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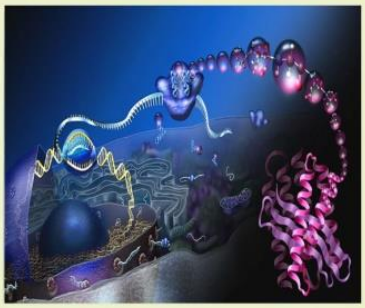

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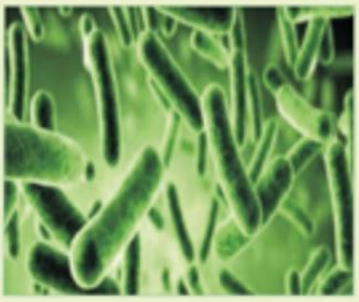

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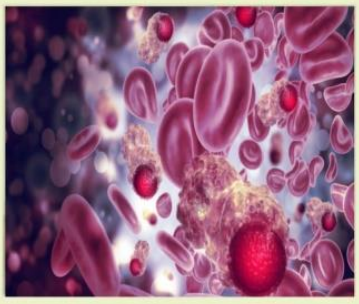

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ORIGINAL ARTICLE

PREVALENCE OF CHRONIC KIDNEY DISEASE AMONG COMMUNITY REMOTE AREAS IN SABAH: POPULATION-BASED STUDY

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ABSTRACT

In this population-based study, we determined the prevalence of chronic kidney disease (CKD) of community in remote areas of Ranau, Sabah to have accurate information for health-care planning. It also investigated the association of risk factors with the prevalence of CKD. A sample of 270 individuals, compared to the study of the National Health and Morbidity Survey 2011, of the adult population (over 18 years old) undertaken in West Malaysia. We measured the estimated glomerular filtration rate (eGFR) using this CKD-EPI equation. The total prevalence of CKD in this group was 53%. An estimated 3.3% had stage 1 CKD (eGFR >90 ml/min per 1.73m^2), 32.6% had stage 2 (eGFR 60–89 ml/min per 1.73m^2), 4.1% had stage 3 (eGFR 30–59 ml/min per 1.73m^2), 7% had stage 4 (eGFR 15–29 ml/min per 1.73m^2), and 6% had stage 5 CKD (eGFR <15 ml/min per 1.73m^2). Only 4% of respondents with CKD were aware of their diagnosis. The significant risk factors included family history of kidney disease, alcohol consumption, smoking status, hypertension, diabetes mellitus, and dyslipidemia. Thus, CKD in East Malaysia are common and warrants early detection, and treatment to potentially improve outcomes can be implemented.

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INTRODUCTION

Chronic Kidney Disease (CKD) is a significant public health issue[1]. It is a worldwide burden attracting major attention due to its rapidly progressing numbers.[2,3] Recent global CKD prevalence is estimated to be between 10 – 15%.[4] A previous study reported 9.1% of West Malaysians to have CKD.[5]

CKD can develop gradually, taking months to years, frequently leading to permanent loss of kidney function over time. Harmful effects of CKD are the accumulation of water, waste, and toxic substances in the body that are excreted by the kidneys. The loss of kidney function is known to cause anemia, high blood pressure, bone diseases, and acidosis disorders (excessive acidity of body fluids) associated with cholesterol and fatty acids. As CKD continues to progress, the glomerular filtration rate decrease and remaining nephrons are unable to effectively eliminate metabolic wastes and environmental toxicants from the body. This inability may escalate the mortality and/or morbidity of an individual[1].

As the renal replacement therapy (RRT) in Sabah has been increased up to 2,047 patients and RRT places a large burden on the health-care budget[15]. Therefore, it is important to obtain accurate local data on CKD to facilitate health care planning, especially in remote areas. The objective of this population-based study was to determine the prevalence of CKD among community aged over 18 years in remote areas of Ranau, Sabah. We also studied the association of risk factors with the prevalence of CKD.

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MATERIALS AND METHODOLOGY

2.1 Study Area

The study was conducted in the district of Ranau, Sabah, North Borneo of Malaysia which comprises a total population of 94,029. More than 85% of the population comprises of the Dusun tribe.[16]

2.2 Patient background

This study was carried out at the Nephrology Health Care Clinic in Ranau Hospital. Most of the patients aged 18 to 65 years, who gave their consent, were diagnosed as CKD and referred to be assessed by physicians. Simple random sampling was used. Pediatric patients, pregnant women, infections disease patients such as those suffering from HIV, and Hepatitis were excluded.

2.3 Sampling method

All respondents were randomly interviewed by trained data collectors using a standard validated questionnaire with fully written consent. This was a cross-sectional study where we evaluated 270 respondents. The questionnaires included demographic characteristics, socioeconomic and health status. Physical examination and blood tests were performed.

Blood pressure (BP) was measured by Omron Japan Model HEM-907 (Tokyo, Japan),[19] which has been validated and calibrated. BP was measured with the respondent at rest in a sitting position, with the BP set and appropriate-sized cuff at chest level. Two readings were taken 15 min apart, and the average measurement was used for analysis.

2.3.1 Blood Sampling Method

Written consent was obtained from the respondents for blood sampling and it was done to determine the serum creatinine (SCr), in which 5ml of blood samples were taken by using a disposable syringe from the vein and collected in a capped plastic sterile tube. The procedures were carried out aseptically and precautions taken during the use of a tourniquet to prevent blood contamination as per protocols. The blood samples were transported by using a cool box and the temperature was maintained at 4ºC and sent immediately to the laboratory within 24 hours.

The serum creatinine level was measured by the enzymatic laboratory method of Sabah Gribbles Laboratory, Malaysia. The estimated GFR (measured in millimeters per minute per 1.73m^2) was calculated using the CKD-EPI creatinine formula[20], where e-GFR= 141 x min (Scr / k, 1) ^{a} x max (SCr / k, 1) $^{-1,209}$ x 0.993^{age} x 1.018 (if female) SCr is serum creatinine (mg / dL), k = 0.7 (female) and 0.9 (male), a = - 0.248 (female) and -0.207 (male), min is the minimum of SCr /k or l and max is the maximum of SCr/k or l.

Fasting blood sugar and total cholesterol were estimated by dry method (CardioChek PA, Gribbles Sabah, MY), which has been validated.[18]

2.4 Definitions

CKD stages 1 and 2 was defined as eGFR > 90 ml/min per 1.73m^2 and 60–89 ml/min per 1.73m^2, respectively. Stages 3, 4, and 5 were defined as eGFR 30–59, 15–29, and <15 ml/min per 1.73m^2, respectively, regardless of kidney damage.

Diabetes mellitus was defined as a fasting capillary blood glucose level > 6.1 mmol/l on CardioChek, or self-reported diabetes diagnosed by medical personnel, or random capillary blood glucose >11.1 mmol/l.

Hypercholesterolemia was defined as random or fasting blood cholesterol > 5.2 mmol/l or self-reported hypercholesterolemia diagnosed by medical personnel.

Hypertension was defined as the average of two BP readings with systolic BP >140 and/or diastolic BP > 90mmHg20 and/or self-reported hypertension previously diagnosed by medical personnel.

2.5 Statistical analysis

Statistical analyses of data were performed by using SPSS version 26 to identify whether there was any significant prevalence of CKD among the respondents. Data were presented as mean and median for continuous variables and proportion for categorical variables. Prevalence estimates of all outcomes were performed. Factors associated with CKD were assessed using logistic regression. Unadjusted odds ratio between exposure variables and indicators of CKD was determined. Adjusted odds ratios and 95% confidence intervals were estimated. The P-value of <0.05 is considered significant.

2.6 Ethical approval and consent

Approval and ethical clearance were given by the National Medical Research Register (NMRR) (Ethics Approval Number: NMRR-18-2615-44151) and the UMS Research committee. The approval also was obtained from the Director of the State Health Department for blood sampling which was conducted by the staff of the health department. All respondents were required to sign a written informed consent form before enrolment.

RESULT AND FINDINGS

There were 270 respondents consented to participate out of initially 400 targeted, giving a response rate of 68%. Table 1 compares the overall National Health and Morbidity Survey (NHMS) 2011 cohort in West Malaysia aged > 18 years (N=15,147) with the CKD study (N=270). There was no difference observed in the profile of both studies.

Table 1 Comparison between National Health and Morbidity Survey (NHMS) cohort samples and CKD samples

Socio-demographic Characteristics	NHMS cohort (>18 years), N=15,147			CKD Study, N=270			
	Number	Mean	Median	Number	Mean	Median	IQR
Age (years)	15,147	42.2	41.0	270	45.1	46.0	20
Systolic blood Pressure(mmHg)	14,631	129.5	127.0	270	134.7	134.0	20
Diastolic blood pressure (mmHg)	14,630	80.2	80.0	270	84.1	84.0	12
Glucose level (mmol/l)	13,436	6.1	5.4	270	5.3	5.0	1.3
Cholesterol level (mmol/l)	13,742	4.9	4.8	270	5.4	5.1	1.3

Abbreviations: CKD, chronic kidney disease; IQR, interquartile range.

Table 2. Prevalence of CKD stages (N=270)

CKD Stage	Number of respondents	Prevalence of CKD (%)
Normal	127	0.0
Stage 1	9	3.3
Stage 2	88	32.6
Stage 3	11	4.1
Stage 4	19	7.0
Stage 5	16	6.0
Total	270	53%

Abbreviations: CKD, chronic kidney disease

Out of 270 respondents, 143 (53%) were diagnosed with CKD based on eGFR measurements (Table 2). Overall, 47% of the respondents had eGFR >90 ml/min per 1.73m^2 which was normal, 3.3% had 4.1% stage 1 CKD, 32.6% had stage 2 CKD, 4.1% had stage 3 CKD, 7.0% had stage 4 CKD and 6.0% had stage 5 CKD (eGFR < 15 ml/min per 1.73m^2). Using univariate analysis, the factors associated with significantly increased prevalence of CKD were smoker, alcohol drinker, diabetes, hypertension, dyslipidemia, and family history of kidney disease (Table 3). All the factors associated with CKD was significant (p<0.05).

Table 3. Factors associated with CKD Prevalence by Univariate Analysis (N=143)

Variable	n (%)	Adjusted OR (95% CI)	P-value
Smoking status		2.72 (0.48-3.32)	0.041
Smoker	89 (62.2)		
Alcohol consumption		3. 28 (2.13- 13.89)	0.005
Drinker	92 (64.3)		
Diabetes	51 (35.7)	2.89 (1.83-4.06)	0.005
Hypertension	114 (79.7)	3.01 (1.37-8.93)	0.001
Dyslipidemia	69 (48.3)	2.01 (1.12- 1.05)	0.047
Family history of kidney disease	109 (76.2)	5.12 (2.75-9.60)	0.000

OR= odds ratio, CI= confidence interval; P<0.05 with chi-square test

DISCUSSIONS

CKD is defined by using the Modification of Diet in Renal Disease (MDRD) equation together with CKD-EPI.[6] In South Korea, Taiwan, and Thailand. CKD was defined by using the MDRD equation with eGFR< 60 ml/min per 1.73m^2. In Beijing, eGFR was measured using calibrated serum creatinine while the Japanese used eGFR and dipstick to define CKD.

The demographic characteristic of the CKD study was similar to that of the overall NHMS 2011 cohort (Table 1). There was no difference in the profile of both cohorts except for certain respondents in the CKD sample. This suggests that the CKD study was conducted on a valid representative sample for the population of the remote area i.e. Ranau, Sabah. There was a good response rate of 68%.

This study assessed the prevalence of CKD among respondents living in Ranau, Sabah using the GFR. The overall prevalence of CKD in the study was 53%. The prevalence of CKD by stages 1,2,3,4, and 5 were 3.3%, 32.6%, 4.1%, 7.0% and 6.0% respectively. In a previous population-based study reported that the prevalence of CKD stage 5 in Malaysia was 0.36% in people above 18 years of age[5]. Our estimated prevalence of stage 5 CKD was higher than in other studies. This difference in CKD prevalence might be due to the difference in case studies and variables.

The prevalence of CKD in West Malaysia of 9.07% is similar to their rate in the region. The prevalence of CKD in Asia varies within South Asia: 10.2% in India, 17.3% in Bangladesh, 16.9% in Pakistan, and 10.6% in Nepal[6, 7]. While, in other Asian regions it was: 17.5% in Thailand, 13% in Japan, 6.8% South Korea, 12% in Taiwan, and 13% in Beijing. The prevalence depends on methodology, CKD definition, and study design incorporated[5].

In this study, a significant association between family history and CKD has been found[8]. Previous studies use lower eGFR and albuminuria to define CKD[9]. The result obtained was positive correlation even after adjusting for age, sex, race, diabetes, hypertension, and socioeconomic background.

This study found a significant correlation between smoking and CKD. Tobacco in cigarettes heavily increases the risk for a wide range of chronic conditions including cancer, cardiovascular disease, and respiratory disease. A study found CKD and its relationship with smoking[13]. The study found that smoking increases the risk for both atherosclerotic and non-atherosclerotic vascular disease, hence, directly increasing the vascular and nonvascular morbidity and mortality in patients with CKD.

This study also found a significant correlation between alcohol consumption and CKD. Excessive alcohol consumption generally leads to liver damage but few studies have also found that ethanol can cause kidney damage[10]. Along with an unhealthy diet and lifestyle, heavy alcohol consumption can greatly contribute to CKD. However, few studies show that there is no obvious correlation between alcohol and CKD due to confounding factors such as smoking, drug

abuse, used of NSAIDS, high fat diet, and coffee that may interfere in study.[17]

Diabetes is associated with hypertension was closely associated with the development of CKD.[11] This is due to an increase in deterioration in glomerular filtration in renal damage caused by diabetes together with hypertension amplifying vascular damage which later leads to renal insufficiency. Elevation of blood pressure both caused by and resulting in increased progression of kidney disease leads to an intermingled cause and effect relationship between hypertension and CKD.

CKD was independently associated with type 2 DM and longer duration of DM. This corresponds with the finding of several studies that reported that the likelihood of developing CKD was greater among patients with a longer duration of diabetes. CKD is estimated to affect 50% of patients with type 2 DM. Improvement in cardiovascular survival in a patient with type 2 DM has contributed to patients surviving longer, allowing sufficient time to develop renal disease[14].

The study also found a significant association between CKD and dyslipidemia. Dyslipidemia is a common complication associated with the decline in GFR. Patients with CKD usually have dyslipidemia or more specifically hypertriglyceridemia due to increased concentration of lipoprotein that is rich with triglyceride. Hypertriglyceridemia occurs because of two reasons; delayed catabolism and the increase in hepatic production of triglyceride-rich lipoproteins. Delayed catabolism is mainly responsible for increasing the concentration of triglyceride-rich lipoprotein in CKD patients[12].

In this study, the following limitations should be considered. First, we were not able to take the underlying risk factors into accounts such as ethnicity, geographical, nationality, and type of herbal medication used. Second, the cross-sectional design of the study makes it impossible to infer the causal relationship between indicators of CKD and associated factors. Third, as Ranau is just one of the districts in the state of Sabah, the prevalence of CKD reported could not be generalized to the whole Sabah population. Fourth, people who were aware that they had CKD were more likely to agree to participate in the study which may lead to overestimation in the prevalence of CKD. Fifth, there is also a possibility of overestimation of CKD due to potential selection bias from missing data. Lastly, the study subjects were recruited from a single hospital which may limit the generalizations of the findings of this study. Therefore, these findings cannot represent symptoms of CKD of the whole population.

Thus, the prevalence of CKD is higher than what is reported in other studies on kidney disease (probably due to sample sizes and different geographical areas). It is also dependent upon smoking, alcohol consumption, hypertension, diabetes mellitus, dyslipidemia, and family history. These factors should be considered 'high risk' in Malaysia, and early detection of CKD in these groups should be implemented.

CONCLUSION

Prevalence of CKD among community remote areas Sabah was 53%. The significant risk factors associated with CKD in this study were family history of kidney disease, alcohol consumption, smoking status, hypertension, dyslipidemia, and diabetes mellitus. Thus, CKD in East Malaysia is common, early detection and treatment among these communities to potentially improve outcomes can be implemented. Further research should look into the impact of other variables such as type of occupation, and source of water intake as these are potential risk factors for impairment of renal function.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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ABBREVIATION AND SYMBOLS

CKD = Chronic Kidney Disease
DM= Diabetes Mellitus
e-GFR= Estimated Glomerular Filtration
ESRD= End-Stage Renal Disease
NKF= National Kidney Foundation
NSAID= Non-steroid Anti-Inflammatory Drugs
SCr = Serum Creatinine

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ORIGINAL ARTICLE

THE EFFECT OF CITICOLIN IN MOTORIC IMPROVEMENT OF ACUTE ISCHEMIC STROKE PATIENTS IN SITI KHODIJAH SEPANJANG HOSPITAL

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ABSTRACT

Background: According to WHO, stroke is most common cause of morbidity and mortality around 5,54 millions death. Stroke is classified into ischemic stroke and hemorrhagic stroke. Ischemic stroke is caused by vascular blockage in the brain, whereas hemorrhagic stroke is caused by vascular ruptures. Ischemic stroke is treated by thrombolytic for reperfuison and anticoagulant or antiplatelet to prevent the formation of thrombus collateral blood brain. Moreover, it also can add neuroprotectant to inhibit further tissue and cellular damage due to cytotoxic effect. The common used of neuroprotectant are piracetam and citicolin. They increase erythrocyte capability in blood vessels without alter shape or function of erytrhocyte. Citicolin improves neuronal cells membrane by increasing synthesis of phosphatidylcholine as main component of cells membrane. Citicolin often chosen because cheaper and there is no significance different effect between both of them. **Objective**: To investigate motoric improvement in acute ischemic stroke patients in Siti Khodijah Sepanjang Hospital. **Methods**: Study design is observational retrospective case-control using medical record from January-September 2019. We devided 72 patients into two groups: control group who received antiplatelet 100 mg/day for 5 days and treatment group who received combination of antiplatelet 100 mg/day and citicolin 500 mg/day for 5 days. Patients were examined using Medical Research Council Manual Muscle Test Scale on first and fifth day. The criteria of motoric improvement is Manual Muscle Testing Scale score increased $\geq$ 1 score in one of extremitas muscles. **Results**: statistic test used chi-square test and wilcoxon test with each significance grade 0,00 and 0,01 (<0,05). **Conclusion**: Our study indicated that citicolin 500 mg/day for 5 days significantly improved motoric in acute ischemic stroke patients in Siti Khodijah Sepanjang Hospital.

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INTRODUCTION

Stroke is the global burden disease that can cause death or disablities problem. Stroke, based on its etiology, classified into ischemic and hemorrhagic stroke. Ischemic stroke is caused by vascular blockage in the brain, whereas hemorrhagic stroke is caused by vascular ruptures. Ischemic and hemorrhagic stroke can be treated with general therapy and special therapy, which is obviously different. Based on its patophysiology, ischemic stroke treatment divided into three steps. The first step is thrombolytic treatment for brain reperfusion. The second step is anticoagulant or antiplatelet to prevent thrombus growth in collateral blood vessels. The third is a neuroprotectant treatment in order to ovoid expansion of neuroglia injury as a result of cytotoxic process[1].

Neuroprotectant commonly used is piracetam and citicoline, both single and combination[2]. Piracetam attempts to increase erythrocyte capability in blood vessels without causing neither transformation nor erythrocyte function. Therefore ischemic brain parenchyma

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will be recovered[3,4]. Citicoline attempts to increase the main component of cell membrane synthesis, phosphatidylcholine that is increasing neuronal cells membrane improvement[4,5].

Ischemic stroke can cause motoric dysfunction, including pareses or muscle weakness. The muscle strength test is used to evaluate muscle weakness. This test is used for patients who are suspected of neurologic abnormality, especially in stroke, head injury, spinal cord injury, and neuropathy. The scale of this test uses Medical Research Council Manual Muscle Testing Scale (MMTS) [6].

Based on previous studies, the evaluation of neuroprotectant effect in motoric function, cognitive, consciousness and activity daily living of stroke ischemic patients, that have been reviewed with NIHSS (National Institutes of Health Stroke Scale), GCS (Glasgow Coma Scale), Barthel Index and another score showed different result. Therefore, this study aimed to evaluate the effect of neuroprotectant treatment for motoric improvement used Medical Research Council Manual Muscle Testing Scale (MMTS) in acute ischemic stroke patients.

STUDY METHOD

This study was observational with case-control approach. The design of this study was retrospective by analyzing ischemic stroke patient medical records. This study used a medical record of ischemic stroke patients on the period January-September 2019. The total sample was 72 patients divided into two groups, control group, and treatment group, each of them was 36 patients. This study used patients who fit to exclusion and inclusion criteria. The inclusion criteria were ischemic (i) stroke patients who got first attack, (ii) diagnosed with < (-1) siriraj score, (iii) obtained standard antiplatelet therapy (aspilet 100 mg per-oral), (iv) strength muscles will be measured by MMTS (Manual Muscle Testing Scale) scale in a range 0-4 and was graded by comparing the left and right body side[6]. The patient's motoric strength was examined in *Musculus biseps brachii* and *Musculus quadriseps femoris.* The exclusion criteria were patients who had repetitive stroke profiles and being hospitalization less than 5 days.

In siriraj interpretation < (-1) score means ischemic and > 1 score means hemorrhagic stroke. Control group was given antiplatelet 100 mg/day for 5 days. While treatment group was given the combination of antiplatelet 100 mg/day and citicoline 500 mg/day for 5 days. The patient's motoric strength was examined using MMTS on the first and fifth day of therapy. Criteria for motoric improvement was increasing of MMTS score $\geq$ 1 score in one of the measured extremity muscles. Data collection and statistical analysis procedure used SPSS 25 version (with $p < 0.05$ means a significant result). Health Ethic Research Committee of Siti Khodijah Sepanjang Hospital has approved this study with a code number 024/KET-KEPK/XII-2019.

RESULTS

1. The Characteristic of Ischemic Stroke Patients in Siti Khodijah Sepanjang Hospital

Table 1 indicates that most of the ischemic stroke patients aged was 55-64 years (33,3%). Ischemic stroke patients were dominated by females. Hypertension and

SIRIRAJ SCORE			
(2,5 x consciousness) + (2 x vomit) + (2 x headache) + (0,1 x diastolic pressure) – (3 x atheroma) – 12 =			
	0	1	2
Consciousness	Aware	Sleepy, stupor	Semi-coma, coma
Vomit	No	Yes	
Headache in 2 hours	No	Yes	
Atheroma (diabetes mellitus, angina)	No	Yes	

diabetes mellitus were the risk factors of ischemic stroke. From 72 ischemic stroke patients, there were 56 (77,8%) patients who had hypertension, and more than half patients had diabetes mellitus.

Table 1 The Characteristic of Ischemic Stroke Patients

The Characteristic of Ischemic Stroke Patients		Frequency	Persentage
Age	33-44	7	9.7
	45-54	17	23.6
	55-64	24	33.3
	65-74	15	20.8
	>75	9	12.5
Gender	Female	43	59.7
	Male	29	40.3
Hipertension	Having hipertension profile	56	77.8
	Nothing hipertension profile	16	22.2
Diabetes mellitus	Having diabetes profile	39	54.2
	Nothing diabetes profile	33	45.8

2. Result of motoric capability on the first day and fifth day

Table 2 MMTS score of control group and treatment group on the first day of therapy

MMTS score	Control group				Treatment group			
	Superior dextra	Superior sinistra	Inferior dextra	Inferior sinistra	Superior dextra	Superior sinistra	Inferior dextra	Inferior sinistra
	N	N	N	N	N	N	N	N
1	0	3	0	3	1	1	1	1
%	0%	8.3%	0%	8.3%	2.8%	2.8%	2.8%	2.8%
2	3	5	3	5	3	5	3	5
%	8.3%	13.9%	8.3%	13.9%	8.3%	13.9%	8.3%	13.9%
3	2	3	2	3	1	2	2	2
%	5.6%	8.3%	5.6%	8.3%	2.8%	5.6%	5.6%	5.6%
4	17	12	17	12	20	17	19	17
%	47.2%	33.3%	47.2%	33.3%	55.6%	47.2%	52.8%	47.2%
5	14	13	14	13	11	11	11	11
%	38.9%	36.1%	38.9%	36.1%	30.6%	30.6%	30.6%	30.6%
N	36	36	36	36	36	36	36	36

Table 2 indicates that MMTS score of control group and treatment group at the first day therapy were not quite different.

Table 3 MMTS score of control group and treatment on fifth day of therapy

MMTS score	Control group				Case group			
	Superior dextra	Superior sinistra	Inferior dextra	Inferior sinistra	Superior dextra	Superior sinistra	Inferior dextra	Inferior sinistra
1	2	3	2	3	0	1	0	1

%	5.6%	8.3%	5.6%	8.3%	0%	2.8%	0%	2.8%
2	2	4	2	4	0	1	0	1
%	5.6%	11.1%	5.6%	11.1%	0%	2.8%	0%	2.8%
3	6	3	6	4	3	0	3	0
%	16.7%	8.3%	16.7%	11.1%	8.3%	0%	8.3%	0%
4	10	16	10	15	14	15	14	15
%	27.8%	44.4%	27.8%	41.7%	38.9%	41.7%	38.9%	41.7%
5	16	10	16	10	19	19	19	19
%	44.4%	27.8%	44.4%	27.8%	52.8%	52.8%	52.8%	52.8%
N	36	36	36	36	36	36	36	1

Tables 2 and 3 indicate that there are some changes in every score of control group. The number of patients in dextra superior extremity and dextra inferior escalated on score 5, 3 and 1. Score 5 from 38.9% becomes 44.4%, score 3, from 5.6% becomes 16.7% and score 1, from 0% becomes 5.6%. Score 2 and 4 have decreased, from 8.3% becomes 5.6% and score 4 from 47.2% becomes 27.8%.

The number of control group in sinistra superior extremity decreased on score 5 of 36.1% becomes 27.8%, and score 2 from 13.9% becomes 11.1%, while score 4 increased 33.3% becomes 44.4% and another score is constant. On sinistra inferior extremity, number of patients escalated on score 4 from 33.3% becomes 41.7%, and score 5 decreased from 36.1% becomes 27.8%.

Whereas, alteration score of treatment group indicates that the number of patients on dextra superior extremity and dextra inferior escalated on score 5 and 3. Score 5 escalated from 30.6% becomes 52.8%, score 3 escalated from 2.8% (dextra superior extremity) and 5.6% (dextra inferior extremity) becomes 8.3%. Score 4 deflated 16.7% (dextra superior extremity) and 13.9% (dextra inferior extremity). Score 1 and 2 deflated become 0%.

Number of patients on sinistra inferior and sinistra superior extremity were escalated. Score 5 from 30.6% becomes 52.8%, while score 2, 3 and 4 deflated 11.1%, 5.6% and 5.5%, respectively. While score 1 is constant 2.8%.

Table 4 Median of control group and treatment group on first day and fifth day

Group	Extremity	First median	Final median	N	*p*
Control group	Superior dextra	4	4	36	0,256
	Superior sinistra	4	4	36	0,768
	Inferior dextra	4	4	36	0,256
	Inferior sinistra	4	4	36	0,572
Treatment group	Superior dextra	4	5	36	0,01
	Superior sinistra	4	5	36	0,01
	Inferior dextra	4	5	36	0,01
	Inferior sinistra	4	5	36	0,01

Table 4 indicates that control group is in same median on first day and fifth day. It can be seen from significant result by alfa wilcoxon test that > 0,05. While in treatment group, there was increasing median from 4 to 5. After wilcoxon test was done, derived alfa 0.01 ($p<0.05$) can be concluded that there is a significant motoric improvement in a treatment group.

3. Correlation of Citicolin Treatment with Motoric Improvement Based on MMTS

Table 5 Quantity of ischemic stroke sample in Siti Khodijah Sepanjang Hospital

Group	Motoric improvement				Total		*p**	*p***
	Good		Not good					
	N		N		N			
Treatment group	23	31.9%	13	18%	36	50%	0.000	0.434
Control group	6	8.3%	30	41.6%	36	50%		

*: chi-square test

**: contingency coefficient test

Table 5 indicates that ischemic stroke patients experience motoric improvement on treatment group are 23 patients (63.8%), while patients who do not experience motoric improvement are 13 patients (36.2%). And ischemic stroke patients who experienced motoric improvement on control group are 6 patients (16.6%) and patients who do not experience motoric improvement are 43 patients (58.9%).

The result of the chi-square test indicates that citicoline treatment in ischemic stroke patients with motoric improvement based on MMTS has a significance result amount of 0.000 (p<0.05). This result indicates that there is a significant effect from citicoline treatment in motoric improvement patients. The contingency coefficient test was effectuated to evaluate the correlation between of citicoline and motoric improvement; the result was found that p=0.434 positive. It can be concluded that motoric improvement by citicoline treatment in ischemic stroke patients has an effective amount of 0.434, it means the effect is moderate.

DISCUSSION

Ischemic stroke is the dynamic process whereby the occlusion of the brain blood vessel can cause large infarct, so the goal of treatment is to re-open the occlusion and to stop the sequence of neuron cell injury. Ischemic stroke can cause impairment motoric and cognitive function. This study revealed that ischemic stroke attacks more on females rather than males. This happened due to the fact that every human has a different condition. The risk ischemic stroke can be reduced by healthful lifestyle such as minimize greasy food, eating more fruits, and quit smoking that glucose is well controlled. This study is in line with a previous study that showed stroke patients on female was 54,17%, whereas male was 45,81%[7].

Hypertension and Diabetes Mellitus are the risk factors for stroke ischemic. This study revealed that most patients had hypertension. This study is in line with previous studies that showed from 60 ischemic stroke patients, 44 patients had hypertension (73,33%)[7]. Hypertension causes lesion on tunica intima endothelial's blood vessels that disturb a real function of blood vessels, anti-thrombosis. Hypertension causes platelet aggregation or the clumping of platelet in the blood that triggers brain tissue hyperfusion[8].

Besides hypertension, most of the patients had diabetes mellitus. Diabetes mellitus can cause a lesion on tunica intima so it can cause platelet aggregation and ischemic due to blood vessel constriction. This study is related to a previous study in RSUD dr. Moerwardi in 2010, they showed that from 66 ischemic stroke patients, there were 47 (71,2%) patients who had diabetes mellitus[9].

Basically, ischemic stroke patients related to several factors that result in different outcomes according to the condition. The factors that influenced the outcomes of ischemic stroke are the patient's age, disease profile, lesion size in a brain, and GCS (Glasgow Coma Scale) during attack. Age is related to decreasing of neuronal regeneration process and decreasing

blood vessel elasticity. Likewise, another pathology condition such as hyperglycemia and hypertension, also have an effect on reducing neuron cell recovery[10]. The level of consciousness also affects ischemic stroke outcome. It has been proven from previous study that showed stroke patients who had low consciousness with GCS<11 had poor functional improvement than GCS >11[11].

This study was accomplished by analyzing ischemic stroke patient medical records who given citicoline treatment provided per-oral with 500 mg/day, which was provided for first five days of stroke attack. Citicoline is composed from two essential element of phospholipids; cytidine and coline. Citicolin attempts to increase the main component of cells membrane synthesis, phosphatidylcoline that increasing neuronal cells membrane improvement[4,5].

The data collection procedure was accomplished by citicoline treatment for five days due to the fact that most stroke patients used BPJS. BPJS only allowed provided citicoline therapy for five days for acute ischemic stroke patients during hospitalization. In addition, the effectivity of the first five-days citicoline treatment period is consistent with Ulfa's study (2017). Her study showed that there was a significant improvement in first until fifth-day therapy, while in the next days, there was insignificance improvement[12].

This study used citicoline treatment with 500 mg doses/day. This dosage is in line with Davalos *et al* study (2010) about oral citicoline dosage in an acute ischemic stroke. They studied different doses of oral citicoline for acute ischemic stroke patients; 500 mg/day, 1000 mg/day, and 2000 mg/day. The study showed that oral citicoline with 500 mg and 2000 mg doses/day gave significance improvement for acute ischemic stroke patients[13].

Patients in a treatment group had a significant motoric improvement rather than in the control group. This study result is in line with Taufiqurrahman and Merry's case report (2016) about the benefit of citicoline in non-hemorrhagic stroke patients. They reported that the patient firstly came with complaining about facial paralysis and dropped in the right side of the body, GCS 456, 3/5 superior dextra or sinistra extremity by MMTS examination, 3/5 dextra sinistra inferior extremity by MMTS examination and scored 9 by NIHSS (National Institutes of Health Stroke Scale) examination. After that, 500 mg/day of citicoline and aspilet were provided. In the third day, the patient had 4/5 MMTS score and began to speak slowly. Therapy continued until the sixth day, and the result is patients can talk as good as usual and got 5/5 for muscle strength score, and also 2 for NIHSS[14].

This study found out that patients with 500 mg/day citicoline treatment for five days have significant motoric improvement as big as muscles examined, *Musculus biseps brachii and Musculus quadriseps femoris*. Citicoline has several stages of therapy effect in acute ischemic stroke. First, it stabilizes cell membranes by increasing phosphatidylcholine and sphingomyelin synthesis[15]. Citicoline inhibits the release of free fatty acids and glutamate during ischemia[16]. Citicoline can decrease the free radical and delayed the ischemic brain injury process[17]. It can also increase synaptic outgrowth and neuroplasticity[18]. These several mechanisms of citicoline can allow the improvement of motoric functional in ischemic stroke patients. However, the researcher realizes that this study needs more, larger sample and long term periods. The direct research to patients and the same examiner can increase validity and minimize valuation subjectivities in MMTS scoring.

CONCLUSION

This study showed citicoline gives benefits for ischemic stroke patients. There is a significant motoric improvement in ischemic stroke patients with treatment by citicoline 500 mg/day for 5 days. Further studies required to prove the effectivity of citicoline for the long term period.

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ORIGINAL ARTICLE

SIT TO STAND TEST OSTEOARTHRITIS PATIENTS

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ABSTRACT

Osteoarthritis (OA) is a degenerative disease found in the elderly. The prevalence of total osteoarthritis OA in Indonesia was 34.3 million in 2002 and reached 36.5 million in 2007. It is estimated that 40% of the population above 70 years old will suffer from OA. Moreover, about 80% of the A patients have limitations in mobility, which in degrees from mild to severe. It leads to a reduction in the quality of life. The development of a simple approach to quantitatively estimating the functional motor performance of various age is crucial to detect the locomotive syndrome (LS) earlier. One available method is the sitting to stand test (STST). Up to recently there a lack of studies that conduct the STST in Indonesia. This study aims to investigate the average and the cut off of the STST scores in OA patients at Ahmad Yani Hospital, Surabaya. We used secondary data, from medical records of the rehabilitation outpatient clinic in 2019 from August to September. We obtain the time of five repetion sit to stand. Then using SPSS 21.0 for analizing the data. The results indicate that the mean and standard deviation of STST scores in osteoathritis patients is 15.72 + 3.45. STST data based on age and its determinants is needed for further research

INTRODUCTION

The Central Statistics Agency predicts the number of population aged 65 years and over in 2010-2035 rose from 5.0 percent to 10.6 percent. This changed in structure resulted in a dependency ratio decreasing from 50.5 percent in 2010 to 47.3 percent in 2035. The decrease in the dependency ratio shows the reduced economic burden for the productive age population (working age) which bears the unproductive age population. These findings will automatically affect the health burden because age is a risk factor that is very closely related to degenerative diseases[1].

Osteoarthritis is a degenerative disease that found specifically in the elderly. According to the World Health Organization (WHO) in 2004, it is known that osteoarthritis affects 151 million people worldwide and reaches 24 million in Southeast Asia. The prevalence of total osteoarthritis in Indonesia was 34.3 million in 2002 and reached 36.5 million in 2007. It is estimated that 40% of the population above 70 years old suffer from osteoarthritis, and 80% of osteoarthritis patients have limited mobility in various degrees from mild to severe which results in reducing the quality of life due to a fairly high prevalence[2]. Primary / generalized osteoarthritis can attack the joints, knees, and hands especially the distal interphalangeal joint (DIP) and proximal interphalangeal (PIP)[3]. This disease causes pain and disability in patients therefore it interferes with daily activities.

One of the conservative treatments for knee osteoarthritis is exercise therapy to improve performance, improving function, increasing local muscle strength and

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endurance, increasing muscle relaxation ability properly, increasing general fitness, all of which play a role in functional capacity. Static or dynamic strengthening exercises can maintain or increase the strength of the periarticular muscles to improve or prevent biomechanical abnormalities and their contribution to joint dysfunction and degeneration. The development of a simple approach to quantitatively estimating the performance of functional motors in various ages is very important for early detection of the locomotive syndrome (LS), one of which is the sit to stand test (STST).

The STST is conducted by arms folded on the chest, participants rise from their chairs and return to a sitting position as quickly as possible. The time to complete five reps is recorded for two separate experiments, with an interval of 1 minute between each trial. STST results or time scores will be very useful for determining the functional status of individual motors as well as for assessing fall risk. In the Mong study (2010), a score of 8.9 + 0.7 was obtained in the young group and 10.8 + 1.7 in the control group (healthy elderly). Whereas in other literature states that the higher the STST score can increase the risk of falling. Based on Buatois, et al., 2008, the cut-off point from the STST score is 15 seconds. A score of 12-15 seconds needs to be reassessed to assess the risk of falling. Until recently, there is a lack of studies that discuss STST in Indonesia, therefore the cut-off point and the average time may need to be determined. There may be different results that can be influenced by differences in culture, demographics, activities, or treatment regimens. Based on the problem above, research is needed to find out what the average STS Test score is, especially in osteoarthritis sufferers in Indonesia.

METHODS

This research is a cross-sectional study by observing STST in the Medical Records of patients at the Medical Rehabilitation outpatient clinic, Ahmad Yani Hospital in Surabaya. This study was done in August-September 2019. Sampling using the accidental sampling method that met the inclusion criteria. The inclusion criteria in this study were that respondents were OA sufferers who were diagnosed clinically by the in charged physician and the results of supporting data, and was tested for STST (had STST data on medical records). The exclusion criteria were: respondents were suffering from physical disabilities or mental disorders during the examination. The measured variable is the STST Score, with the condition that the STST score is the time between sitting to stand for 5x as measured in seconds using a chair and stopwatch. The method of data collection is done by recording the patient's time in completing five sitting repetitions with arms folded on the chest-the participant rises from the chair and returns to the sitting position as quickly as possible. Data analysis was performed using descriptive statistic in SPSS 17.0 program, and kolmogorov- smirnov to test the normality.

RESULTS

There were 44 samples met the inclusion criteria. The characteristics of the samples are provided in Table 1. It can be seen that the distribution of samples in terms of age is evenly distributed between the ages of 50-79 years with the age group 60-69 years dominating (38.6%). The average age is 63.61 years (Table 1) Furthermore, the number of female samples (86.4%) is higher than the male (13.6%). More than half had low back pain (LBP) with OA (52.35), then followed by people with OA as much as 36.4% (Table 1). The patient duration of illness or length of illness samples ranged in the range of 1-5 years (79.5%). Table 1 shows that the average length of illness from 44 samples is 2.2 years with a standard deviation of 1.912.

Table 1 Sample Characteristics

		Frequency (n=44)	Persentage
Age	40-49	1	2.3
	50-59	15	34.1
	60-69	17	38.6
	70-79	10	22.7
	80-89	1	2.3
Gender	Men	6	13.6
	Women	38	86.4
Diagnosis	OA	16	36.4
	LBP	5	11.4
	LBP with OA	23	52.3
Duration of sick	< 1 year	8	18.2
	1-5 year	35	79.5
	>5 year	1	2.3
Shalah (Prayer) position	Normal	25	56.8
	Sitting	17	38.6
	Sitting prostration	2	4.5

From the SPSS statistical test results (Table 2), the minimum value of the STST score is 8.32 seconds, a maximum of 26.24 seconds. The average score is 15.61 seconds with a standard deviation of 3.61 seconds. Furthermore, the data was tested for normality with Kolmogorov-Smirnov, so that the p value was 0.200 (> 0.05) which means that the data was normally distributed

Tabel 2 Descriptive Statistics

	Frequency	Minimum Value	Maximum Value	Mean Value
STS Test	44	8.32	26.24	15.72

DISCUSSION

Osteoarthritis is a disease that is found specifically in the elderly or often called degenerative disease. It is estimated that 40% of the population above 70 years of age suffer from osteoarthritis, and 80% of osteoarthritis patients have limited mobility in various degrees from mild to severe resulting in reduced quality of life due to a fairly high prevalence[2]. This disease causes pain and disability in patients so that it interferes with daily activities.

This is in line with the results of our study which showed that the 60-69 year age group dominated the sample (38.6%). Whereas in the 70-79 age group ranks third with 22.7%. Then it was also seen that 43.1% of the samples had experienced disturbances when doing daily activities, namely prayer. As many as 4.5% of patients could not bow down and then changed into a sitting position, and 38.6%

of patients could only pray by sitting. The average of Visual Analog Scale (VAS) n this study was 6.4 ± 1.66. The highest proportion of VAS scores is 7 (31.8%.) The possibility of this value that causes movement limitations in patients so that interferes with daily activities.

In this study, the STST average value was slightly higher than the other studies, which was 15.7 seconds. In a study conducted by Buatois, et al., 2008, the cut-off point from the STST score was 15 seconds which was a difference of 0.7 seconds longer. In a study conducted by Mong[4], a score of 8.9 + 0.7 was found in the young group and 10.8 + 1.7 in the control group (healthy elderly) where there was a difference of 6.8 seconds longer in the young group and 4.9 seconds longer in the group control (healthy elderly). The literature also states that the STS Test score is influenced by age. The older the age, the higher the score. In the Bohannon[6] metaanalysis the STS Test scores are classified. If the study was dominated by the 60-69 year age, the normal STS Test score will be 11.4 seconds. This score is far below the result study. However, in this study, the STST scores were not categorized based on age. Therefore need further research to confirm.

CONCLUSION

The results of this study indicate that the average of STST scores in Osteoathritis patients at Ahmad Yani Hospital, Surabaya is 15.72±3,45. This score is higher than the other study. It means that there is possibility that OA patient here has worse quality of life

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CASE REPORTS

CONSERVATIVE CARE COST ANALYSIS OF PATIENTS OF LONG BONE FRACTURE IN EMERGENCY ROOM. A REVIEW TO SEE THE SUFFICIENCY OF HEALTH INSURANCE COSTS

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ABSTRACT

Introduction: Long bones are bones that include the humerus, radius, ulna, femur, tibia and fibula. Aside from fibula, the main function of long bones is supporting weight and facilitate movement. Therefore, fracture in the long bone will cause liited movement or even loss. Long bone fracture is still a global problem because the number of events is quite large. This is in line with the increase in socioeconomic status and the incidence of traffic accidents which is one of the causes of fractures. **Method:** This is a Prospective study to determine the magnitude of the cost of treatment conservatively in cases of long bone fractures in RSUD dr. Soetomo. The study design used was a prospective cohort. The sample size used in this study was determined by consecutive sampling, ie patients who met the inclusion criteria in the period May - August 2017. **Results:** From the observations for four months from May 2017 - August 2017 at Emergency Room Soetomo General Hospital, we found 77 patients with long bone fractures that were casted. Of these patients, 38 patients were placed in a slab and 39 patients were placed in a circular cast. Among the 39 people, 17 patients were excluded according to the exclusion criteria and 22 patients were included as the study sample according to the inclusion criteria. By using a statistical test using paired sample T test with a value of $\alpha = 0.05$, a significance of 0.025 was obtained. Because the significance value is $0.025 < 0.05$ (α). **Discussion:** From the results, there was a difference between the BPJS rate of installing circular cast and the real cost of installing circular cast on long bone fractures. In addition, we get that the average value of the BPJS rate is greater than the real cost value, which means we can conclude that the BPJS cost can cover the cost of conservative therapy in cases of long bone fractures. **Conclusion:** In the economic aspect, the longer stay means higher costs that must be paid by the patient (the payer) and accepted by the hospital. This only applies to real tariffs, whereas to INACBG's long or short length of stay does not affect the cost.

INTRODUCTION

Long bones is a main framework for movement. Fracture of long bone can limited movement. The occurrence of long bone fracture is still a global problem because the number of events is quite large. This is in line with the increase in socioeconomic status and the incidence of traffic accidents which is one of the causes of fractures [1].

Long bone fractures mainly result from significant trauma. Data shows incidence of long bone fractures is 21 fractures per 1000 people per year in United States, men is higher than women. Similar data also reported in Norway and United Kingdom[2]. Approxi-

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mately, 2109 patients seeking ED to Orthopedics and Traumatology at the Soetomo General Hospital itself, in 2016, about 360 (17%) were patients with long bone fractures treated with conservative therapy[3.]

In every case of long fracture, it is necessary to choose the right therapy. In general, therapy for long bone fractures is divided into conservative (non-operative) and operative therapy. The costs between conservatively and operative therapy are quite different. James Heckman in 1997 showed that the cost of therapy in tibia fracture cases is 65% lower conservatively compared to operative therapy[4].

Recently, health financing model In Indonesia is mainly centered on BPJS (Social Security Organizing Agency) Health and health insurance. Funding with Health BPJS based on the INA-CBGs (Indonesia Case Base Groups) package makes it possible to carry out conservative treatment of long bone fractures comprehensively. In BPJS, the products covered are regulated by national formulary[5].

Therefore, to estimate adequacy of conservative therapy treatment costs for long bone fractures and its efficiency, this study focus on the costs incurred by the INA-CBG package and the amount the need for conservative therapy of patients with long bone fractures at dr. Soetomo General Hospital[3].

CASE(S)

From 22 patients included in inclusion criteria, there were 14 patients (65%) male and 8 female patients (35%). From these patients we get a number of cases with diagnoses of fractures in the upper limb, such as: closed fracture antebrachia, closed fracture distal radius, and Galeazzi fracture and closed fractures in the lower extremities such as: closed tibia fractures, calcaneus fractures, and metatarsal fractures. Most of them, we found most cases were fractures in the antebrachial section.

In antebrachial fractures, we do closed reduction management and immobilization using a long arm cast, while distal radius fracture, immobilization is done by placing a long arm cast. In lower extremities, most fractures ensue in tibia. It could be done conservatively that is closed reduction and immobilization with long leg cast, whereas metatarsal fracture, conservative management was performed under knee cast.

RESULTS

Afer four months observation, from May 2017 - August 2017 at Emergency Room Dr. Soetomo General Hospital, we found 77 patients with long bone fractures that were casted. Of these patients, 38 patients were placed in a slab, 39 patients were placed in a circular cast. Among 39 patients, 17 patients were excluded according to criteria and 22 patients were included as subject on this study. The cast installation was performed by PPDS Orthopedics and Traumatology Hospital Dr. Soetomo - Faculty of Medicine, Airlangga University who has received casting academy training.

Table 1. Sample distribution based on age

Group age	Number	(%)
≤10 Years old	8	36,4
11-20 Years old	5	22,7
21-30 Years old	2	9,1
31-40 Years old	4	18,2
41-50 Years old	2	9,1
61-70 Years old	1	4,5
Total	22	100,0

From data, it was found that the highest incidence of closed fractures occurred in the range of first and second life periods. Children run into dramatic change in motoric development so as they tend to fall like from furniture or stairs. Meanwhile, in second decade of life, the trauma mechanism mainly occurs during outdoor activities. This is almost in line with study conducted by Hedstrom EM et all in 2010 in Sweden[6].

Table 2. Sample Distribution based on gender

No	Genders	Total	(%)
	Men	14	63.7
	Women	8	26.3
	Total	22	100

From table 2, the highest incidence of closed fractures is found in men twice than women. It caused by trauma, especially trauma due to traffic accidents, workplace accidents and activities/ sports.

Table 3. Sample Distribution based on Conservative treatment

Conservative Treatment	Total	%
Long arm cast	8	36
Below elbow cast	1	4
Long leg cast	3	13
Below knee cast	3	13
Long arm cast dengan general anesthesia	6	27
Long arm cast + below knee cast	1	4
Total	22	100

Based from table 3, it was found that the incidence of fractures is more common in the upper limb than the lower limb

Table 4. Distribution of Average Comparison of Real Cost Rates and BPJS Rates

Conservative Treatmnet	Total	Average of Real Cost	BPJS Insurace Cost
Long arm cast	8	Rp. 548.750	Rp. 579.700
Below elbow cast	1	Rp. 641.000	Rp. 579.700
Long leg cast	3	Rp. 411.666	Rp..579.700
Below knee cast	3	Rp. 641.000	Rp. 579.700
Long arm cast dengan general anesthesia	6	Rp. 5.605.333	5.724.600
Long arm cast + below knee cast	1	Rp. 821000	Rp. 579.700

DISCUSSION

By using a statistical test using paired sample T test with a value of $\alpha = 0.05$, a significance of 0.025 was obtained. Because the significance value is $0.025 < 0.05$ (α), it can be concluded that Ho is rejected, which means there is a difference between the BPJS and real cost of installing circular cast on long bone fractures. In addition, average value of BPJS rate is greater than real cost value. It means that the BPJS cost can cover cost of conservative therapy in cases of long bone fractures. This happens because in patients who are treated conservatively do not require a long treatment time.

According to Cleverly (1997), one way that costs for a package payment system (Cased Base Groups) can be reduced by reducing patient length of stay (Cleverley, 1997). Meanwhile Sudra (2009) reported, from medical aspect the longer patient stay at hospital, quality of medical performance is declining because the patient must be treated longer (longer recovery). Conversely, the quality of medical performance is good in case patients treated in shorter period [7]. From economic aspect, the longer the length of stay means the higher the costs that must be paid by the patient (the payer) and accepted by the hospital. This only applies to the real tariff, whereas the tariff of INACBG's long or short length of stay does not affect the cost [8].

The results of this study are almost in line with study conducted at Kalisat Hospital Jember in January - June 2015 in which there was a statistically significant difference between real cost rate and INA-CBG package rates on the payment of diabetes mellitus patient claims. In this case a lower real cost rate is obtained[9].

However, different results were obtained in study conducted at RSUD dr. Achmad Mochtar Bukittinggi in January to December 2016. In this study, the difference in negative rates that illustrates hospital rates is greater than the payment of INA-CBG rates.

Negative rate difference is found in surgical cases involving operative medical measures [10].

Weaknesses of this study involve: period is too short, only 4 months (May to August 2017), so that the number of cases obtained is relatively low. Then further study is needed to assess especially in terms of patient satisfaction and operator satisfaction. In addition, this study also received funding from sponsors in accordance with agreed cooperation.

CONCLUSION

Conservative therapy with circular cast for closed bones with long bones is still one of the main choices today, especially in children. The current health cost financing model mainly uses BPJS based on the INA-CBGs package. The rate of the INA-CBG package is greater than the real cost rate for patients with closed fractures that are treated conservatively in Emergency Room Dr. Soetomo General Hospital.

Further research is needed to review more deeply about conservative therapy in the treatment of closed fractures, especially in terms patient satisfaction as well as from operator or doctor's point of view.

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CASE REPORTS

LONG TERM EVALUATION OF RADIOGRAPHICALLY UNDETECTED ACUTE OSTEOMYELITIS RESULTING CHRONIC OSTEOMYELITIS WITH MRSA

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ABSTRACT

Osteomyelitis is an infection and inflammation of the bone that may spread into all parts of the bone. Methicillin-resistant Staphylococcus aureus or MRSA complicates the management of diseases, 28% of hospitals in Indonesia are suspected to be MRSA endemic. Osteomyelitis combined with MRSA have obscured prognosis knowing its assessment and management are still being developed. Presenting a case of Chronic Osteomyelitis and MRSA of an 11-year old girl that had been monitored for 5 years after the reported onset in July 2015. The patient complained of severe pain in the left hip region causing her to stop using her left limb in July 2015. Signs of acute osteomyelitis couldn't be confirmed by sequential assessments of X-Ray and USG examination. Cefazolin and Gentamicin injections were administered for 23 days. The family requested the patient to be discharged, claiming they were unable to see significant clinical improvement. Intravenous of antibiotic regimens were changed into oral regimens, consisting; Co-Amoxiclav and Gentamicin. The patient was never present for routine check-up, her family conceded that they went to traditional alternative medication and stated the patient's clinical outcomes were showing signs of improvement; in which the patient was able to walk normally. 6 months after, the patient's mother observed abnormal gait, however the patient didn't mention nor complain of anything. Furthermore, an X-ray assessment was performed, with the result of the entire left femoral head being reportedly destroyed. In January 2016 the patient was referred to Dr.Soetomo Hospital, then diagnosed with chronic osteomyelitis and pathological fracture of 1/3 proximal left femur with a suspicion of avascular necrosis. The patient was given prophylactic antibiotics. Closed biopsy couldn't be performed, hence open biopsy was suggested. The patient had routine check-ups to monitor the disease progression, alongside radiologic assessment and laboratory assessments prior to the surgery. Episodes of localised swelling and tenderness in the hip area were present. Scenes of seropurulent discharges were additionally reported. In june 2017 patients had surgical debridement and sequestrectomy in addition to an open biopsy, where MRSA was diagnosed. No antibiotics had been given after the surgery and had routine wash with Chlorhexidine Gluconate 4%. Currently, the patient still undergoes routine check-ups at the outpatient facility, as radiologic and laboratory examination are routinely observed. As of now, the patient has no issue in its daily living activities. However, there is still limited range of movement at the infected site, with 90 degree of hip flexion and constrained internal rotation. A lower limb length discrepancy is present due to local growth aggravation at the left hip. The patient wears a lift modified shoe on her left leg. In any case, there has not been any complaints of pain, swollen or seropurulent releases throughout the last 18 months

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INTRODUCTION

Osteomyelitis is a bone infection that grows from trabecular areas of the bone. This infection could also invade the bone marrow, bone cortex, periosteum and surrounding tissues[1].

Approximately 75% of osteomyelitis is caused by gram-positive *Staphylococcus* that arise from blood vessels or from adjascent soft tissues. In facts, although the most common bacteria causes osteomyelitis are *S. aureus* and *S.epidermidis*, bone biopsy remains the Gold Standard for starting treatment. Biopsy may determine the most sensitive antibiotics, besides to detect MRSA (*Methicillin Resistant Staphylococcus aureus*) or MRSE (*Methicillin Resistant Staphylococcus epidermidis*) as early as possible to eliminate further complication[2].

Some areas have shown higher incidence of antibiotic resistance for osteomyelitis, especially in Asia. Lack of antibiotics regulations have resulted in an increased number of antibiotics abuse, leading to greater transmission and antibiotics resistance. As a result, some Asian countries have one of the highest prevalence of MRSA incidence, it is common for hospitals in Asia to be MRSA endemic. In early 2010s, the estimation of hospitals with MRSA endemic were 28% in Indonesia and Hong Kong and >t-;' 70% in South Korea[3].

In 2016 a research from Dr. Soetomo Academic General Hospital Surabaya -- teaching hospital in Indonesia, showed 8% of all surgery patients suffered from MRSA (including the inpatients). From the results, there is a continuous increase of numbers of MRSA patients within Hospitals in Indonesia[4].

Children with acute osteomyelitis in developing countries often came too late to be treated, due to lack of awareness and proper medical facilities. Not only chronic osteomyelitis that had worsened with multiple antibiotics resistance reported, but also it is also hard to differentiate between osteomyelitis and malignancies. This issue causes chronic osteomyelitis in developing countries to be the main factor of musculoskeletal disabilities and morbidities [5,6].

CASE REPORT

We present a case of chronic osteomyelitis and MRSA of an 11-year-old girl, this patient had been monitored for the last 5 years after the reported onset since July 2015. The patient monitored routinely, routine physical examination and radiologic examination on her left hip region to assesed patient's improvement.

The patient complained of severe pain and continuous pain in the left hip region causing her to stop using her left limb in July 2015. It is reported the patient did not want her left hip region to be touched because it would escalate the pain resulting limited range of movement. The pain decreased when she didn't move her left hip. She had felt this complaint for approximately 1 week. Slight fever also reported. The patient was finally brought to the hospital, physical examination and radiological examination were performed. Signs of acute osteomyelitis couldn't be confirmed from X-Ray and USG examinations (figure 1a and 1b). Patient then referred as an inpatient. Cefazolin and Gentamicin injections were administered for 23 days and her left hip joint movement was limited. After her first week in the hospital, repeated radiologic and USG examinations performed, however signs of acute osteomyelitis couldn't be confirmed from the sequential assessments (figure 1c and 1d). MRI examination was not an option considering the patient's background.

(a)

(b)

(c)

(d)

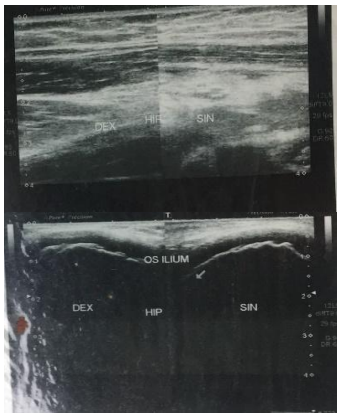

Figure 1. (a and b) First radiological examination, signs of acute osteomyelitis couldn't be confirmed; (c and d) sequential assessments with radiological and USG examination, signs of acute osteomyelitis couldn't be confirmed yet.

The family requested the patient to be discharged, claiming they were unable to see significant clinical improvement. Intravenous antibiotic regimens were changed into oral regimens, consisting; Co-Amoxiclav and Gentamicin. The patient was never present for routine check-up, her family conceded that they went to traditional alternative medication and stated the patient's clinical outcomes were showing signs of improvement; in which the patient was able to walk normally.

Six months later, the patient's mother observed abnormal gait, however the patient didn't mention nor complaint of anything. The patient also reported having difficulties in her P.E. class, limited range of movement in her left hip, especially when squatting. Patient did not complaint about pain, swelling and fever. An X-ray assessment was performed, with the result of the entire left femoral head being reportedly destroyed. In January 2016 the patient was referred to Dr.Soetomo General Hospital, where the patient was then diagnosed with chronic osteomyelitis and pathological fracture of 1/3 proximal left femur with a suspicion of avascular necrosis. (figure 2)

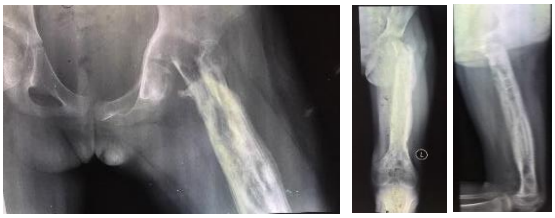

Figure 2 Left femoral head destruction present, accompanied by the sequester and involucrum on the left femur with solid periosteal reaction. Femoral head deformity present. From these images, concluded that the patient had osteomyelitis and a pathological fracture of 1/3 proximal left femur with a suspicion of avascular necrosis on the left femoral head.

The patient was given prophylactics antibiotics. Closed biopsy couldn't be performed, hence open biopsy was suggested. The patient had routine check-ups to monitor the disease progression, alongside radiologic assessment and laboratory assessments prior to the surgery. Episodes of localised swelling and tenderness in the hip area were present. Scenes of seropurulent discharges were additionally reported. Closed biopsy couldn't be performed hence open biopsy was suggested.

In june 2017 patients had surgical debridement and sequestrectomy in addition to an open biopsy, where MRSA was diagnosed. No antibiotics had been given after the surgery and had routine wash with Chlorhexidine Gluconate 4%. Currently, the patient still undergoes monthly check-ups at the outpatient facility for the next 1,5 years, radiologic and laboratory examinations were routinely observed.

RESULTS

As per 19th January 2020, the patient no longer had any issues in its daily living activities. In any case, there had been no complaint of pain, swelling or seropurulent discharges throughout the last 18 months.

There is still limited range of movement at the infected site, with 90 degree hip flexion

and constrained internal rotation, however, according to them these complaints do not really affect her daily activities

A lower limb leg-length discrepancy is present due to local growth aggravation at the left hip. The patient wears a lift modified shoe (orthotic) on her left leg. The patient had already replaced her orthotic once. (figure3)

(a)

(b)

(c)

Figure 3 (a) Limited range of movement is present on her left hip, with 90 degree of hip flexion at best (b) A leg-length discrepancy is present (c) The patient wears a lift modified shoe on her left leg (orthotic).

From the latest radiological examination (Figure 4) Bone trabeculation outside of the lesion, joint gap and the joint surface appeared well. Lucency on distal third of the left femur could be interpreted as a representation of an active lesion.

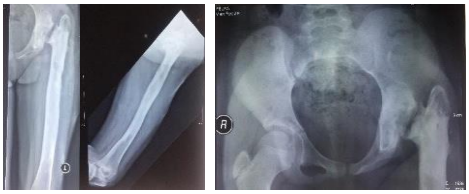

Figure 4 Latest radiological examination

DISCUSSION

There are two hypotheses that are able to explain the pathophysiological findings on children with osteomyelitis, that are Inside Outside Theory and Outside Inside Theory. The focus on Inside Outside theory is the inability of children's immunity to suppress the process of inflammation, and the intramedullary pressure causing sinuses and capillaries suppression which would cause bone infarction. Outside Inside Theory focuses more on the pathogen invasion abilities to enter periosteum causing periosteal abscess, eventually damaging the bone structure[7].

The pathophysiology, radiological description and its classifications are complex due to its connection with multiple factors; such as patient's age, duration, route of infection, immunity and patient's vascular condition on the infected site[6].

Differences in mode of infection, intraosseous vascular anatomy and subperiosteal abscess formation in children caused different clinical manifestations compared to adults. In paediatrics patients, long bones such as tibia and femur are the most common site of infection, whereas on adult patients, axial structures are the most common site. Femur (36%), tibia (33%), humerus (10%) and pelvis (2,8%) are the most common site of infection[,8,9].

Routes of infections are also varied. In children, hematogenous routes are more common[9]. Hematogenous osteomyelitis in long bones frequently attacks the metaphysis, slowing down the blood flow on metaphysis (which is closed with the epiphysis) and directing the microbes deposition that eventually leading to focal infection. Focal infection triggers an inflammatory response that increases the medullary pressure. This pressure can compress cortex and periosteal blood vessels, resulting bone necrosis. Microbial factors also play an important role of the disease progression, Adhesins on *S. aureus* able to identify the molecular matrix that its main function is to connect the polysaccharide structures and have connections to fibronectin, fibrinogen, collagen and heparin which are the structures that maintained the bone matrix. *S. aureus* that is ingested by the osteoclast still could survive and might become more resistant to antibiotics[10]. Osteomyelitis that is essentially a bone marrow inflammation could develop to

osteonecrosis, bone destruction and septic arthritis, ending as a permanent disability[8].

Radiographic presentation of osteomyelitis depends on the clinical presentation and age of the patient[9]. Simple X-Ray imaging has low sensitivity and low specificity to detect acute osteomyelitis. 80% of patients that come at least 2 weeks after the onset will have normal radiographic presentation due to its incapability to detect the spreading infection in the bone tissue. Few osteomyelitis aspects that could be shown by simple x-ray are periosteal reactions, because of the increasing periosteal thickness; tissue swelling visible at least 2 week after the onset and the border between that differs thickness of the bone appears clearly with intraosseous abscess. But these features are not specific on osteomyelitis and could also be seen in stress fracture, bone tumour and tissue's infection. Therefore the radiological examination is possible to postpone for 10 to 14 days from the onset to confirm the diagnosis 8[,9,10].

Ultrasound examination is also limited because of its inability to examine the bone, bone marrow and competence of operator. This examination is decently accurate, fast and adequately effective to compare both extremities, but with its limitations, this examination is rarely used as a first line additional examination. In acute osteomyelitis this examination used mainly to observe the progressing infections in subperiosteal area because of the loosening on the tissue attachments at periosteum. Color Doppler is also able to identify tissue swelling with its ability to locate hyper vascularities around the bone. Ultrasound is also helpful to guide needle aspiration if tissue swelling is observed 7[,9,10]

Although with its limitations, simple x-ray is still the first line examination to confirm acute osteomyelitis and to exclude other diagnoses such as fractures. Simple X-Ray can also be used to observe disease's progression. Simple X-Ray is still recommended as a first step and Ultrasound Examination could performed if needed[,9,10]

The disease causing microbes also contributes to the clinical presentation and the severity of the osteomyelitis. *S. aureus* caused 80% of osteomyelitis, where *methicillin sensitive Staphylococcus aureus* (MSSA) and *methicillin resistant Staphylococcus aureus* (MRSA) are also the two most common pathogens. Some forms of more aggressive osteomyelitis reported caused by MRSA/MSSA, it is known that these two pathogens contain genotype-300, pvl and fnbB that affect fibronectin where this polysaccharide associated with the binding force and severity of infection. Two previous studies in America showed increasing numbers of osteomyelitis incidents and more severe cases are associated with higher prevalence of MRSA and most of them are community acquired. Higher incidence of MRSA infection associated with extra-osseous events, increasing number surgical intervention and duration of hospitalization. At the same time, the more severe the infection contributes to longer duration of hospitalization. Where osteomyelitis is not treated adequately, chronic osteomyelitis could develop into osteonecrosis, intraosseous disruption and disruption of periosteal vascularization 7[,8,10].

CONCLUSION

Acute osteomyelitis is a clinical diagnosis. Simple X-Rays need to be routinely performed in inpatients, with an addition of Ultrasound Examination. Thorough and intensive education plays important role for the patient and patient's family to achieve comprehensive understanding of the disease. For some cases in which the diagnosis is not yet confirmed, complete and accurate treatments are supposed to prevent bone necrosis, later contributing to the formation of irreversible leg-length discrepancy and limited range of movement with the result that permanent limited daily functions.

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REVIEW ARTICLE

META-ANALYSIS : COMPARISON OF NEOVAGINA SUCCESS RATE WITH VECCHIETTI'S LAPAROSCOPIC METHOD AND DAVYDOV'S LAPAROSCOPIC METHOD IN MAYER-ROKITANSKY-KUSTER-HAUSER SYNDROME (MRKH) PATIENTS

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Mayer-Rokitansky-Kuster-Hauser Syndrome, Laparoscopic Davydov, Laparoscopic Vecchietti, Vaginal Length, FSFI Score

ABSTRACT

Background: Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKH) is caused by an embryological growth disorder of the mullerian duct. Laparoscopic Vecchietti and Davydov are laparoscopic surgery techniques that are often used for neovaginal surgery. **Objective:** This study aimed to compare the success rate of neovagina with the Vecchietti laparoscopic method and Davydov's laparoscopic method in patients with Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKH). **Methods**: A systematic data search was performed on a medical database (PUBMED, MEDLINE, Cochrane Database, Google Scholar). Inclusion criteria: (1) randomized study of the Vecchietti Laparoscopic Method with Davydov's Laparoscopy, (2) all inclusive papers can be accessed completely, and (3) the data obtained can be accurately analyzed. **Data acquisition and analysis**: We searched for a random blind study (RCT) with the following keywords: (1) Vecchietti Laparoscopy [title] AND (2) Davydov's Laparoscopy [title] AND Mayer-Rokitansky-Kuster-Hauser syndrome [title]. **Results**: Three RCTs comparing neovaginal success with the Vecchietti laparoscopic method and Davydov's laparoscopic method a total of 122 patients were analyzed. Average vaginal length (mean difference [MD] -0.70, and 95% [CI] -0.99 to -0.41 (P <0.00001), Average number of Female Sexual Function Index scores (mean difference [MD] -1.34, and 95% [CI] -1.71 through -0.96. (P <0.00001). **Conclusion:** This meta-analysis concludes that Davydov's Laparoscopic Method is better in terms of postoperative vaginal length and the Female Sexual Function Index Score

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INTRODUCTION

Mayer-Rokitansky-Ku¨ster-Hauser syndrome (MRKH) is an embryological growth disorder of the mullerian ductus which results in no uterine formation and/ or 2/3 of the vaginal area in women with normal secondary sex growth and normal karyotyping 46, XX. This syndrome is found 1 every 4500-5000 women [1].

Mayer-Rokitansky-Kuuster-Hauser syndrome (MRKH) consists of two types. Type 1 is MRKH type that does not form the uterus and vagina completely (Rokitansky sequence). Whereas Type 2 is a type of MRKH that does not form the uterus and vaginal perfectly and is accompanied by other malformations (MURCS association). Patients with MRKH syndrome usually present with complaints of never having menstruation with a physical examination showing normal secondary sex growth but a dead end vagina. Investigations can be done in the form of transabdominal ultrasound, MRI, or karyotyping. Transabdominal ultrasound and MRI are performed to evaluate the uterus, vagina and abnormalities in the urogenital

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tract. In karyotyping patients with MRKH syndrome, the phenotype XX is obtained. This is needed to distinguish between Androgen Insensitivity Syndrome [1,2].

Differential diagnosis of MRKH syndrome includes vaginal atresia, WNT 4 syndrome, Androgen Insensitivity Syndrome. The difference between MRKH syndrome and vaginal atresia is that the uterus and the upper part of the vagina are found, whereas in WNT 4 syndrome and Androgen Insensitivity Syndrome, there is testicular or masculized ovary and XY phenotype[3].

The major issue in these patients (MRKH) is vaginal agenesis, which affects sexuality and alters quality of life. Classic vaginal agenesis management is to create a cavity that allows satisfying painless penetrative intercourse. Vaginoplasty can be achieved either surgically or by progressive dilation of the vaginal dimple. Most surgical or nonsurgical techniques are reported to provide good anatomical and functional results of at least 70%.

The first management of MRKH syndrome patients is patient and family counseling about the patient's condition and plans for making neovagines for the patient's sexual needs. Making neovagina can use non-operative methods and operative methods. The non-operative method consists of the Frank method, a method with a vaginal dilatator. Operative methods include the Vechietti, Mc-Indoe, and Daydov methods[5].

Surgery is a choice for women who are unsuccessful with dilators or who prefer surgery and after a thorough discussion about advantages and disadvantages of various neovaginal techniques. It is very important for patients to realize that surgical procedures she still needs to use a vaginal dilator in the postoperative period to avoid stricture or stenosis. Classically, Vecchietti surgery is an abdominal procedure performed through a Pfannenstiel skin incision; However, it has been modified into the laparoscopic approach. There is limited data because this is a relatively new technique. Another laparoscopic approach is the adaptation of Davydov's procedure. The Davydov laparoscopic technique is a three-stage operation which includes dissection of the rectovesical space, mobilization of the peritoneal abdomen to make vaginal division, and adhesion of the peritoneum to the introitus.

New surgical methods have recently been developed in which laparoscopy has replaced traditional surgery. Because of it, this study analyzed which presents the most advantages.

We chance to compare the two techniques in terms of sexual satisfaction and effectiveness (vaginal length), which affects sexuality and alters quality of life in a relatively large cohort of patients with Rokitansky syndrome. This syndrome has been treated by a wide variety of techniques proposed for the creation of a neovagina, demonstrating that the inventiveness of the gynecologic surgeons is infinite, and that the ideal procedure still has to be found. Therefore, this study compares the only and we believe two techniques (with a laparoscopic approach) constitute a desirable combination of minimal invasiveness and good results, and can be considered in developing country especially in Indonesia.

METHODS

Data Search Strategy

A systematic literatures search were carried out using PUBMED, Google Scholar, and the Cochrane Central Register of Controlled Trials to obtain randomized randomized studies (RCTs) in the span of the year 2010 to 2020, using keywords: (1) Mayer-Rokitansky-Ku¨ster-Hauser; (2) Vecchietti Laparoscopy and Davydov Laparoscopy

Inclusion Criteria

The following criteria had been used in the selection: (1) randomized and observational randomized observations of the Vecchietti Laparoscopy and Davydov Laparoscopy in patients with Mayer-Rokitansky-Ku¨ster-Hauser (2) all inclusive

papers are completely accessible, and (3) all the data were obtained, can be analyzed accurately.

Study Quality Assessment

The authors independently assessed the validity of each study using the criteria stated in the Cochrane Handbook for Systematic Reviews of Interventions6. Each study was grouped and assessed according to quality categories: A, studies have a low risk of bias; B, studies have a high risk of bias, or C, studies have unclear risk (unclear risk of bias).

Data Extraction

Data extraction was carried out to obtain the objectives, objectives and research questions of this study. Clinical outcomes compared were expected vaginal length and patient FSFI score.

Statistical Analysis and Meta-Analysis

Meta-Analysis was compiled using Review Manager (RevMan) version 5.3. (Cochrane Collaboration, Oxford, UK). Mean difference (MD) is derived from averages and standard deviations and is used when results are reported using an identical scale. When the scale was used differently, standard MD (SMD) was calculated using RevMan. The confidence interval used is 95%.

RESULTS AND DISCUSSION

Study Selection

Searching data on PubMed and Google Scholar returned 538 articles. Screening based on the inclusion criteria described previously, a total of 3 articles were included for meta-analysis. The screening and selection process is illustrated using a study selection flowchart (Figure 1).

Study Characteristics

The characteristics that comparing intervention of the Vecchietti laparoscopic method and the Davydov laparoscopic method are summarized in table 1.

Number of Samples

Our study included three articles which included 122 patients with Mayer-Rokitansky-Ku¨ster-Hauser syndrome (MRKH) who made neovagina. A total of 59 patients underwent the Vecchietti laparoscopic methods and 63 Davydov's laparoscopic methods.

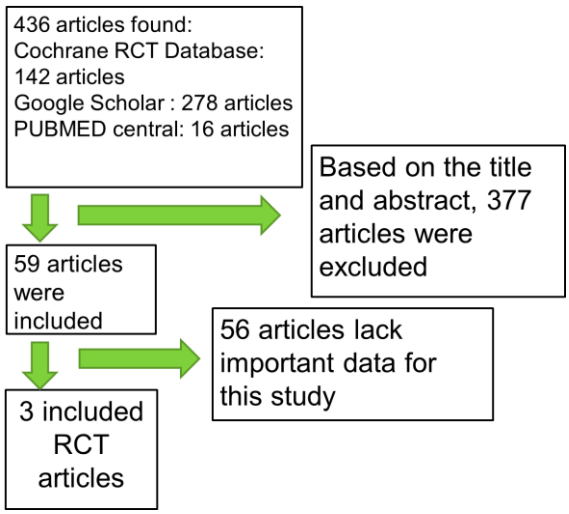

Figure 1. Study selection flowchart

Design study

All three studies from Alaa et al, Bianchi et al, and Dong X et al are retrospective cohorts.

Follow-up time

The three studies from Alaa et al, Bianchi et al, and Dong X et al were followed up for at least 1 year after neovaginal measures.

Risk of bias

We have explicitly assessed whether related studies have a high risk bias based on the criteria stated in the Handbook[6]. An assessment of the risk of bias from each study can be seen in Figures 2 and 3. Based on the assessments, it can be concluded that the related studies have a low risk bias.

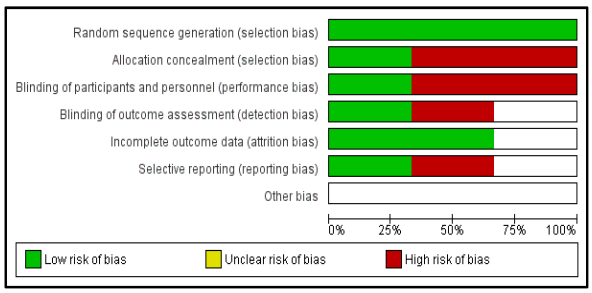

Figure 2. Conclusions from risk stratification bias in all articles in this meta-analysis.

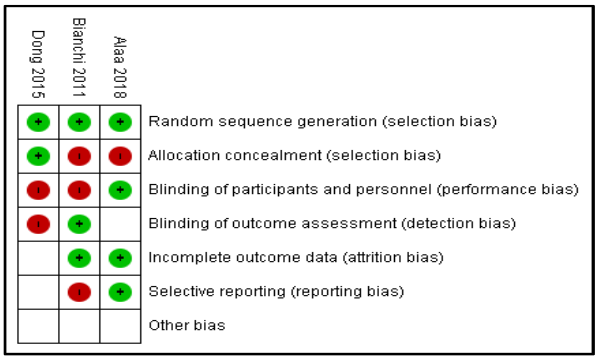

Figure 3. The risk assessment of the author's bias against each article involved.

The meta-analysis was compiled using Review Manager (RevMan) version 5.3. (Cochrane Collaboration, Oxford, UK). This paper assesses the comparison of neovagina success rates with the Vecchietti laparoscopic and Davydov laparoscopic methods by assessing vaginal length and FSFI score[6,7]. We use fixed-effects and random-effects Meta-analyzes for data combinations that can be logically assumed that several studies estimate the same therapeutic effect.

Strengths and limitations

The strength of our study was its methodology. We exclude other cases of vaginal agenesis, as MRKH syndrome, vaginal dimples may be different from those of complete androgen insensitivity syndrome patient in terms of embryologic development. Moreover, a 46, XY karyotype may have a significant impact on quality of life, independently from the absence of vagina. Study reported that vaginal aplasia had a higher psychological impact in MRKH syndrome patients. The accuracy of our results was supported by the use of validated quality of life questionnaires and the standardized pelvic exam performed by an independent evaluator.

Some limitations at the level of our review should also be highlighted. We pooled studies with, to a limited extent, heterogeneous stage and intervention methodology. In our studies, 122 patients were treated with laparoscopic surgery, 59 with Vecchietti's method and 63 with Davydov's method which cannot describe the actual results, so it can't be a base for recommendations. Future research and study is still needed, with a larger sample of patients.

Interpretation

Our results from comparing neovaginal success with the Vecchietti laparoscopic method and Davydov's laparoscopic method with a total of 122 patients were analyzed. From Davydov method average vaginal length 0,7 cm longer with range 0,41-0,99 cm (see Figure 4). This analysis shows, Davydov's laparoscopic method has a better success rate in terms of clinical outcome from the depth or length of the vagina than Vecchietti's laparoscopic method P <0.00001).

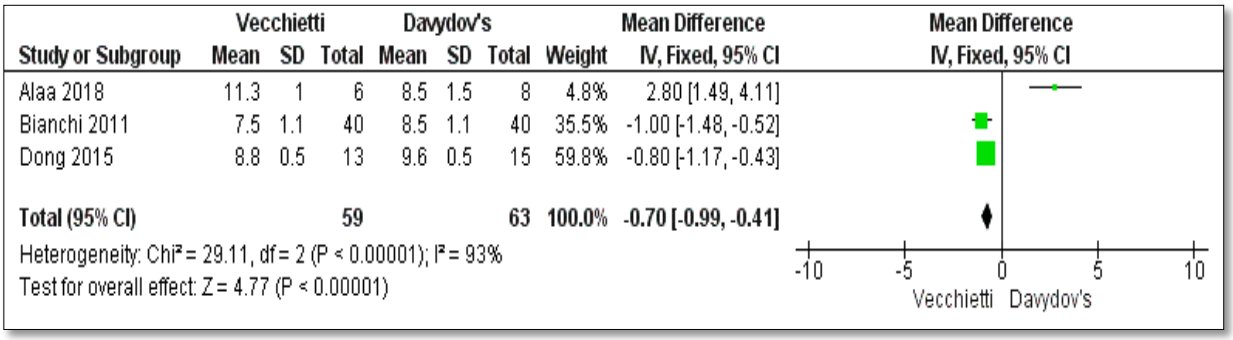

Figure 4. Forest plot showing a comparison of clinical outcomes for vaginal depth

Table 1. Study Characteristic

Reference	Year	Country	Study Design	Inclusion Criteria	Intervention	Outcome
Dong X, et al, 2015	2015	China	Retrospective Cohort Study	All women diagnosed with MRKH syndrome aged > 18 during January 2010 - December 2013	Neo-vaginal Method with Vecchietti Laparoscopy and Davydov Laparoscopy for Patients with MRKH Syndrome	Operation outcome, Vaginal length, sexual quality with FSFI standardization
Bianchi S et al, 2011	2011	Italy	Retrospective Cohort Study	Women with MRKH syndrome aged > 18 years who underwent neovagina procedures from October 2003 to August 2008.	Neo-vaginal methods with Vecchietti Laparoscopy and Davydov Laparoscopy for Patients with Vaginal Agenesis	Operation outcome, Vaginal length, sexual quality with FSFI standardization
Alaa, et al, 2018	2018	France	Retrospective Cohort Study	Patients included exclusively MRKH syndrome patients aged > 18 years, who began management of Agenesis Vagina from year 1995 until 2015. Evaluation by an independent and experienced single gynecologist	Comparing dilatation and surgical techniques in patients with vaginal agenesis in Mayer-Rokitansky-Ku-ster-Hauser syndrome, assessed in terms of quality of life, outcome of operations, and complications	WHO Quality of Life Instruments as well as FSFI and FSDI Scale (quality of sexual life) Group: dilation therapy, surgery and sexual Intercourse

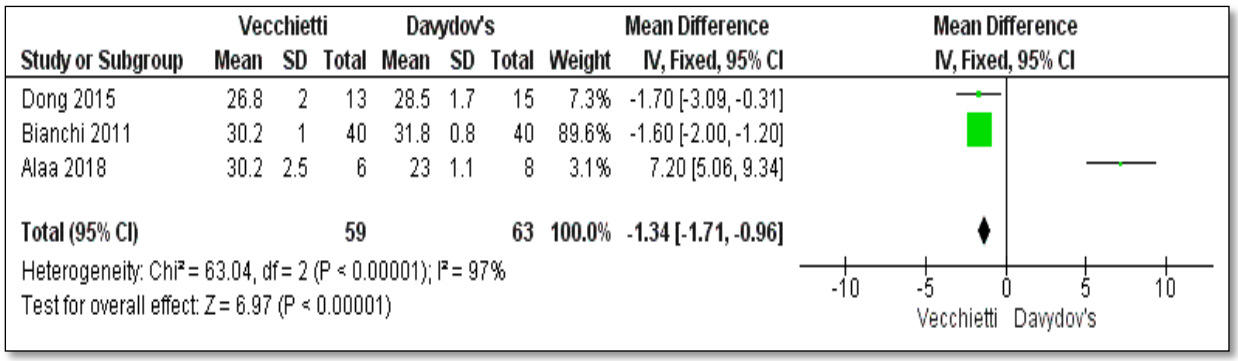

Figure 5. Forest plot showing the comparison of sexual satisfaction (FSFI score)

We obtained FSFI score results from total 122 patients, with 59 patients were treated by Vechhietti's laparoscopic method and Davydov's laparoscopic method in 63 patients. The Davydov's average number of Female Sexual Function Index score was 1,34 point better with range 0,96 – 1,71. Figure 5 shows Davydov's Laparoscopic method has a significant difference in patient sexual satisfaction in terms of FSFI score (P <0.00001).

SUMMARY

This sudy concludes that Davydov's Laparoscopic Method is better , in terms of postoperative vaginal length, and sexual satisfaction (Female Sexual Function Index – FSFI). Davydov's laparoscopic method can be considered as the therapeutic choice of laparoscopic surgery in MRKH patients. Although further research and study is still needed with a larger number of samples to be a recommendation for future therapy

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REVIEW ARTICLE

THE EFFECTIVENESS OF PRASTERONE VS PLACEBO THERAPY AS THE VULVOVAGINAL ATROPHY TREATMENT IN MENOPAUSAL WOMEN: META-ANALYSIS STUDY

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ABSTRACT

Background : Vulvovaginal atrophy is a condition that often occurs in menopausal women due to Estrogen decreased. Prasterone (DHEA) is a steroid hormone that can be converted into Estrogen in the target tissue**. Objective :** A Meta-analysis study was conducted to evaluate the effectiveness of administering Prasterone as Vulvovaginal Atrophy therapy in menopausal women, by evaluate the number of Superficial Cells, Parabasal Cells, vaginal pH, and Dyspareunia**. Methods :** A systematic data search was performed on a medical database (PUBMED, Google scholar, Cochrane). Inclusion criteria: (1) randomized study of Prasterone as Vulvovaginal Atrophy therapy in postmenopausal women, (2) all-inclusive papers can be accessed completely (from 583 articles found, we excluded 580 articles, the result is 3 RCT analyzed) and (3) the data obtained can be accurately analyzed**. Results:** Three RCTs with a total of 696 patients were analyzed. The average number of Superficial Cells (mean difference [MD] 7.63, and 95% [CI] 7.57 to 7.70 (P <0.00001). The average number of Parabasal Cells (mean difference [MD] -29.84, and 95% [CI] -30.25 to -29.44 (P <0.00001). The average number of vaginal pH (mean difference [MD] -0.69, and 95% [CI] -0.70 to -0.68 (P <0.00001). The average number of Dyspareunia (mean difference [MD] -0.38, and 95% [CI] -0.39 to -0.37 (P <0.00001). All diamonds do not intersect the vertical line, and have p <0.05, it proves that there are significant differences between the two groups. All non-hysterectomized women have an atrophic or inactive endometrium. Side effects that are often complained of are headache and application site discharge. **Conclusion** This meta-analysis concludes that Prasterone therapy has a significant therapeutic effect for Vulvovaginal Atrophy in menopausal women

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INTRODUCTION

The layers of vaginal walls consist of 4 layers, namely Basal cells, Parabasal cells, Intermediate cells, and Superficial cells. In the women with normal estrogen levels, around 15%-30% of cells were Superficial cells and the remaining were Intermediate cells. If Parabasal cells were found, it might be due to the Estrogen deficiency that happened in the women. One of the factors of Estrogen deficiency was menopause.

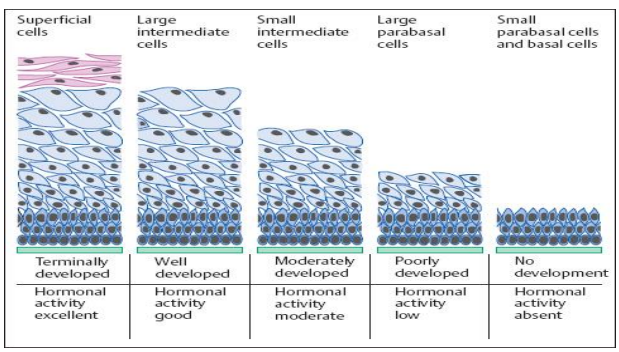

Figure 1. The Layers of Vaginal Walls

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Vulvovaginal Atrophy (VVA) is a condition the frequently occurs in menopausal women. It is characterized by thinning of the vaginal epithelium, reduced vaginal lubrication, and increased fragility of the epithelium. The symptoms of VVA include the drying of the vagina, inflammation, burning sensation, and pain during sexual activities (Dyspareunia). The menopause-related hormone changes, especially lack of estrogen secretion, are the primary causes of VVA[1]. Before reaching menopause, the dominant cells are the superficial cells, and they only exist in some parabasal cells. Meanwhile, after menopause, the total parabasal cells increase followed by the absence of superficial cells [2].

The frequently used therapies for VVA treatment are non-hormonal therapy (lubricant) and hormonal therapy (topical estrogen), and the selective estrogen receptor modulators/SERMs (Ospemifene). The systemic estrogen is not given to avoid the potential stimulation effect of estrogen in the endometrium and breasts [3].

DHEA (Dehydroepiandrosterone) is a steroid hormone produced by the adrenal gland that is then changed into testosterone and estrogen. During menopause, DHEA becomes the main source of estrogen. However, the DHEA levels decrease as people get older and only 25% of menopausal women are estimated to have enough DHEA to avoid menopause symptoms, such as VVA[3]. DHEA replacement therapy is an effective approach that minimizes the potential risk related to estrogen-based therapy [3].

Prasterone is a synthetic DHEA that is biologically and biochemically identical to the endogenous human DHEA. In the peripheral target tissues, DHEA is altered into active intracellular estrogen and androgen by tissue-specific steroidogenic enzymes. Intravaginal prasterone (Intrarosa) has been used in Europe for VVA treatment in menopausal women[5]. Prasterone has been approved in the U.S. for Dyspareunia treatment due to menopause [6]. The dosage used is 6.5 mg of the vaginal suppository.

This paper was arranged to evaluate the effectiveness of prasterone vs placebo therapy as the VVA treatment in menopausal women using Meta-analysis method.

METHOD

Data Search Strategy

The search for literature systematically had been done using PUBMED, Google Scholar, and Cochrane Central Register of Controlled Trials to collect randomized studies (Randomized Controlled Trials/RCT) that investigated the use of Prasterone in menopausal women suffering from VVA. The researchers tried to find the database using the combination of some terms, such as "Prasterone, Placebo, VVA, menopause, and RCT".

Inclusion Criteria

Some of the following criteria had been used in the selection. (1) Randomized study

Table 1. The Quality Assessment of each Study. A: all qualities for criteria are fulfilled; ITT: intention-to-treat; ANCOVA: Analysis of Covariance; Pr: Prasterone; Pl: Placebo

Study	Allocation sequence	Hidden Allocation	Therapy Group	Control Group	*Blinding*	Sample size calculation	Statistic Analysis	ITT Analysis	Level of study quality
Labrie (2011)	A	A	Pr	Pl	A	yes	ANCOVA	Yes	A
Archer (2015)	A	A	Pr	Pl	A	yes	ANCOVA	Yes	A
Labrie (2018)	A	A	Pr	Pl	A	yes	ANCOVA	Yes	A

(randomized controlled trials) on Prasterone as the Vulvovaginal Atrophy (VVA) treatment in menopausal women, (2) all inclusion papers can be accessed completely, and (3) the collected data can be analysed accurately.

Quality Assessment of the Study

We assessed the validity of each study independently by using the criteria mentioned in the Cochrane Handbook for Systematic Reviews of Interventions. We discussed the topic if there was a different point of view. Each study was put into some classifications and assessed based on the category of quality, namely, quality A if the study had low risk of bias; quality B if the study had moderate risk of bias, or quality C if the study had high risk of bias (Figure 2 and Figure 3).

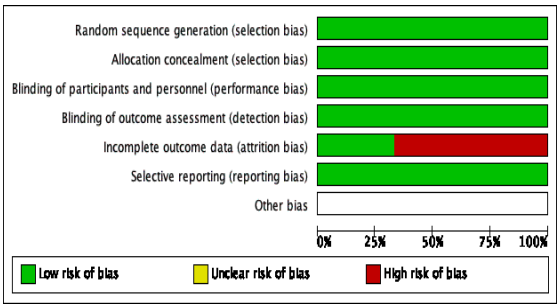

Figure 2. The Conclusion of the Stratification of the Risk of Bias in All Articles in This Meta-analysis

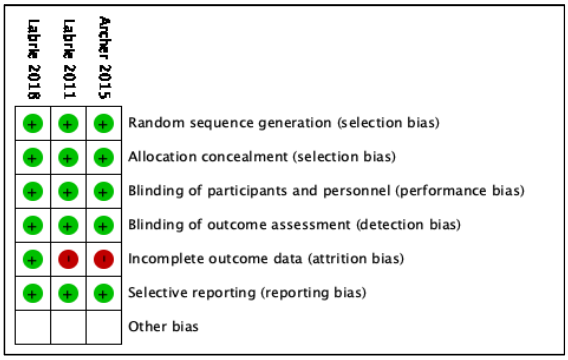

Figure 3. The Assessment of the Writer's Risk of Bias Against Each Inclusion Article

Data Extraction

The followings are the important information collected from each study: (1) main author; (2) the country of the research location; (3) total sample; (4) year of publication; (5) therapy in patients; (6) the data of the mean score of superficial cells; (7) the mean score of parabasal cells; (8) the mean score of vaginal pH; (9) and the mean score of Dyspareunia complaints.

Statistical Analysis and Meta-Analysis

The effect of therapy is expressed using the comparison of the outcome from the therapy group and the control group. In this paper, the outcome was reported as the continuous variables, whereby it had several possible results. The effect of the therapy was expressed as the 'mean score difference'. This score calculated by obtaining the mean scores in both the therapy group and the control group, and then the difference was calculated.

Meta-analysis was arranged using the Review Manager (RevMan) version 5.3. (Cochrane Collaboration, Oxford, UK). This paper assessed the mean difference of superficial cells, the mean difference of superficial cells, the mean difference of parabasal cells, the mean difference of vaginal pH, and the mean difference of Dyspareunia complaints.

The researchers used the fixed-effect and random-effect of meta-analysis for data combination, whereby it assumed logically that several studies had a similar therapy effect estimation.

RESULT

Characteristic of the Studies

Data search resulted in 583 articles. A total of 585 studies had been excluded based on the description in the abstract by seeing the inclusion and exclusion criteria that had been described before. After a series of the selection process, it collected 3 inclusion articles in total for meta-analysis (Figure 3). Table 1 shows additional information related to inclusion articles.

Individual Quality of the Study

All inclusion studies were random and double-blind, and all articles had been passed the randomization process. All inclusion RCTs performed the calculation of power in determining the optimum total sample (Table 1).

We had assessed explicitly whether the relevant studies had a high risk of bias based on the criteria mentioned in the Handbook[7]. Based on the assessment, we assessed the degrees of possibility and the direction of bias and the possibility of these points to influence the outcome of the study. We then analysed the sensitivity in exploring the effect of bias.

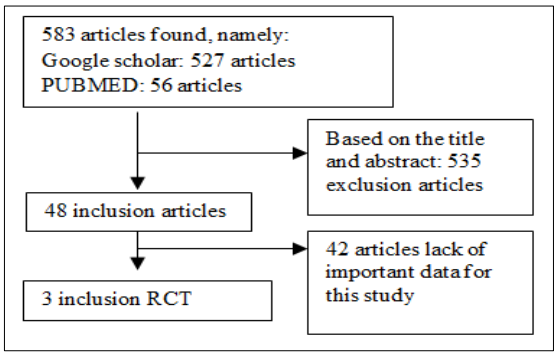

Figure 3. Path Diagram of the Process of Selecting Studies.

Effectiveness

The Mean Score of Superficial Cells

Three inclusion RCTs with the outcome of the mean score of superficial cells, from the cohort, contained 696 samples (436 samples in the Prasterone group and 260 samples in the placebo group) (Figure 4). The estimation of fixed-effects from the mean score difference was 7.63 and 95% CI was around 7.57 to 7.70 (P <0.0001). This analysis result showed that Prasterone had a more significant effect on increasing the mean score of superficial cells than that of Placebo.

The Mean Score of Parabasal Cells

Three RCTs contained 696 samples in total (436 samples in the Prasterone group and 260 samples in the Placebo group) (Figure 5). The estimation of fixed-effects from the mean difference was -29.84 and 95% CI was around -30.25 to -29.44 (P <0.0001). The result of this analysis showed that Prasterone had a more significant effect on decreasing the mean score of parabasal cells than that of Placebo.

The Mean Score of Vaginal pH

Three RCTs contained 696 samples in total (436 samples in the Prasterone group and 260 samples in the placebo group) (Figure 6). The estimation of fixed-effects from the mean difference was -0.69 and 95% CI was around -0.70 to –0.68 (P <0.0001). The result of this analysis showed that Prasterone had a more significant effect on decreasing the mean score of vaginal pH than that of Placebo.

Dyspareunia Complaints

Three RCTs contained 696 samples in total (436 samples in the Prasterone group and 260 samples in the placebo group) (Figure 6). The estimation of fixed-effects from the mean difference was -0.38 and 95% CI was around -0.39 to –0,37 (P <0.0001). This analysis result showed that Prasterone had a more significant effect on decreasing the Diyspareunia complaints than that of Placebo.

From the four forest plots, the diamond was not tangential to the vertical line. Hence, it might be inferred that the was a difference in the result between the experimental group and the control group. The four analyses had a p-value of less than 0.05, proving that there was a significant difference between the two variables. The three studies above were heterogenous since not all of the Confidence Interval intersected the vertical line of the diamond.

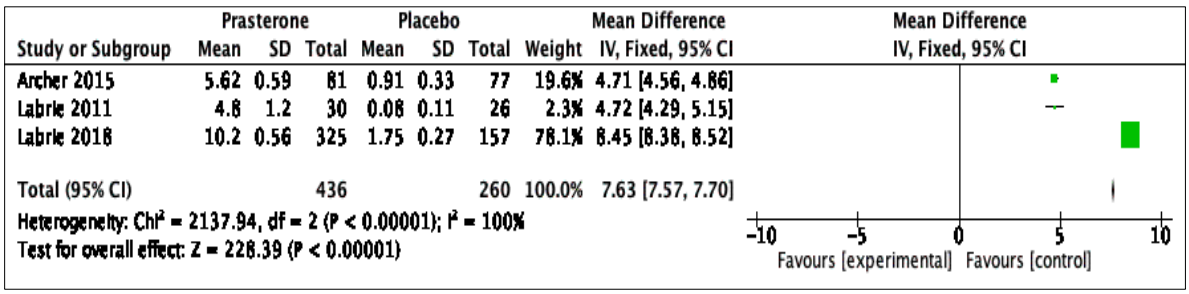

Figure 4. The Forest plot shows the mean difference in superficial cells. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

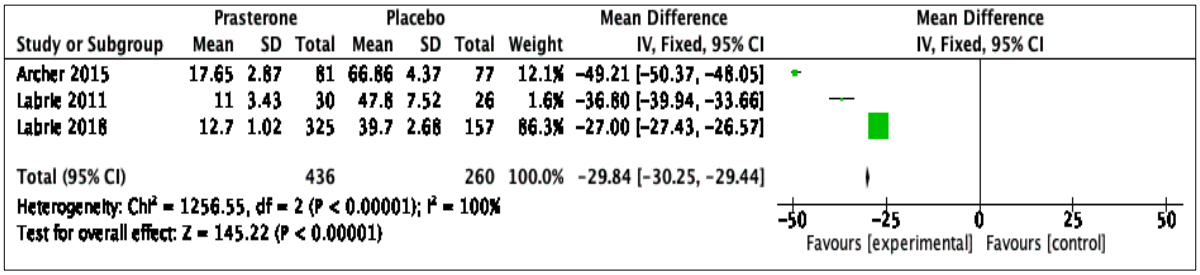

Figure 5. The Forest plot shows the mean difference in Parabasal cells. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

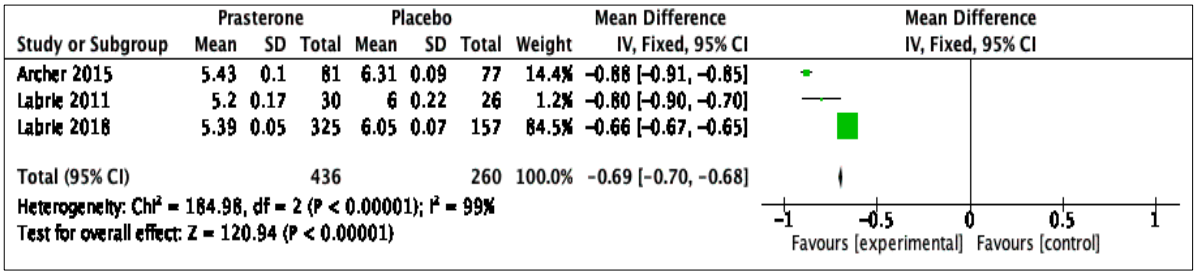

Figure 6. The Forest plot shows the mean difference in vaginal pH. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

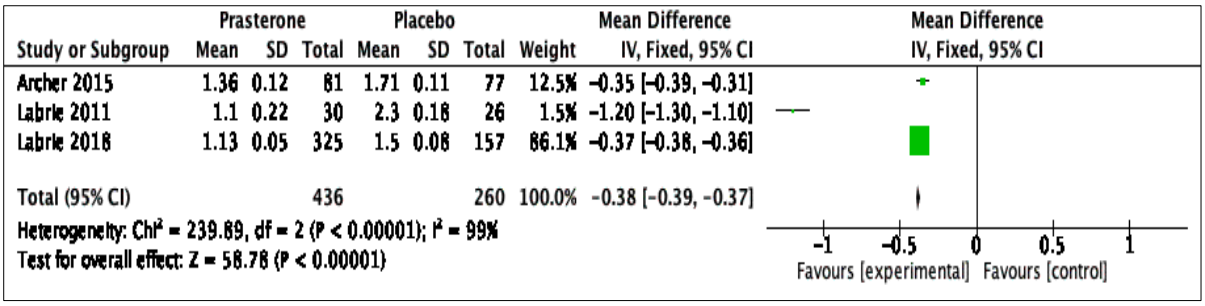

Figure 7. The Forest plot shows the mean difference in Dyspareunia complaints. SD, standard deviation: IV. inverse variance: CI. confidence interval: df. degrees of freedom.

DISCUSSION

Prasterone has been used in the U.S. and Europe since 2016 as the VVA treatment in menopausal women. The following is the pharmacologic treatment for VVA complaints.

The excellence of giving the Prasterone was that it did not cause significant changes in steroid hormone levels in the serum. The Estrogen and Testosterone levels were still at the normal range for menopausal women, and they were known [9].

From the result of the 2 RCTs that had been analyzed, besides the improvement of 4 investigated variables, Prasterone also had advantageous Androgen effects, such as the decreased of the drying in the vagina, the decreased irritation/itchiness in the vagina, the decreased vaginal fluid, and the improved integrity of vaginal epithelium [9].

Drug	Available Strengths	Cost[b]
Oral		
Osphena (Shionogi)	60 mg ospemifene/tab	$556.60
Vaginal		
Rings		
Estring (Pfizer)	2 mg/ring (0.0075 mg estradiol/d)[c]	406.90
Femring (Allergan)	0.05, 0.1 mg estradiol/d[c]	422.50
Inserts		
Intrarosa (Endoceutics)	6.5 mg prasterone/insert	525.00
Vagifem (Novo Nordisk)[d]	0.01 mg estradiol/tab	765.70[e]
Creams		
Estrace (Allergan)	0.01% cream (0.1 mg estradiol/gram)	287.60[f]
Premarin Vaginal Cream (Pfizer)	0.625 mg conjugated estrogens/gram	345.40[g]

Figure 8. The Pharmacologic Treatment for VVA

The side effects that the RCT subjects complained about were white vaginal discharge/leucorrhoea, urinary tract infection (UTI), and headache. The endometrial conditions that had been evaluated in the 12th week mostly resulted in endometrial atrophy. No significant histological finding existed in all of the results of biopsy[9].

This Meta-analysis only included double-blind RCT. The quality of all studies in this meta-analysis was quite high based on the assessment criteria of Review Manager 5.3 program. However, the total inclusion study was not adequate in compiling the clinical recommendation against the patients. In addition, the long-term effect (effectiveness and side effects) could not be proven in this study. Consequently, the writers suggest a further investigation from big-scale studies in the patient population of this study.

CONCLUSION

This Meta-analysis concludes that Prasterone has significant therapeutic effects in patients experiencing Vulvovaginal Atrophy due to Menopause, and it has been proven safe to be consumed.

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REVIEW ARTICLE

COMPARISON THE SUCCESS RATE OF VESICOVAGINAL FISTULA REPAIR SURGERY WITH TRANSVAGINAL AND TRANSABDOMINAL PROCEDURE: META ANALYSIS

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Keywords: vesicovaginal fistule, transvaginal repair, transabdominal repair, omental flap interposition and Martius labial flap.

ABSTRACT

Objective: This paper aims to evaluate the success rate of vesicovaginal fistula (VVF) repair surgery by transvaginal (TVAG) and transabdominal (TPA) procedure. **Method:** Literatures were searched on the online database, PUBMED and Google Scholar. All of the studies should be belonging on to inclusion criteria. The literatures had qualitative analyze by the authors and bias criteria based on *Review Manager 5.3* application. It also had quantitative analyzed by the same application. **Results:** The literatures have 191 patients (transvaginal-n=107; transabdominal-n=84). The data was homogen (Chi^2<df; P>0,05). The forest plot showed that TPA has a higher success rate than TVAG, still not statistically significant (test overall effect P>0,05; 95%CI was 0,59 to 5,30). **Conclusion**: Transabdominal procedure has a higher success rate.

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INTRODUCTION

Vesicovaginal fistula (VVF) is an abnormal channel between the bladder and the vaginal that cause prolonged and continuous urinary incontinence. Number of cases are high in developing country[1]. Incidence rate at Sub-Saharan Africa were 2 million women per 50,000 – 10,000 populations [2,3]. The etiology of VVF can be acquired and congenital. In developed country, obstetric trauma is the common etiology of acquired VVF [4]. The following number of the common etiology is total abdominal hysterectomy[5]. Malignant infiltration from various pelvic cancers is the third cause of VVF[6]. Pelvic tumor radiation also can be the cause of VVF. It may appears a couple years after the therapy[6]. The others cause could be trauma and iatrogenic from obstetric, gynecologic, or urological surgery[1,7]. The patophysiology of VVF in obstetric trauma is an ischemic fibrous while having a labour. In delayed labour, the bladder neck and the uretra pressed by the head of the fetus and symphisis pubic. This condition cause fibrous ischemia and anterior vagina wall necrosis. The necrosis will detach and remove after day tenth[8,9].

The major symptoms of VVF is consistent urine leakage from the vagina[(6)], bad smell and wet sensation that were interfere life quality of the patients[1,10]. Patients complaint the continuous urine leakage from vagina that cannot be held. Also, there were history of obstetric trauma, gynecologic procedure or radiation therapy. The examiner will obtaine small granulated lesion, hyperemia and not specific hollow while did vaginal touche. Methylen blue test will be positive at VVF patients. Imaging examination will support the diagnosis of this case, such as cystoscopy, intravena pyelography (IVP), retrograde and voiding cysto-urethrography, MRI fistulography, pelvic CT Scan and USG[(1)(4)]. Cycstoscopy will provide the specific anatomical origin of the leakage[4,6].

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Management of VVF can be divide by two approaches, they are conservative and surgical. Conservative managements are urine catheterization, fibrin-collagen sealant and platelet rich plasma (PRP) injection. Conservative therapies for reccurent VVF use percutaneous nephrostomy (PCN) or modified with ureter occlussion bilateral, sabutyl-2-cyanoacrylate injection, detachable or non-detachable ballons, and sponges made from nylon, plugs, coils or gelatin[4,6]. Simple VVF is indicated for conservatives with 4-6 weeks of recovery[(11)]. There are various approach for surgical management, such as transvaginal, transabdominal, laparoscopy, and combination[4]. Complex and radiated type VVF are indicated for surgical repair. The expected outcome from these therapies are the closure lesion, better quality of life, and sexual functions[7].

In the UK and developed world, Warner R et al. suggests that vaginal repair is significantly more cost-effective than abdominal repair owing to the shorter operative time and length of stay with no significant difference in the success rates. [7]Tatar B et al. researched that vaginal approach to VVF repair is more cost-effective because the mean hospitalization time is less compared with transabdominal repair, and this difference emphasizes the vaginal route as the first choice without compromising the success rate[4]. This paper aims to evaluate the success rate of vesicovaginal fistula (VVF) repair surgery by transvaginal (TVAG) and transabdominal (TPA) procedure.

METHODS

Data Search Strategy

The literature was obtained from online search engine, PUBMED and Google Scholar. The keywords used are vesicovaginal fistule, transvaginal repair, transabdominal repair, omental flap interposition and Martius labial flap. Then, all of the literatures (n=68) selected by the title and abstract after the duplicate removed. Fifty articles were excluded for the use of languages other than English and Indonesian. Eighteen articles were screened, then twelve articles excluded because of the unavailable of full text studies. Six full-texted articles were evaluated and furthermore, two articles were excluded because these studies used laparoscopy and robotic surgery. Four articles were included (fig. 1) and analyzed using *Review Manager 5.3* (Cochrane Collaboration, Oxford, UK).

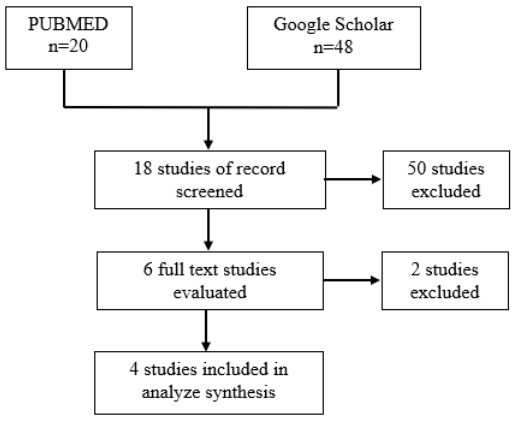

Figure 1. Flowchart of the searched literature

Inclusion Criteria

Inclusion criteria of this review: (1) cross sectional and cohort study, (2) English and Bahasa full text study, (3) vesicovaginal fistule sample, (4) comparison the clinical outcome of VVF repair with transvaginal (TVAG) - Martius labial interposition flap procedure and transabdominal (TPA)-Omental flap interposition procedure, (5) all inclusion papers can be fully accessed, and (6) the data obtained can be analyzed accurately.

Study Quality Assessment

Four of the studies were qualitatively and independently appraised by the authors using bias criteria from *Review Manager 5.3* application. The author discussed and assessed the category of each criteria (low-risk bias, intermediate bias, or high-risk bias). Most of the included literature have high risk of bias. It is shown from the red line of the outcome in funnel plots (fig. 2 and fig. 3).

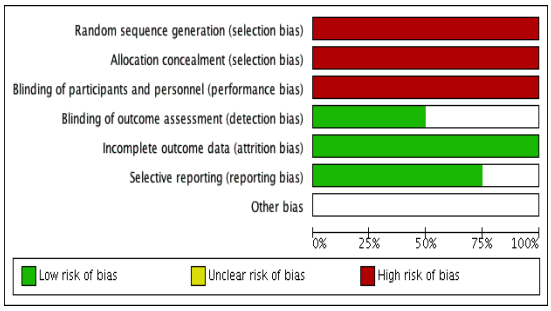

Figure 2. bias stratification risk of articles in this study

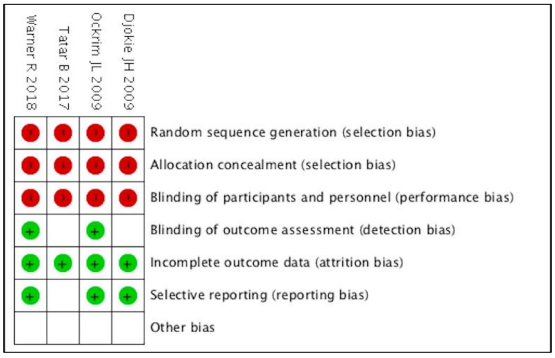

Figure 3. Assessment of the risk of author bias for each inclusion article

Data Extraction

The criteria to extract the data: (1) main author; (2) year of publication; (3) country of the study; (4) design study; (5) inclusion criteria; (6) intervention; (7) success rate of the VVF repair; (8) reccurence rate of the VVF repair. This study compares the success rate of VVF repair intervention by compared TVAG and TPA procedure. The outcome expressed by odd ratio (OR) and the significance represented by P value, then analyzed by *Review Manager version 5.3*. (Cochrane Collaboration, Oxford, UK). Beside of number, there is a forest plot that will provide summarize outcome of this study.

RESULT

Study Characteristics

Four literatures were reviewed as a retrospective study. Three of them are cross sectional[4,7,12], one is a cohort study[6]. One study with prospective data, but reviewed as a retrospective[7]. All of studies have VVF case with variance of age, etiology and time span. A study of Djokic et al, 2009 have 220 participants with the longest time span (1978-2004). Intervention in the literatures had surgical repair with TVAG and TPA. Other approaches were done by another studies, they were Djokic et al, 2009 (Transvesical-TVES n=129) and Tatar et al, 2017 (laparoscopic n=2; urinary diversion (UD) n=2). Still in this review focused on TVAG and TPA approach to compare the reccurent rate for getting the success rate between the approaches. All of the studies have no significant difference in recurrent cases. Some additional outcome also obtained in those literature. Djokic et al, 2009 states that TVAG reffers to simple VVF than TPA for complex VVF and big size lesion and radiologic caused prefer use TPA. A case of VVF in Ockrim et al, 2008 had failed healing because 3 cm of lesion and no omental interposition. Warner et al, 2019 study with prospective data stated that TPA approach has longer operating time, longer length of hospital staying (length of stay-LOS) and higher cost than TVAG approach. Detail data of each study showed in table 1.

Table 1. characteristic of the data from each article

Author	Design Study	Person	Intervention	Comparison	Outcome
JH Djokic et al, 2009	Retrospective – Cohort study	VVF case between 1978-2004 n=220	1. TVAG – martius labial interposition 2. TPA – Flap interposition (omental flap interposition) 3. TVES – extraperitoneal cystostomi approach	reccurence rate of TVAG, TPA, and TVES	success rate: 1.TVAG-56/59 patients (94,9%) 2.TPA-30/32 patients (93,8%) 3.TVES-122/129 patients (94,6%) reccurence rate: primary: 1. TVAG-3/59 (5,1%) 2. TPA-2/32 (6,2%) 3. TVES-7/129 (5,4%)

					secondary: 1. TVAG-1/3 (33,3%) 2. TPA 0/2 (0%-all patients full recovery) 3. TVES-2/7 (28,6%)
Jeremy L. Ockrim et al, 2008	Retrospective – Cross sectional study	32 of VVF cases between 2000-2006	1.TVAG – martius labial interposition 2.TPA – Flap interposition (omental flap interposition)	reccurence rate of TVAG and TPA	Success rate: 1.TVAG-11/11 patients (100%) 2.TPA-18/21 patients (85,7%) reccurence rate: secondary: PA-2/3 (66,7%) 1 patient had failed surgery with VVF post radiotherapy, >4cm size lesion, no omental interposition.
Burak tatar et al, 2017	Retrospective – cross sectional study	20 of VVF cases between 2006-2015	1. TVAG – martius labial interposition 2. TPA – Flap interposition (omental flap interposition) 3. Laparoscopic 4. Urinary diversion – Ileal conduit technique	reccurence rate of TVAG, TPA, laparoscopic and urinary diversion (UD).	success rate: 1.TVAG-5/5 patients (100%) 2.TPA-11/11 patients (100%) 3.laparoscopy-1/2 patients (50%) 4.SLPE-UD (n=1); ILPE-UD (n=1) reccurence rate: laparoscopy 1 patient SLPE: Supra-levator pelvic exenteratio ILPE: Intra-levator pelvic exenteratio
Ross warner et al, 2019	Retrospective – cross sectional study	47 of VVF cases between 2007-2015	1. TVAG – martius labial interposition 2. and TPA – Flap interposition (omental flap interposition)	1. the mean cost 2. duration of operating time 3. length of hospital stay (LOS) 4. the success number of the repair 5. fistula complexity	Primary outcome: success rate: 1. TVAG-29/32 patients (90,6%) 2. TPA-13/15 patients (86,7%) reccurence rate: 1. TVAG-3 patients 2. TPA 2 patients secondary outcome: 1. total cost of TVAG lower than TPA 2. mean operative time – TVAG 196,89 min; TPA 223,4 min 3. LOS – TVAG 5,3 days; TPA 9,1 days 4. size of the fistula similar at TVAG and TPA

Comparison of The Success Rate at VVF Repair Between TVAG and TPA Approach

Four literatures were analyzed by *Review Manager 5.3* application then the outcome shown in a Forest Plot (fig. 4). The accumulative data are 191 patients (transvaginal-n=107; transabdominal-n=84). point of estimate located at the right side, it means that transabdominal has success rate higher than transvaginal. Then, the heterogenicity should be considered. From the forest plot, it is known that all of the studies have homogen data (Chi^2 < df; P>0,05). However, the accumulative data has no significant effect (test overall effect P>0,05; 95%CI was 0,59 to 5,30).

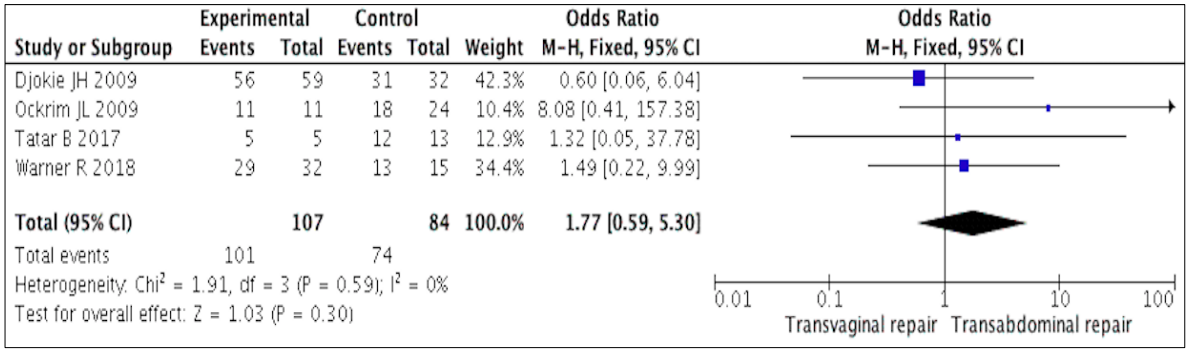

Figure 4. Forest plot of TVAG and TPA VVF repair surgery (experimental= tranvaginal; control=transabdominal; CI-confidence interval; df-degrees of freedom)

DISCUSSION

Surgical therapy for vesicovaginal fistule repair has kind of approaches, they were transvaginal, transabdominal, transvesical, laparoscopy, and urine divertion. The most frequent approaches that used by gynecologist in developing countries are transvaginal and transabdominal. Transvaginal (TVAG) approach was used for simple, small, first attempt repair, and distal fistulas[6]. Transabdominal (TPA) approach frequently used for large size of VVF (>2cm)[4] and the location close to orificium urethra. This condition categorize as a complicated VVF case, yet there is no consensus coincident which fistulas indicated as complicated[(4)]. The complex VVF operated by urologist commonly using the TPA procedure. Behind all of those reasons, there were advantages and disadvantages from both approaches. The advantages of TVAG with martius labial interposition flap were easy to operate, easy to modified, stronger stitches, protect the urethra, shorter duration of operating time, low morbidity, low cost and shorter length of stay, then the disadvantages of TVAG approach were pain at flap retrieval and asymetrism. On other approach, TPA with omental flap interposition had better vascularity so that the flap can stick out better. The disadvantages of TPA were post-operative pain, temporary ileus, over bleeding, longer operating time, higher cost and longer length of stay. Notwithstanding with all of those evidences based on the literatures which was reviewed in this study, there is no significant different success rate between TVAG and TPA[4,6,7,12]. In the study of Burak et al, 2017 it said that the range of success rate of VVF were 70-100%[11,13,14], while the TPA was around 90-100%[14]. Some of VVF cases with large size or complicated fistula operated by urologist, and they prefer to the TPA approach. This literature also states that, TVAG had less length of stay of the patients and low complication of the surgery. It would be reasonable to say that TPA should be considered if the VVF is a complex and large lesion[4]. Djokic et al, 2009 also stated that TVAG should be considered in non-complicated cases and flap procedure in TPA approach is the most secure technique[6]. It is hard to compare the success rate because of the surgeon's prefferences, the complexity, and co-morbidity of the patients[6]. No interposition also be the risk factor of the failed rate of surgery[12]. Tertiary unit which has wide range of etiology also be the factor of this study statement, such as emergency caesarean section, radiotherapy, multiple complex anti-incontinence interventions and infection[12]. The study of Warner et al, 2019 which has prospective data, said that TVAG should be the first options for the simple VVF because it has lower cost, shorter LOS, shorter duration operating, minimal pain and morbidity[7].

Three of the literatures had a little number of participants (Burak et al, 2017 n=20; Ockrim et al, 2008 n=32; Warner et al, 2019 n=47), while one literature had the most number participants which is it had the longest

duration time span (Djokic et al, 2009 n=220). The complexity of fistula also not homogen from each other. Moreover, the study of Ockrim et al, 2008 based on tertiary unit. Different operator is the limitation of the study because the difference level of their skills, although Warner et al, 2019 has the single data surgeon. The bigger participant should be established in this field of study, furthermore a multi-center study is preferable for this kind of problem.

Eventhough all of the literatures had mentioned their preference approach of VVF repair surgery, this study is not be able to conclude, because the statistic analyze was not significant. The type study of the literatures are cross sectional and cohort, it means that it is difficult to randomized the data. But, at the forest plot, the data showed its homogenicity. The forest plot also talked about confidence of interval that means the effect's significancy. Because the effect was not significant, it cannot be concluded the overall effect, although the estimate point showed at the transabdominal side. At the future study, the literature should be more than this, so as the statistic will be significant. If there is randomized controlled study it will be better to gain the clinically relevant conclussion.

CONCLUSSION

The approach is depended on the complexity and the size of the fistule, the operator preferences, the kind of the fistula primary or the reccurence fistula. TPA has a higher success rate than TVAG, still not statistically significant

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