-67 protein expression to assess cell proliferation index with cervical lymphoid node status (N0, N1, N2 and N3) in NPC patients was proven to be significant. The substance from statistical analysis result was the elevation of Ki-67 expression which was connected to the enlargement of cervical lymphoid node and both of the research variable had a strong correlation (r = 0.758). The expression of Ki-67 protein to assess cell proliferation index could be used to evaluate cancer cell progressivity with cervical lymphoid node enlargement as clinical manifestation can be used as therapeutical-intervention consideration toward NPC patients. Enlargement of cervical lymphoid node was one of the prognostic indicator in NPC patients, in turn Ki-67 expression could become alternative to pinpoint the prognosis of NPC patients. However, prospective research was still need to be conducted to pinpoint the prognostic value with Ki-67 protein in NPC patients.

The result from this research matches with Zhixin and Shaofeng research was conducted in 2002 in Guangxi which studied about the correlation of Ki-67 protein expression to evaluate cell proliferation index in 66 NPC patients has resulted that a significant correlation was acquired between the elevation of cell proliferation index and metastasis. Thus, cell proliferation index could be used as NPC patients prognostic indicator (Zhuxin & Shaofeng 2013). Shi et al in 2005 conducted a study in to 62 NPC patients, a significant correlation between Ki-67 protein expression and cervical lymphoid node status in NPC patient was acquired, but there was no correlation to cancer stages (Shi et al 2005). Liu et al 2008 conducted a research in Guangzhou toward 43 NPC patients, significant correlation was acquired between Ki-67 protein expression with incident of cervical lymphoid node in NPC patients (Liu et al 2008).

Furthermore, there were also researches with different results. Taweevisit et al in 2010 conducted a study in Thailand to 60 NPC patients, and resulted no significant correlation between cell proliferation index and cervical lymphoid node status in NPC patients (Taweevisit et al 2010). Ozel et al in 2004 conducted a study and acquired no significant correlation between expression of Ki-67 with NPC stages (Ozel et al 2004).

The differences in cell proliferation index by assessing Ki-67 protein expression which in turn connected to cervical lymphoid node status research results may be caused by some reason, because there are factors from NPC patients involved in the research including stadium factor, and type of histopathology; factor of researcher's accuracy in pinpointing the hot spot to assess Ki-67 protein expression; difference in the usage of cell proliferation index assessment standard which was between cut off below 10% and 30%, when using cut off below 10%, significant result will be gained, unlike when using cut off below 30% (Taweevisit et al 2010). The expression of Ki-67 protein could be used to assess the accumulation of many carcinogenesis factors. This caused the possibility to estimate progressivity of cancer cell and prognostic; prediction to therapeutical response, pre and post therapy evaluation; and malignancy patients survival rate (Eccles 2011, Harahap 2009).

Some researches that were conducted to study the correlation between cell proliferation index with carcinogenesis process done by researchers. Taweevisit

(2007) conducted a study to search the correlation of Ki-67 protein expression with mutant p53 protein expression as tumor suppressor protein in 60 NPC patients and get a significant correlation as the result between expression of Ki-67 and mutant p53 proteins. The elevation of p53 tumor supressor protein expression would cause uncontrolled cell proliferation, this was shown by the increase in Ki-67 protein.

Cell proliferation was connected with the mutation of protooncogen into oncogene. This caused malignant tumor to stimulate intracellular growth factor without extracellular stimulation (Eccles 2011). Liu et al (2008) conducted a research to study the correlation between LMP and STAT with cell proliferation in 43 NPC patients in Guangzhou and acquired a significant correlation between Ki-67 protein expression and incident of cervical lymphoid node enlargement in NPC patients.

Ki-67 protein expression to assess cell proliferation index was correlated with cyclin-D1 expression as cell cycle regulator, EGFR and HER2. Hu and Shi (2004) conducted a research to study the correlation between cyclin D1 as cell cycle regulator and Ki-67 protein expression to assess cell proliferation index in 56 NPC patients and acquired significant result, elevation of cyclin-D1 would increase cell proliferation (Tan et al 2005). Ma et al (2003) conducted a research to study the relationship between cell proliferation index, angiogenesis, p53, EGFR and HER2 toward 78 NPC patients and acquired a result which stated that those factors were reciprocal correlation, influencing the clinical condition and prognosis of NPC patients.

Taweevisit et al (2010) conducted a research in Thailand on 60 NPC patients and acquired a significant relationship between microvascular density to evaluate engiogenesis and cell proliferation index which was assessed by expression of Ki-67 protein as the result. They found significant relationship between Ki-67 protein expression and microvascular density with NPC patients' prognostic. Some studies on Ki-67 protein expression were also being used to assess the prognosis of malignancy patients (Eccles 2011). Lavertu et al (2001) conducted a a study on 50 squamous cell malignancy in head and neck and found out that elevation of Ki67 protein to assess cell proliferation index was significant related with lower survival (Lavertu et al 2001). Taweevisit et al (2010) in Thailand recommended proliferation index by assessing Ki-67 protein expression as the prognostic indicator of NPC patients, because it only required a small amount of tissue to assess the expression of Ki-67 protein.

In short, the expressions of Ki-67 protein were also being used to assess other malignancy prognostic cancer in between them were gall blader malignancy, prostate, breast, endometrium. The evaluation of malignancy patients' prognosis based on Ki-67 protein expression using criterion value of less than (<) 10 % concluded that the patients had good prognostic, 10%-25% indicated medium prognosis, and > 25% indicated a bad prognosis (Li et al 2008, Lin 2010, Eccles 2011).

CONCLUSION

This study acquired a significant relationship between cell proliferation index and cervical lymphoid node status in NPC patient with strong correlation. This caused the checking of Ki-67 protein expression to evaluate cell proliferation index to be able to be used as indicator of progressivity, material for interventional therapy, and alternative to pinpoint prognostic factor in NPC patients. Further studies needed to search the correlation between Ki-67 protein expression and kinds of histopathology, stadium, nasopharyngeal primary tumor and metastatic incidence and survival rate in NPC patients. It also needed to compare Ki-67 protein before and after therapy as post therapy assessment and evaluation in NPC patients.

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AMRTA-X: GRASP KINEMATIC ANALYSIS DURING MYOELECTRIC PREHENSION ORTHOSIS AND BODY POWERED PREHENSION ORTHOSIS'S USAGE ON BRACHIAL PLEXUS INJURY PATIENTS

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ABSTRACT

Brachial Plexus Injury (BPI) results in decreased motor function in upper extremity and leads to reduced hand grasping movement. Orthotic prehension is designed to create artificial grasp movements in paralyzed hand. This study was to compare grasp kinematic improvement between body powered and myoelectric prehension orthosis usage in patients with BPI. This study was a single group without control and post test with experimental study. The subjects of the study (n = 11) were brachial plexus injury patients with non-functional hand strength. Joint motion and angular velocity of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joint of index finger were evaluated. There was an improvement in joint motion and angular velocity after both orthosis usage. Joint motion in MCP and PIP, Angular velocity in MCP were not significantly different between myoelectric and body powered and myoelectric prehension orthosis usage. PIP angular velocity improvement were better after body powered prehension orthosis usage (p= 0.03).In conclusion, body powered and myolectric prehension orthosis usage improved kinematic parameter of index finger's MCP and PIP joint. PIP angular velocity was better after body powered prehension orthosis usage.

***Keywords**: kinematic analysis; brachial plexus injury; body powered prehension orthosis; myoelectric prehension orthosis*

ABSTRAK

Cedera Pleksus Brakhialis (CPB) menyebabkan penurunan fungsi motorik ekstremitas atas dan mengganggu gerakan menggenggam. Ortosis prehension dirancang untuk menciptakan gerakan menggenggam buatan pada tangan yang mengalami kelumpuhan. Perbandingan perbaikan kinematika gerakan menggenggam antara penggunaan ortosis prehension body powered dengan ortosis prehension myoelektrik pada subyek penderita CPB. Studi ini adalah studi eksperimental single group, post test only. Subyek penelitian (n = 11) adalah pasien CPB dengan kekuatan tangan non-fungsional (MMT<3). Analisis kinematic dilakukan dengan mengevaluasi pergerakan dan kecepatan sudut sendi metacarpophalangeal (MCP) dan interphalangeal proksimal (PIP) jari telunjuk pada proses menggenggam. Terdapat perbaikan pergerakan dan kecepatan sudut sendi setelah penggunaan kedua jenis ortosis. Pergerakan sendi MCP dan PIP, serta kecepatan sudut sendi MCP tidak berbeda signifikan antara penggunaan kedua jenis ortosis. Peningkatan kecepatan sudut PIP lebih baik setelah penggunaan orthosis prehension body powered (p = 0,03). Sebagai simpulan, penggunaan ortosis prehension body powered dan myolektrik dapat meningkatkan parameter kinematik pada sendi MCP dan PIP jari telunjuk saat gerakan menggenggam. Perbaikan kecepatan sudut sendi PIP lebih baik setelah penggunaan ortosis prehension body powered.

***Kata kunci**: analisis kinematik; cedera pleksus brakialis; ortosis prehension body powered; ortosis prehension myoelektrik*

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INTRODUCTION

Strong and sudden trauma that affects the shoulder region may result in damage to the shoulder and other structures that surrounds it, including muscles, fascia, skin, bones, and neuromuscular structures. In neuromuscular damage, the brachial plexus may be affected by this trauma. The brachial plexus injury

(BPI) is a lesion on nerve tissue originating from the 5th cervical roots to the 1st thoracic root (C5-Th1). These lesions carry consequences, occurrence of neurological deficits in various structures that innervated by these nerve roots (Kang & Wolfe 2011, Kelly & Leonard 2012).

The incidence of BPI increased every year in Dr. Soetomo Academic Hospital Surabaya. Most of all were males (86%) in the 21-30 years old (37%). The most frequent injury mechanisms were motorcycle accidents (90%), and the right side of injury was the right side (77%). The levels of injury were 24% C5-6 postganglionic, 19% C5-7 postganglionic, 3% postganglionic C8-T1, 54% C5-T1. In the complete BPI, the postganglionic C5-7 and preganglionic C8-T1 combinations occurred in 33% of cases (Rachmawati et al 2016, Suroto 2011, Suroto 2015).

Generally, human hands play an important role in human interaction with the environment. In BPI, motor disturbances can result in loss of grip strength and hand function. According to data between January 2005 - December 2009 in Dr. Soetomo, from 14 patients postoperative BPI, 7 patients had a motor power with more than or equal to 3, and 7 patients had muscle strength less than 3 (Kelly & Leonard 2012, Rachmawati et al 2016, Gustus et al 2012, Suroto 2011).

Brachial Plexus Injury (BPI) causes impaired motor and sensory function in the upper extremity. Impaired motor function in the shoulder, elbow and wrist caused disruption of the ability of stabilization, positioning and placement of the upper motion. While impaired motor function in both of extrinsic and intrinsic hand muscle caused disruption of hand prehension ability. The combination of all of those impairment added with exteroceptive and proprioceptive sensory dysfunction caused hand dexterity disruption (Jones 1996, Wardhani et al 2011).

In the BPI rehabilitation program, the use of shoulder-elbow-wrist orthosis improves the stabilization, positioning and placement of upper extremity in functional position. Meanwhile, the use of prehension orthosis is intended to improve the ability of hand prehension. Although in practice, the use of prehension orthosis in Dr. Soetomo Academic Hospital for the BPI cases had never been given (Wardhani et al 2011, Bengtson & Shin 2008, Lunsford & DiBello 2008, Smania et al 2012, Hapsari et al 2017). In this case, there are two types of prehension orthosis; body powered prehension orthosis is prehension orthosis that used other healthy part of body to empower prehension ability. On the other hand, an externally powered prehension orthosis uses external source to create artificial grasp action (Lunsford & DiBello 2008).

This study intended to compare kinematic improvement effect after body powered and myoelectric prehension orthosis usage in BPI patient. Body powered prehension orthosis that was used was a shoulder-driven prehension orthosis with the same principle design as in Lehneis publication. Thumb was fixated in an opposition position to the 2nd and 3rd fingers; the 2nd and 3rd fingers are driven by voluntary closed mechanical system through a cable drawn by the contralateral side through a shoulder harness (Lehneis 1968, Michael & Nunley 1992, Lunsford & DiBello 2008).

Figure 1. Body powered (shoulder driven) prehension orthosis installed on subject

Myoelectric prehension orthosis that were used were developed by the Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Academic Hospital. This myoelectric signal were taken from electrode that were placed over Platysma and Sternocleiodmastoideus muscle and processed later on surface EMG (sEMG) hardware (Myoware and Teensy board) and Arduino based-on software developed by the Faculty of Biomedical Technic of Science and Technology,Universitas Airlangga. The energy source for High torque motor servo and sEMG were 5V Battery 7500 mAH. The mechanical components were 3D printed polylactic acid (PLA), and designed to enable the orthosis to make a three-jaw chuck position. This orthosis is a development of the Powered Dynamic Hand Orthosis (PDHO) (Lehneis 1968, Brown & Roberts 2008, Fundhi et al 2016, Geethanjali 2016, Saharan et al 2017, Salamat et al 2017, Pawana 2016).

Kinematic parameters that were evaluated were joint movement and angular velocity at metacapophalangeal (MCP) and proximal interphalangeal (PIP) joint of index finger. Both of it were two of upmost kinematic parameters being analyzed.The kinematic analysis were conducted by using software Kinovea that had a quality, validity and reliability for measuring motion analysis

(Charmant 2017, Chen et al 2015, Cordella et al 2014, Grigg et al 2017, Puig-Divi et al 2017, Mohamed 2015).

Figure 2. Myoelectric prehension orthosis installed on subject.

MATERIALS AND METHODS

In this single group without control, post-test research design was conducted on 11 patients with right brachial plexus injury in Medical Rehabilitation Installation of Dr. Soetomo Academic Hospital that fulfilled inclusion and exclusion criteria and recruited as research subjects. The inclusion criteria were right brachial plexus injury with hand muscle strength less than 3, could understand and followed instructions, agreed to be the subject of research as well as following the entire series of research by signing informed consent form. The exclusion criteria were limitation of range of motion that inhibited orthosis installation, weakness of the left shoulder muscles, upper extremity acute inflammation, upper limb skin lesions, the size of the orthosis that did not match the suject body size. The subjects would be ruled out from the study if they developed an allergic reaction to the orthosis or could not complete the entire series of studies.

Table 1. Baseline characteristic

Character	Value
N	11
Sex	Male 11 (100%)
Age (years)	27,18 ± 5,95
Height (cm)	166,45 ± 4,61
Weight (kg)	64.91 ± 10,11
BMI (kg/m2)	23,36 ± 3,44
BPI side	Right side 11 (100%)
Root affected	Total C5-Th1 11 (100%)
Degree of lesion	Complete 10 (91%)
Duration (years)	3,8 ± 2,74
BPI's surgery history	FFMT 8 (72,7%)
Rehabilitation program	Routinely 9 (81,8%)

All subjects used shoulder-elbow orthosis to eliminate shoulder and elbow motoric disturbance. Then, they used both types of prehension orthosis alternately. First, subjects used body-powered prehension orthosis, and performed orthotic control exercises for 15 minutes. Then, grasp simulation video were recorded. After washout period for 7 days, the subjects used myoelectric prehension orthosis, and performed orthotic control exercises for 15 minutes. Then, grasp simulation video were recorded again. All videos were recorded with Sony Handycam HDR-CX240E in special grasp simulation platform. Then, these recordings were kinematically analyzed with Kinovea ver. 0.8.26.

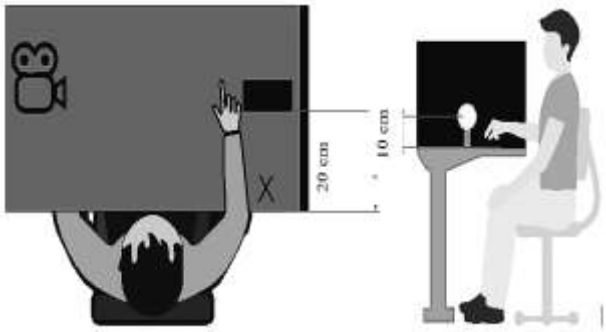

Figure. 3. Grasp simulation special platform.

The subject were instructed to grasp the 3 cm-diameter cylinder three times. The fastest grasp was being analyzed. All of the data were collected and analyzed using SPSS version 17 software. This study was ethically approved by Health Research Ethical Comittee of Dr. Soetomo Academic Hospital Surabaya.

RESULTS

The study involved 11 male, right total BPI, age range of 22-36 years. All subjects were total BPI patients, 91% had complete lesions, 55% BPI at trunk level, 91% had BPI due to motorcycle accidents, 82% had undergone free functioning muscle transfer (FFMT) operation, performed routine rehabilitation, BPI occurs between 4 months - 10 years, and all subjects have intrinsic and non-functional hand muscle strength (Table 1).

The initial and final angle of the MCP joint showed that there was no significant difference between the use of body-powered prehension orthosis with myoelectric ortosis. While in the initial and final angle parameters PIP showed that there was a significant difference between the use of body-based prehension orthosis with myoelectric ortosis. In the joint angle motion parameters, myoelectric prehension orthosis did not differ significantly in the MCP and PIP joint angle

motion parameters compared to the body powered orthosis (Table 2).

The joint angular velocity parameters showed that body powered prehension orthosis is significantly superior than compared with myoelectric prehension orthosis in the PIP angular velocity parameter, while in the MCP angular velocity parameter, body powered prehension orthosis did not differ significantly from myoelectric prehension orthosis (Table 2).

DISCUSSION

This study was the first experimental study that compared between body powered prehension orthosis and myoelectric prehension orthosis usage in BPI subjects. There were some literatures that discussed prehension orthosis usage in BPI, but no one conducted any comparison between two types of prehension orthosis. Browns and Slack only mentioned externally powered prehension orthosis usage in BPI, while Michael and Lehneis mentioned body powered prehension orthosis (Brown & Roberts 2008, Slack & Berbrayer 1992, Michael & Nunley 1992, Lehneis 1968).

The subjects of this study were 11 male patients with BPI aged 20-36 years. All subjects were total BPI patients, 91% had complete lesions, 55% BPI at trunk level, 91% had BPI due to motorcycle accidents, 82% had undergone free functioning muscle transfer (FFMT) operation, performed routine rehabilitation. The BPI occured between 4 months to 10 years, and all subjects had intrinsic and non-functional hand muscle strength (MMT <3) (table 1). The baseline characteristics of subjects were suitable with some literatures. The Department of Orthopedic and Traumatology Dr. Soetomo Academic Hospital mentioned that BPI sufferers were mostly male with young adult age (25-35 years old), and as suspects of motorcycle accidents. Narakas mentioned that 70% of BPI involved motorcycle traffic accidents. Rachmawati mentioned that half of BPI patients had functional upper muscle strength after FFMT procedures (Kang & Wolfe 2011, Suroto 2011, Rachmawati et al 2016).

Figure 4. Kinematic analysis of MCP and PIP joints during myoelectric prehension orthosis usage. **Left:** initial position; **Right:** Final position

All subjects could complete the entire research phase until finished. It showed that subjects can adapt to the use of shoulder-angled orthosis as well as both types of prehension orthosis and had an ability to control the orthosis after a 15 minutes orthosis control exercise session. The use of orthosis prehension in the subject wasa form of environmental change that was intended to overcome the existing impairment on the subject. The ability to operate the orthosis showed a succesful adaptation to a new environment (WHO 2001, Johnson & Mansfield 2014).

The ability of subject to control basic movement of prehension orthosis was also a great first step; considering that this was the first time he had experienced for using, feeling and controlling the orthosis. The ability of the subject to be able to move his hands back consciously had a great psychological impact, the change from being immobile limb to being mobile could be a big motivation for him. Instead of just moving the fingers, the control exercises also ensured that the orthosis worked well, where three jaw chuck movements that became the goal of finger movement were also achieved (Suroto 2011).

This study also showed that both orthosis design were safe to be used since there were no major or fatal side effect. The side effect that occured in this study was one subject being exhausted after body powered orthosis usage and another one subject felt uncomfortable in her neck and face after myoelectric prehension orthosis usage.

Table 2. Kinematic parameter comparison of MCP and PIP joint

Kinematic Parameter	n	Body Powered Orthosis		Myoelektric Orthosis		*p*	Sig.
		Value	SD/Range	Value	SD/Range		
MCP initial angle (º)	11	-14	-36 – (-5)	-8	-54 – (-4)	0,857 [b]	
MCP final angle (º)	11	5	-25 – 28	13	-50 – 30	0,350 [b]	
MCP joint movement (º)	11	22	7,27	25	10,25	0.441[a]	
PIP initial angle (º)	11	50	11,24	22	10,81	0,000 [a]	**
PIP final angle (º)	11	61	42 - 77	31	21 – 78	0,04 [b]	**
PIP joint movement (º)	11	11	5 - 31	14	6 – 42	0,181 [b]	
MCP angular velocity (º/s)	11	44	22,78	33	9,88	0,218 [a]	
PIP angle velocity (º/s)	11	24	20-80	17	7 - 43	0,03 [b]	**

The joint movement comparison result suggests that there is an advantage in the mechanical design of myoelectric prehension orthosis, ie the presence of a second joint in the finger bar that allows flexion movement in the PIP joints to be minimal. But the superiority of the design brings another consequence, in which the size and mechanical design of myoelectric prehension orthosis becomes larger and more complex. In fact, in terms of successful performing the task of grasping, both types of orthosis is successfully solve it. Thus, when viewed from the side of effectiveness, a more simple design is certainly preferred. Bos also mentions that it should be a consideration in designing of a functional hand tool (in this case orthosis prehension) that less complex design but still give a good function (Bos, et al., 2016).

The results of the research on the parameters of joint movement of both types of orthosis show that there is movement of MCP joints of 22-25º and PIP 11-14º joints. With such a wide range of joint motion is still very far from the area of normal joint motion, only about 25% (MCP joint) and 15% (PIP joint). The joint movement is suitable with the Sancho-Bru research, which states that Holding a cylinder with a diameter of 64 mm movement need MCP joint flexion of 10.2º and PIP joint flexion 37.6º. Hayashi mentioned that it is necessary to move the MCP joints at least 100º, which begins with extension 30º and ends at flexion 70º so that there is no disruption of hand function. Bain's research states that the functional joint extent required to perform 20 items of function tests holding Sollerman's hands for MCP joints is 19-71º flexion (48% of total joint joints of MCP joints) and PIP 23-87º joints (59% total joint PIP). So, it can be predicted that with the use of both this study's orthosis, they wouldn't able to mimic normal hand function or complete the task of daily activity (Duncan, et al., 2013; Hayashi, et al., 2014; Bain, et al., 2015; Sancho-Bru, et al., 2014).

Other mechanical design problems for a good prehension orthosis include the space in the hand is narrow. This is a design challenge, because imperfect mechanical design will produce not perfect finger movements. Improper mechanical design may also results in joint misalignment in hand, which may lead to discomfort in users, rejection in use, even to pressure sore occurrence (Bos, et al., 2016).

Angular velocity parameter comparison result suggests that body powered prehension orthosis can work to close the grasp faster, the factor that causes the speed of orthosis prehension body powered angle can be faster is because the closing speed of the grip is produced through direct body movement transmission, in this case the shoulder adduction movement. Whereas in myoelectric prehension othosis, the angular velocity is limited by the inherent specifications of the electric motors used, the magnitude of the energy source voltage as well as the efficiency of the mechanical components of the orthoses. The restriction of shoulder adduction movement is a motor learning process that is still in its early stages, only through a 15 minute adaptation process during the exercise of orthotic control, and a brief adaptation process also makes the subject to ensure that gripping movements have succeeded only from visual feedback.

Goebl's research mentions that through regular and rigorous exercise, a neurostructural organization will produce a more efficient movement. The imperfection of the sEMG system and the added lack of mechanical feedback and relatively short training time will result in the subject's adaptation process with more difficult myoelectric prehension orthosis (Goebl and Palmer, 2013; Carey, et al., 2015; Bos, et al., 2016; Hitec Multiplex, 2018).

The resultant angular velocity produced by both types of orthosis is still far from the normal value mentioned by Chen's research which states that the normal male hand angle velocity at MCP joints is 12,16 rad/s equivalent to 696.95 º/s and in the PIP joint 15,03 rad/s equivalent to 860,93 º/s. However, the speed of grasping it is still faster than the Dorenfeld's developmental orthosis that takes time to close the grip by 60° in 4.17 seconds, or has an angular velocity of 14.3 º/s (Chen, et al., 2013; Dorenfeld, et al., 2013).

In the study there are some limitations of research, namely: orthosis prehension body powered and myoelektrik only available in 1 size, whereas research subjects have variations of body size, so it is possible there is an orthosis that is not fit for the body size of the subject.

There is difficulty in the process of recognition of movement by using a marker, the marker can not be attached completely to the wick joints of the wrist, MCP, PIP and DIP because the design of mechanical systems and orthotic materials sometimes cover the axis of the joint

CONCLUSION

Body powered shoulder-driven prehension orthosis and myoelectric prehension orthosis usage improves kinematics parameters of MCP and PIP joints of the second finger on BPI grip movements. Body powered shoulder-driven prehension orthosis usage is no better than myoelectric prehension orthosis prehension in improving movement of the MCP and PIP joints also MCP joint angular velocity. Body powered shoulder-driven prehension orthosis usage is better than the use of myoelectric prehension orthosis in improving the angular velocity of the second PIP joint joint in the BPI grip movement.

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HYPERBARIC OXYGEN EFFECTS ON CONTRAST AND MACULAR LIGHT SENSITIVITY IN DRY TYPE AGE-RELATED MACULAR DEGENERATION PATIENTS

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ABSTRACT

This study was to compare the effectiveness of hyperbaric oxygen therapy (HBOT) on contrast and macular light sensitivity improvement in dry type age-related macular degeneration (AMD) patients. The subjects were eyes that had been diagnosed with dry type AMD which met inclusion criteria. The subjects were divided into two groups. The first group was given antioxidants and HBOT. The second group was given only antioxidants. Contrast and macular light sensitivity test were done using MARS contrast sensitivity chart and Humphrey Field Analyzer-3 for three times, pre-therapy, day-1 and 14 post- therapy. This study found that 25 eyes were included for analysis, 14 subjects in first group, and 11 subjects in second group. Statistical analysis results showed that there were significant increase on contrast sensitivity in intervention group between one-day post-therapy with pre-therapy, P = 0.003 (P <0.05), and between 14-days post-therapy with pre-therapy, P = 0,015 (P <0.05). From pre- and post-analysis, there were no significant difference found on contrast sensitivity in control group and macular light sensitivity in intervention group. In control group, there were significant increase on superotemporal, superonasal, and inferonasal area between one-day post-therapy and pra-therapy with P = 0.004, P = 0.013 and P = 0.008 (P <0.05), respectively, and there was significant decrease on inferonasal area between 14-days post-therapy and one-day post-therapy, P = 0.003 (P <0.05). In conclusion, patients with AMD who were subjected to HBOT achieved improvement in contrast sensitivity in cases considered as having low prognosis. HBOT should be considered as promising intervention for AMD management adjuvant and further research are needed to find optimal dosage.

***Keywords**: AMD; hyperbaric oxygen; contrast sensitivity; light sensitivity*

ABSTRAK

Penelitian ini bertujuan untuk membuktikan pengaruh dari terapi oksigen hiperbarik pada perbaikan sensitivitas kontras dan cahaya makula pada penderita Age-related Macular Degeneration (AMD) tipe kering. Subjek adalah mata penderita yang telah terdiagnosis AMD tipe kering yang memenuhi kriteria inklusi. Subjek dibagi ke dalam dua kelompok. Kelompok pertama diberikan antioksidan dan HBOT. Kelompok kedua diberikan antioksidan saja. Sensitivitas kontras dan cahaya makula diperiksa menggunakan grafik sensitivitas kontras MARS dan Humphrey Field Analyzer-3. Pemeriksaan dilakukan sebanyak tiga kali, praterapi, satu hari dan 14 hari pascaterapi. Dalam penelitian ini, 25 mata dimasukkan untuk dianalisis, 14 pada kelompok pertama dan 11 pada kelompok kedua. Hasil analisis statistik menunjukkan didapatkan peningkatan yang signifikan pada sensitivitas kontras di kelompok pertama antara satu hari pascaterapi dengan praterapi, P = 0,003 (P <0,05), dan antara 14 hari pascaterapi dengan praterapi, P = 0,015 (P <0,05). Pada analisis pre- dan post-, tidak didapatkan perbedaan yang signifikan pada sensitivitas kontras di kelompok kedua dan sensitivitas cahaya makula di kelompok pertama. Pada kelompok kedua didapatkan peningkatan yang signifikan pada area superotemporal, superonasal, dan inferonasal antara satu hari pascaterapi dengan praterapi dengan P = 0,004, P = 0,013, P = 0,008 (P <0,005) secara berurutan, dan didapatkan penurunan yang signifikan pada area inferonasal antara 14 hari pascaterapi dan satu hari pascaterapi, P = 0,003 (P <0,05). Sebagai simpulan, pasien dengan AMD yang menjalani HBOT mengalami perbaikan sensitivitas kontras pada kasus yang dianggap memiliki prognosis buruk. HBOT dapat dijadikan pilihan intervensi yang menjanjikan pada tatalaksana tambahan AMD dan penelitian lanjutan dibutuhkan untuk menemukan dosis yang optimal.

***Kata kunci**: AMD; oksigen hiperbarik; sensitivitas kontras; sensitivitas cahaya*

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world in people over 50 years of age (McCannel et al 2017). There are two forms of AMD which are dry and wet form. The dry form accounts for approximately 85 to 90% of AMD cases (Chandramohan et al 2016). It is estimated that among North Americans, 15 million (85%–90% of all AMD patients) currently have dry (nonneovascular, or nonexudative) AMD and 1.7 million people (10%–15% of all AMD patients) have wet (neovascular) AMD (McCannel et al 2017). Age-Related Eye Disease Study (AREDS) divide AMD into 4 categories according to the size and extent of drusen in each eye, the presence of advanced AMD and visual acuity. AREDS AMD category 1 consisted of persons free of AMD with less than 5 small drusen (<63 µm). Category 2 participants had early AMD with multiple small drusen or non-extensive intermediate drusen (63 to 124 µm), pigment abnormalities or a combination of the two. Category 3 participants had no advanced AMD but had at least 1 large drusen (125 µm), extensive area of intermediate drusen or geographic atrophy (GA) not involving the center of macula. Category 4 participants had advanced AMD, central geographic atrophy (CGA) or neovascular AMD in one eye (Chew et al 2013).

A previous research has suggested several aspects of macular visual function can be impaired in early AMD, both cone-mediated and rod-mediated functions. These include spatial contrast sensitivity, visual acuity under low luminance and/or low contrast, photopic and scotopic light sensitivity, flicker sensitivity and dark adaptation (Owsley et al 2015). Contrast sensitivity is a measure of the amount of lightness or darkness an object has compared with its background. Although there is a moderate correlation between visual acuity and CS, they are independent measures of visual function and not necessarily interchangeable. Contrast sensitivity can detect visual dysfunction that is not apparent when visual acuity alone is tested (Faria et al 2015). Photoreceptor degeneration in early AMD is associated with decreased light sensitivity in the macula and slowed dark adaptation despite normal visual acuity (Sevilla et al 2016).

AREDS first established the benefit of vitamin and zinc supplementation in reducing the risk of vision loss in nonexudative AMD. In the study, supplementation with the antioxidant vitamins C (500 mg) and E (400 IU), beta carotene (15 mg), and the micronutrient zinc (80 mg zinc oxide and 2 mg cupric oxide to prevent zinc-induced anemia) in patients with intermediate or advanced AMD showed a 25% risk reduction for progression to more-advanced stages of AMD and a 19% risk reduction in rates of moderate vision loss (>=3 lines of visual acuity) at 5 years (McCannel et al 2017).

In dry AMD, Stefansson et al suggested that the diffusion of oxygen to photoreceptors would be impaired by drusen, and that merely the increased distance of the photoreceptors from the choroid could be significant in causing retinal hypoxia (Stefansson et al 2011). This conclusion was based largely on the analysis of retinal detachment, in which we showed that even very small detachments could impair O2 transport. While it is not easy to know the causal relationship, photoreceptor loss is localized to areas of large drusen (Sadigh et al 2013), so this appears to be a reasonable suggestion.

Hyperbaric oxygen therapy (HBOT) has many biologic affects including activation of endogenous antioxidants, decrease in lipid peroxidation, microbicidal actions, and as a regulator of inflammation, which may theoretically affect the development and/or progression of AMD. A study by Weiss on 14 patients with advanced AMD that was given a one-hour session of HBOT had resulted eight patients were treated at 1.75 ATA, and six patients were treated at 1.5 ATA for one hour. Significant improvements in visual acuity and/or visual field with improvements in the activities of daily living were observed. There were no complications, and the visual benefits achieved appear to be maintained at follow-up visits (Weiss 2010). HBOT dosage that was used at Department of Hyperbaric, Naval Health Institute, Surabaya, Indonesia was breathing 100% oxygen at 2.4 ATA (Widodo et al 2016).

MATERIALS AND METHODS

This quasi-experimental study was conducted at Department of Hyperbaric, Naval Health Institute, Surabaya and vitreoretinal division of ophthalmology outpatient clinic at Dr Soetomo Hospital Surabaya from April 2018 to July 2018. This study was approved by Medical Research Ethic Comittee of Dr Soetomo Academic Hospital Surabaya. Informed consent was obtained from participants after the nature and purpose of the study was described.

Patients could be eligible if 1 or both eyes met the following criteria: patients with previously known dry type AMD, visual acuity less than 1.3 LogMAR, systolic blood pressure was below 140 mmHg, no abnormalities on ear-nose-throat and chest x-ray examination, agreed to have a restrictive diet (low fat and no alcohol), and if the patient was a smoker, he/she agreed to stop smoking for minimum 4 days before therapy until 1 day after therapy. Participants also asked to avoid sunlight exposure for minimum 4 days before

therapy until 1 day after therapy. Diagnosis of dry type AMD was based on AREDS classification stage 1, 2, and 3. The diagnosis were confirmed by two vitreoretinal senior consultants. Exclusion criteria included any of the following: having chronic restrictive pulmonary disease, wet type AMD, maculopathy caused by other disease, and inability to read. Drop out criteria were unable to follow the follow-up schedule, refusal to complete the study, and death.

Functional Testing

Visual acuity and all functional tests were performed before fundus imaging. Best-corrected visual acuity was assessed by one refractionist using ETDRS (Early Treatment of Diabetic Retinopathy) Chart under photopic conditions (189-377 lux). The results were recorded in logarithm of the minimum angle of resolution (logMAR). Subjects wore their best correction for all tests.

Contrast sensitivity testing with MARS numeral contrast sensitivity chart. The test system was a set of three printed charts, supplied in three forms for independent left eye, right eye and binocular testing. The three forms, whose number was identified at the bottom of each chart were identical except for the sequence of numerals. Each chart form consists of 48 numerals, each subtending 2 deg at a 50 cm test distance, arranged in eight rows of six numerals each. The contrast of each numeral, reading from left to right, and continuing on successive lines, decreased by a constant factor (0.04 log unit). The patient simply read the numerals across lines and down the chart as in standard letter acuity measurement. Instead of the numerals decreasing in size, however they decreased in contrast. The contrast of the final numeral before which the patient misidentified two consecutive numerals with a correction for earlier incorrect responses, determined the log contrast sensitivity (CS).

This study used static automated white-on-white threshold perimetry with Humphrey Field Analyzer-3 (Carl Zeiss Meditec), and 10-2 Swedish Interactive Threshold Algorithm (SITA) Standard Test to examine macular light sensitivity. When the fixation lost and the false-positive/false-negative rates were less than 20%, the results were considered reliable. This study analysed only use the reliable test data. All tests were done for three times, namely baseline (before therapy), one day post therapy, and 14 days post therapy.

Statistical Analysis

The data obtained were analyzed with frequency and descriptive statistics. The comparison between groups were assessed using Mann-whitney and independent samples T-test. For pre- and post- analyses were using Wilcoxon signed rank test. Qualitative data were analyzed using chi square and Fisher's exact test. All statistical values were considered significant if p value was < 0.05. All statistical analyses were carried out using SPSS version 20.0.

RESULTS

Table 1 presented the demographic characteristics of 25 eyes from 15 AMD patiens enrolled in the study. There were no statistically significant difference between both groups' demographic characteristics with P >0.05.

Table 1. Demographic characteristics of the study population

	HBOT (n=14)	Control (n=11)	p value
Gender (M/F)	0/14	0/11	-
Age (y)	64.50 ± 8.57	64.36 ± 6.36	0.965
Diabetes (Y/N)	4/10	8/3	0.073
Hypertension (Y/N)	2/12	4/7	0.350
Obesity (Y/N)	6/8	3/8	0.677

*p was significant if <0.05
M: male, F: female, y: years, Y: yes, N: no

Table 2 presented contrast sensitivity value on both groups at different times. The mean logCS at baseline was 1.47 ± 0.28 and 1.51 ± 0.13 logCS in HBOT and control group respectively (P = 0.934; table 2). At one day post therapy, the corresponding values were 1.57 ± 0.29 and 1.54 ± 0.15 logCS (P = 0.241), and at 14 days post therapy, they were 1.57 ± 0.25 and 1.52 ± 0.15 (P = 0.098). There were no statistically significant differences in contrast sensitivity between groups. Subjects in HBOT group had statistically significant contrast sensitivity improvement at one day and 14 days follow-up (P = 0.03 and 0.015, respectively, table 3). Subjects in control group had no statistically significant contrast sensitivity improvement either at one day or 14 days follow-up compared to baseline (P = 0.553, 0.720, respectively).

Table 2. Contrast sensitivity values during the course of the study

Time	Mean	SD	Median	Min.	Max.	p value
Baseline:						
HBOT	1.47	0.28	1.56	0.64	1.68	0.934
control	1.51	0.13	1.48	1.30	1.72	
1 day post-therapy:	1.57	0.29	1.68	0.64	1.76	0.241

HBOT control 14 days post therapy:	1.54	0.15	1.52	1.28	1.72	
HBOT Control	1.57 1.52	0.25 0.15	1.68 1.56	0.88 1.24	1.76 1.68	0.098

*p was significant if <0.05
SD: standard deviation

Table 3. Contrast sensitivity changes

Time	p value
	HBOT
1 day post therapy - baseline	0.003*
14 days post therapy - baseline	0.015*
14 days post therapy - 1 day post therapy	0.731
	Control
	0.502
	0.720
	0.377

*p was significant if <0.05

Table 4 presented macular light sensitivity values on both groups at different times. The macular light sensitivity was divided into 4 areas, which were superotemporal, superonasal, inferotemporal, and inferonasal, as seen in figure 1. The mean value in each area was stated in table 4.

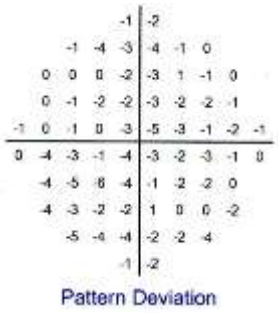

Figure 1. Humphrey Field Analyzer-3 (10-2 pattern, SITA standard) pattern deviation results

There were no statistically significant difference found between both groups in every areas and times (P >0.05; Table 4).

Table 4. Macular light sensitivity values during the course of the study

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	Mean	SD	Median	Min.	Max.	p value
Superotemporal						
Baseline:						
HBOT	-2.87	3.70	-1.44	-14.65	-0.47	0.084‡
Control	-3.03	1.43	-2.59	-5.53	-1.24	
One day post therapy:						
HBOT	-2.77	4.20	-1.35	-16.06	-0.18	0.784‡
Control	-1.53	0.76	-1.41	-3.53	-0.71	
14 days post therapy:						
HBOT	-2.81	3.39	-1.59	-13.35	-0.53	0.366‡
Control	-2.54	1.83	-2.29	-7.53	-0.59	
Superonasal						
Baseline:						
HBOT	-1.98	1.39	-1.53	-4.47	-0.35	0.155†
Control	-2.99	2.08	-2.82	-6.65	-0.71	
One day post therapy:						
HBOT	-2.08	2.10	-1.06	-7.76	-0.29	0.381‡
Control	-2.03	1.37	-1.65	-5.18	-0.41	
14 days post therapy:						
HBOT	-2.49	2.46	-1.71	-10.06	-0.59	0.285‡
Control	-3.04	2.00	-2.59	-7.12	-1.12	
Inferotemporal						
Baseline:						
HBOT	-2.76	2.80	-1.85	-11.41	-0.53	0.661‡
Control	-2.13	1.33	-1.94	-4.71	-1.00	
One day post therapy:						
HBOT	-3.05	3.82	-1.91	-15.12	-0.53	0.956‡
Control	-1.99	0.79	-1.88	-3.82	-0.82	
14 days post therapy:						
HBOT	-2.94	3.55	-1.82	-14.65	-1.12	0.826‡
Control	-2.41	1.55	-1.59	-5.41	-0.94	
Inferonasal						
Baseline:						
HBOT	-1.99	1.30	-1.38	-5.12	-1.00	0.198‡
Control	-2.66	2.07	-2.12	-8.24	-0.88	
One day post therapy:						
HBOT	-1.97	1.16	-1.88	-5.06	-0.47	0.213†
Control	-1.50	0.46	-1.59	-2.35	-0.94	
14 days post therapy:						
HBOT	-2.18	1.08	-2.17	-3.94	-0.71	0.78†
Control	-2.30	1.01	-2.24	-4.24	-1.00	

*p was significant if <0.05
† Based on independent samples T-test
‡ Based on Mann-whitney test

Table 5. Macular light sensitivity changes

Time	p value HBOT	Control
Superotemporal :		
1 day post therapy - baseline	0.489	0.004*
14 days post therapy - baseline	0.900	0.154
14 days post therapy - 1 day post therapy	0.330	0.062
Superonasal :		
1 day post therapy - baseline	0.900	0.013*
14 days post therapy - baseline	0.221	0.722
14 days post therapy - 1 day post therapy	0.096	0.109
Inferotemporal :		
1 day post therapy - baseline	0.625	0.563
14 days post therapy - baseline	0.889	0.689
14 days post therapy - 1 day post therapy	0.850	0.504
Inferonasal :		
1 day post therapy - baseline	0.807	0.008*
14 days post therapy - baseline	0.433	0.534
14 days post therapy - 1 day post therapy	0.505	0.003*

*p was significant if <0.05

The changes of macular light sensitivity were significantly increased in control group, between 1 day post therapy and baseline at superotemporal, superonasal and inferonasal area (p = 0.004, 0.013, and 0.008, respectively, table 5). At inferonasal area, there was statistically significant decrease in macular light sensitivity changes (p = 0.003). In HBOT group, although not statistically significant, there were slight improvement in all area between one day post therapy and baseline.

DISCUSSION

This clinical trial showed benefits of treatment with hyperbaric oxygen for dry type AMD. Most studies on this subject have visual acuity as an endpoint. Our study was the first to use contrast and macular light sensitivity as endpoints. This was based on previous study that stated that visual acuity is inadeaquate as an endpoint for evaluating treatments for early and intermediate AMD since visual acuity is largely undisturbed during these disease stages (Owsley, Huisingh, Clark, Jackson, & McGwin Jr, 2015).

At one-day follow-up, there were significant improvement on contrast sensitivity in HBOT group, which was in line with previous study by Weiss, showing improvement in visual function 2-days follow-up after one hour session of HBOT in AMD patients (Weiss, 2010). Keane found that the strongest correlatian detected between decreased contrast sensitivity and increased total volume of subretinal tissue (Keane, et al., 2010). Previous study by Chao stated that HBOT can decrease the release of TNF-α by RPE cells therefore decreased inflammation (Chao & Chao, 2017). We believed the improvement on contrast sensitivity in our patients were becaused of the decreased inflammation on subretinal tissue by HBOT. At 14-days follow-up, eventhough there were significant improvement compared to baseline, we could not the same results when compared to one-day follow-up. This showed that improvement on contrast sensitivity happened at one-day follow up and it was stable until 14-days follow-up.

Although macular light sensitivity improved in HBOT group during one-day of follow up, the trend was not statistically significant. this can be explained from previous study that stated photoreceptor consumed a large amount of oxygen to convert light energy into readable neuronal signals for the brain to translate (Chao & Chao, 2017). The pivotal role of oxygen for photoreceptor survival was reported. When retina was exposed by bright light, direct exposure to the sunlight or even by continous ambient light, it activated phototransduction persistently. This proccess consumed large amount of oxygen and could cause oxidative stress (Panfoli, Calzia, Ravera, Morelli, & Traverso, 2012). Our subjects in HBOT group had more sunlight exposure than subjects in control group. This was showed in 14-days follow-up results in control group we can see a sugnificant decrease of macular light sensitivity since the restriction on sunlight exposure only until one day of follow up.

A study by Linsenmeier stated that 100% oxygen could be beneficial if given episodically (Linsenmeier & Zhang, 2017). In our study, HBOT was only given for one session, with no maintenance dosage. Further research would be needed to investigate the optimal dosage for AMD patients.

Our main bias was lack of patients' blindness. It was impossible to do a true double-blind study because HBOT needs patients to be cooperative. Another limitation of the study was no randomization alocation on subjects due to difficulty to maintain HBOT schedule for people living out of town. Other limitations to the study were short duration of follow-up, and difficulty to control confounding variables (such as diet, sunlight exposure, smoke and air pollution exposure).

CONCLUSION

In this study 14 subjects with AMD is given HBOT and achieved improvement in contrast sensitivity in cases considered low prognosis. In summary, our findings reveal some beneficial effects of hyperbaric oxygen for the adjuvant management of early and intermediate AMD compared to antioxidant only. HBOT should be considered as promising intervention for AMD management adjuvant and further research are needed to find optimal dosage.

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RADIOLOGY PERSPECTIVE: ONE-YEAR STUDY OF HIRSCHSPRUNG DISEASE

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ABSTRACT

Hirschsprung disease is a rare developmental disorder of the enteric nervous system. This study purposed to give an epidemiological database and current trend analysis from radiological perspective of Hirschsprung disease. A prospective descriptive study was conducted for a year in 2017 at Sanglah Public General Hospital, Bali. Colon in loop examination using either water-soluble or barium was conducted. The parameters evaluated in this study were all baseline characteristics, contrast media used, and HD types. Hirschsprung accounted for 2.16% from all 1018 newborn. Male was 3.4 times more prone to Hirschsprung disease. Age distribution was predominant during 0 – 4 weeks after birth (36.4%). Ultrashort, short, and long segments were 45.5%, 45.5%, and 9% respectively. Contrast media was used and mainly barium rather than water soluble in a proportion of 8:3 due to standard operating procedure adapted by some pediatric surgeon. Ultrashort and short segment HD had the same contribution. Barium was dominated, although water soluble was chosen in most literatures for infant due to its ability as diagnostic as well as therapeutic effect. Hence, further research was expected to support and change the perspective in making the diagnosis.

***Keywords**: hirschsprung disease; colon in loop; barium enema; pediatric; radiology*

ABSTRAK

Penyakit Hirschsprung merupakan kelainan perkembangan yang menyerang sistem saraf system enterik yang jarang. Tujuan studi ini untuk memberikan gambaran epidemiologi penyakit Hirschsprung dari sudut pandang radiologi Metode penelitian ini bersifat deskriptif prospektif yang dilakukan selama satu tahun pada tahun 2017 di Rumah Sakit Umum Pusat Sanglah (RSUP Sanglah). Pemeriksaan colon in loop digunakan sebagai tombak pada diagnosis penyakit Hirschsprung baik menggunakan kontras barium atau water-soluble. Seluruh karakteristik dasar, kontras media yang digunakan, tipe segmen Hirschsprung merupakan parameter yang dievaluasi. Angka kejadian Hirscpsprung disease di RSUP sanglah pada tahun 2017 adalah 2.16% dari 1018 bayi lahir hidup. Predileksi usia 0-4 minggu setelah lahir 36,4%, dominasi laki-laki (77%). Ultrashort,short, long segment yang ditemukan sebanyak 45,5%, 45,5%, dan 9%. Barium merupakan media kontras yang lebih sering digunakan dengan rasio 8:3 dengan kontras water soluble. Hal ini disebabkan oleh standar operasional prosedur yang diaplikasikan oleh beberapa klinisi. Ultrashort dan short segment memiliki insiden yang sama. Penggunaan barium mendominasi pada studi ini, walaupun kontras water-soluble merupakan media kontras yang lebih dipilih pada bayi usia kurang dari 1 tahun oleh karena memiliki efek terapeutik dan diagnostic. Oleh karena itu penelitian lebih lanjut perlu dilakukan untuk mendukung dan mengubah prespective dalam menegakkan diagnosis.

***Kata kunci**: penyakit hirschsprung; colon in loop; barium enema; pediatri; radiologi*

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INTRODUCTION

Hirschsprung disease is a congenital disorder where there is an absence in distal enteric ganglion cells called as Auerbach and meissner plexus that are often found at recto-sigmoid level (Benarroch et al 2014, Weinert & Rios 2016). This is due to the inhibition of craniocaudal migration of neural crest cells to embryonic

development and resulting in colorectal relaxation failure (Weinert & Rios 2016, Schoenwolf et al 2015). These ganglion cells are responsible for normal peristaltis. Therefore, hirschsprung disease will cause functional intestinal obstruction at the aganglionic level (Langer 2012). Hirschsprung has a tonic contraction characteristic at distal colon depicting the lack of NO or VIP neuron inhibition (Benarroch et al 2014).

In Indonesia, the incidence of Hirschsprung Disease (HD) is not known for sure but several studies conducted resulted with ratio of one in 5000 live births. Indonesia population is 220 million, and the birth rate is 35 per mils. It is predicted that every year, 1540 babies will be born with HD. There was 40 to 60 patients with HD were referred to Cipto Mangunkusumo Hospital Jakarta (Kartono 2004). In addition with HD, they usually presented with other congenital disorder, such as down syndrome and urogenital disorder (Riwanto et al 2011; Kessman 2006). HD frequently affects male compare to female with 4:1 ratio in short segment type of HD, but the gender predilection is almost the same for long segment HD (Weinert & Rios 2016, Schoenwolf et al 2015, Riwanto et al 2011).

Clinical manifestation of HD started at birth with 99% of at term newborn have delay meconium passage within 48 hours after birth. HD frequently occurs in the first 6 weeks of life with symptoms, such as abdominal distension, vomiting, and constipation (Benarroch et al 2014, Weinert & Rios 2016). The pathognomonic sign of HD is the late passage of meconium with additional abdominal distention and green vomiting respectively as the important symptoms not to be missed. Several newborns may also present with diarrhea and foul smelling stomach as well as fever (Bishop & Ebach 2017).

HD is classified based on the aganglionic segment. Ultrashort segment (incidence of 13.4%) is defined when the aganglionic zone is confined to anal sphincter or up to 3-4 cm distal rectum due to its very short aganglionic area the manifestation of this type of HD. Ultrashort segment is not as prominent as the other types, and it can be detected at older age (Meier-Ruge et al 2004).

Short segment HD account for 75% and is the most common type of HD. Short segment defines where the aganglionic zones reach up to rectosigmoid level. Long segment HD reach up to splenic flexure, while total aganglionic type involves distal ileus from 1/3 transverse colon with incidence rate of 8-10%. Ultra long segment HD is the rarest type if the aganglionic zone reaches small bowel segment and is more than 50 cm long of aganglionic zone. If the aganglionic zone of HD involves the entire small intestine, it is called Zuelzers disease (Paterson et al 2015, Moore 2016).

Colon in loop is the examination of choice with water solulable contrast. Contrast enema is both diagnostic and therapeutic. With a soft small cathether introduce to anal spincther without balloon inflation, so that it will not give a false dilatation picture at distal colon. Under fluoroscopy in lateral position, it may give a description of the transisional zone (Weinert & Rios 2016). Dilatation of sigmoid more than rectum through rectosigmoid index (RSI) calculation will confirm HD if the RSI is below 1, and it is one of HD diagnosis characteristic with contrast enema (Meier-Ruge et al 2004) (Moore 2016).

Histology analysis showed absence of intrinsic parasimpatethic ganglion cells in Auerbach's and Meissner plexus in intestinal wall, associated with increased positive acetylcholinesterase nerve fibers in the aganglionic region of the intestine (Benarroch et al 2014; Paterson et al 2015). This study aimed to give an epidemiological database and current trend analysis from radiological perspective of HD.

MATERIALS AND METHODS

This study was descriptive prospective study conducted at Radiology department of Sanglah Public General Hospital Bali and involved all patients suspected with HD in 2017. The patients went to colon in loop examination either barium or water-soluble contrast, and it was used for test or measurement. A marker was taped on the anal dimple and about 50-100 cc of contrast, barium 1:8 with saline solution or 1:3 water soluble non-iodinated with saline salutation was used using small catheter which was introduced to anal sphincter without balloon inflation, and the contrast media was injected under fluoroscopy guidance, true lateral, oblique, and antero-posterior (AP) projection photos were taken. The incidence and baseline characteristic, such as age and gender, and contrast media used for colon in loop procedure and HD type from radiological perspective (ultrashort, short, long, and total HD) were the parameters being evaluated in this study. This study defined ultrashort as 4 cm less aganglionic zone from anal spincther, short segment where aganglionic-hypoganglionic zone reached to sigmoid colon, long segment defined as aganglionic-hypoganglionic zone up to above sigmoid colon to lienalis flexure, and total aganglionic was beyond that up to distal ileum or ileocaecal junction (Weinert & Rios 2016).

RESULTS

All live births at Sanglah Public General Hospital Denpasar-Bali in 2017 were 1018 consisting of 534 males and 468 females. There were 31 patients clinically suspicious with HD.

Table 1. Contrast study result in patient clinically suspicious with HD contrast study

Contrast study	N	Percentage
Hirscprung disease	22	71%
Non Hirscprung disease	9	29%
Total	31	100%

There were 22 patients confirmed HD from colon in loop examination out of 31 patients clinically suspicious of HD (71%), while 9 patients (29%) did not show HD from contrast examination. The incidence rate of HD at Sanglah Public General Hospital in 2017 was 2.16% from all live births.

Table 2. Gender distribution of patients with HD confirmed through colon in loop

Gender	N	Percentage
Male	17	77%
Female	5	23%
Total	**22**	**100%**

The gender predilection on this study showed 77% was male. Male was 3.4 more than female from all patients with HD

Table 3. Age distribution of patients with HD

Age	N	Percentage
0-<1 Month	8	36.4%
1-12 Months	5	22.7%
1-5 Months	6	27.3%
6-14 Years	2	9.1%
15-25 Years	1	4.5%
Total	22	100%

There was 36.4% patients confirmed HD through colon in loop examination who showed early manifestation less than 4 weeks old.

Table 4. Contras media used in colon in loop in all patients clinically suspicious of HD

Contrast Media	N	Percentage
Barium	24	77%
Water soluble	7	23%
TOTAL	31	100%

Table 5. Contrast media used in patient confirmed HD through colon in loop study

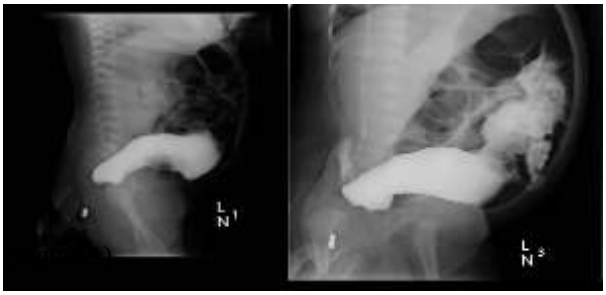
Contrast Media	N	Percentage
Barium	16	73%
Water soluble	6	27%
TOTAL	22	100%

Out of all 31 patients only 7 patients (23%) using water soluble contrast while 77% using barium (Table 4). Barium was still the mostly chosen contrast media in all patients confirmed HD through colon in loop study, accounts for 73% and 27% of them were using water soluble (Table 5).

Table 6. HD Type from Radiological examination HD

HD Type	N	Percentage
Ultra short segment	10	45.5%
Short segment	10	45.5%
Long segment	2	9.0%
TOTAL	22	100%

This study demonstrates that ultrashort and short segment has ratio of 1:1 incidence, while long segment HD only 1/11.



A B

Figure 1. Water soluble contrast study, Lateral (A) and oblique (B) projections. Aganglionic zone was less than 4 cm, demonstrate ultrashort segment HD.Source : Radiology Departement Sanglah Public General Hospital Bali, published with permission

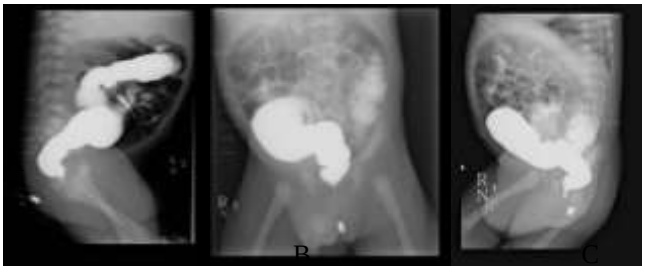


Figure 2. Barium Contrast study, (A) Lateral, (B) AP supine, (C) right oblique, (D) Aganglionic zone at distal sigmoid with cone shape transitional zone, resembles short segment HD. Source : Radiology Departement

Sanglah Public General Hospital Bali, published with permission

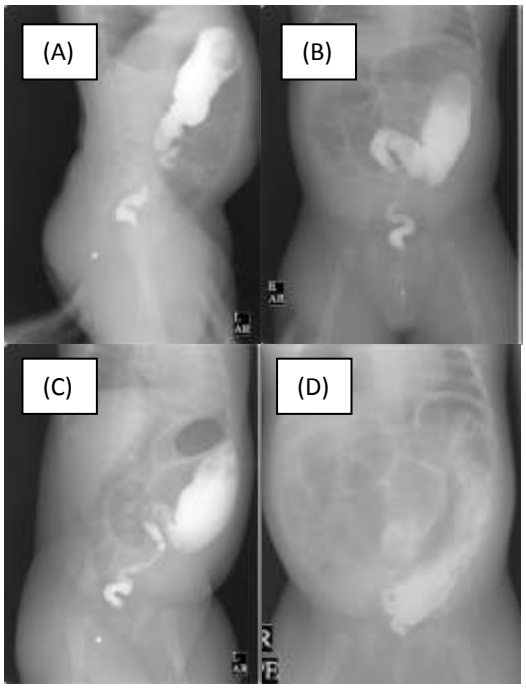


Figure 3. Water soluble contrast study. Aganglionic zone and hypoganglionic zone was seen from rectum to sigmoid and distal colon descenden with transisional zone from mid descenden colon to lienalis flexure. (D) post evacuation 24 hour shows retention and antiperistaltis.

Source: Radiology Departement Sanglah Public General Hospital Bali, published with permission.

DISCUSSION

Clinical manifestation of HD, such as late meconium passage as well as abdominal distention will lead clinicians to HD diagnosis suspicion. As much as 71% out all of suspicion confirmed HD diagnosis, while other could be suit differential diagnosis of HD, such as anorectal malformation and multisystem disorder consisting of muscular dystrophy, cystic fibrosis, diabetes mellitus, developmental delay, spinal cord disturbance, meconium plug syndrome (left colon syndrome) celiac disease, meconium ileus, ileal atresia, maternal drug used (Bishop & Ebach 2017, Moore 2016).

The incidence rate of HD at Sanglah Public General Hospital was 2.61% with 3.2% risk for male and 1% for female. This study showed male predominant. The early manifestation of HD which was less than 1 month old was also in synchronized with prior study, that was the first 6 weeks of living. The use of barium or water soluble contrast is still in debate in several center in Indonesia, while several published studies showed water soluble contrast was the chosen media for baby infant with less than a year of age for both diagnostic and therapeutic (Donnelly 2017, Ralls et al 2017).

Water-soluble contrast could give lavement effect and release the colonic tension (Donnelly 2017, Kraus 2017). Barium contrast was less used due to several other differential diagnosis of HD, such as meconium ileus or meconium plug syndrome where barium would hold up meconium evacuation and camouflage the diagnosis (Donnelly 2017). Water-soluble contrast had given about 87% sensitivity and 83% specificity from the study at Oxford UK (Castillo et al 2012). This study showed that barium was still the selected contrast media due to the lack of support from the standard operational procedure in the hospital, where most clinician still believed the use of barium superior to water soluble. This was going to need further discussion with all clinicians involved for the use of water-soluble. Further study stressing the sensitivity and specificity for water-soluble contrast in diagnosing HD in the hospital should be proposed, so that the result could be the backbone for the new standard operational procedure in colon in loop examination for HD.

Short segment HD has to be the most common HD type in literature, while this study reported that ultrashort and short segment contributed the same value, so that long segment and other type were in significant with literature as rare type (Moore 2016).

CONCLUSION

The incidence rate of HD in 2017 at Sanglah Public Regional Hospital was 2.16% from all live births with approximately 1.8 cases of HD in every month. HD was manifested in patients less than 4 weeks of age. Male was 3 times for prone to HD compare to female. Ultrashort and short segment HD in the hospital contributed the same number. Barium was used often in the hospital due to standard operational procedure adapted by the clinicians, even tough the most recent update study showed that water soluble was more useful especially for infant less than 1 year due to other different diagnosis which might be camouflaged by the presence of barium. Water-soluble contrast had more advantage for both diagnostic and therapeutic lavement effect. Therefore, further study was recommended to change the perspective of clinicians to be a backbone for the new better standard operational procedure in diagnosing HD.

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DETERMINANT FACTORS OF DEPRESSION IN BETA MAJOR THALASSEMIA CHILDREN

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ABSTRACT

Thalassemia is a chronic disease with long-term treatment that increases the potential for impact on physical, cognitive, and psychological conditions. About 80% of patients with major thalassemia have at least one psychiatric disorder. Depression is one of the most frequently reported, especially in prepubertal and puberty periods. The study aimed to evaluate determinant factors of depression in beta mayor thalassemia children. This study was a cross-sectional study on patients aged 9 to 17 years at hematology outpatient clinic in Dr Soetomo Academic Hospital from September to Desember 2018. The level of depression determinded by Children Depression Inventory (CDI) questionnaire. The data were collected and analyzed using the IBM SPSS Statistics version 21. It was statistically significant with p<0.05. Forty five participants were included in this study, 15 participants with mild depression and 30 participants without depression. Gender (P = 0.462), age of diagnosis (P = 0.385), frequency of tranfussion (P = 0.065), family history of depression (P = 0.350), physical change (P = 0.711), duration of illness (P = 0.674) had no significant value as a determinant factor while complication (P = 0.049) and serum cortisol level (P = 0.037) had significant value as determinant factors of depression in Beta Major Thalassemia children. In conclusion, mild depression was more common in thalassemia patients who experienced complications and had high serum cortisol levels.

***Keywords**: beta major thalassemia; level of depression; children depression inventory (cdi)*

ABSTRAK

Thalassemia adalah penyakit kronis dengan pengobatan jangka panjang yang meningkatkan potensi dampak pada kondisi fisik, kognitif, dan psikologis. Sekitar 80% pasien dengan thalassemia mayor memiliki setidaknya satu gangguan kejiwaan, depresi adalah salah satu yang paling sering dilaporkan, terutama pada periode prapubertas dan masa pubertas. Tujuan dari penelitian ini adalah untuk mengevaluasi faktor-faktor penentu depresi pada anak-anak thalassemia beta mayor. Penelitian ini adalah studi cross-sectional pada pasien berusia 9 hingga 17 tahun di klinik rawat jalan hematologi di Rumah Sakit Umum Dr Soetomo dari September hingga Desember 2018. Tingkat depresi ditentukan oleh kuesioner Children Depression Inventory (CDI). Data dikumpulkan dan dianalisis menggunakan IBM SPSS Statistics versi 21. Nilai signifikan secara statistik adalah p <0,05. Empat puluh lima peserta dilibatkan dalam penelitian ini, 15 peserta dengan depresi ringan dan 30 peserta tanpa depresi. Jenis kelamin (P = 0,462), usia diagnosis (P = 0,385), frekuensi tranfusi (P = 0,065), riwayat keluarga depresi (P = 0,350), perubahan fisik (P = 0,711), lama sakit (P = 0,674)) memiliki nilai yang tidak signifikan, sedangkan komplikasi (P = 0,049) dan kadar kortisol serum (P = 0,037) signifikan sebagai faktor penentu depresi pada anak Beta Major Thalassemia. Sebagai simpulan depresi ringan lebih sering terjadi pada pasien talasemia yang mengalami komplikasi dan kadar serum kortisol yang tinggi.

***Kata kunci**: beta major thalassemia; tingkat depresi; inventarisasi depresi anak (cdi)*

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INTRODUCTION

Thalassemia is an autosomal recessive genetic disease group characterized by failure to produce a synthesis of normal ß-globin chains (Olivieri & Weatherall 2006, Hastings et al 2012, Sarker & Shahriar 2017). Thalassemia has the characteristics of severe anemia, hepatosplenomegaly, bone deformity and endocrine

abnormalities include growth and development disorders, late puberty which can be accompanied by damage to the hypothalamic-pituitary axis (Nasiri et al 2014).

Patients with thalassemia need a long period treatment that has potential to have an physical, cognitive, and psychological impact (Permono & Ugrasena 2006, Mednick et al 2010). Psychological disorders occured in 1: 4 of 38 patients with thalassemia major aged 6-18 years in Turkey, and about 24% experienced depression (Aydinok et al 2005). Another study showed thalassemia patients aged 7-18 years as many as 49% experience depression and 62.7% with irritable and anxious. More than 43% had a desire to commit suicide and 27.3% died of suicide (Ghanizadeh et al 2006).

Chronicity of the disease and long-term treatment can be stressors that cause depression and susceptible to other stressors. This condition triggers an imbalance from the factors that influence the emergence of depression disorders. Depression will be responded by the hypothalamic-pituitary-adrenal (HPA) axis, causing an increase in basal cortisol levels, which will cause continuing symptoms of depression, damage the brain, reduce endurance and worsen the course of the disease. Under other condition the state of Iron toxicity can affect the HPA axis at different levels indicated by the presence of lower ACTH levels (Baldini et al 2017).

The increased risk of psychological and behavioral disorders in patients with thalassemia indicates the importance of long-term psychosocial support and prevention of the emergence of mental disorders in order to improve the quality of life. It was concluded that psychological evaluation needs to be routinely done (Bush et al 1998, Messina et al 2008). The impact of depression at young age have associated with negative long-term outcomes of mental and functional health, including disorders that occurred during school, and substance abuse interpersonal relationship and suicide attemps (Gladstone & Beardslee 2009).

Many studies published about psychiatric problems in patients with Beta Major Thalassemia, but there are limited number of studies investigating the determinant factor of depression in Beta Major Thalassemia in Dr Soetomo Academic Hospital. In the present study, this study aimed to identify the prevalence of depression in children with thalassemia major and its determinant factors. Identifying factors could help with prevention and increased the quality of life.

MATERIALS AND METHODS

A cross-sectional study was conducted in the Hematologic outpatient clinic of Dr. Soetomo Academic Hospital, Surabaya, Indonesia in September to November 2018. The subjects were children aged 7 to 18 years old who were diagnosed as Beta Mayor Thalassemia by haematology and oncology consultant. In all subjects, the degree of depression was evaluated using Children Depression Inventory (CDI) questionnaire which divided into mild (13-17), moderate (18-23) and severe depression (24-54) according to the CDI score. Serum cortisol test was using the Immunochemiluminescence method, collected from venous blood in the cubiti region. Blood sampling for serum cortisol was carried out at 08.00-10.00 am. The subjects were excluded if they had another chronic disease apart from thalassemia and its complications, drugs that affected blood cortisol levels, acure illness or conditions that could increase serum cortisol levels.

This study determined gender, age of diagnosis, frequency of tranfusion, family history of depression, physical change, duration of illness, complication and serum cortisol level as factors that influenced depression in Thalassemia children. Statistical analysis was performed using SPSS 21. Significant was indicated by p-value ($P < 0.05$). This study was approved by the Ethics Committee of Dr. Soetomo Academic Hospital.

RESULTS

Of 56 beta major thalassemia patients in the Hematology outpatient clinic 45 met the inclusion criteria during the study period. We excluded 11 patients, 4 patients with alpha thalassemia and 7 patient with the age below 7 years old (Figure 1). The characteristics of the subject were listed in Table 1.

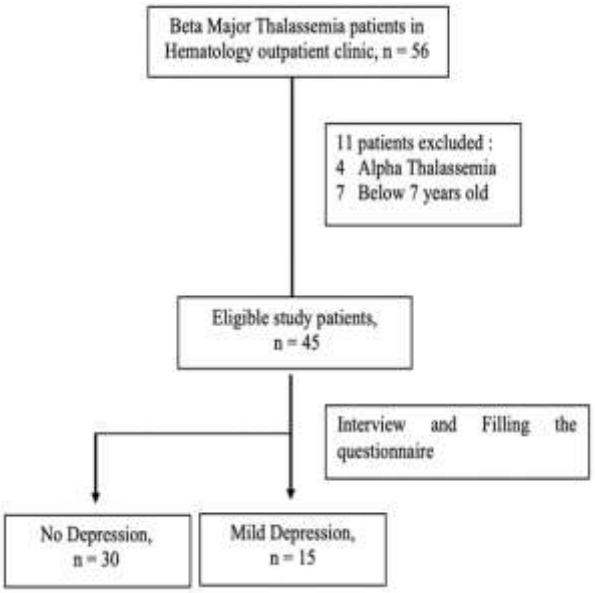


Figure 1. Subject recruitment

Table 1. Subject Characteristics

Characteristics	(n)	(%)
Gender		
Male	22	49
Female	23	51
Age, median (min-maks)	11.7 (7-17) years old	
Age (Year)		
7-10	24	53
11-14	14	31
15-18	7	16
Nutritional Status		
Normal	35	78
Moderate Malnutrition	10	22
Hb pretransfusion rate		
< 6 g/dL	1	2.2
6-8 g/dL	41	91.1
>8 g/dL	3	6.7
Ferritin level		
< 1000	3	6.7
≥1000	42	93.3
Chelating Agent Type		
DFP	29	64
DFX	16	36
Degree of depression (CDI score)		
No depression		
Mild	30	66.7
Moderate	15	33.3
Severe	0	0
	0	0

Out of 45 patients, 30 patient categorized as no depression and 15 patients with mild depression, determinant factors of the degree of depression all shown in **Table 2**. Determinant factors that influence the level of depression significantly were complication and serum cortisol levels. The scatterplot describe the correlations between the serum cortisol level with the degree of depression in Beta Major Thalassemia (**Figure 2**)

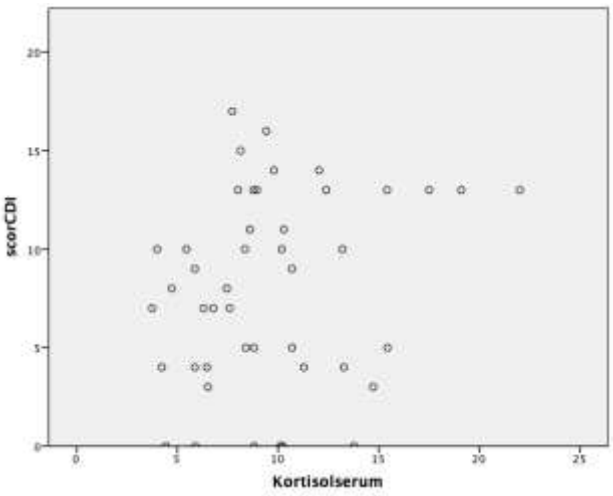
Table 2. Determinant factors of mild depression in Beta Major Thalassemia

Determinant factors	No depression N (%)	Mild Depression N (%)	P
Gender			
Male	15 (46.9)	7 (58.8)	0.462
Female	17 (53.1)	6 (46.2)	
Age at diagnosis (year)			
< 1	6 (18.7)	4 (30.8)	0.385
1-5	17 (53.1)	4 (30.8)	
> 5	9 (28.2)	5 (38.4)	
Frequency of tranfusion			
< 12 x/year	2 (6.3)	1 (7.7)	0.065
>12x/year	30 (93.7)	12 (92.3)	
History of Splenectomy			
Yes	0 (0)	1 (7.7)	0.289
No	32 (100)	12 (92.3)	
Family History of Depression			
Yes	3 (9)	0 (0)	0.350
No	29 (91)	13 (100)	
Family History of Thalassemia			
Yes	8 (25)	0 (0)	0.078
No	2 (6.2)	0 (0)	
Not Test	22 (68.8)	13 (100)	

Physical Change			
Facies Cooley	15 (33.3)	8 (61.5)	0.711
Hyperpigmentation	25 (55.6)	10 (76.9)	
Abdominal enlargement	21 (46.7)	12 (92.3)	
Duration of Illness (year)			
< 1	0 (0)	0	0.674
1-5	3 (9.4)	1 (7.7)	
> 5	29 (90.6)	12(92.3)	
Complications			
Yes	24 (75)	13 (100)	0.049*
No	8 (25)	0 (0)	
Cortisol serum level			
Normal	23 (71.9)	12 (92.3)	0.037*
Low	9 (28.1)	0 (0)	
High	0 (0)	1 (7.7)	
Cortisol serum rate	Median 8.80 (SD $\pm$ 4.07)		

*Chi-Square test; Fisher exact test, $p \leq 0.05$

Figure 2. Scatter plot of cortisol serum level and level of depression (CDI Score)



DISCUSSION

Previous studies had received reports of depressive disorders in patients with Beta Major Thalassemia. Savari (2007) reported depression occurred in 14% of patients with Beta Major Thalassemia and Intermedia, while Aydinok (2005) reported that 24% of patients with Beta Major Thalassemia experienced psychiatric disorders, such as depression (Aydinok et al 2005). Fifty percent of children aged 13-18 years with thalassemia major who seek treatment at the Thalassemia Center Department of Child Health FKUI Cipto Mangunkusumo Hospital had a poor quality of life, as many as 77.3% of subjects had poor psychosocial functions (Aji et al 2009). Thalassemia is a chronic disease that presents serious clinical and psychological challenges. The side effects of thalassemia on physical appearance can cause changes in body shape, growth disorders, and delayed puberty. Changes in physical appearance also contribute to a bad self-image. Serious complications that can occur such as heart failure, arrhythmia, liver disorders, endocrine complications and infections (Behdani et al 2015).

Clinical characteristic showed that there were no significant different in gender, ages, nutritional status, social economy status, and education. There were 23 males (49%) and 22 females (51%). Seven male participants and 8 female participants were mild depression. gender, age of diagnosis, frequency of tranfusion, family history of depression, physical change, duration of illness, complication and serum cortisol level suspected to had significant value as determinant factors of depression in Beta Major Thalassemia children.

There were 22 males (49%) and 23 females (51%) children with beta major thalassemia. A total of 7 male

and 8 female experienced mild depression. In this study, there were no significant differences between male and female patients with Beta Major Thalassemia on the emergence of depression. The proportion of sex in this study was balanced between men and women. In accordance with Mariani et al study in 2011 showed that there were no significant differences between the quality of life of boys and girls (Mariani et al 2011). In the study, that the major beta thalassemia was inherited autosomal recessively regardless of gender.

The age at diagnosis of beta major thalassemia could affect the length of treatment and complications arising from the disease. Diagnosis and treatment of thalassemia was one of the severe stressors that could cause various emotional challenges and psychological disorders (Velasco-Rodriguez et al 2014). This study had several age groups when diagnosed with beta major thalassemia, including less than 1 year as many as 4 out of 10 children (40%) experiencing depression, age 1-5 years as many as 5 out of 21 children (24%) experiencing depression and more than 5 In the year 6 out of 14 children (43%) experienced depression. Yet, the age difference was not significantly different. The amount of parental, family and environmental support greatly influenced the patient's resistance to stressors that appeared as thalassemia patients.

From this study, there were 93.3% of patients ran blood transfusions as much as 12 times per year. Blood transfusion is the main treatment in major beta thalassemia patients. Chronic transfusion prevents most complications, but complications related to blood transfusion were the major sources of thalassemia morbidity. Beta thalassemia major had a large negative impact on children. Children with thalassemia faced stressful effects throughout their lives, including frequent blood sampling for laboratory tests, frequency of transfusions and frequent subcutaneous injections and oral therapy of iron chelator drugs, all of which mad patients vulnerable to psychiatric loads such as depression and anxiety (Pattanashetti et al 2017). Venty's study showed no correlation between the frequency of blood transfusions, pre-transfusion hemoglobin levels and depression (Venty et al 2018). However, it was different from other studies which showed a correlation between the frequency of blood transfusion and depression. Blood transfusion more often caused an increase in school absenteeism and affects patients interacting socially with their peers. Therefore, they felt isolated and vulnerable to depression (Venty et al 2018).

A history of splenectomy in 1 child with mild depression, 44 children without splenectomy as many as 14 children experienced mild depression. Splenectomy was performed on thalassemia patients who had recurrent blood transfusion, symptomatic splenomegaly and failure to thrive (Mazzone et al 2009). The action of splenectomy was expected to reduce the frequency of transfusion and iron chelation therapy. A family history of depression could have an influence on the level of biology-genetic or lead to cognitive or social-behavioral vulnerability. The history of psychiatric disorders in families had received attention, especially in children who experience chronic pain as a risk factor for depression (Khurana et al 2006). In this study, there were 3 children (7%) who had families with a history of depression and 42 children (93%) had no family with a history of depression, but statistically the two groups did not have significant differences. The number of patients who did not had a family history of depression in this study was far more than those who had a family depression. None of the children with a family history of depression did not suffer from depression, so that there was no relationship between family history of depression and the emergence of depression in patients with beta major thalassemia in this study.

Thalassemia is not contagious but it is inherited, transmitted from parents to boys in an autosomal recessive pattern (Sun & Wang 2014). In this study group, there were 12 children (27%) who had a history of thalassemia in the family, 2 children (4%) had no history of thalassemia in the family and 31 children (69%) had never been examined. There were no significant differences between the three groups with values. It was difficult to ascertain the cause of not significant history of thalassemia in the family against the emergence of depression, because the number of parents who were not examined was quite a lot.

Disease and treatment that people undergoing thalassemia can cause several problems. When compared with healthy children, children with thalassemia have more physical symptoms and somatic complaints. Physical changes they experience due to chronic anemia and treatment that causes iron deposits in the organs of the body (Bulan 2009). Physical changes that occur include clinical pallor, enlarged spleen, facies cooley, hyperpigmentation, distended stomach. Research conducted by Bulan found that spleen size was a significant factor in quality of life. Enlargement of the spleen causes the abdomen to bulge, causing pressure on the abdominal cavity resulting in decreased mobility and appetite for children. Physical changes also occurred in the sample of this study group, including facies cooley of 17 children with 7 children (41.2%) experiencing mild depression, hyperpigmentation of 35 children with 11 children (31.4%) experiencing mild depression and distended abdomen 36 children (38.9%) with 14 children

experiencing mild depression. The overall characteristics have no significant difference in depression. Physical changes in patients do not become stressors that affect susceptibility to depression, judging from the number who experience mild depression in groups that do not have physical changes, it is quite comparable. The support of parents, family, environment and self esteem greatly affects the level of vulnerability to depression.

The duration of illness and the degree of depression did not have a significant relationship (P = 0.674). The number of participants who suffered from mild depression was 73.3% in the duration of illness more than 5 years. No significant result could be influenced by the presence of environmental factors, like family, social, personal factors that strengthen resistance to depression. The same results were obtained in the study by Venty, that the duration of illness with an average value of 8 years (SD 4) did not find a significant relationship with depression. According to the study, the difference in his study was also influenced by genetic factors, social demographic factors, psychological factors, social factors and different types of questionnaires used in each study (Venty et al 2018). In contrast to previous studies by Khurana which explained that the longer the patient suffers from an illness, the higher degree of depression, because the longer patient got uncomfortable treatment from symptoms of persistent disease and actions during treatment (taking blood, repeated transfusion and continuing continuously) (Khurana et al 2006).

The complications of illness and the level of depression had a significant relationship (P <0.05). The influence of disease complications on the degree of depression was significant. The greater the incidence of complications, the greater the possibility of mild depression. Complications of the disease in this study included growth disorders, liver disorders, heart failure, physical changes. These complications increase the stressor (frequency of transfusion, adverse effects of chelating agent, comorbidities, anxiety about the development of the disease), thereby increasing susceptibility to the appearance of depression. The existence of physical changes from splenomegaly, bone marrow expansion, short body, and various symptoms caused by the process of hemolysis. Physical differences compared to normal children wereimportant factors that influenced personality development and social function (Yengil et al 2014). Most of the studies had result of depression were mild depression. Thalassemia had a risk factor for causing mild depression by 2.3 times compared with moderate or severe depression. There was no theory that clearly explained the factors that affected a patient's ability to deal with depression, but there were several factors that influenced a patient's ability to deal with stress, including interpersonal and personal factors. Other studies suggested that the longer the duration of the disease, the more often patients were hospitalized regularly to get transfusions that led to higher risk of complications until depression appeared (Sharpe & Rossiter 2002).

The degree of depression were influenced by the serum cortisol levels with significant relationship (P <0.05). The greater the incidence of depression, the greater possibility of increasing serum cortisol levels. In this study, the increase in serum cortisol levels was influenced by the presence of chronic stress suffered by thalassemia patients. The disadvantage in this study was that there was no data on the value of other hormones produced by the anterior hypothalamus as a comparison of whether normal cortisol values were normal or a result of a condition of endocrine complications due to thalassemia. Some studies clarified that depression affected cortisol levels. In line with this, Balbo and Aisa study reinforced that HPA axis hyperactivity occured to associate with psychiatric disorders and clinical syndromes, such as depression and insomnia. This study supported the results of previous studies that depression hypercortisolism could arise due to adrenal cortex dysfunction in which the secretion of cortisol independently from ACTH that produced irregular cortisol secretion. Almost all types of physical or mental stress could cause increased secretion of ACTH and cortisol, cortisol increases by as much as 20 times. This effect was seen in the secretory response of adrenocortical after trauma (Balbo et al 2010).

CONCLUSION

Prevalence of mild depression in children with thalassemia major was 33.3%. Complication of illness and serum cortisol level were significant as determinant factors of depression in Beta Major Thalassemia children.

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BODY MASS INDEX, WAIST-HIP RATIO AND FASTING BLOOD GLUCOSE LEVELS AMONGST UNIVERSITY STUDENTS

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ABSTRACT

Overweight and obesity have been correlated to the higher risk for developing metabolic diseases in later life, such as DM type 2. This study reseached the body mass index (BMI), the waist to hip ratio (WHR) and the fasting blood glucose levels (FBG) in the seemingly healthy university students to comprehend these variables amongst the youth in Indonesia in 2019. The BMI and WHR of 150 male and female students aged 18-22 years old of the IIKBW, Kediri were measured by standardised anthropometry. The FBG was measured after 8 hours-minimum of fasting from the capillary blood drop using glucometer. Data was then analysed using SPSS 17 with level of significance of P <0.05. According to Asia-Pacific BMI classification, students were 30.7% obese with males significantly higher than females (P = 0.016), 18% overweight (significantly higher in females, P = 0.04), 36% normal and 15.3% underweight. When compared between genders, the WHR was significantly higher in males (P <0.001); while there were no significant differences in FBG (P = 0.6). 4 males and 5 females with FBG >=100 mg/dl, whereas others were within normal limits. There were positive significant correlations between BMI and WHR in males and females (r = 0.777, P <0.001; r = 0.54, P <0.001, respectively). There was a significant positive correlation between the BMI and FBG with r = 0.217, P = 0.008; and between the WHR and FBG with r = 0.21, P = 0.01 amongst all students. In this study, male students have significantly higher BMI and WHR than females. Higher FBG was well observed in students with either higher BMI or WHR.

***Keywords**: BMI; diabetes mellitus; obesity*

ABSTRAK

Obesitas dan kelebihan berat badan berkorelasi dengan tingginya resiko mengidap berbagai penyakit metabolik di kemudian hari, termasuk DM tipe 2. Penelitian ini bertujuan menganalisis hubungan indeks massa tubuh (IMT), rasio lingkar pinggang-panggul (WHR) dan kadar glukosa darah puasa (GDP) pada mahasiswa laki-laki dan perempuan usia 18-22 tahun di IIKBW, Kediri tahun 2019. IMT dan WHR dari 150 mahasiswa dinilai dengan metode antropometri terstandarisasi. GDP dari darah kapiler diukur menggunakan glukometer minimal 8 jam pasca puasa. Data dianalisis dengan menggunakan SPSS 17 dengan tingkat signifikansi P <0,05. Berdasarkan klasifikasi IMT Asia Pasifik, 30,7% subjek mengalami obesitas (IMT laki-laki lebih besar dibandingkan perempuan; P = 0,016), 18% gemuk (IMT lebih besar pada perempuan, P = 0,04), 36% normal dan 15,3% kurus. WHR lebih besar pada laki-laki (P <0,001) meskipun tidak terdapat perbedaan bermakna antara GDP laki-laki dan perempuan (P = 0,6). Didapatkan 4 laki-laki dan 5 perempuan memiliki GDP >=100 mg/dl. Terdapat korelasi yang bermakna antara IMT dan WHR pada laki-laki dan perempuan (r = 0,777, P <0,001; r = 0,54, P <0,001). Terdapat korelasi positif dan bermakna antara IMT dan GDP dengan r = 0,217, P = 0,008; dan antara WHR dan GDP dengan r = 0,21, P = 0,01 dari seluruh mahasiswa. Pada penelitian ini, IMT dan WHR mahasiswa laki-laki lebih besar secara bermakna daripada perempuan. GDP yang tinggi cenderung ditemukan pada mahasiswa dengan IMT atau WHR yang lebih besar.

***Kata kunci**: IMT; diabetes mellitus; obesitas*

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INTRODUCTION

The prevalence of overweight and obesity are increasing thus becoming a global health concern (Mehdad et al 2012, Poobalan & Aucott 2016). These conditions have also been reported amongst the youth, which might increase the risk to suffer various metabolic diseases in later life (Poobalan & Aucott 2016). Several metabolic diseases correlated to obesity i.e. type-2 diabetes mellitus (T2DM) (Stroud et al 2015, Portero et al 2014).

Early identification of overweight and obesity in the young adults is warranted. World Health Organisation (WHO) has recommended the measurement of body mass index (BMI) as the simplest way for defining obesity (Mishra et al 2014). However, the BMI is an indirect measurement for body fat because the fat mass and the lean body mass components are not differentiated, as such in the measurement of the waist-hip ratio (WHR). WHR that is more accurate in measuring body fat distribution, can predict visceral fat/central obesity (apple-shaped or pear-shaped obesity), after adjusting to the BMI (Doustjalal et al 2016, Gadekar et al 2018, Fu et al 2015). In this study, we analysed the BMI and WHR in the seemingly healthy male and female university students and correlated these variables to the fasting blood glucose levels (FBG) as one indicator of prediabetes.

MATERIALS AND METHODS

The study was conducted amongst 74 male and 76 female students of the Faculty of Dentistry, Institut Ilmu Kesehatan Bhakti Wiyata (IIKBW), Kediri, East Java, Indonesia aged 18-22 years old. Ethical clearance was obtained from the Research and Ethical Committee of Universitas Airlangga, Surabaya, Indonesia. After informed consent and information for consent were signed, all subjects were fasting overnight from 10.00 pm until the study began at approximately 07.00 am in the next morning. The weight, height, waist circumference and hip circumference were measured using standard anthropometry. Body weight was measured to the nearest 0.1 kg using Omron HN289 (Omron, Japan) digital weighing scale placed on a firm, flat ground with subjects wearing light clothing and no shoes; belts and other accessories were removed and pockets emptied. Height was measured to the nearest 0.1 cm using a wall-mounted tape measure (GEA, Indonesia) with the subjects standing erect, barefoot, heels together and looking straight ahead in the Frankfurt plane.

The BMI was calculated as weight in kilograms divided by height squared in metres. Subjects with BMI of less than 18.5kg/m2 were classified as underweight, 18.5-22.9 kg/m2 were classified as normal weight, 23.0-24.9 kg/m2 were classified as overweight, 25.0-29.9 kg/m2 were classified as obese I and BMI greater than or equal to 30 kg/m2 were defined as obese II (WHO 2000). Waist circumference and hip circumference (both in cm) was measured using the tape measure SECA 201 (SECA, Germany) according to WHO guidelines (WHO 2011). Waist circumference was measured to the nearest 0.1 cm in standing position at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest and at the end of normal expiration. Hip circumference was measured to the nearest 0.1 cm at the widest diameter around the hip and having the greater trochanter as the landmark. The WHR was calculated as waist circumference divided by the hip circumference. The waist-hip ratio cutt-off point for Asian was 0.90 and 0.80 for male and female, respectively. Apple-shaped obesity was defined as high BMI (BMI ? 23 kg/m2) with high WHR (WHR > 0.90 for male and > 0.80 for female), while pear-shaped obesity was defined as high BMI (BMI ? 23 kg/m2) with low WHR (WHR <0.90 for male and <0.80 for female) (Fu et al 2015, WHO 2000, WHO 2011). Capillary blood sample was taken to measure the FBG using Accu-Chek Active® glucometer (Germany); after the index or middle finger had been cleaned with alcohol swab.

The finger site was then dried and finger-prick done with single-use lancet or a lancing device to draw blood for each subject. Fasting blood glucose (FBG) was classified according to the recommendation of Perkumpulan Endokrinologi Indonesia (PERKENI) (2015); FBG <100 mg/dL is normal fasting glucose; FBG 100-125 mg/dL was prediabetes and FBG ? 126 mg/dL was provisional diagnosis of diabetes. According to American Diabetes Association (2005), prediabetes is similar to impaired fasting glucose (PERKENI 2015, ADA 2005). The data were analyzed using SPSS 17.0 for Windows. For difference of variables in male and female students. t-test or Mann–Whitney U test for independent samples were used to compare mean scores, and the Chi-square was used to compare frequencies. Pearson correlations of BMI, WHR and FBG of the subjects were assessed. P <0.05 was regarded as significant.

RESULTS

Data on various anthropological parameters and fasting blood glucose were given in Table 1. According to Asia-Pacific BMI classification, students were 30.7% obese with males significantly higher than females (P = 0.016), 18% overweight (significantly more in females, P = 0.04), 36% normal and 15.3% underweight. However, the overall BMI showed no significant differences between males and females (P = 0.41). The apple-shaped obesity was higher in females (18.4%) than in males (14.9%), whilepear-shaped obesity was higher in males (36.5%) than in females (27.6%) although not significantly different (P >0.05). When compared between genders, the WHR was significantly higher in males (P <0.001); while there was no significance in FBG (P = 0.6).

Table 1. Anthropometry parameters and fasting blood glucose of males and females

Variables	All	Males (n = 74)	Females (n = 76)	*p* value
Weight (kg) (μ (SD))	62.3 (14.9)	67.9 (15.9)	56.7(11.5)	<0.001
Height (cm) (μ (SD))	162.1 (8.3)	168.2 (5.8)	156.1 (5.6)	<0.001
BMI (kg/m2) (μ (SD))	23.6 (4.8)	23.9 (5.1)	23.3 (4.5)	0.411
Underweight (n (%))	23 (15.3)	12 (16.2)	11 (14.5)	0.945
Normal (n (%))	54 (36)	24 (32.4)	30 (39.5)	0.467
Overweight (n (%))	27 (18)	8 (10.8)	19 (25)	0.040
Obese I & II (n (%))	46 (30.7)	30 (40.5)	16 (21)	0.016
BMI ≥ 23 kg/m^2 (n (%))	73 (48.7)	38 (51.4)	35 (46.1)	0.627
WC (cm) (μ (SD))	78.3 (12.4)	82.1 (13.8)	74.6 (9.6)	0.001
HC (cm) (μ (SD))	97.1 (9.2)	97.2 (9.8)	96.9 (8.7)	0.865
WHR (μ (SD))	0.80 (0.07)	0.84 (0.07)	0.77 (0.05)	<0.001
Apple-shaped [a] (n (%))	25 (16.7%)	11 (14.9%)	14 (18.4%)	0.715
Pear-shaped [b] (n (%))	48 (32%)	27 (36.5%)	21 (27.6%)	0.324
FBG (mg/dl) (μ (SD))	87.8 (7.3)	88.1 (7.5)	87.5 (7.3)	0.600
FBG ≥100 mg/dl (n (%))	9 (6%)	4 (5.4%)	5 (6.6%)	1

BMI: body mass index, WC: waist circumference, HC: hip circumference, WHR: waist-hip ratio, FBG: fasting blood glucose. [a]BMI ≥ 23 kg/m^2, WHR > 0.90 for male and > 0.80 for female. [b]BMI ≥ 23 kg/m^2, WHR < 0.90 for male and < 0.80 for female.

Table 2. Pearson's correlation coefficients (r) of BMI with WHR

Subject	*r* value	*p* value
Overall (Males & Females)	0.617	<0.001
Male	0.777	<0.001
Female	0.54	<0.001

BMI: body mass index, WHR: waist-hip ratio

Table 3. Pearson's correlation coefficients (r) of FBG with BMI and WHR

Subject	FBG	
	BMI	WHR
Overall (Males & Females)		
r value	0.217	0.210
p value	0.008	0.010
Male		
r value	0.226	0.232
p value	0.053	0.046
Female		
r value	0.203	0.207
p value	0.079	0.072

BMI: body mass index, WHR: waist-hip ratio, FBG: fasting blood glucose

DISCUSSION

From this study we found the overweight and obesity have becoming a common issue either in male or in female students. The prevalence is higher when compared to the previous study conducted in Indonesia in 2014-2015 (34.3%) (Pengpid & Peltzer 2017), and to other studies in Pakistan (31.1%), Thailand (20.8%) and Bangladesh (20%) (Khan et al 2016, Pengpid & Peltzer 2015, Howlader et al 2018). In our study, the prevalence of the obesity was slightly higher in males compared to in females. This might be due to the genetics and/ or environment, such as restrictive diet life style amongst females is arguably more popular to stay slim (Khan et al 2016, Chao et al 2012, Al-Kilani et al 2012). The BMI and WHR differences were found between genders; from both we could determine the fat deposition pattern in the body (Fu et al 2015, WHO 2000, WHO 2011). In male students, the pear-shaped obesity was more commonly found than in females. On the other hand, the apple-shaped obesity was more common amongst females, which indicates the central type obesity that has been reported to a higher risk to develop the cardiovascular disease than those with pear-shaped (Gadekar et al 2018, Fu et al 2015, WHO 2000). Apple-shaped obesity is considered more dangerous than pear-shaped obesity because of the accumulation of fat in the deep abdominal area around the visceral organs that can lead to the development of arterial hypertension and insulin resistance which may lead to the heart diseases, dyslipidemia and T2DM in later life (Gadekar et al 2018, Klop et al 2013, Rolland et al 2007).

We found that students with higher BMI, or WHR, would have significant positive correlation to the higher FBG (>=100 mg/dl). This showed an indication of an impaired fasting glucose, a condition which might lead to the prediabetes if it was not well managed. Higher FBG levels were more common in females than in males. The prevalence of high FBG found in the current study was higher to the previous study in Eastern China due to the difference in the study methodology and sampling (Hao et al 2014, Somers et al 2006, Huang et al 2004). However, in Bangladesh and South Africa, there were no significant correlations between the FBG and the BMI amongst the university students (Howlader et al 2018, Yang et al 2002). Students with higher BMI

tend to have higher WHR; an elevated free fatty acid inflow to the liver tend to occur, and generated the abdominal adiposity. This would contribute to the insulin sensitivity impairment through the secretion of adipokines that might impair the glucose tolerance (Gadekar et al 2018, Klop et al 2013). Furthermore, the adiponectin is lower in the obese patients; a condition that might give some degree of higher risks to develop T2DM. Adiponectin was another type of adipokines which could improve the insulin secretion and sensitivity also the fatty acid oxidation to prevent the atherosclerosis and T2DM by decreasing the inflammatory process (Somers et al 2006, Huang et al 2004, Yang et al 2002).

CONCLUSION

This study has resulted that male students had significantly higher BMI and WHR than the female students. Higher FBG was significantly observed in students with higher BMI and/ or WHR.

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PHYSICAL CONDITION COMPARISON BETWEEN FEMALE ATHLETE INDOOR HOCKEY OF EAST JAVA TEAM AND NATIONAL TEAM

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ABSTRACT

This study purposed to describe physical condition differences between indoor hockey female athletes of East Java Team and National Team. Data sampling were taken from 12 indoor hockey female athletes of PON 2016 with age range 17-28 years old and 12 athletes of indoor hockey of Indonesia's National Team at SEA Games 2017 with age range 19-28 years old for comparison. Physical conditions measured were VO2max to represent endurance, abdominal muscle strength, speed and flexibility. Obtained data were then analyzed using SPSS. VO2max of East Java Team was 39.54 ± 4.18 ml/kg/minute and for National Team was 43.43 ± 7.59 ml/kg/minute (?=0.14). For abdominal muscle strength, East Java Team had 41.50 ± 7.01 kg and National Team had 51.83 ± 3.32 kg (?=0.00). For speed, East Java Team had 3.59 ± 0.30 second and National Team had 3.94 ± 0.38 second (?=0.51). For flexibility, East Java Team had 23.75 ± 5.10 cm and National Team had 29.50 ± 4.91 cm (?=0.01). This study concluded that East Java Team physical condition was under National Team and it had significant differences at flexibility and abdominal muscle strength. Furthermore, optimal interventions were needed to improve both of those physical conditions.

***Keywords**: hockey; endurance; flexibility; strength; speed*

ABSTRAK

Tujuan dari penelitian ini adalah untuk mendeskripsikan perbedaan kondisi fisik pada hoki indoor putri atlet Tim Jatim dan Timnas. Pengambilan sampel data diambil dari 12 atlet hoki indoor putri PON 2016 dengan rentang usia 17-28 tahun dan 12 atlet hoki indoor Timnas Indonesia SEA Games 2017 dengan rentang usia 19-28 tahun sebagai pembanding. Kondisi fisik yang diukur adalah VO2max yang mewakili daya tahan, kekuatan otot perut, kecepatan dan kelenturan. Data yang diperoleh kemudian dianalisis menggunakan SPSS. VO2max Tim Jawa Timur 39,54 ± 4,18 ml / kg / menit dan untuk Timnas 43,43 ± 7,59 ml / kg / menit (? = 0,14). Untuk kekuatan otot perut, Tim Jawa Timur 41,50 ± 7,01 kg dan Timnas 51,83 ± 3,32 kg (? = 0,00). Untuk kecepatan, Tim Jatim punya waktu 3,59 ± 0,30 detik dan Timnas 3,94 ± 0,38 detik (? = 0,51). Untuk fleksibilitas, Tim Jawa Timur memiliki 23,75 ± 5,10 cm dan Tim Nasional 29,50 ± 4,91 cm (? = 0,01). Dari data tersebut dapat disimpulkan bahwa kondisi fisik Tim Jawa Timur berada di bawah Timnas dan terdapat perbedaan yang signifikan pada kelenturan dan kekuatan otot perut. Selain itu, diperlukan intervensi yang optimal untuk memperbaiki kedua kondisi fisik tersebut.

***Kata kunci**: hoki; ketahanan; fleksibilitas; kekuatan; kecepatan*

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INTRODUCTION

Hockey is a sport with achievement that categorized as a sport game. In the hockey game, there are two teams that play against each other to score as much as possible. There are two kinds of hockey games that played up to the world championship which is field hockey, indoor hockey, dan ice hockey (FIH.com). The types of hockey that grow rapidly in Indonesia are field and indoor hockey. Indonesia's participation in international championship at indoor hockey in SEA

Games 2017 has achieve silver medals and this potential is available for further development.

Every sports has its own characteristic that become identity and used as milestone to arrange training program (Mansur 2011). Indoor hockey has similar characteristic with futsal or basketball which, there is no limitation to exchange player and it also grouped as intermitten sport. Intermitten sport is a sport that need ability to suddenly changes direction even though in high speed (Mansur 2011). Based on those two characteristics, prime physical condition of athlete is requested and evenly distributed to all team member. Main physical conditions that needed in achievement sport athlete are endurance, abdominal muscle strength, speed and flexibility (Sajoto 1988). Cardiovascular endurance is an ability to effectively and efficiently using heart system, respitory and blood circulation continuously (Mukesh 2015) and this condition can be measured using VO2 max. Abdominal muscle strength is an ability to assemble maximum work at abdominal muscle. This condition is important for short movement, fast movement, sport performance and stabilization during explosive movement from extrimicity (Pintar et al 2009). Speed is an ability to do continuous movement in similar form at a short time. This ability is needed by hockey player for convinience during the game (Saini 2016). Flexibility is an ability of a person to move his/her body and some part of the body in one motion room as wide as possible without experience and result any injury at muscle joints. Flexibility is main necessity to run alter training program (Bozic et al 2010).

East Java is one of regions that has some good achievements at Indonesia's indoor hockey in student, undergraduate student, club, or regional championships. Therefore, it needs some attentions related to athlete's physical condition to gain better achievement. This study was to describe the difference of main physical condition between female East Java athlete and National athlete at indoor hockey sport used as milestone to train and arrange some training program from early stage at school until preparation of PON 2020. Given the differences in performance's quality between those players that were not far viewed from the game level, experience, and training duration.

MATERIALS AND METHODS

This study used analytical observation method. The population of the study consisted of 12 female athletes indoor hockey of East Java from PON 2016 with age range 17-28 years old and 12 female athletes indoor hockey of National from SEA Games 2017 with age range 19-28 years old. Physical conditions measured in this study were endurance, abdominal muscle strength, flexibility, and speed. Measurement being performed was a routine test carried out by KONI of East Java.

Endurance

To measure cardiovascular efficiency, physical work capacity test and VO2max had been developed to use in laboratory and field situation to help the scientist, physical teacher and trainer (Kumar, 2015). Endurance test being measured was cardiovascular endurance to know athlete's VO2max using multi fitness test (MFT) method (Kumar 2017). Unit that was resulted after conversion was ml/kg/minute.

Abdominal Muscle Strength

This abdominal muscle strength test was measured by sit up test for 60 seconds. The athletes were doing a sit up as much as possible for 60 seconds. This test was done in only one experiment. The more number of sit up gained from the athletes, the better category they were in. The result of this measurement was using times of doing.

Speed

This speed test was done by the athletes by running as fast as possible in 20 meters. This test was done in two experiments, and the best time was chosen from both of them. The less period of time gained by the athletes, the better speed of physical condition category they were in. This measurement was using stopwatch, and use second as unit.

Flexibility

This flexibility test was done using 'sit' and 'reach' flexibility tool. The athletes sat with both of their leg forward or touched the measurement beam, then both of their hands were stack straight and push both of their hands on a measurement ruler as far as possible without bending their knee. Number of measurement was placed at the farthest reach of the hand that pushed, so that the farther the push the better flexibility that the athletes had. The final result of this measurement was using centimeter unit.

RESULTS

This study has resulted data of profile from female athlete of indoor hockey of East Team and National Team. The comparison data of cardiovascular endurance of physical condition (VO2max), speed, abdominal muscle strength, and flexibility can be seen in the following tables:

Table 1. Profile data from indoor hockey female athletes of East Java Team and National Team

Group		Age X ± SD (yr)	Weight X ± SD (Kg)	Height X ± SD (cm)
East Java Team	12	21.75 ± 3.11	51.50 ± 8.76	156.92 ± 6.29
Indonesian National Team	12	23.75 ± 2.80	51.58 ± 6.34	155.83 ± 4.99

Table 2. Analytical result of endurance comparison (VO2max) between East Java Team and National Team

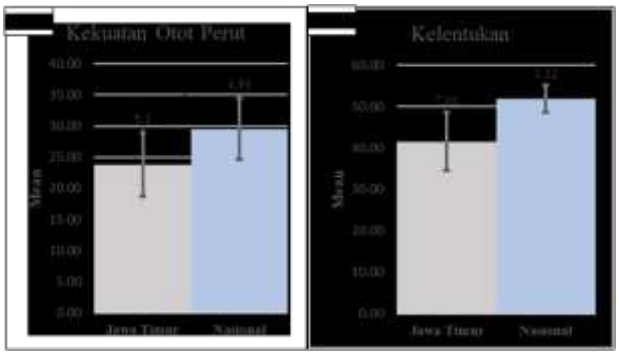
ENDURANCE (ml/kg/min)					
Group	mean±SD	Min	Max	Range	P value
East Java	34.30±4.18	34.30	47.40	13.10	0.14
National	43.43±7.59	33.90	57.60	23.70	

From the previous result of analytical data, the VO2max average of East Java Team was lower compare to National team. The comparison of VO2max between female athlete indoor hockey of East Java team and National team did not show significant difference with ? value = 0.14.

Table 3. Analytical result of speed comparison between East Java Team and National Team

SPEED (sec)					
Group	mean±SD	Min	Max	Range	P value
East Java	3.59±0.30	4.06	3.09	0.97	0.51
National	3.49±0,39	3.88	2.62	1.26	

From the previous result of analytical data, East Java Team and National Team did not show significant difference with ? value = 0.51. However, time difference of them was not far, where East Java team was 3.59 and National team was 3.49.



1.a 1.b

Figure 1. At 1.a. Showed the differences of abdominal muscle strength. 1.b. Showed the differences of flexibility.
*There were significant differences with ?<0.05 at t-test.

From the previous result of analytical data, graphic 1. a. showed that the difference of average of abdominal muscle strength physical condition of East Java Team (23.75) was lower than National Team (29.5). The graphic 1. b. showed that the difference of average of flexibility physical condition of East Java Team was lower than National Team which was only 41.50 and 51.83 in each.

DISCUSSION

From the comparison of abdominal strength, it showed that there was a significant difference between East Java player (41,50) and National Player (51,83) with ? value = 0,00. National athlete team showed a better result compared to East Java team. From previous research about abdominal muscle strength on professional female player in India, there were about 48 repetition (Qinney 1984). That difference was not too far for East Java Team to catch if they want to maximize their abdominal muscle strength, so that they could optimum achievement, whereas in this case, there was a supporting research result that discussed how abdominal muscle strength influenced athlete's achivement (Pintar et al 2009).

From the result of flexibility comparison of East Java Team and National Team, there were significant difference between national player with ? value=0.01. If

we compare them with a study on flexibility in Finland which had been participated at international championship, they had an average flexibility of 17.67 cm (Saini 2016). Meanwhile, the East Java Team was not too far different from them. Flexibility is important aspect of physical condition that the athletes should possess, because it is a basic aspect to perform at training program (Saini 2016). As of East Java Team physical condition could be maintained to be better, so that they could perform in optimum training program.

From the analytical data result of physical condition of cardiovascular endurance by knowing VO2max of both teams' athletes, they were not showing significant difference, but National Team still had better highest number compared to East Java Team, although the lowest number of National Team was lower than East Java Team, so that the result had created a wide range of number. The indoor hockey female athlete of Findland National Team that had previously been measured in previous study gave result of average VO2max of 49.5 ml/kg/min (Peltone 2015). Meanwhile, East Java's athlete had average VO2max of 43.43 ml/kg/min, and its difference was still from National's athlete or Finland National athlete. Those differences were proven of fact that experienced athlete showed better level of average and consistency. It wasimportant for the coach/trainer to improve VO2max of East Java's athlete to gain better achievement, because endurance was defined as a condition where the body was able to work in long period without getting over exhausted after completing the job (Harsono 1988 in Hendra 2014).

From analytical data result of physical condition of flexibility, the East Java Team and National Team showed significant difference among National athletes with ? value=0,01. The significant difference between National athlete and East Java athlete was supported by a wide range of differences between them. Yet, the range was designed not to be too wide. If we compared it with the previous research on flexibility of Finland athletes that had joined in world championship, they had an average of flexibility 17.67 cm (Saini 2016) and East Java Team was not too far from it. Flexibility is important aspect of physical condition that athletes should possess, because it is a basic aspect to perform training program (Saini 2016). Therefore, by physical condition of East Java Team, they could perform in optimum training program.

The analytical data result of physical condition of speed between East Java Team and National Team was almost the same. The analytic result of speed did not show significant result with ? value=0,51. Physical condition of speed analysis did not show significant difference between East Java team and National team. However, National Team showed a result that they were faster than East Java Team. In comparison, the previous research between hockey athlete and female soccer athlete in India showed a result that hockey athlete has a better speed than soccer athlete in 4.16/4.18 second (Saini 2016). The difference of speed with foreign athlete was not too far, so that it is depends on effort of the coach/trainer to improve the speed physical condition of East Java Team, so that they could be better (Saini 2016).

Physical conditon is an important aspect in sport achievement, because it directly impacts on athlete's performance (Tanner & Gore 2013). Success in sport is usually a result of planning, hard working, commitment, and athlete's training. All successful athletes are trained individuals who have the best performance at certain physical activity and usually joined long term training program (Bompa & Carrera 2015).

CONCLUSION

Indoor hockey female athletes of the National Team had better physical conditions in the components, such as abdominal muscles strength and flexibility, compared to the female athletes of East Java Team. Therefore, it is recommended to improve the physical condition of abdominal muscles strength and flexibility of East Java athlete while keep maintaining other physical condition.

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RELATIONSHIP BETWEEN HIGH SENSITIVITY-C REACTIVE PROTEIN LEVEL AND IMPAIRED COGNITIVE FUNCTION IN HIV PATIENTS

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ABSTRACT

Human Immunodeficiency Virus (HIV) infection was one of the most serious health challenges in the world. The Ministry of Health of the Republic of Indonesia reports the number of HIV cases in Indonesia as of June 2019 as many as 349,882. At present, although antiretroviral combination therapy has been found, the prevalence of neurocognitive disorders in the form of HIV-associated neurocognitive disorders (HAND) reaches 50% of HIV patients. This study aimed to determine the relationship between high sensitivity-C Reactive Protein (hs-CRP) level and cognitive impairment assessed using MoCA-INA score in HIV patients at the UPIPI Dr. Soetomo Academic Hospital Surabaya. This cross-sectional study used consecutive sampling that fulfilled inclusion and exclusion criteria. The cognitive function of the subjects was examined by MoCA-INA score and blood samples were collected for measuring hs-CRP level. Of 100 subjects, 41 had abnormal MoCA-INA score and 59 had normal score. The number of subjects with high level of hs-CRP (>= 5) who had abnormal and normal MoCA-INA score were 22 (53,7%) and 6 (10,2%) respectively. This result was significantly difference with p = 0,0001, RO = 28,072 (95% CI, 5,470-144,052). Therefore, there was a significant relationship between hs-CRP level and cognitive function, where a subject with a high hs-CRP level was more likely to have impaired cognitive function.

***Keywords**: HAND; HIV; hs-CRP; MoCA-INA*

ABSTRAK

Infeksi Human Immunodeficiency Virus (HIV) merupakan salah satu tantangan kesehatan yang paling serius di dunia. Kementerian Kesehatan Republik Indonesia melaporkan jumlah kasus HIV di Indonesia sampai dengan Juni 2019 sebanyak 349.882. Saat ini, meskipun telah ditemukan terapi kombinasi antiretrovirus, namun prevalensi gangguan neurokognitif berupa HIV-associated neurocognitive disorders (HAND) mencapai 50% dari pasien HIV. Tujuan penelitian ini adalah mengetahui hubungan antara kadar high sensitivity-C Reactive Protein (hs-CRP) dengan gangguan fungsi kognitif yang dinilai dengan MoCA-INA pada pasien HIV di poli UPIPI RSUD Dr. Soetomo Surabaya. Penelitian cross sectional menggunakan consecutive sampling yang memenuhi kriteria inklusi dan ekslusi. Subjek penelitian dilakukan pemeriksaan kognitif menggunakan MoCA-INA kemudian dilakukan pengambilan darah untuk pemeriksaan kadar high sensitivity-C Reactive Protein (hs-CRP). Pada 100 subjek penelitian didapatkan 41 subjek dengan MoCA-INA terganggu dan 59 subjek dengan MoCA-INA normal. Hasil analisis penelitian ini didapatkan bahwa subjek penelitian yang memiliki kadar high sensitivity-C Reactive Protein (hs-CRP) ? 5 dengan MoCA-INA terganggu yaitu 22 subjek (53,7 %) lebih besar dibandingkan dengan MoCA-INA normal yaitu 6 subjek (10,2 %). Hasil tersebut dinyatakan signifikan secara statistik dengan nilai p = 0,0001, RO = 28,072 (IK 95%, 5,470-144,052). Terdapat hubungan yang signifikan antara kadar high sensitivity-C Reactive Protein (hs-CRP) dengan gangguan fungsi kognitif, di mana subjek dengan level hs-CRP tinggi lebih cenderung memiliki gangguan fungsi kognitif.

***Kata kunci**: HAND; HIV; hs-CRP; MoCA-INA*

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INTRODUCTION

Human immunodeficiency virus (HIV) infection that causes AIDS (Acquired Immunodeficiency Syndrome) was one of the most serious health challenges in the world since the first case reported in 1981. According to data from the Joint United Nations Program on HIV/AIDS (UNAIDS), there were 37.9 million people were living with HIV at the end of 2018. AIDS-related deaths in the world in 2018 reached 770,000 cases. As

many as 61% of new cases come from Sub-Sahara Africa (Joint United Nations Programme on HIV/AIDS 2019).

HIV-AIDS was first discovered in Indonesia in 1987 in the province of Bali. The Ministry of Health of the Republic of Indonesia reported the number of HIV cases in Indonesia as of June 2019 as many as 349,882. The highest number of HIV infections were reported in DKI Jakarta (62,108), followed by East Java (51,990), West Java (36,853), Papua (34,473), and Central Java (30,257). While the number of AIDS cases from 1987 to June 2019 was 117,064 people. There were 5 provinces with the highest number of AIDS; Papua (22,554), East Java (20,412), Central Java (10,858), DKI Jakarta (10,242), and Bali (8,147) (P2P Division, Indonesia Ministry of Health 2019).

At present, although antiretroviral therapy has been found, the prevalence of neurocognitive disorders in the form of HIV-associated neurocognitive disorders (HAND) remains high. Globally, it is estimated that 50% of HIV-positive people have neurocognitive disorders (Heaton et al 2010). A study by Chan et al, in 2012 reported that about 1 in 5 HIV-positive patients in South Asia was estimated to have HIV-associated neurocognitive disorders (HAND) (Chan et al 2012). HAND was a complication that has an impact on the quality of life and functional outcomes (Heaton et al 2010).

Montreal Cognitive Assessment (MoCA) was a screening tool designed to detect neurocognitive disorders and identifying HAND, even in mild form, including in mild degrees. MoCA has been widely used to filter cognitive dysfunction by assessing 8 cognitive domains, conscious only one page and takes only 10 minutes to complete the test. The validity and reliability test for the Indonesian version of the MoCA (MoCA-INA) proved to be valid according to the transcultural validation protocol (Husein et al 2010).

High sensitivity C-reactive protein (hs-CRP) was an acute-phase inflammatory molecule that has an important role in the human immune system. Recently, the relationship between hs-CRP concentration and cognitive function has been investigated by several observational studies. However, a study on the relationship between hs-CRP and HAND was still limited. A study conducted by Schouten et al in 2016 reported that inflammatory markers such as hs-CRP were one of the factors that significantly decreased cognitive function in HIV patients with $p < 0.05$ (Schouten et al 2016). Another study by Watanabe et al (2016) showed a correlation between higher CRP concentrations and lower cognitive functions. Likewise, Rubin et al (2018) in their study reported that high level of C-reactive protein (CRP) were the strongest predictors of cognitive impairment in HIV patients.

However, another study by Burdo et al (2013) reported that neurocognitive disorders in HIV patients receiving antiretrovirals were not associated with hs-CRP. The study of Brandon et al in 2016 showed that there was no relationship between hs-CRP and cognitive decline in HIV patients (Imp et al 2016). There are inconsistent differences in results from several studies, and the use of hs-CRP as a neurocognitive biomarker in HIV was still rare. Further studies were needed to conclude a causal correlation between hs-CRP level and cognitive function measured by MoCA-INA in HIV patients.

MATERIALS AND METHODS

This study was a cross sectional observational analytic study. The subjects were HIV patients receiving antiretroviral treatment at UPIPI Unit Dr. Soetomo Academic Hospital aged 18 years and older recruited between September and October 2019. The subjects who had GCS score lower than 15 or had depression, or had a history of brain structural lesion were excluded.

The subjects were selected from consecutive admission at the UPIPI Unit Dr. Soetomo Academic Hospital until the determined number of samples had been reached. Cognitive tests were carried out using the Moca-INA score with a cut off point less than 26 was defined as abnormal and blood sampling was performed for the patient to examine the hs-CRP level. Statistical analysis was performed with SPSS 25. Categorical data that had been collected was performed by the chi-square test.

RESULTS

This research was conducted for two months from September to October 2019 at the UPIPI Unit Dr. Soetomo Academic Hospital Surabaya. There were 100 subjects recruited in this study. Demographic characteristics included age, sex, and level of education. Based on demographic data, most of the study subjects were male (56%), age <=50 years (85%) and graduated from Senior high school (55%). The clinical characteristics of the subjects included body mass index, vascular risk factors, hs-CRP level and MoCA-INA.

Table 1. Demographic characteristics of subjects

Variable (N = 100)	n (%)	Average ± SB
Gender		
Man	56 (56)	
Woman	44 (44)	
Age		39,98 ± 9,618
> 50 years old	15 (15)	
≤ 50 years old	85 (85)	
Duration of Education (year)		11,65 ± 2,724
Level of education		
Elementary school	9 (9)	
Junior high school	15 (15)	
Senior high school	55 (55)	
Diploma / Bachelor Degree	21 (21)	

Table 2. Clinical characteristics of research subjects

Variable	n (%)	Average ± SB
Body mass index		22,264 ± 3,606
Thin	11 (11)	
Normal	64 (64)	
Overweight	23 (23)	
Obesity	2 (2)	
Vascular Risk Factors		
Yes	6 (6)	
No	94 (94)	
hs-CRP		5,38 ± 9,387
< 5	72 (72)	
≥ 5	28 (28)	
MoCA-INA		24,48 ± 3,761
< 26	41 (41)	
≥ 26	59 (59)	

The results of the analysis for the relationship between confounding variables such as gender, body mass index and vascular risk factors with impaired cognitive function in this study showed no statistically significant effect. Based on multivariate analysis, it was found that the age, education and hs-CRP variables had a statistically significant effect on impaired cognitive function as assessed by MoCA-INA with a p-value <0.05. Data analysis of these confounding variables can be seen in the table below with values considered significant if p <0.05.

Table 3. Relationship between age and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Age				
> 50 years old	11 (26,8)	4 (6,8)	0,013	5,042 (1,477-17,211)
≤ 50 years old	30 (73,2)	55 (93)		
Total	41 (100)	59 (100)		

Table 4. Relationship between gender and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Gender				
Woman	20 (48,8)	24 (40,7)	0,550	1,389 (0,622-3,100)
Man	21 (51,2)	35 (59,3)		
Total	41 (100)	59 (100)		

Table 5. Relationship between level of education and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Level of education				
Elementary-senior high school	39 (95,1)	40 (67,8)	0,002	0,108 (0,024-0,495)
Diploma-Bachelor Degree	2 (4,9)	19 (32,2)		
Total	41 (100)	59 (100)		

Table 6. Relationship between Body Mass Index and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Body mass index				
Overweight obesity	7 (17,1)	18 (30,5)	0,197	0,469 (0,175-1,255)
Thin – Normal	34 (82,9)	41 (69,5)		
Total	41 (100)	59 (100)		

Table 7. Relationship between vascular risk factors and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Vascular Risk Factors				
Yes	2 (4,9)	4 (6,8)	1,000	0,705 (0,123-

No	39 (95,1)	55 (93,2)	4,043)
Total	41 (100)	59 (100)	

The results demonstrated statistically significant relationship between the level of hs-CRP with impaired cognitive function (p-value of 0.0001, Odd Ratio: 10,228 (95% CI, 3,601-29,048). It indicates that subjects who had the level of hs-CRP? 5 had a risk of 10,228 times greater of having impaired cognitive function than those whose level was less than 5. This result can be seen in table 8.

Table 8. Relationship between hs-CRP level with impaired cognitive function (MoCA-INA)

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Level of hsCRP				
< 5	19 (46,3)	53 (89,8)	0,0001	10,228 (3,601-29,048)
≥ 5	22 (53,7)	6 (10,2)		
Total	41 (100)	59 (100)		

The results of the analysis for the relationship between confounding variables and impaired cognitive function showed statistically significant difference for age and education variables hence we proceed to multivariate analysis. This result can be seen in table 9.

Table 9. Results of multivariate logistic regression analysis

Variable	P value	Adjusted OR	IK 95%	
			Min	Max
Age	0,004	8,297	1,957	35,174
Level of education	0,002	0,039	0,005	0,294
hs-CRP	0,0001	28,072	5,470	144,052

Based on this multivariate analysis, it was found that age, education, and hs-CRP variables had a statistically significant effect on cognitive impairment with a P <0.05. From the three variables above it can be concluded that the variables which affect cognitive function were age, education, and hs-CRP. Variables that strongly influence cognitive function were hs-CRP (P of 0.0001; OR: 28,072). This result validates that patients with hs-CRP >=5 were 28,072 times more likely to experience cognitive impairment than those whose level was less than 5.

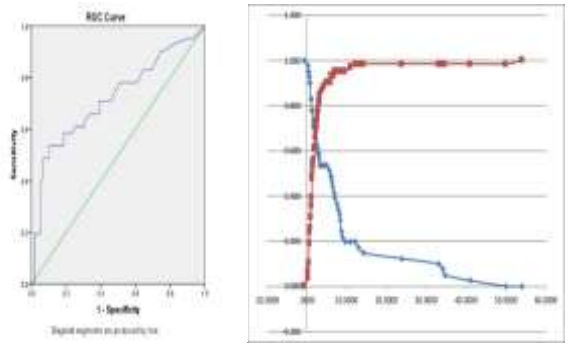

Figure 1. Cut off hs-CRP against cognitive impairment

Based on this study, the cut-off of hs-CRP level for cognitive impairment was 2.2 (p 0,003, OR : 3,761 (95% IK, 1,622-8,720)). It means that subjects whose hs-CRP level were >=2.2 had a risk of 3,761 times greater of having abnormal MoCA-INA score compared to those whose level was <2.2. This result can be seen in Table 10.

Table 10. Relationship between hs-CRP level using 2.2 cut-off with impaired cognitive function (MoCA-INA)

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Level of hsCRP				
< 2,2	14 (34,1)	39 (66,1)	0,003	3,761 (1,622-8,720)
≥ 2,2	27 (65,9)	20 (33,9)		
Total	41 (100)	59 (100)		

DISCUSSION

This study was an observational analytic study with a cross-sectional design to determine the relationship between hs-CRP level and impaired cognitive function which was assessed using MoCA-INA score in HIV patients in The UPIPI Dr. Soetomo Academic Hospital, Surabaya.

This study found that subjects who were older than 50 years old tend to have abnormal MoCA-INA scores (P 0.004). A study by Jade et al in 2017 in South Africa found that age > 50 years was associated with the risk of developing HAND (P = 0.003) (Mogambery et al 2017). A Study by McCombe et al. in 2012 in Canada also obtained results that age was a predictor of HAND in HIV/AIDS patients even though they have received a combination of antiretroviral (P <0.05) (Mccombe et al 2013). Another cross-sectional study in 2010 in Botswana showed an increase in the prevalence of cognitive impairment in HIV patients with increasing age (Lawler et al 2010). According to Kamkwalala and Newhouse (2017), many factors influence brain aging in the HIV-positive population. Infiltration of HIV at an

early age could trigger an inflammatory and neurodegenerative process that would eventually cause HAND. Hence, older HIV-positive patients were more likely to have impaired cognitive function than younger ones.

This study also shows the relationship between sex and cognitive impairment assessed using the MoCA-INA score was not statistically significant with P = 0.550. This was consistent with research by Garrido et al in 2013 that reported no significant differences were found between sex and cognitive impairment in the HIV patient population (Garrido et al 2013). The same results were obtained in a study by McCutchan et al (2012) that reported there were no statistically significant differences between the sexes and impaired cognitive function with p 0.92.

In this study, the results of the analysis of the relationship between education and cognitive function disorders found statistically significant differences with p 0,002. Individuals who were highly educated reportedly showed a slower decline in cognitive function compared to those with poorly educated. This was because education has a protective effect on cognitive function (Catroppa & Anderson 2010). A study by Kathy et al in 2010 found that education level significantly affected cognitive functions in HIV patients (Lawler et al 2010). A study by Kabuba et al (2018) found that higher education was protective against the occurrence of HIV-associated neurocognitive disorder (HAND).

Overweight and obesity were associated with chronic systemic inflammation. In this study, the results of the analysis of the relationship between body mass index with impaired cognitive function did not demonstrate a statistically significant difference with P = 0.197. These results were consistent with a study by Okafor et al in 2017 who reported that body mass index ie overweight and obesity were not statistically related to cognitive function (Okafor et al 2017). The same results were obtained in Ku et al's study in 2014 which concluded that body mass index was not statistically significant with HAND (P = 0.105) (Ku et al 2014).

Vascular risk factors associated with poorer cognitive function include hypertension and diabetes. Mechanically, these factors cause inflammation and oxidative stress in blood vessels and cause cerebral hypoxia-ischemia and endothelial dysfunction of blood vessels (Tedaldi et al 2015). In this study, the results of the analysis of the relationship between vascular risk factors and cognitive impairment assessed using MoCA-INA did not have a statistically significant relationship with P = 1,000. These results were following previous studies conducted by McCutchan, et al. in 2012 who reported that vascular risk factors were not statistically significant with impaired cognitive function with P = 0.07 (McCutchan et al 2012).

The results of the analysis of the relationship between hs-CRP level with impaired cognitive function assessed using MoCA-INA showed statistically significant results with P = 0.0001 and an Odds Ratio value of 28,072 (95% CI, 5,470-144,052). It means that the subjects who had level of hs-CRP >=5 had a 28,072 times greater risk of experiencing MoCA-INA disturbed than patients who had hs-CRP level <5. The results of this study were consistent with the study by Rubin et al. who reported that a high levels of hs-CRP were the strongest predictors of impaired cognitive function in HIV patients (Rubin et al 2018). A study conducted by Schouten et al in 2016 reported that inflammatory markers such as hs-CRP were one of the factors that significantly influenced cognitive decline in HIV patients with a p-value < 0.05 (Schouten et al 2016). The results of the analysis of the relationship between hs-CRP level with impaired cognitive function assessed using MoCA-INA showed statistically significant results, but these results could also be influenced by other conditions in the form of opportunistic infections, such as lung, brain, eye, nose and ear infections mouth and acute skin infections were mostly found in HIV patients. To reduce the bias due to these conditions, researchers sought to take the sample of the study in the Internal disease unit in The UPIPI on patients who came to control anti-retroviral therapy. This study did not take samples from other units at UPIPI such as pulmonology, ophthalmology, dermatology, ENT (ear nose and throat), or neurology unit.

In this study, a cut off level of hs-CRP was 2.2 for cognitive impairment. The results found that subjects who had hs-CRP level >=2.2 with impaired and normal MoCA-INA were 27 subjects (65,9%) and 20 subjects (33,9%) respectively. Whereas subjects whose hs-CRP level <2.2 with abnormal and normal MoCA-INA scores were 14 (34,1%) and 39 (66,1%) respectively. The above results were statistically significant (p-value of 0,003, OR: 3,761 (95% IK, 1,622-8,720)). It suggested that subjects who had hs-CRP level ? 2,2 had a risk of 3,761 times greater of having abnormal MoCA-INA compared to those whose level was less than 2,2.

The limitation of this study was that this study did not classify any affected cognitive domains of the subjects. The value of this study was that this study was the first study conducted at Dr. Soetomo Academic Hospital concerning the relationship between high C-Reactive Protein (hs-CRP) level and impaired cognitive function

assessed using MoCA-INA in HIV Patients in UPIPI Unit Dr. Soetomo Academic Hospital Surabaya.

Neurodegeneration in HIV-associated neurocognitive disorders (HAND) was associated with neuroglia activity. Damage to the nervous system in HIV infection occurs through 2 mechanisms: 1.) Toxicity occurs directly (direct) from HIV itself or through the release of viral proteins, such as Tat and gp120). Indirect toxicity was mediated by monocyte/macrophage cells (Hong & Banks 2016). The HIV-infected monocyte pathway was activated across the blood-brain barrier, infecting microglia and macrophages. Activation of macrophages and microglia would release proinflammatory products, such as IL-6 (Hong & Banks 2016). These proinflammatory cytokines could induce hepatocyte cells to synthesize CRP. CRP would cause the accumulation of reactive oxygen species (ROS) and vice versa. Reactive Oxygen Species (ROS) would cause an inflammatory process. Inflammasome regulated the activation of caspase-1. Caspase-1 functions to break down IL-1 cytokines into active forms namely IL-1? and IL-18 and cause pyroptosis and inflammation which ultimately resulted in HIV-related complications, such as HIV-associated neurocognitive disorders (HAND) (Galloway et al 2015).

Various neurotoxin and increased free radicals in the form of Reactive Oxygen Species (ROS) that caused inflammation processes had an important role in the incidence of HIV-associated neurocognitive disorders (HAND). Antiretrovirals were only able to reduce the density of the virus in the patient's body but were unable to overcome the influence of Reactive Oxygen Species (ROS) which were formed in many HIV patients (Nasronudin 2014). Even with a combination of suppressive antiretroviral, HIV-induced neuroinflammation continues (Rubin et al 2018).

CONCLUSION

There was a significant relationship between hs-CRP level and cognitive function, where subject with high hs-CRP level was more likely to have impaired cognitive function.

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MECHANISM OF PHYSICAL EXERCISE ON LOWERING LEVELS OF C-REACTIVE PROTEIN (CRP) IN OVERWEIGHT AND OBESE

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ABSTRACT

The cases of overweight and obesity in the world increased continuously. In 2016, obesity increased by 3% in men and 6% in women compared to 1975. Overweight cases also increased by 20% in men and 23% in women compared to 1975. Overweight and obesity have been linked to an increase in adipose tissue in the body. Increased adipose tissue associated with inflammation, where one of its characteristics is an increase levels of C - Reactive Protein (CRP). This study aimed to describe the mechanism of physical exercise to diminish CRP level in overweight and obesity. Adipose tissue produced and released various pro-inflammatory and anti-inflammatory factors, such as leptin, adiponectin, resistin, TNF-?, IL-6, MCP-1 and CRP. One of the prevention and treatment of inflammatory for overweight and obesity cases was to do physical exercise. In cases of overweight and obesity, the physical exercise aims to increase energy expenditure. Physical exercise decreased the volume and amount of adipose and pre-adipose tissue as well as the number of endothelial cells and macrophages in adipose that contained pro-inflammation, such as IL-1, TNF-?, CRP, serum amyloid protein (SAA), and cytokines. Physical exercise risen anti-inflammatory properties, such as IL-10, IL-1ra which played a role in inhibiting the transduction of IL-1? signals and inhibiting TNF-? synthesis. Physical exercise also amplified antioxidant enzymes, such as SOD and GPX. The antioxidants played a role in fighting free radicals to reduce inflammation.

***Keywords**: overweight; obesity; inflammation; CRP; exercise; anti-inflammatory*

ABSTRAK

Kasus overweight dan obesitas di dunia terus mengalami peningkatan. Pada tahun 2016 obesitas mengalami peningkatan 3% pada laki-laki dan 6% pada perempuan dibandingkan tahun 1975. Kasus overweight juga mengalami peningkatan yaitu 20% pada laki-laki dan 23% pada perempuan dibandingkan tahun 1975. Overweight dan obesitas telah banyak dikaitkan dengan peningkatan jaringan adiposa di dalam tubuh. Peningkatan jaringan adiposa berhubungan dengan terjadinya inflamasi, yang ditandai antara lain dengan adanya peningkatan kadar C-Reactive Protein (CRP). Artikel ini bertujuan untuk memapaparkan mekanisme latihan fisik terhadap penurunan kadar CRP pada overweight dan obesitas. Jaringan adiposa menghasilkan dan melepaskan berbagai faktor pro-inflamasi dan anti-inflamasi seperti leptin, adiponektin, resistin, TNF-?, IL-6, MCP-1 dan CRP. Salah satu pencegahan dan penanganan inflamasi kasus overweight dan obesitas adalah dengan melakukan latihan fisik. Pada kasus overweight dan obesitas, latihan fisik bertujuan untuk meningkatkan pengeluaran energi. Latihan fisik menurunkan volume dan jumlah jaringan adiposa dan pre-adiposa serta jumlah sel endotel dan makrofag di adiposa yang mengandung pro-inflamasi seperti IL-1, TNF-?, CRP, serum amiloid protein (SAA), dan sitokin. Latihan fisik meningkatkan anti-inflamasi seperti IL-10, IL-1ra yang berperan dalam menghambat transduksi sinyal IL-1? dan menghambat sintesis TNF-?. Latihan fisik juga meningkatkan enzim antioksidan seperti SOD dan GPX. Peningkatan antioksidan berperan dalam melawan radikal bebas sehingga menurunkan terjadinya inflamasi.

***Kata kunci**: overweight; obesitas; inflamasi; CRP; latihan fisik; anti-inflamasi*

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INTRODUCTION

Heart disease, atherosclerosis, hypertension, and type 2 diabetes mellitus are the risk of diseases caused by overweight and obesity. The cases of obesity in the world in 2016 has increased by 3% in men and 6% in women compared to 1975 (World Health Organization 2016). Whereas overweight cases have increased by

20% in men and 23% in women compared to 1975 (World Health Organization 2016). In Indonesia, cases of obesity in 2018 amounted to 21.8% of Indonesia's population and 13.6% including overweight (Basic Health Research, 2018). This indicates that there is a need for prevention and treatment of overweight and obesity for reducing the prevalence.

The increase of overweight and obesity is partly due to the high-calorie intake (high-calorie diet) and the lack of physical activity. Kurdanti et al (2015) found that obese adolescents had a higher average energy intake than non-obese adolescents. The adolescent who had more active physical activity, had a lower risk of obesity compared to inactive one. This can occur, because calories excess in the body is stored in the form of glycogen and fat. The lack of physical activity also supports an increase of fat (triglycerides) as a result of lower energy expenditure than energy intake. This also leads to an increase of C-reactive protein (CRP).

C-reactive protein (CRP) is an indicator used to determine risk factors for various diseases, such as hypertension, heart disease, and atherosclerosis and the level of systemic inflammation. Overweight and obesity have a significant correlation with CRP, because 75% of overweight and 93.5% of obesity have high CRP levels (Lavanya et al 2017). The CRP level more than 3 mg/L have an increased risk of coronary heart disease and diabetes (Soinio et al 2006). Lavanya et al (2017) found average CRP levels in normal people about 2.37 mg/L, in overweight people about 6.63 mg/L, and obese people about 10.22 mg/L.

Physical exercise can prevent and treat overweight and obesity through one the several the mechanisms including the reduction of CRP levels. Continuous physical exercise significantly reduces CRP levels in obese and breast cancer women (Tizdast et al 2016). Continuous aerobic exercise also significantly reduces CRP levels in cases of type 2 DM (Alizadeh et al., 2012). Continuous physical exercise with moderate-intensity (55-59% HRR) can also reduce CRP levels in cases of obesity (Vella et al 2017). Based on previous evidence, this study aimed to describe the mechanism of physical exercise to diminish CRP level in overweight and obesity.

OVERVIEW

C-Reactive Protein

C-Reactive Protein (CRP) is a protein secreted mainly by hepatocyte cells in response to inflammation, injury, and infection. Tillet and Francis in 1930 firstly identified CRP in the blood of patients infected with Pneumoccocal pneumonia by identifying substances that can precipitate and interact with phosphorylcholine residues from C polysaccharides, and their ability to precipitate calcium ions (Tillet & Francis 1930). The CRP belongs to the amino acid family of short pentraxin with high phylogenetic conservation (Mantovani et al 2008). CRP is one of an important regulators of the body's immune system and mediators of acute responses which link to various chronic or systemic inflammatory diseases.

CRP plays a role in inflammation of the body's immune system. CRP binds to phospholipids especially lysophospholipids and recognizes bacterial lipids as well as parts of the innate immune system (Strang & Schunkert 2014). CRP binds to bacteria or cells and interacts with NK cells and monocytes, activates endothelial cells to increase the adhesion of molecules, chemokines, and cytokines and mediates LDL uptake into macrophages (Chandrashekara 2014). CRP also strengthens the inflammatory response in both acute and chronic.

CRP is mainly synthesized by liver cells (hepatocytes). In healthy individuals, the CRP serum levels are around 1 mg/dl (Zhou et al 2016). When receiving a stimulus, such as a bacterial infection and tissue injury, hepatocytes will synthesize and secrete CRP to the blood circulation 1000 times higher than the basal condition (Zhou et al 2016). Hepatocytes are stimulated by IL-6 and gradually rise by IL-1? and TNF-? (Salazar et al 2014). STAT3, C/EBPs, and NF?B play a role in increasing CRP transcription (Zhou et al 2016). Obesity or an increase in fatty tissue (hypertrophy or hyperplasia) causes an increase in chronic inflammation. Increased inflammation triggers an increase in the synthesis of cytokines and cell pro-inflammatory proteins, such as neutrophils, monocytes, IL-6, and TNF-? (Teixeira et al 2014). An increment of IL-6 causes a raise of CRP production in hepatocytes. If the increment of IL-6 continues, the serum CRP levels will be higher due to chronic inflammation.

On the other hand, CRP is not only synthesized in the liver, but in other cells where mRNA is located and can respond to inflammation. The mRNAs that have been found in extra-hepatic sites include adipose tissue, lungs, atherosclerotic lesions, renal tubular epithelial cells, lymphocytes, macrophages, and smooth muscle cells (Salazar et al 2014). CRP is synthesized as a monomer and then converted to a pentamer in the endoplasmic reticulum. In hepatocyte cells, pentameric protein is retained in the endoplasmic reticulum and CRP is released slowly at rest (non-inflammatory) (Sproston & Ashworth 2018). When it gets an inflammatory stimulus, CRP is secreted in the blood

vessels quickly. Then serum CRP levels tend to increase significantly 6-8 hours after the initial stimulus and reach a peak at 24-48 hours, with a half-life of about 19 hours and the concentration is determined by the rate of synthesis (Salazar et al 2014).

Other effect of CRP is that the CRP influences an apoptosis. Devaraj et al. (2005) found that CRP stimulates the production of pro-apoptotic cytokines and pro-inflammatory mediators such as IL-1?, TNF-?, and reactive oxygen compounds. CRP also regulates p35 in monocytes and affects CD32 thereby inducing apoptosis (Kim et al 2014). CD32 has been shown to trigger apoptotic signals and is expressed on monocytes that are polarized into pro-inflammatory macrophages (Tugal et al 2013). This presents that CRP could cause apoptosis in monocytes.

CRP has a role in cardiovascular disorders. CRP is involved in monocyte adhesion and recruitment of intracellular molecules such as E-selectin and monocyte chemoattractant protein-1 (MCP-1) in atherosclerotic plaques (Sproston & Ashworth 2018). CRP also plays a role in increasing LDL uptake in macrophages and activating the complement system that leads to atherogenesis (the process of plaques formation in arteries). The role of CRP in atherosclerosis is what makes CRP as an indicator of cardiovascular risk. CRP also causes apoptosis of smooth muscle cells in the human coronary heart mediated by caspase 3 (Blaschke et al 2004).

CRP has been extensively studied concerning cardiovascular diseases, such as atherosclerosis, heart failure, and myocarditis. High sensitivity CRP reagent is also used to detect basal CRP levels in patients at risk of cardiovascular disease. Individuals who have CRP levels higher than 3 mg/L have an increased risk of coronary heart disease and this risk is increased in cases of diabetes (Soinio et al 2006). The importance of CRP measurement is to detect early risk of cardiovascular disease so that prevention and treatment can be done.

Table 1. CRP levels for the risk of cardiovascular

CRP Levels	The Level of Cardiovascular Risk
<1 mg/L	Low
1-3 mg/L	Medium
>3 mg/L	High

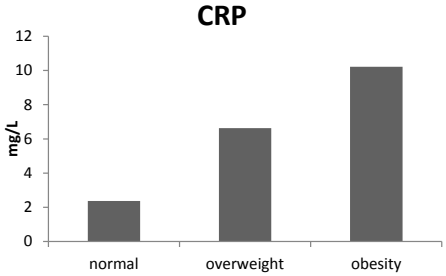
Source: Bonaca and Morrow (2008)

In atherosclerosis, CRP had various influences, such as activating the complement and apoptotic systems, activation of vascular cells, recruitment of monocytes, fat accumulation and thrombosis. CRP also activated NF?? which increases the production of cytokines, chemokines, molecular adhesions, growth factors, and cell immune receptors in atherosclerotic plaques (Salazar et al 2014). CRP also regulated endothelial cell activation and dysfunction, by inducing the expression of intracellular adhesion molecules, E-selectin and monocyte chemoattractant protein-1 (MCP-1) which allowed chemotaxis and binding of monocytes to endothelial cells during the early stages of atherogenesis (Chi et al 2002, Hattori et al 2003). The awareness of the rising level of CRP in atherogenesis should be realized to prevent the risk of plaques formation in in blood vessels.

CRP on Overweight and Obese

Overweight and obesity had more adipose tissue in the body than normal people. There were 2 kind of adipose tissues, namely brown and white adipose tissue. In newborns, brown adipose tissue helped to regulate energy expenditure through thermogenesis mediated by the expression of Uncoupling protein-1 (UCP-1) (Aaron et al., 2009). White adipose tissues had an active role in regulating physiological and pathological processes, such as immunity and inflammation (Karastergiou & Mohamed-Ali 2010). Increased adipose tissue associated with inflammation was characterized by an increase in C-Reactive Protein (CRP). Various studies had proven that CRP levels of overweight and obesity were higher than non-overweight and obese persons (Dayal et al 2014, Ishii et al 2012, Lavanya et al 2017, Mirhoseini et al 2018, Shilpa et al 2014).

The average CRP level in normal people was around 2.37 mg/L in overweight people around 6.63 mg/L and obese people around 10.22 mg/L with aged from 20 to 70 years (Lavanya et al 2017). Dayal et al (2014) found an average CRP level in overweight and obese adolescents around 3.92 mg/L and normal/non-obese adolescents around 2.15 mg/L in India with an average age of 11 years. Normal adults had an average CRP level of around 1.2 mg/dl, overweight and obese adults had an average CRP level of about 3.8 mg /dl withan average age of 32-34 years (Shilpa et al 2014).



Source: Lavanya et al (2017)

Figure 1. CRP serum level in a person with normal, overweight, obesity BMI-70 year-old

Inflammation that occured in overweight and obesity was chronic inflammation. This was marked by lymphocytes, macrophages, the proliferation of blood vessels and connective tissue (Seki et al 2009). Macrophages were a component of adipose tissue and actively participate in the immune system (Ellulu et al 2017). Adipose tissue produced and released various pro-inflammatory and anti-inflammatory factors, such as leptin, adiponectin, resistin, TNF-?, IL-6, MCP-, and CRP. One-third of the total IL-6 concentration came from adipose tissue (Fontana et al 2007). Excessive pro-inflammatory cytokines in overweight and obesity had been considered as links to inflammation.

The exessive nutrients that entered the body were responded by adipose tissue through adipocyte hyperplasia and hypertrophy. An enlargement that occured in adipocytes progressively caused the blood supply to adipocytes to decrease, thereby causing hypoxia (Cinti et al 2005). Hypoxia triggered necrosis and infiltration of macrophages into adipose tissue and causes increased production of pro-inflammatory cytokines. Macrophages produced three pro-inflammatory mediators including TNF-?, IL-6 and adiponectin (Karastergiou & Mohamed-Ali 2010). IL-6 was a stimulus for hepatocytes to produce and secrete CRP and assisted by TNF-? and IL-1? (Salazar et al 2014, Zhang et al 2009). The accumulation of free fatty acids in overweight and obesity activated the pro-inflammatory serine kinase cascade, such as IkB kinase and c-Jun N-terminal kinase which promoted adipose tissue to release IL-6 and triggered hepatocytes to synthesize and secrete CRP (Rocha & Libby 2009).

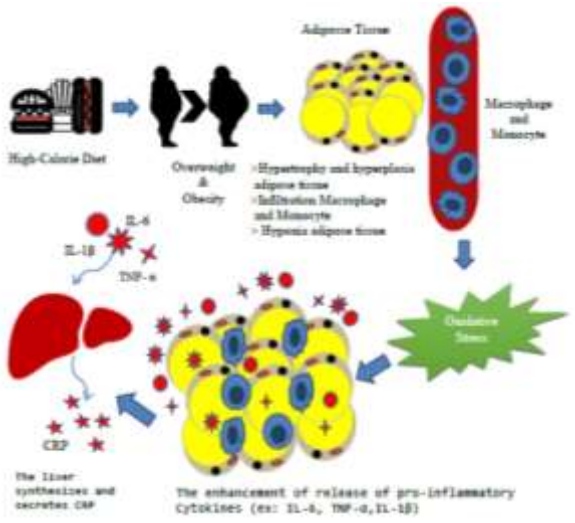


Figure 2. Mechanisms of increasing CRP in overweight and obesity

The relationship between overweight and obesity to CRP has been described as pathophysiological. Klisic et al. (2014) found that CRP and triglyceride (TG) levels were higher in overweight women compared to normal women. Dayal et al (2014) revealed and identified through anthropometric measurements correlate with CRP in children in India, it showed that each increase of 1 unit of BMI could increase the CRP odds ratio by 37%. Increased CRP in overweight and obesity had also been linked to various risks such as atherosclerosis due to decreased endhothelial nitric oxide synthase (eNOS) activity, thereby reducing nitric oxide (NO) levels and increasing concentrations of ET-1 (endhotelin-1) as vasoconstrictors which weaken the endothelium vasodilation process (Teixeira et al 2014). Vasoconstriction caused an increase in shear stress resulting in greater damage to blood vessels and created conditions that led to atherosclerosis and thrombus formation (Teixeira et al 2014).

Physical Exercise on Overweight and Obese Person

Exercise is a physical activity carried out in sequence and repeatedly to improve body fitness. Physical exercise in people with overweight and obesity aims to increase energy expenditure and body physiology and reduce adipose tissue and weight. Physical exercise is also able to increase anti-inflammatory which can suppress pro-inflammation such as CRP. Moderate-intensity aerobic physical exercise for 12 weeks significantly decreases CRP levels in obese children with or without metabolic syndrome in Egypt (Kamal & Ragy 2012). Continuous moderate-intensity exercise reduces CRP levels significantly in women with obesity and breast cancer (Tizdast et al 2016).

Adaptation to physical exercise in overweight and obese people affects the level of inflammation. Physical exercise affects the immune system by reducing the number of mononuclear cells in peripheral blood which are a source of pro-inflammatory cytokines such as (IL-1, IL-6, IL-1?, IL-8, CRP) (Echavez et al 2016). Physical exercise also enhances anti-inflammatories such as IL-10, IL-1ra which have important part in inhibiting the transduction of IL-1? signals and inhibiting TNF-? synthesis (Pedersen 2017). A decrease in IL-6 also affects a decrease in CRP, IL-6 is a stimulator of liver CRP secretion. Continuous moderate exercise can reduce levels of CRP and IL-6 in cases of obesity (Vella et al 2017). These evidences revealed exercise can decrease pro-inflammatory and increase anti-inflammatory thereby reducing the level of systemic inflammation and CRP.

Physical exercise decreased inflammation by reducing fat mass in cases of overweight and obesity. Physical exercise decreased the volume and amount of adipose and pre-adipose tissue and the number of endothelial cells and macrophages in adipose containing pro-inflammatory such as IL-1, TNF-?, CRP, serum amyloid protein (SAA) and cytokines (Nicklas et al 2005, Echavez et al 2016, Sirico et al 2018). Physical exercise decreased fat mass which caused an increase in free radicals and oxidative stress consequently reducing inflammation and CRP levels. Physical exercise also enhanced regulation of the Nrf2 gene where physical exercise increased free radicals which stimulated Nrf2 to increase the transcription of antioxidant enzymes (Done & Traustadóttir 2016). Antioxidants ' function was fighting free radicals as a result the inflammation reduced.

The role of physical exercise in reducing CRP levels and pro-inflammation in overweight and obesity varied depending on the type of exercise as well. Moderate-intensity aerobic exercise using treadmills and elliptical trainers for 6 weeks could reduce CRP levels by 29% in postmenopausal obese women (Ryan et al., 2014). The combination of walking aerobic physical exercise and strength training for 60 minutes with diet also decreased average CRP levels from 7.6 to 5.3 mg/L in overweight and obese adults with knee osteoarthritis with an average age of 65 years (Beavers et al 2015). Continuous moderate-intensity exercise using treadmills, ergometer and elliptical cycles for 8 weeks reduced average CRP levels from 21.9 nmol/L (0.0003942 mg/L) to 14.9 nmol/L (0.0002682 mg/L) in overweight and obese cases with the adult age of 28 years (Vella et al 2017).

Figure 3. Alteration of CRP serum level.

Pre= before training session, Post= after training session. Adopted data from Kamal dan Ragy (2012)*, Vella et al. (2017)** and Beavers et al. (2015)***.

Moderate aerobic exercise with walking and running for 12 weeks decreased the average CRP level from 2.1 mg/L to 1.2 mg/L in obese children with metabolic syndrome in Egypt at the age of 8-12 years (Kamal & Ragy 2012). Endurance training with submaximal intensity running (34 minutes) for 8 weeks reduced average CRP levels from 4620 pg/ml (0.00462 mg/L) to 595 pg/ml (0.000595 mg/L), and resistant exercises, such as pull-down, bench press, leg press, calf exercise, biceps curls, leg curls, lateral raise by dumbbell and overhead press reduced the average CRP level from 4411 pg/ml (0.004411 mg/L) to 666 pg/ml (0.000666 mg/L) in overweight and obese women with a mean age of 22 years (Mogharnasi et al 2019). The selection of the accurate dose of exercise was needed to get maximum results for overweight and obese. However, the principle of physical exercise was that physical exercise should be carried out regularly and progressively (gradually increasing). It would have a positive impact on reducing the level of inflammation including CRP in overweight and obese persons.

CONCLUSION

People with overweight and obesity had risk factors for various diseases, such as heart disease, metabolic syndrome, atherosclerosis, hypertension, and type 2 diabetes mellitus. As risk factors, overweight and obesity were associated with chronic inflammation through increased pro-inflammation such as IL-6, TNF-? and CRP. TNF-? is secreted excessively when overweight and it plays a role in increasing the rate of CRP synthesis. IL-6 is associated with obesity and it stimulated the liver to synthesize and secrete CRP associated with systemic inflammation. Inflammation was also followed by vascular and endothelial dysfunction that is characterized by a decrease in nitric oxide and an increase in reactive oxygen species (ROS) and can cause atherosclerosis, hypertension, changes in

metabolic markers and leads to heart disease. Physical exercise had an important part in increasing the physiology function and energy expenditure of the body. Physical exercise increased antioxidant enzymes, such as superoxide dismutase (SOD) and anti-inflammatories which consisted of IL-10, IL-1ra, and adiponectin that could suppress free radicals and pro-inflammatory. Physical exercise could also reduce fat mass, free fat mass, pro-inflammatory, such as IL-6 TNF-? and CRP.

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CALYCEAL DIVERTICULUM: A CASE REPORT

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ABSTRACT

Calyceal diverticulums are often benign and asymptomatic. On the other hand, some interventions are necessary in several symptoms. Radiological imaging is performed to made dianoses, but somehow can pose misinterpretation of radiological imaging results and mistreatment from the urologist. To present a case of a calyceal diverticulum treated with open diverticulectomy. This study reported a case of a calyceal diverticulum in a 30-year-old man with an almost 1-month history of left flank pain. The patient undergone several imaging diagnostics, before finally diagnosed calyceal diverticulum with a stone inside it. The patient had underwent open diverticulectomy. Initially, cystoscopy and insertion of Double J Stent (DJ Stent) were done, and then using the lumbotomy approach the incision that had been made. This case demonstrated the use of imaging combined with urologist interpretation and surgical management which was successfully treated the patient's clinical problems.

***Keywords**: flank pain; calyceal diverticulum; open diverticulectomy*

ABSTRAK

Divertikel kaliks seringkali jinak dan tidak bergejala. Di sisi lain, intervensi diperlukan bila didapatkan gejala. Pencitraan radiologis dilakukan untuk membuat diagnosis, dengan kemungkinan ketidaktepatan interpretasi hasil pencitraan radiologis dan berpengaruh pada tindakan ahli urologi. Kami melaporkan sebuah kasus divertikel kaliks yang dilakukan divertikulektomi terbuka. Kami melaporkan kasus divertikulum calyceal pada pria berusia 30 tahun dengan riwayat nyeri panggul kiri hampir 1 bulan. Pasien menjalani sejumlah pencitraan, sebelum akhirnya terdiagnosis divertikel kaliks dengan batu di dalamnya. Kami mengerjakan sistoskopi dan pemasangan Double J Stent (DJ Stent) terlebih dahulu, kemudian pasien diposisikan lumbotomi untuk prosedur divertikulektomi terbuka. Kasus ini menunjukkan penggunaan pencitraan dikombinasi dengan interpretasi urologis dan tindakan pembedahannya yang berhasil mengobati keluhan klinis pasien.

***Kata kunci**: nyeri panggul; divertikel kaliks; divertikulektomi terbuka*

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INTRODUCTION

A calyceal diverticulum is an event of the upper collecting system located in the kidney parenchyma and relatively uncommon with various unique clinical, pathological, and therapeutic features (Timmons et al 1975). The formation of the non-secretory sac is limited by transitional epithelial cells and is related to the main collecting system through a narrow channel, so that it allows passive filling of urine (Wein et al 2016). A century before, Prather put forward the term calyx diverticula used today (Dineva et al 2016).

A diverticulum can be caused by secondary factors due to trauma or due to previous surgical processes such as percutaneous nephrolithotomy (PNL) (Middleton & Pfister 1974). Described in most literature, diverticles are divided into 2 types, type I is the type that is more often found, located at the upper pole, and connects with minor calyx, usually the fornix. Whereas type II connects with calyx major or with kidney pelvis and tends to provide clinical symptoms, because its size can develop to be quite large and/due to stone formation (Rapp & Gerber 2004). In this study, we described the treatment of calyceal diverticulum in superior left kidney with open diverticulectomy.

CASE REPORT

A 30-year-old man presented with sudden left dull flank pain, weighing for almost a month. The patient had fever and hematuria intermittently. There was no history of allergies to certain medicine/food, trauma, and previous surgery. Cigarette consumption was confirmed by the patient for approximately 1 pack/2 days. The patient was a Javanese native with no family members who have similar symptoms. His vital signs and physical test were in normal limits. The abnormal laboratory results found in urinalysis leukocytes +2, blood +3, protein +3, from urine sediment obtained leukocytes and full erythrocytes per visual field.

Computed Tomography (CT) - Abdominal scan and Intravenous Pyelogram (IVP) (Figure 1 and Figure 2) were performed. Those 2 modalities were still inadequate to visualized the delayed phase-contrast filling the kidney cystic mass, and later found out it as diverticulum while using Magnetic Resonance Imaging (MRI).

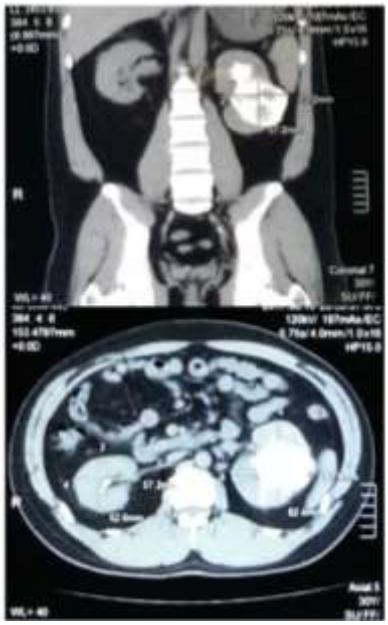

Figure 1. CT scan of the abdomen with contrast, the visible formation of cystic mass on the coronal and axial sides with sizes visible in each image 73.2 x 57.2 mm and 80.9 x 82.4 mm

Figure 2. IVP starts from a plain abdominal radiograph/kidney-ureter-bladder (KUB) x-ray pre-contrast. In the secretion phase in the 5th minute, the left kidney appears behind the right kidney. At 2 hours after filling the contrast, visible mass formation in the left kidney.

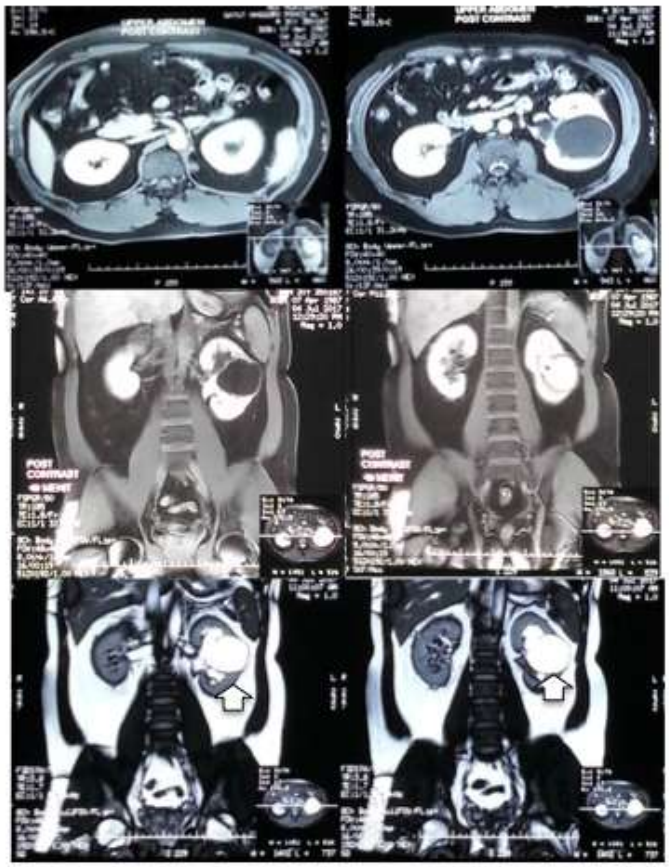

Figure 3. MRI Abdomen wedge Axial, Coronal T1Fat Sat, T2 Fat Sat, 2DFIESTA, 3D MRU without contrast, followed by T1FS with intravenous Gadolinium contrast. The post-contrast filling diverticulum is indicated with a white arrow.

MRI results obtained normal large right kidney, no hydronephrosis, no stones/cysts/nodules were seen. Left kidney appears large, cystic lesions appear related to the calyx of the upper left kidney, small neck diameter 16 mm and stones in neck diverticula size: 12.7 x 9.2 mm, no visible hydronephrosis, no visible solid mass. On the post-contrast, the contrast appears to fill the lesion. The diverticula size: 71 x 49 x 55 mm located between the upper calyx pole and the middle calyx pole of the left kidney when the middle pole is pushed down. Other organs were in normal limits.

The patient was planned for surgery. The surgery was performed with cystoscopy, left Retrograde Pyelography (RPG), and left Double J (DJ) Stent Ch 6 (Figure 4) and Folley Cath 16 Fr first, followed by open diverticulectomy (Figure 5).

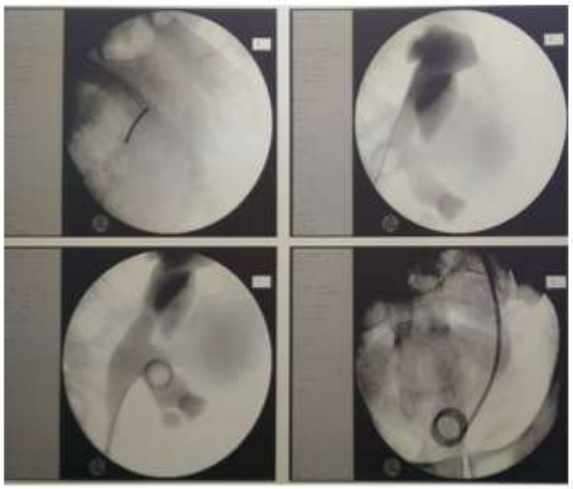

Figure 4. The RPG process and the insertion and correction of left kidney DJ stent.

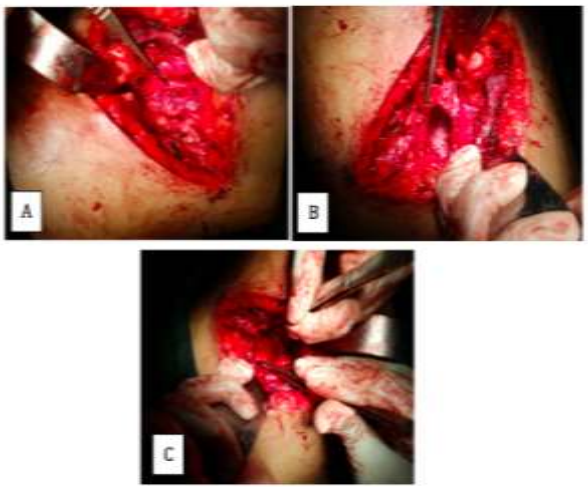

Figure 5. (A). Exploration of the diverticular wall right in the middle of the left kidney; (B, C). Excision of the diverticula wall is approximately half

After excision of the diverticles, the mucosal wall and parenchyma sutured in two layers fashion. The wound was closed layer by layer and the Ch 14 vacuum drain was placed. The results obtained during surgery in the form of left calyx diverticles were examined for anatomic pathology (Figure 6). Microscopic results showed no malignancy, more likely a Cystic Disease of the kidney with Chronic Pyelonephritis.

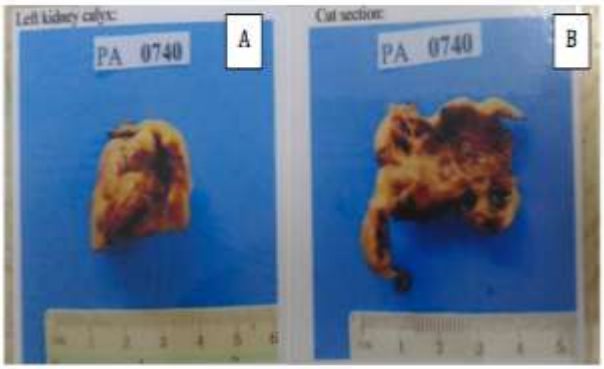

Figure 6. Specimens of left kidney diverticula (A) Part of left calyx kidney tissue, (B) Cut Section of left kidney calyx

After surgery, vital signs, symptoms, urine, and drain production were observed. One day after surgery, all laboratory and clinical results were in good condition. The patient also performed a KUB x-ray later (Figure 7). Continued on the third day after surgery the patient was examined for ultrasonography (USG) Urology (Figure 8). The results of the KUB x-ray and USG, right and left kidney within normal limit with left DJ stent visualized in a good position.

Figure 7. KUB x-ray one day after surgery

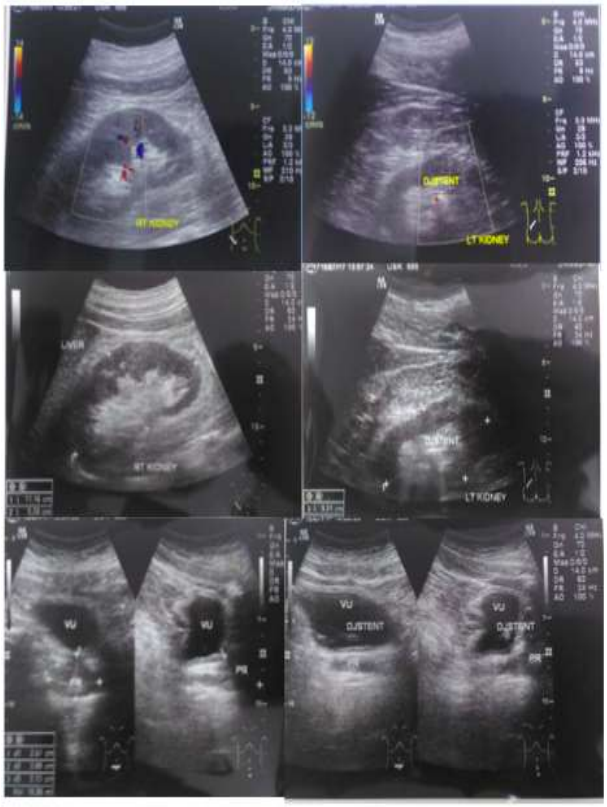

Figure 8. Urology USG showed left kidney after surgery, visualized tip of DJ Stent and no hydronephrosis, mass, stones, and blood clots were obtained. Doppler clearly showed good vascularity on both kidneys. Bladder and prostate are within normal limits.

On the sixth day, the drain was removed. On the seventh day after surgery, the patient was able to mobilize adequately and no other significant symptoms were obtained. The patient was discharged and scheduled for outpatient polyclinic control 1 month later.

DISCUSSION

The diagnosis of calyceal diverticulum relies heavily on radiological imaging. Misinterpretation of imaging later may be misleading the operator to choose surgical intervention methods. Since all of the symptoms (such as hematuria, urinary tract infections, and flank pain) in this patient were mostly considered as clinical kidney tumors. The symptoms that arise in our patients might be caused by diverticular neck obstruction causing calculus, or the calculus itself which obstructed neck's diverticles. Nearly 50% of the calculus in the diverticular cavity was calcium which moved with changes in body position (Tanagho & McAninch 2013, Burns et al 1984). According to the latest theory, the urine collected in the diverticula could be a single factor in the formation of stones (Auge et al 2006). Other

researchers have revealed that metabolic factors contribute to causing lithogenesis. This can be seen in the results of a 24-hour urine test, an abnormal parameter was found (Israel & Bosniak 2003).

MRI results visualized the longitudinal opacity which CT and IVP lacks sensitive when the contrast flew slowly from the neck and filled the diverticula. This phenomena was caused by the slow exchange of urine between the pelvicalyceal and the diverticula system, so that the contrast cannot reflux the diverticula or even visualized any opacity at all and could be interpreted as a kidney tumor or cyst (Ritchie et al 1990). Our patient diverticula size 71 x 49 x 55 mm was quite large, considering the size of the largest diverticles ever reported to be 18 cm (Auge et al 2006). It was assumed that the size of the diverticula increased with time if the patient had no symptoms. In principle, the management of diverticles followed by symptoms included taking stones and expanding infundibular stenosis to prevent urine accumulation or by ablation of the diverticular cavity at the same time (Tanagho & McAninch 2013).

The least invasive therapy was Extracorporeal Shock Wave Lithotripsy (ESWL) and was often chosen by patients and their families, but some studies showed the results of stone-free rates range from only 20-58% (Streem & Yost 1992, Turna et al 2007). The selection criteria for ESWL included stone size <1.5 cm and the neck of the diverticula that must be short and open, where stone fragments could come out and minimize the number of further surgical procedures (Waingankar et al 2014, Tan et al 2013, Rathaus et al 2001).

Endourology procedures, such as ureteroscopy (URS) or PNL might offer substantial benefits regarding size and position from stone or diverticula. Both procedures had varied good stone-free rates (70 % to 100%) and symptom-free rates (77% to 100%) (Tanagho & McAninch 2013, Tan et al 2013). Overall, the stone-free rate of URS was superior compared to SWL, but more inferior to PNL (Waingankar et al 2014).

The laparoscopic approach or robotic surgeries of diverticles neck with stones had been described in a large number of studies and were often used for stones located anteriorly (Wyler et al 2005).Waingankar et al explained that the results obtained using the retroperitoneal and transperitoneal approaches for diverticles located in the posterior are astonishing. The incidence of 100% stone-free rates, ablation of the diverticles reached 92%, and symptoms-free conditions range from 75-87% (Waingankar et al 2014).

Meanwhile, an open approach for stone-forming calyx diverticles treatment became obsolete. There remained a portion role for open surgery where anatomic and/surgical cost consideration, limited instrument availability, and patient or operator preferences excluded their uses. On the other hand, this open approach offered almost 95-100% stone-free rates and almost 90% symptoms-free conditions (Wein et al 2016, Tanagho & McAninch 2013, Ramakumar & Segura 2000).

CONCLUSION

Open surgical in developed countries has remained as the treatment of choice since it is safe, cheaper than the laparoscopic approach, and able to provide good results, coupled with the choice of an incision technique approach by the operator that allows for minimizing surgical scars. Periodic evaluations are needed if recurring symptoms arise with consideration of stone reformation.

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EARLY STUNTING DETECTION EDUCATION AS AN EFFORT TO INCREASE MOTHER'S KNOWLEDGE ABOUT STUNTING PREVENTION

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ABSTRACT

Stunting is one of the main nutritional problems that is still common in children under five and has serious health impacts. The results of National Health Research (Riskesdas) in 2018 showed the prevalence of stunting at 30.8%, indicating that 1 out of 3 Indonesian children are still stunted. Probolinggo Regency is a priority area for stunting handling in 2019 with a prevalence of 50.2% according to a report from the National Team for the Acceleration of Poverty Reduction (TNP2K). One of the factors that directly affect the incidence of stunting is low birth weight (LBW), while the mothers' knowledge level of health is an indirect factor that affects the growth conditions of children under five. The purpose of this study was to analyze the effect of providing stunting early detection education on maternal knowledge regarding stunting prevention. This is a pre experimental research study with one group pre-post test design, children aged 0-24 months as the research subjects. The case group consisted of stunted children (BL/A <-2 SD Z-score), while the control group consisted of normal children according to the BL/U indicator. The number of research subjects for the case and control groups was 40 with mothers of the toddlers as research respondents. The samples were selected using total sampling technique. Data were analyzed using dependent T test and linear regression. The results suggested that at the beginning of the session before provided education about early detection of stunting, mothers with stunting toddlers had lower level of knowledge (73.3%) than those with normal toddlers (77%). After provided with education, the knowledge level of mothers with stunted toddlers appreared to be higher (89%) than those with normal children (87.6%), with significant increase in each group (P <0.05). It could be concluded that education on stunting detection could significantly improve mothers' knowledge regarding the prevention of stunting in children aged 0-24 months. Providing regular education, both by nutrition workers at the health center and integrated service post (posyandu) cadres, was a necessary to prevent stunting to the maximum.

***Keywords**: education; early detection; stunting*

ABSTRAK

Stunting merupakan salah satu permasalahan gizi utama yang masih sering ditemukan pada anak balita dan memiliki dampak kesehatan yang serius. Hasil Riskesdas di tahun 2018 menunjukkan prevalensi stunting sebesar 30,8%, yang artinya 1 dari 3 anak indonesia masih mengalami stunting. Kabupaten Probolinggo menjadi daerah prioritas penanganan stunting yang memiliki prevalensi sebesar 50,2% pada tahun 2019 berdasarkan laporan Tim Nasional Percepatan Penanggulangan Kemiskinan (TNP2K). Salah satu faktor yang mempengaruhi kejadian stunting secara langsung adalah berat badan lahir rendah (BBLR) sedangkan tingkat pengetahuan ibu terhadap kesehatan menjadi factor tidak langsung yang berpengar;uh pada kondisi pertumbuhan balita. Tujuan dari penelitian ini adalah untuk menganalisis pengaruh pemberian edukasi deteksi dini stunting terhadap pengetahuan ibu tentang pencegahan stunting. Penelitian ini adalah studi pre-eksperimental dengan rancangan pre-post tes dalam satu kelompok, subjek penelitian anak usia 0-24 bulan dengan kelompok kasus adalah anak stunting (PB/U < -2 SD Z-score) dan kelompok kontrol adalah anak yang normal berdasarkan indikator PB/U. Jumlah subjek penelitian untuk kelompok kasus dan kontrol sebanyak 40 dengan ibu balita sebagai responden penelitian. Pemilihan sampel menggunakan teknik total sampling. Analisis data menggunakan uji T dependen dan regresi linier. Hasil penelitian menunjukkan pada awal sesi sebelum diberikan edukasi tentang deteksi dini stunting, ibu dengan balita stunting memiliki pengetahuan lebih rendah (73,3%) daripada ibu dengan balita normal (77%), namun setelah edukasi diberikan rata-rata tingkat pengetahuan ibu dengan balita stunting lebih tinggi (89%) daripada ibu dengan balita normal (87,6%) dengan kenaikan pengetahuan yang signifikan pada masing-masing kelompok (P<0,05). Kesimpulan penelitian adalah bahwa edukasi deteksi disi stunting secara signifikan dapat meningkatkan pengetahuan ibu terkait pencegahan stunting pada anak di usia 0-24 bulan. Pemberian edukasi secara berkala baik oleh petugas gizi puskesmas maupun kader posyandu perlu dilakukan sebagai upaya pencegahan stunting secara maksimal.

***Kata kunci**: edukasi; deteksi dini; stunting*

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INTRODUCTION

Stunting is one of the most common nutritional problems in the world and in Indonesia (UNICEF, 2012). Nutritional problems, especially stunting in children, is one of the conditions of malnutrition that has become a major concern in the world, especially in developing countries, as it has impacts on the slow growth of children as well as low level of immunity, intelligence, and productivity (Kurniasih D, Hilmansyah H, Astuti M, Imam S, 2-10). The Ministry of Health (Kemenkes) defines stunting as children under five with a z-score of less than -2SD/(stunted) and less than -3SD (severely stunted) with body length (BL/A) or height (BH/A) according to age compared to the standard WHO-MGRS (Multicentre Growth Reference Study) 2006. The 2013 National Health Research (Riskedas) results show that there has been an increase in the prevalence of stunting from 35.6% in 2010 to 37.2% in 2013, indicating that 1 out of 3 Indonesian children are classified as stunting.

One of the risk factors that influence the incidence of stunting in children under five is a history of low birth weight (LBW) (TNP2K, 2017). As a result, the growth of LBW babies will be disrupted, and if this situation continues with insufficient feeding, frequent infections, and poor health care can cause stunted children. However, the incidence of stunting is also indirectly influenced by socio-economic factors, such as education level, income, and number of household members (RISET KESEHATAN DASAR, 2013).

Several studies have shown that the risks caused by stunting are decreased academic achievement, increased risk of obesity, more susceptibility to non-communicable diseases and an increased risk of degenerative diseases (Kementrian Kesehatan, 2013). Therefore, stunting is a predictor of poor human resources which in turn will affect the development of the nation's potential (Soetjiningsih, 2012). Based on data from the Central abureay of Statistics (BPS) in 2019, the prevalence of children under five experiencing stunting in 2019 in Indonesia is still quite high, namely 27.7% with an estimate of 28 out of 100 toddlers experiencing stunting. East Java Province is one of the provinces whose stunting rate is above the national average (36.81%), with Probolinggo Regency having a prevalence of 50.2%. (EPPGBM, Dinas Kesehatan Jawa Timur, 2019).

One of the solutions to the problems described above can be done through early detection of stunting in mothers of toddlers. This study aims to analyze the effect of education on maternal knowledge regarding Stunting Prevention in Selogudig Village, Pajarakan District, Probolinggo Regency, East Java Province.

MATERIALS AND METHODS

This study was a pre experimental study with one group pre-post test design. This study was conducted in Selogudigkulon village, Pajarakan District, Probolinggo Regency-East Java. The study location was chosen purposively based on the data showing that the prevalence of stunting in Selogudigkulon Village was included in the top 100 (TNP2K 2017). The population in this study were all mothers with toddlers aged 0-24 months with a sample of 20 mothers with stunted toddlers and 20 mothers with normal toddlers selected based on total sampling. The intervention was carried out by providing education on early detection of stunting through lectures and question-and-answer sessions.

Data collection was carried out using a self-assessment questionnaire with the assistance of 2 (two) public health graduates. The knowledge questionnaire on stunting prevention contained fifteen multiple choice questions. The questionnaire was filled twice (before and after the stunting) education intervention was given. The interventions were given in the form of lectures related to stunting, breastfeeding, and clean and healthy living behavior (PHBS) followed by an interactive question and answer session as well as exposure to early detection of stunting using a stunting detection blanket measuring device. The intervention lasted 90 minutes. Data processing was performed using SPSS 22 IBM Statistics with statistical analysis of dependent T test (? <0.05) to see an increase in knowledge.

RESULTS

Respondent characteristics

Selogudigkulon Village is located in Pajarakan District, Probolinggo Regency, East Java Province, Indonesia. This village is located in the south about 12 kilometers from the capital city of Probolinggo Regency. Based on observations, public integrated service post (posyandu)

is conducted once a month with regular nutritionist visits at the time the posyandu is scheduled, but along with the COVID-19 pandemic conditions, posyandu is conducted through direct visits by local cadres. The characteristics of the 40 respondents included maternal age, maternal education, maternal occupation, family income, age at marriage and maternal height.

In this study, the mothers' age was categorized into 2, namely less than 20 years old or over 35 years old and between 20 to 35 years. The characteristics of respondents were presented in Table 1. The results showed that most of the respondents were between the ages of 20-35 years old (65%). A person's productive period was a period where someone easily accepted the learning process and the development of their intellectual power was in the age range of 20-35 years (Rahmawati 2012). A person at the age of 20-35 years was considered to have had enough experience and a growing way of thinking as well as the knowledge on how to provide good complementary feeding to their babies (Sediaoetama 2010).

Furthermore, in the category of education level, it was found that the majority of mothers' education levels were at non-tertiary institutions (non-college) (95%). The level of family education, especially the mothers' education, could be a factor that affected the nutritional status of children and families. Children with malnutrition conditions usually occured due to the lack of parents' attention to children's nutrition; one of which was influenced by the mother's low level of knowledge on nutrition. Mothers' formal education affected maternal nutritional knowledge which in turns affected health behavior to care more about the nutritional status of children and families (Sediaoetama 2010).

Most of the respondents in the Pajarakan Health Center work area became housewives as many as 36 respondents (90%) (Table 1). According to other studies, mothers who do not work will pay more attention to the quality and quantity of food that will be consumed by their children. Mothers who did not work have more time to care for their children, although other factors such as knowledge and parenting also needed to be considered (Bishwakarma & Vanneman 2011). In addition, the fact that the mothers did not work also had an effect on their families' monthly income.

The income category was adjusted to the Regional Minimum Wage for Work (UMK) in Probolinggo as many as IDR 2,319,796.75. Of all respondents, 90% were families who had an income below the UMK. Economic status affected the purchasing power of parents in getting food with high nutritional value. Some studies suggested that income was a factor that greatly affected the ability to choose the quality and quantity of food (Prendergast & Humphrey 2014). The low economic status of a family could negatively impact the children's growth, such as the likelihood of the child becoming thin and short (UNS/SCN 2013).

Table 1. Social demographic characteristics of respondents participating in early detection of stunting education

Characteristics	Number of Respondents (n = 40)	
	n	%
Respondents' Age		
<20 or >35 years old	14	35
20-35 years old	26	65
Respondents' Level of Education		
College	2	5
Non-College	38	95
Occupation		
Teacher	1	2.5
Laborer	1	2.5
Private Company Employee	1	2.5
Village Officials	1	2.5
Not Working/Housewives	36	90
Family Income (UMK 2020)		
<IDR 2,319,796.75	36	90
≥IDR 2,319,796.75	4	10
Age at Marriage		
Teenager (<= 19)	14	35
Normal (> 19)	26	65
Exclusive Breastfeeding		
Yes	40	100
No	0	0
Respondents' Body Height		
Short (< 150)	20	50
Not Short (>= 150)	20	50

In Table 1, the age of the respondents at marriage indirectly related to the age of the mothers having their first pregnancy. Of all respondents in this study, 65% were married at normal ages (>19 years old), while the remaining 35% were married at ?19 years old. A mother who was pregnant in her teenage years is still in her infancy, thus causing the risk of seizure of nutrients between the fetus and the mother's metabolism itself. This situation becoame worse when the mother's nutritional intake was inadequate, causing the fetus to experience growth restriction. This increased the risk of the fetus being born with low birth weight or premature birth, both of which were the factors in the occurrence of stunting in toddlers (WHO 2011).

Based on the respondents' body height data, it was found that 50% of the respondents were in the short category and the other 50% were in the not short category. In this study, the characteristics of the

mothers' heights were divided into 2, namely short with body height of <150 cm and not short with body height of ? 150 cm. The height of a mother also affected the growth and development of the child. This was because the blood flow of the uterus and the growth of the uterus, placenta and fetus in short pregnant women was limited, causing the baby to be boen with low weight. Thus, it was necessary to make improvements to the occurrence of fetal growth slowdown or retardation known as IUGR (Intra Uterine Growth Retardation) and low birth weight (LBW) (Andriani et al 2017). This incident would also take place in the next generation. The problem of stunting between generations was unavoidbale unless there was an improvement in nutrition and adequate health services at that time.

Short mothers did not always have short children (stunting) even though there was a tendency for short mothers to give birth to stunted children. If the parenting, especially the diet was good and included proper complementary feeding, the child would grow up healthy and optimally. The promotion of exclusive breastfeeding for six month-long followed by complementary feeding and breastfeeding was UNICEF's program outline. This was important as an effort to prevent overweight and stunting in infants and toddlers (Bishwakarma & Vanneman 2011). All (100%) respondents in the working area of the Pajarakan Health Center gave exclusive breastfeeding to babies and toddlers. This is a good first step in parenting for growing children and toddlers.

Respondents' Level of Knowledge

Out of the 40, two groups were divided with 20 participants in each group. Mothers with stunting toddlers had lower level knowledge (73.3%) than those with normal toddlers (77%). However, after education was provided, the mean level of knowledge of mothers with stunting toddlers appeared to be higher (89%) than those with normal toddlers (87.6%) with a significant increase in knowledge on each group (P <0.05).

Table 2. Mean values of pre and post test in session 1 (group of mothers with stunting toddlers and session 2 (mothers with normal toddlers)

	N	Mean	SD	SE
SESSION 1 PRE	20	73.333	14.018	3.134
SESSION 1 POST	20	89.000	7.578	1.695
SESSION 2 PRE	20	77.000	16.959	3.792
SESSION 2 POST	20	87.667	13.206	2.953

Table 3. Statistical analysis of increased knowledge in the pre and post test groups of mothers with stunting toddlers and those with normal toddlers

	t	df	p
SESI 1 PRE - SESI 1 POST	-5.887	19	1.142e -5
SESI 2 PRE - SESI 2 POST	-3.470	19	0.003

Note. Student's t-test.

In the carried out paired T test, in tables 2 and 3, it is found that the average level of knowledge in mothers with normal toddlers and mothers with stunted toddlers has increased significantly after education, indicated by a p value of <0.05. This suggests that the influence exerted by this study was a positive influence for respondents with an increase in understanding and knowledge. The results of this study are in line with Andriani's research in 2017 conducted in the working area of Public Health Center (Puskesmas) Puluwatu, Kendari City, suggesting that there was a significant difference in knowledge before and after the mothers being given the Mother Smart Grounding (MSG) program in preventing stunting (Andriani et al 2017). There is also another research on measuring the nutritional status of toddlers as an effort to prevent stunting conducted in the Randugunting Hamlet, Sleman. The study revealed that there was a difference of means between the values before being given training and the values after being given training, proving the provision of education, training and simulations to be effective in increasing respondents' knowledge.

In a research on monitoring the nutritional status of toddlers for Posyandu cadres by Zaki et al (2018), the results of the activities evaluation showed that there was an increase in knowledge and skills scores before and after being given training and monitoring on the nutritional status of toddlers to cadres. The improvement can be seen from the participants' ability to correctly weigh standing toddlers, measure the weight of babies of less than two years old, measure the height of toddlers, and fill out the Growth Card (KMS). Furthermore, the training of health cadres in early detection of nutritional disorders also showed an increase in knowledge and skills. The impact is that the health cadres have shown improvements in making referrals for nutritional disorders for children under five, while mentoring by cadres has a positive impact on nutrition health services for children under five (Hati & Pratiwi 2019).

The nutritional health of infants and toddlers is highly important for parents to pay attention. A healthy child is

not susceptible to disease, including infectious diseases which are dominant in nutritional problems. This is because a healthy child has a good immune system. The immune system changes according to the nutritional health of the child's body. If a child's nutritional health is good, his immune system will increase. Conversely, if the nutritional health condition decreases, then his immune system will decrease (Kosasih et al 2012). Parental education is one of the important factors in children's development since adequate education can affect the behavior of stimulating children's growth and development by parents. The lack of stimulation of children can cause growth and development disorders of children and even persistent disorders (Soetjiningsih & Ranuh 2014).

Table 4. Analysis of the respondent's level of knowledge on each question item (scale 0-100)

No	Question Item	Number of Correct Answer n (%)			
		Session 1		Session 2	
		Pre-test	Post-test	Pre-test	Post-test
1	What is the other name for stunting?	16 (80)	19 (95)	18 (90)	19 (95)
2	Stunting occurs due to the lack of nutritions in a long term, namely?	12 (60)	19 (95)	13 (65)	17 (85)
3	What are the long-term impacts of stunting?	13 (65)	12 (60)	18 (90)	18 (90)
4	Which of these following statements are **not** included as the stunting prevention?	11 (55)	11 (55)	13 (65)	11 (55)
5	Which of these followings statements are included as the simple steps to prevent stunting toddlers?	17 (85)	20 (100)	18 (90)	19 (95)
6	Until what age should breastfeed be given to an infant?	19 (95)	16 (80)	17 (85)	14 (70)
7	What are the benefits of breastfeeding?	8 (40)	16 (80)	11 (55)	16 (80)
8	What is the correct duration of breastfeeding?	6 (20)	20 (100)	12 (60)	18
9	Is it allowed to give a banana to infants of <6 months to help them feel full quicker?	17 (85)	20 (100)	15 (75)	19 (95)
10	What do you do if your nipples blister or bleed?	18 (90)	20 (100)	18 (90)	19 (95)
11	What is Clean and Healthy Living Behavior (PHBS)?	13 (65)	20 (100)	10	20 (100)
12	Which of the following are PHBS in a household?	20 (100)	20 (100)	18 (90)	20 (100)
13	Which of the following are **not** the requirements for a healthy toilet?	14 (70)	14 (70)	11 (55)	17 (85)
14	Is daily consumption of fruit and vegetable a part of PHBS?	18 (90)	20 (100)	20 (100)	20 (100)
15	Why should you implement PHBS?	20 (100)	20 (100)	19 (95)	20 (100)

As seen in table 4, it is found that the level of changes in the knowledge of the two groups has increased. The highest score on the pre-test in the first session group, namely mothers with stunted toddlers, was 100 points and the lowest was 20 points. Meanwhile, there is a high increase in the post-test score with 55 being the lowest score. Changes in the level of knowledge also occurred in the second group, namely mothers with normal toddlers, with the lowest value being greater than those in the first group. In the pre-test, 50 was the lowest score and one respondent obtained 100 points as the highest score.

In the second group's post-test score, the lowest score was 70 points and the highest was still 100 points, but the number of respondents who obtained it increased by 4 people. The correct answers most commonly found in both groups were on the topic of questions about breastfeeding, PHBS, and followed by stunting in the last position. This indicates that the respondents' understanding of stunting was still less than the topics of breastfeeding and PHBS. Based on this, it could be seen that the level of knowledge of mothers with normal children under five was better than mothers with stunting in the pre-test and post-test scores with the pre-test mean value of the first group being 14.8±75 and the second group 15.4±80. In the post test results, the mean of the first and second groups had the same value, such as 17.8 ±95

CONCLUSION

This study showed that providing education on early detection of stunting could significantly increase

mothers' knowledge regarding the prevention of stunting in children aged 0-24 months. The provision of regular nutrition education by nutritional workers at the health center and posyandu cadres was necessary as an effort to prevent stunting.

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- Rose ME, Huerbin MB, Melick J, et al (2002). Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res935, 40-46

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Meltzer PS, Kallioniemi A, Trent JM (2002). Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW (eds). The genetic basis of human cancer, New York, McGraw-Hill, p 93-113

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