Vol. 10 No. 3 October 2022 – January 2023

MEDICINUS

JURNAL KEDOKTERAN
UNIVERSITAS PELITA HARAPAN

Diterbitkan oleh Fakultas Kedokteran, Universitas Pelita Harapan, Indonesia
ISSN 1978 - 3094
E ISSN 2622 - 6995

MEDICINUS

Journal of Faculty of Medicine
University of Pelita Harapan

Vol.10 No. 3
October 2022 – January 2022
ISSN 1978-3094
E-ISSN 2622-6995

Clinical Article & Review Article

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Publish: October 2022

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Publish

February – June – October

The Difference of Low Density Lipoprotein Cholesterol Levels on Different Severity of Coronary Artery Disease Patients in Siloam Hospital Lippo Village

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Citation: Tanaka Michael, Santoso Wilbert, Anggraini Novita. The difference of low density lipoprotein cholesterol levels on different severity of coronary artery disease patients in Siloam Hospital Lippo Village. Medicinus. 2022 October; 10(3):103-109.
Keywords: Coronary artery disease; Low-density lipoprotein; Number of vessel disease.
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Online First: October 2022

Abstract

Background: Coronary artery disease (CAD) is one of the highest causes of death in the world. Hypercholesterolemia, especially low-density lipoprotein (LDL) levels, is a major risk factor, because it is the main precursor of atherosclerosis. Previous studies showed the relationship between LDL level and the number of vessel disease is still inconsistent, therefore it needs to be observed further. The objective of this study was to know the effect of LDL levels on the number of vessel disease in CAD patients who underwent coronary angiography.
Methods: It was a cross-sectional and retrospective study, where data were taken from medical records of CAD patients who underwent coronary angiography at Siloam Hospital Lippo Village between January to June 2018. Patients with at least one vessel disease were included. The number of vessel disease was categorized into 3 groups: one-vessel, two-vessels, and multi-vessel. The relationship between LDL levels and the number of vessel disease was analyzed using one way ANOVA.
Result: The data includes 90 patients; 70 (77.8%) were male with average age of 56±9 years. There were 32 (35.6%) patients in one-vessel group; 27 (30%) in two-vessel group; and 31 (34.4%) in multi-vessel group with an average LDL levels of 106.43±40.51 mg/dl; 111.15±39.43 mg/dl; and 114.52±32.55 mg/dl respectively. Although it seemed that the increase in LDL cholesterol levels was in line with the number of vessel disease, there was no statistically significant relationship between the two variables (p=0.694).
Conclusions: LDL cholesterol level does not affect the number of vessel disease in CAD patients.

Introduction

Coronary artery disease (CAD) is one of the highest causes of mortality and morbidity in the world[1]. CAD also has the highest prevalence (1.5%)[2] and the second highest cause of mortality (12.9%)[3] in Indonesia for cardiovascular diseases. High concentration of low-density lipoprotein (LDL) is one of the major modifiable risk factors for CAD and has a direct causality for the disease[4, 5, 6] aside from hypertension, smoking, diabetes mellitus, obesity, and sedentary lifestyle[7].

High levels of LDL are the precursor of atherosclerosis. LDL molecules migrate through endothelium, form a buildup of plaque, then narrows the blood vessel overtime. The cap of the plaque then gets thinner and become prone to rupture, causing thrombosis[8]. Atherosclerotic lesions are evaluated using coronary angiography and then classified as obstructive (diameter narrowing of ≥70%; ≥50% for LMCA) or non-obstructive (diameter narrowing of >20% and <70%; >20% and <50% for LMCA). Obstructive lesion is clinically significant and

considered as vessel disease in CAD patients[9].

Several studies have been conducted to find the association between the LDL concentration and the number of vessel disease in CAD. Previous studies by Saito et al.[10] and Chieng et al.[11] have suggested that higher LDL concentration will lead to a more complex and an increase in the number of vessel disease in CAD patients (p<0.01; p<0.05 respectively), which then contradicted by two other studies from Brazil[12] and Iran[13] where neither significance nor correlation is found between the two variables (p=0.1; p=0.73 respectively).

The hypothesis is that the higher the concentration of LDL in the blood, the higher the number of vessel disease in CAD patients. The correlation between the two variables remains inconsistent and contradictory based on the previous studies, therefore this study aimed to know and add more evidence about the effect of LDL on the number of vessel disease in CAD patients.

Material And Methods

Subjects

This retrospective study was conducted in Siloam Hospitals Lippo Village, Tangerang, Indonesia. The data were taken from medical record of patients who underwent coronary angiography within the period of January – June 2018. Subjects were included if they had at least one clinically significant lesion (diameter narrowing of ≥70%; ≥50% for Left Main Coronary Artrery) of coronary arteries. The laboratory result of LDL levels must be taken within 6 months from the time of coronary angiography[14].

The samples were then categorized into three groups: one-vessel; two-vessels; and multivessel based on the number and location of the obstruction. The LDL concentration were compared and analysed along with the other essential variables between these groups. The effect of LDL levels on the number of vessel disease in CAD patients were analysed using one-way ANOVA with a p value of <0.05 to be considered statistically significant. The rest of the confounding variables were presented as descriptive data.

Additional information (if present) such as electrocardiogram (ECG), echocardiogram, diagnosis, and the therapy given were also collected from the medical record and presented in this study as part of the characteristic of subjects. The frequency of the locations of vessel disease such as left main coronary artery (LMCA), right coronary artery (RCA), left anterior descending artery (LAD), and left circumflex artery (LCX) were also presented.

Statistical analysis

The program used for statistical analysis was SPSS 22.0 for Windows (SPSS Inc, USA). The normality and homogeneity test were performed on the data which resulted in normal distribution. The data were then presented by mean ± standard deviation (SD) for variables such as the LDL levels and age, while the rest (male gender; history of hypertension; diabetes; hypertriglyceridemia; and smoking) were presented as frequencies and percentage.

Result

Out of 427 patients who underwent coronary angiography in Siloam Hospitals Lippo Village, 162 were excluded due to non-existent significant lesion, 175 were excluded because of insufficient data, resulting in the final sample of 90 patients. Baseline characteristics were shown in Table 1. The predominant samples in this study were male (77.8%) with average age was 56 ± 9 years. There were 32 samples (35.6%) in the one-vessel group, 27 samples (30%) in the two-vessels group, and 31 samples (34.4%) in the multivessel group. Left Anterior Descending was the most affected coronary artery in this study (80%).

The average LDL cholesterol level was 110.63 ± 37.34 mg/dl, with majority of samples in the <100 mg/dl category (n=36;

40%). A total of 77 patients (85.6%) had a history of hypertension, 47 patients (52.2%) had a history of diabetes, and 59 patients (65.6%) had a history of smoking.

Table 1. Baseline Characteristics

Characteristic	Frequency (n=90)	Percentage (%)
Gender		
Male	70	77,8
Female	20	22,2
Age (years)	56 ± 9*	
< 40	3	3,3
40-49	23	25,6
50-59	30	33,3
60-69	28	31,1
70-79	5	5,6
>80	1	1,1
Number of vessel disease		
One-vessel	32	35,6
Two-vessels	27	30,0
Multivessel	31	34,4
Location of vessel disease		
LMCA	9	10,0
LAD	72	80,0
LCX	53	58,9
RCA	53	58,9
Diagnosis		
ACS (without further explanation)	14	15,6
STEMI	19	21,1
NSTEMI	16	17,8
UAP	9	10,0
SAP	10	11,1
N/A	22	24,4
LDL-c levels (mg/dl)	110,63±37*	
<100	36	40,0
100-129	32	35,6
130-159	12	13,2
160-189	7	7,8
≥190	3	3,3
Risk factors		
Hypertension	77	85,6
Diabetes	47	52,2
Hyper TG	29	32,2
Smoking	59	65,6
Therapy		
Antiplatelet	84	93,3
Anticoagulant	21	23,3
Beta blocker	48	55,6
ACEI/ARB	34	37,8
Nitrate	43	47,8
Statin	81	90,0
Spironolactone	4	4,4
CCB	24	26,7
ECG		
Sinus rhythm	51	56,7
Atrial rhythm	3	3,4
ST elevation	19	21,1
ST depression	14	15,6
T inversion	10	11,1
Q wave	13	14,4
LVH	8	8,9
N/A	27	30,0
Echocardiogram		
Dilated LV	8	8,9
EF (≥ 50%)	20	22,2
RWMA	13	14,4
N/A	62	68,9

*Mean ± standard deviation

ACEI/ARB - angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ACS - acute coronary syndrome; CCB - calcium chanel blocker; EF - ejection fraction; LAD - left anterior descending; LCX - left circumflex artery; LDL – low density lipoprotein; LMCA - left main coronary artery; LV – left ventricle; LVH – left ventricle hypertrophy; N/A – not available; NSTEMI - non ST elevation myocardial infarction; RCA - right coronary artery; RWMA: regional wall motion abnormality; SAP – stable angina pectoris; STEMI - ST elevation myocardial infarction; UAP - unstable angina pectoris.

Most of them were given antiplatelet therapy (93.3%) and statins (90%). ECG results found from samples showed sinus rhythm for 51 patients (56.7%) and most of them experienced myocardial infarction with the presence of ST elevation (21.1%). Samples with echocardiogram results showed that there was no significant ventricular dilatation of the heart (21.1%) with the ejection fraction of ≥50% (22.2%) for most patients.

The predominant samples in this study were male (77.8%) with average age was 56 ± 9 years. There were 32 samples (35.6%) in the one-vessel group, 27 samples (30%) in the two-vessels group, and 31 samples (34.4%) in the multivessel group. Left Anterior Descending was the most affected coronary artery in this study (80%).

The average LDL cholesterol level was 110.63 ± 37.34 mg/dl, with majority of samples in the <100 mg/dl category (*n*=36; 40%). A total of 77 patients (85.6%) had a history of hypertension, 47 patients (52.2%) had a history of diabetes, and 59 patients

(65.6%) had a history of smoking. Most of them were given antiplatelet therapy (93.3%) and statins (90%). ECG results found from samples showed sinus rhythm for 51 patients (56.7%) and most of them experienced myocardial infarction with the presence of ST elevation (21.1%). Samples with echocardiogram results showed that there was no significant ventricular dilatation of the heart (21.1%) with the ejection fraction of ≥50% (22.2%) for most patients.

To determine the effect of LDL levels on the number of vessel disease, one-way ANOVA test were performed and shown on the table (Table 2). The average LDL cholesterol level in one-vessel, two-vessels, and multivessel group respectively was 106.43 ± 40.51 mg/dl, 111.15 ± 39.43 mg/dl, and 114.52 ± 32.55 mg/dl. Although LDL levels were directly proportional to the number of vessel disease, there was no statistically significant relationship between the two variables (p=0.694).

Other collected variables (risk factors for CAD) were compared descriptively between each vessel group (Table 3). The average age tends to be higher as the number of vessel disease increases. The percentage of samples who had hypertension, diabetes, and had a history of smoking are also increased in the two-vessels and multivessel group. In contrast, male gender and hypertriglyceridemia did not show any relationship to the number of vessel disease.

Table 2. Relationship Between Number of Vessel Disease and LDL Cholesterol Levels

	N (%)	LDL level (mg/dl)	P value
One-vessel	32 (35,6%)	106,43 ± 40,51	0,694
Two-vessel	27 (30%)	111,15 ± 39,43	
Multivessel	31 (34,4%)	114,52 ± 32,55	

Table 3. Descriptive comparison between risk factors to the number of vessel disease in CAD patients

Risk factor	One (n=32)	Two (n=27)	Multi (n=31)
Age (years)	54 ± 7	55 ± 10	58 ± 11
Male gender	25 (78,1%)	22 (81,5%)	23 (74,2%)
Hypertension	25 (78,1%)	22 (81,5%)	30 (96,8%)
Diabetes	13 (40,6%)	13 (48,1%)	21 (67,7%)

Discussion

Most patients in this study belong in the one-vessel group, which consists of 32 samples (35.6%), followed by multivessel group with 31 samples (34.4%), and two-vessels group with 27 samples (30%). The most frequently affected artery was LAD (n = 72, 80%), followed by LCX and RCA arteries with the same frequency (n = 53, 58.9%), then LMCA (n = 9, 10%). This is consistent with the theory and research described by Wasilewski et al, where the septal perforator in LAD tends to have a "milking effect" which causes the distribution of atherosclerotic plaque to be more dominant in this artery than the others.[15, 16]

The LDL cholesterol levels were shown to be increased in the two-vessels group and multivessel group. LDL levels had an average of 106.43 ± 40.51 mg/dl in one-vessel group, 111.15 ± 39.43 mg/dl in two-vessels group, and 114.52 ± 32.55 mg/dl in multivessel group. There was no statistical significance found after the data was analysed with one-way ANOVA (p = 0.694). The result of this study was similar with another study conducted by Penalva et al, in which LDL levels and the number of vessel disease does not have statistically significant relationship, although the data similarly showed that the increase in LDL levels was also consistent with the increase of the number of vessel disease. The researcher assumed that his sample of 107 patients was still relatively

small in order to obtain any statistical significance in his research[14]. This could also be one of the factors that caused no statistical difference in this study because of the relatively small number of samples (*n* = 90 samples). A study conducted by Khashayar et al, described that there was no correlation between the two variables at all. According to their study, there was other factor that affects the number of vessel disease besides LDL levels, which is the high-density lipoprotein (HDL)[13]. HDL levels were not included in this study and it was unknown whether it had any influence on the outcome and the number of vessel disease.

In contrast, a study by Gruzdeva et al. found a significant effect between LDL levels and the number vessel disease in CAD patients. Their method was that angiography procedure and the laboratory examination are carried out strictly and only within a few hours after the onset of the disease, with the number of samples as many as 400 samples[17]. In this study the data were obtained retrospectively from medical records and the time between the LDL examination and angiography procedure was not necessarily uniform between one sample to another. These difference of time period between each sample might be a factor for a less representative data, which then affected the outcome of this study to be statistically insignificant.

In theory, a high level of blood LDL will cause more lesions in coronary arteries because the process of atherosclerosis is initiated by a high number of LDL molecules that invades the endothelium. High LDL levels can also form free radicals that also damage the function of endothelial cells, making LDL particles penetrate more easily through endothelial cells. Although the results obtained in this study were not statistically significant, high LDL levels remain as the major precursor of plaque formation in coronary artery disease. Therefore, LDL levels is still considered for estimating the severity of lesions in CAD.

Limitation of study

The design of this study is cross-sectional retrospective, which includes some limitations such as: time of examination of LDL levels that are not uniform between one sample to another; and lack of information whether the patient's LDL cholesterol level is controlled. The assessment of complexity and severity of lesion in this study was only qualitative in nature and did not use standardized scores such as SYNTAX, hence another limitation that can be improved in the future. Besides, this study did not analyze other risk factors for coronary artery disease. Hypertension, diabetes, smoking, and family history are traditonal risk factors that may influence severity of coronary artery disease. Further studies are needed to evaluate those factors together with LDL levels to predict the outcome in coronary artery disease population.

Conclusion

In conclusion, LDL cholesterol levels have no effect on the number of vessel disease in patients with CAD. Patients in the higher vessel group tend to be older, have a history of hypertension, diabetes, and smoking.

References

1. Cardiovascular diseases (CVDs) [Internet]. World Health Organization. 2018 [cited 17 August 2018]. Available from: http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

2. Kemenkes RI. Laporan Riset Kesehatan Dasar. Jakarta: Kemenkes RI; 2013

3. Kemenkes RI. Indonesia: Sample Registration System 2014. Jakarta: Kemenkes RI; 2014

4. Stone NJ, Robinson JG, Lichtenstein AH, Merz NB, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25PtB): 2889-934. https://doi.org/10.1016/j.jacc.2013.11.002

5. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype Clinical perspective. Circulation. 2016;134(1):9–19. https://doi.org/10.1161/circulationaha.116.022335

6. Ference B, Ginsberg H, Graham I, Ray K, Packard C, Bruckert E et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies: A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459-2472. https://doi.org/10.1093%2Feurheartj%2Fehx144

7. Risk Factors [Internet]. World Health Organization. 2018 [cited 17 August 2018]. Available from: http://www.who.int/cardiovascular_diseases/en/cvd_atlas_03_risk_factors.pdf?ua=1

8. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: Process, Indicators, Risk Factors and New Hopes. Int J Prev Med. 2014;5(8):927-946. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4258672/

9. Levine G, Bates E, Blankenship J, Bailey S, Bittl J, Cercek B et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):e574-e651. https://doi.org/10.1161/cir.0b013e31823ba622

10. Saito R, Kawai Y, Watanabe M, Motoyama A, Ishida R, Kitayama M et al. 362 Atherogenic Lipid Profile and Development of Multivessel Coronary Artery Disease in Women. Atherosclerosis Supp. 2011;12(1):78. http://dx.doi.org/10.1016/S1567-5688(11)70363-4

11. Chieng D, Pang J, Ellis K, Hillis G, Watts G, Schultz C. Elevated lipoprotein(a) and low-density lipoprotein cholesterol as predictors of the severity and complexity of angiographic lesions in patients with premature coronary artery disease. J Clin Lipidol. 2018;12(4):1019-1026. https://doi.org/10.1016/j.jacl.2018.03.090

12. Penalva RA, Huoya Mde O, Correia LC, Feitosa GS, Ladeia AM. Lipid profile and intensity of atherosclerosis disease in acute coronary syndrome. Arq Bras Cardiol. 2008;90(1):24-30. https://doi.org/10.1590/s0066-782x2008000100005

13. Khashayar P, Mohagheghi A. The correlation between dyslipidemia and coronary artery disease based on angiographic findings in an Iranian population. Acta Med Indones. 2010;42(2):82-5.

14. Rojas F, De Frutos T, Ponte A, Chacón J, Vitale G. Coronary Heart Disease and Dyslipidemia: A Cross-Sectional Evaluation of Prevalence, Current Treatment, and Clinical

Control in a Large Cohort of Spanish High-Risk Patients: The PRINCEPS Study. Prev Cardiol. 2009;12(2):65-71. https://doi.org/10.1111/j.1751-7141.2008.00022.x

15. Wasilewski J, Niedziela J, Osadnik T, Duszańska A, Sraga W, Desperak P et al. Predominant location of coronary artery atherosclerosis in the left anterior descending artery. The impact of septal perforators and the myocardial bridging effect. Kardiochir Torakochirurgia Pol. 2015;4:379- 385. https://doi.org/10.5114/kitp.2015.56795

16. Wasilewski J, Niedziela J, Osadnik T, Roleder M, Nowakowski A, Glowacki J et al. The Role of Septal Perforators and "Myocardial Bridging Effect" in Atherosclerotic Plaque Distribution in the Coronary Artery Disease. Pol J Radiol. 2015;80:195-201. https://doi.org/10.12659%2FPJR.893227

17. Gruzdeva O, Uchasova E, Dyleva Y, Belik E, Karetnikova V, Shilov A et al. Multivessel coronary artery disease, free fatty acids, oxidized LDL and its antibody in myocardial infarction. Lipids Health Dis. 2014;13(1):111. https://doi.org/10.1186%2F1476-511X-13-111

Factors Associated With Atopic Dermatitis In Elementary School Children In Suburban Area In Indonesia: Original Research

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Citation : Gunawan Catherine, Satriajaya Anthony, Vatvani Akhil Deepak, Waren Kalis, Broto Resza, Kalumpiu Jane Florida, Tan Sylvia. Factors Associated With Atopic Dermatitis In Elementary School Children In Suburban Area In Indonesia: Original Research. Medicinus. 2022 October; 10(3):110-115.
Keywords: Atopic dermatitis; Associated factors; Atopy; ISAAC; School children
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Abstract

Background: There was limited data of Atopic Dermatitis (AD) prevalence and its associated factors in Indonesia. Therefore, the aim of this study was to identify and evaluate the AD prevalence and factors associated with AD in elementary school children in suburban area in Banten.

Methods: A cross-sectional study was conducted in 3 elementary schools children age 6 – 7 years old who were randomly selected. Information was obtained through an Indonesian version of the International Study of Asthma and Allergies in Childhood questionnaire (ISAAC).

Results: From 304 school children in semi-urban area, AD was reported as ever had an itchy rash which was reccurent for at least 6 months in 17.4% of the children, 19.5% of the children had this itchy rash at any time in the past 12 months, and 11.4 % reported doctor-diagnosed AD. The factors found to be associated with an increased risk of AD were allergic rhinitis (OR 2.151 CI: 1.086-4.261), history of premature birth (<37 weeks) (OR 5.306, CI:1.577-17.858), exclusive breastfeeding (OR 3.126 CI:1.314-7.439), and food allergy (OR 2.912 CI:1.386-6.119).

Conclusion: The results of this study showed that allergic rhinitis, history of premature birth (<37 weeks), exclusive breastfeeding, and food allergy were factors associated with AD in Indonesian schoolchildren.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder, characterized by cutaneous dryness, intense itching, scratching, skin damage, and secondary infections. Atopic dermatitis (AD) is one of the most common skin diseases in the world, particularly in neonates, children, and adolescents.[1] AD is caused by a combination of genetic and environmental factors. The disease is closely associated with asthma and allergic rhinitis. Although this disorder is not fatal, it can lead to skin damages, secondary infections, sleep disorders in children and parents, reduced quality of life, high costs, loss of confidence, and reduced functional capacity that can interfere athletic activities and social relationships.[2,3]

As a result of previous studies based on ISAAC, the incidence of AD in the infant population was estimated to be 15–20%, showing an increase in prevalence. It has also compared the prevalence among the different countries and showed differences in each region.[4] The prevalence of AD is reported to be 17.2% in American children, 15.6% in European Children, 24% in Japanese children aged 5-6 years old, 19.1% in Korea, and 20% in other countries. The prevalence of allergic

diseases has increased not only in high income but also in low-to-middle income countries (LMIC), such as Indonesia.[1]

There is a wide spectrum of presentations of atopic eczema, from minimal flexural eczema to erythroderma. The skin of a child with eczema is generally dry. The eczema can occur anywhere, but there are particular patterns that are more common at certain ages. The face is usually the first to be affected. In crawling infants the forearms, extensor aspects of the knees, and the ankle flexures are often the most affected. In older children the flexor aspects of the elbows and the knees are mostly affected. The eczema may be moist and weeping or may be thickened (lichenified) and dry. In children with darker skin the rash may have a papular nature. Scratch marks are always seen. [1]

For primary, secondary and tertiary prevention of childhood AD, it is crucial to determine the factors which are associated with the development or exacerbation of AD. Known associated factors linked to the incidence of AD from previous studies were the presence of asthma or rhinitis symptoms,positive family history for allergic diseases[5], indoor allergens such as dust mite, animal dander and fur[6], environmental tobacco smoke (ETS)[7], exclusive breastfeeding history[8], low birth weight, prematurity, house mould, higher exposure to air pollution, smaller families with less exposure to infections, animal contact in first year of life and within the last year, higher maternal age, consumption of paracetamol in first year of life and within the last year[9], and a wider range of foods.[2,3,10] The association between atopic eczema and food allergy is complex, though it is usually children with severe atopic eczema have food allergy.[2]

There was limited data of AD prevalence and its associated factors in Indonesia. Therefore, the aim of this study was to identify and evaluate the AD prevalence and factors associated with AD in elementary school children in suburban area in Indonesia.

Material And Methods

Study design and subjects

This cross-sectional study was performed in January 2018. A total of 304 children, chosen from a random sample of 3 elementary schools in Tangerang, Indonesia, were included in this study. After coordination with the schools under study, researchers presented letters referred to schools according to ISAAC protocol, and obtain informed consent. Based on ISSAC protocol, after distributing the questionnaires, each question was explained by a trained interviewer. The questionnaires were completed preferably by the parents and by the students themselves if the parents were absent. The data collected were entered into Microsoft Excel.

Questionnaires

Allergic disorders were assessed with a validated questionnaire for age 6-7 years old developed by International Study of Asthma and Allergy in Childhood (ISAAC) which had been translated into Bahasa Indonesia to accommodate local study requirements. AD ever was defined as a positive response to the question “Have you ever had an itchy rash which was coming and going for at least 6 months?” The prevalence of asthma symptoms were obtained from the questions: “Has your child and family member ever had wheeze?” The prevalence of rhinitis symptoms were obtained from the following questions: “Has your child and family member ever had a problem with sneezing or a runny or blocked nose when you (he/she) did not have a cold or the flu?”

An additional questionnaire was administered to obtain demographic data, socioeconomic status, parental education, parental occupation, and other potential associated factors for the development of allergies. The potential associated factors that were investigated included the following: gender, birth weight, delivery time, number of siblings, exclusive breastfeeding history, parental asthma or allergic rhinitis or atopic dermatitis,

exposure to animals in the first year of life and within the last year, exposure to tobacco smoke in at home, dampness and mold in the house, food allergy, cooking method in the house, and paracetamol consumption in the first year of life and within the last year.

Written informed consent was obtained from parent or guardian of each child. The study was approved by the Ethical Committee of the Medical Faculty, University of Pelita Harapan (ethical clearance ref: 006/K-LKJ/ETIK/VIII/2017)

Statistical analysis

The collected data were analyzed using SPSS ver.22 (IBM, 2018). To investigate the relationship between associated factors and AD, the analysis was carried out using the *Chi- square* test, and its odds ratio (OR) and confidence interval of 95% were calculated. Statistical significance was set at P<0.05.

Result

Data were collected from 304 school children in semi-urban area. AD was reported as ever had recurrent itchy rash for at least 6 months in 17.4% of the children, 19.5% of the children had this itchy rash at any time in the past 12 months, and 11.4 % reported doctor-diagnosed AD. The associated factors for AD were described in table 1. In this study, the Odd ratio of asthma in patients with AD was 1.08, CI: 0.388-3.006, p value 0.884 and Odd ratio of allergic rhinitis patients with AD was 2.151 CI: 1.086-4.261, p value 0.026. Of the children with AD, 4.8% were born prematurely (<37 weeks), OR 5.306, CI:1.577-17.858, p value 0.003, 61.3% had exclusive breastfeeding (breastfed for 6 months or more), OR 3.126 CI:1.314-7.439, p value 0.007, and 17.2% had food allergy, OR 2.912, CI:1.386-6.119, p value 0.004. Household pets during infancy (in the first year of child's life) was present in 79.9% of the children, OR 0.639, CI: 0.305-1.339, p value 0.233, household pets at present (in the last 1 year) was present in 94.2% of the children, OR 0.432, CI: 0.143-1.306, p value 0.127. The Odd ratio of exposure to cigarette smoke (at present) in children with AD was 1.679, CI:0.894-3.153, p value 0.105. The family income were described in table 2.

The factors found to be associated with an increased risk of AD were allergic rhinitis, history of premature birth (<37 weeks), exclusive breastfeeding, and food allergy. However, gender, asthma, household pets (during infancy), household pets (at present), exposure to cigarette smoke (at present), and family income showed no statistical significance as a associated factor for AD.

Table 1. Factors associated with atopic dermatitis in children

Risk factors	%	OR (95% CI)	P value
Gender (female)	47.6 %	1.36 (0.74-2.52)	0.315
Asthma	9.6 %	1.08 (0.388-3.006)	0.884
Allergic rhinitis	60 %	2.151 (1.086-4.261)	**0.026**
Prematurity	4.8 %	5.306 (1.577-17.858)	**0.003**
Exclusive breastfeeding	61.3 %	3.126 (1.314-7.439)	**0.007**
Food allergy	17.2 %	2.912 (1.386-6.119)	**0.004**
Household pets (during infancy)	79.9 %	0.639 (0.305-1.339)	0.233
Household pets (at present)	94.2 %	0.432 (0.143-1.306)	0.127
Exposure to cigarette smoke (at present)	50.7 %	1.679 (0.894-3.153)	0.105
Family income			0.374

Table 2. Family income

Family income	%
< Rp 1,000,000	19.1%
Rp 1,000,000 – 3,000,000	38.1%
Rp 3,000,000 – 5,000,000	28.9%
>Rp 5,000,000	13.9%

Discussion

In our study, factors found to be associated with an increased risk of AD were allergic rhinitis, history of premature birth (<37 weeks), exclusive breastfeeding, and food allergy. However, we did not find any relation between AD and other risk factors including gender, asthma, household pets (during infancy), household pets (at present), exposure to cigarette smoke (at present), and family income. Our finding were consistent with the previous studies which showed that presence of allergic rhinitis, history of premature birth (<37 weeks), and food allergy were associated with increase risk of AD.[10]

Patients with AD have higher rates of allergic diseases than the general population. 80% of children with AD develop asthma and/or allergic rhinitis later in life and referred to as the "allergic march" or "atopic march". The cutaneous manifestations of atopy often represent the beginning of the atopic march. Approximately half of AD patients will develop asthma, particularly with severe AD, and two thirds will develop allergic rhinitis. Epicutaneous sensitization with subsequent migration of sensitized T cells into the nose and airways, causing upper and lower airway disease.[11]
Ten to twenty percent of patients with AD have food-induced urticaria/anaphylaxis compared with 1-3% of the general population.[12] The current hypothesis is that cutaneous sensitization through disrupted skin barrier leads to food sensitization and food allergies. Defects in serine peptidase inhibitor, Kazal type 5 (SPINK5) are associated with food challenge-proven food allergy.[13,14] In addition, skin barrier impairment at birth which is measured by higher transepidermal water loss (TEWL) predicts food allergy at two years of age.[15] Earlier onset (<3 months of age) and more severe AD is associated with high egg, milk, and/or peanut-specific IgE.[16] Patients with AD and concomitant egg, peanut, or dust mite allergy are more likely to have AD that persists beyond five years of age.[17] Infants and young children with AD are more commonly sensitized to foods[18], whereas children over five years and adults are more commonly sensitized to aeroallergens (dust mite sensitization is most prevalent in both children and adults).[19] And vice versa, food allergies play a role in exacerbating AD in up to 33% of patients with severe AD, 10 – 20% with moderate AD, and 6% with mild AD. Elimination of food allergens in patients with AD and confirmed food allergy can lead to significant AD improvement.

Relation of breast-feeding with IgE as allergic marker in childhood is complex and early production of food-specific IgE is associated with an elevated risk for allergic outcomes. Among children of mothers with high IgE levels, breast-feeding was associated with elevated IgE levels relative to never breast-fed children in that maternal IgE strata. Thus exclusive breastfeeding cause immediate, continuing, and high-volume exposure to antigens, including bacteria and allergens, which might alter inherited predisposition toward IgE production. Other explanation is that breast-feeding associated with lower infections in early life which might stimulate the infant immune system toward an allergic (TH2) rather than an antimicrobial (TH1) response and encourage persistence of the TH2 immunity, particularly in the context of a genetic predisposition toward IgE production.[20] Premature birth (<37 weeks) infants might have higher risk of AD because they have immature skin barrier that cause increased permeability and transepidermal water loss.[21]

Exclusive breastfeeding, household pets during infancy and at present effects on AD is still controversial, where exclusive breastfeeding, household pets (during infancy), and household pets (at present) were found as both risk and protective factors of AD. Previous studies showed that female gender, asthma, exposure to cigarette smoke (at present), and high family income were significant risk factor for AD, which were not in agreement with our result.

The limitation of this study was our study design was a cross-sectional survey which cannot identify the causal relationship. In addition, the diagnosis of AD was based on a questionnaire, not by detailed history and physical examination. Further investigation by prospective cohort study is required to prove the causal relationship between the development of AD and risk factors in Indonesian children. Because AD might be an 'entry point' for the subsequent development of asthma or allergic rhinitis, children with AD need proper management to prevent epicutaneous sensitisation leading to systemic immune response. There was no conflict of interest in this study.

Conclusion

The results of this study showed that allergic rhinitis, history of premature birth (<37 weeks), exclusive breastfeeding, and food allergy were factors associated with AD in Indonesian schoolchildren.

Acknowledgment

The authors thank the team from Faculty of Medicine, University of Pelita Harapan, preceptors, and most of all the study participants from these elementary schools, Tangerang, Indonesia.

References

1. Kiken DA, Silverberg NB. Atopic dermatitis in children, part I: epidemiology, clinical features, and complications. Cutis. 2006;78(4):241-7.

2. Barnetson R. Childhood atopic eczema. BMJ. 2002;324(7350):1376-1379. https://doi.org/10.1136/bmj.324.7350.1376

3. Kalmarzi RN, Ataee P, Homagostar G, Tajik M, Ali Shekari, Daem Roshani, Vahid Ghobadi Dana, Sairan Nili. Prevalence of Atopic Dermatitis Symptoms among Students in Kurdistan: a North-west Province of Iran. Int J Pediatr. 2016;4: 1205-1214.

4. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet. 1998;351:1225-32.

5. Girolomoni G, Abeni D, Masini C, Sera F, Ayala F, Belloni-Fortina A, et al. The epidemiology of atopic dermatitis in Italian schoolchildren. Allergy. 2003;58(5):420-5. https://doi.org/10.1034/j.1398-9995.2003.00112.x

6. Harris JM, Williams HC, White C, Moffat S, Mills P, Newman AJ, et al. Early allergen exposure and atopic eczema. Br J Dermatol. 2007;156(4):698-704. https://doi.org/10.1111/j.1365-2133.2006.07710.x

7. Arruda LK, Sole D, Baena-Cagnani CE, Naspitz CK. Risk factors for asthma and atopy. Curr Opin Allergy Clin Immunol. 2005;5(2):153-9. https://doi.org/10.1097/01.all.0000162308.89857.6c

8. Peat JK, Allen J, Oddy W, Webb K. Breastfeeding and asthma: appraising the controversy. Pediatr Pulmonol. 2003;35(5):331-4. https://doi.org/10.1002/ppul.10276

9. Beasley R, Clayton T, Crane J, von Mutius E, Lai C, Montefort S et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme. The Lancet. 2008;372(9643):1039-1048. https://doi.org/10.1016/s0140-6736(08)61445-2

10. Park YM, Lee SY, Kim WK, Han MY, Kim J, Chae Y, et al. Risk factors of atopic dermatitis in Korean schoolchildren: 2010 international study of asthma and allergies in childhood. Asian Pac J Allergy Immunol. 2015; 34(1):65-72. https://doi.org/10.12932/ap0621.34.1.2016

11. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol. 2003;112(6):S118-S27. https://doi.org/10.1016/j.jaci.2003.09.033

12. Eigenmann PA, Calza AM. Diagnosis of IgE-mediated food allergy among Swiss children with atopic dermatitis. Pediatr Allergy Immunol. 2000; 11(2):95-100. https://doi.org/10.1034/j.1399-3038.2000.00071.x

13. Johansson EK, Bergström A, Kull I, Lind T, Söderhäll C, van Hage M, et al. IgE sensitization in relation to preschool eczema and filaggrin mutation. J Allergy Clin Immunol. 2017; 140(6):1572-1579. https://doi.org/10.1016/j.jaci.2017.04.008

14. Ashley SE, Tan HT, Vuillermin P, Dharmage SC, Tang MLK, Koplin, et al. The skin barrier function gene SPINK5 is associated with challenge-proven IgE-mediated food allergy in infants. Allergy. 2017; 72(9):1356-64. https://doi.org/10.1111/all.13143

15. Kelleher MM, Dunn-Galvin A, Gray C, Murray DM, Kiely M, Kenny L, et al. Skin barrier impairment at birth predicts food allergy at 2 years of age. J Allergy Clin Immunol. 2016; 137(4):1111-6. https://doi.org/10.1016/j.jaci.2015.12.1312

16. Hill DJ, Hosking CS, de Benedictis FM, Oranje AP, Diepgen TL, Bauchau V, et al. Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study. Clin Exp Allergy. 2008; 38(1):161-8. https://doi.org/10.1111/j.1365-2222.2007.02861.x

17. Horwitz AA, Hossain J, Yousef E. Correlates of outcome for atopic dermatitis. Ann Allergy Asthma Immunol. 2009; 103(2):146-51. https://doi.org/10.1016/s1081-1206(10)60168-8

18. Eller E, Kjaer HF, Høst A, Andersen KE, Bindslev-Jensen C. Food allergy and food sensitization in early childhood: results from the DARC cohort. Allergy. 2009; 64(7):1023-9. https://doi.org/10.1111/j.1398-9995.2009.01952.x

19. Pónyai G, Hidvégi B, Németh I, Sas A, Temesvári E, Kárpáti S. Contact and aeroallergens in adulthood atopic dermatitis. J Eur Acad Dermatol Venereol. 2008; 22(11):1346-55. https://doi.org/10.1111/j.1468-3083.2008.02886.x

20. Wright AL, Sherrill D, Holberg CJ, Halonen M, Martinez FD. Breastfeeding, maternal IgE, and total serum IgE in childhood. J Allergy Clin Immunol. 1999;104(3Pt1):589–594. https://doi.org/10.1016/s0091-6749(99)70328-3

21. Rudikoff D, Cohen S, Scheinfeld N. Atopic Dermatitis and Eczematous Disorders. Florida: Taylor & Francis Group; 2014. p.87

Relationship of Sexual Violence to Depression in Female Students of Faculty of Medicine, Pelita Harapan University

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Citation : Xaviera Luqyana Ghina, Kristiani Erna, Suryadinata Neneng. Relationship of Sexual Violence to Depression in Female Students of Faculty of Medicine, Pelita Harapan University. Medicinus. 2022 October; 10(3):116-121
Keywords: Sexual violence; Depression; Female students
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Online First : October 2022

Abstract

Background: Sexual violence can take many forms to anyone. The increase in the number of sexual violence against women in Indonesia is quite significant. These incidents are reported to occur frequently in women in young adulthood. These experiences can have long-term effects, one of which is depression. There are several studies that show an association between sexual violence and the incidence of depression. However, there has not been much quantitative research to look at the relationship on this matter in Indonesia, especially on female students. This study aims to understand the relationship between sexual violence and the incidence of depression in female students of the Faculty of Medicine, Universitas Pelita Harapan.

Methods: This study use a cross-sectional study design. The data has been collected using questionnaires filled in by the respondents. This study involved 149 female students of the Faculty of Medicine, Pelita Harapan University. The results of the study were processed and statistically analyzed using SPSS 25.

Result: Based on research data, there are 149 respondents from female students of the Faculty of Medicine, Universitas Pelita Harapan. with a mean age of 19.29 (SD = 1.086). The youngest age of the respondent is 17 years old and the oldest is 24 years old. A total of 55 respondents had experienced sexual violence. Based on the results of the Beck's Depression Inventory (BDI) questionnaire, 16% had mild depression, 9% had moderate depression, and 2% had severe depression. Chi-square test showed a significant relationship between experiences of sexual violence and the incidence of depression, with $p < 0.001$.

Conclusions: Sexual violence is related to the incidence of depression in female students of the Faculty of Medicine, Pelita Harapan University.

Introduction

Sexual violence without realizing it becomes a thing that is often found in people's lives, which can occur in various forms. This event can happen to anyone, regardless of age or gender. However, more forms of sexual violence against women are reported and are often in the spotlight.[1,2]

Based on the Annual Records of the National Commission on Violence Against Women, it was found that the incidence of violence against women has increased almost eight times over a period of 12 years. These data are the result of reported cases, so it is said that this incident is still an iceberg phenomenon.[3]

Sexual violence is theoretically said to be a major stressor to the mental and physical health of the victims.[4,5] Psychological problems that are often found as a result of sexual violence include depression, anxiety, and anger.[6] In addition to mental health, these experiences can also have an impact on the physical and

reproductive condition of the victim.[7] Besides that, sexual violence ranks as the second type of violence in the personal realm, where most of the victims are in the early adult age group.[3] The female students belong to the early adult age group, and these data indicate that there are quite a number of incidents of sexual violence in the age group belonging to female students, so that female students can be said to be one of the risk factors.[8]

This study aims to examine the relationship between sexual violence and depression in female students of Faculty of Medicine, Pelita Harapan University.

Material And Methods

This analytical study had been conducted in female students of faculty of medicine Pelita Harapan University between January 2021 and March 2021. Informed consent had been conducted from all of the students.

Inclusion criteria is students of faculty of medicine Pelita Harapan University who are willing to fill out research questionnaires. Exclusion criteria is students of faculty of medicine Pelita Harapan University who are nor willing to fill out research questionnaires, have a history of mental disorders, have a metabolic or chronic disease, have experience of other types of violence, and who are not filling out the questionnaire completely.

The research design applied in this study was a cross-sectional analytic study. Statistical analysis was performed by using SPSS 25 version and Microsoft Office Excel 2010 version. Statistical tests have been carried out using the chi-square method.

Result

There were 171 respondents who were successfully collected, with 22 respondents included in the exclusion criteria. Samples characteristics: batch 2018 (41%), batch 2019 (28%) batch 2020 (31%), never experienced sexual violence (63%), have experienced sexual violence at the age of <6 (4%), 6 – 12 (3%), >12 – 16 (15%), >16 (15%). Of the 15 types of sexual violence based on Komnas Perempuan, only seven types of sexual violence were experienced by respondents. The most common types of sexual violence experienced by respondents were sexual harassment (53 respondents), followed by sexual intimidation (six respondents), sexual control (four respondents), sexual exploitation (two respondents), inhumane punishment and sexual nuances (one respondent), and the practice of sexually nuanced traditions (one respondent).

Table 1. Sample characteristics

Characteristics	Frequency (n= 149)
Age	
Mean	19.29 (SD= 1.086)
Batch	
2018	61 (41%)
2019	42 (28%)
2020	46 (31%)
History of Mental Disorder	0 (0%)
Metabolic or Chronic Disease	0 (0%)
Other Types of Violence	0 (0%)
Experience of Sexual Violence	
Never	94 (63%)
Age <6	6 (4%)
Age 6 – 12	5 (3%)
Age >12 – 16	22 (15%)
Age >16	22 (15%)
Types of Sexual Violence*	
Sexual Harassment	53
Sexual Intimidation	6
Sexual Exploitation	2
Inhumane Punishment	1
and Sexual Nuances	1
The practice of sexually	4
nuanced traditions	
Sexual Control	
Amount of Sexual Violence	
1 type	44 (80%)
>1 type	11 (20%)
Depression Incidence	
Yes	41 (27,5%)
No	108 (72,5%)
Depression Scale	
Normal	108 (73%)
Mild	24 (16%)
Moderate	14 (9%)
Severe	3 (2%)

*Cannot be used as a percentage

The description of the relationship between the experience of sexual violence and the incidence of depression in students of the Faculty of Medicine, Pelita Harapan University can be seen in Table 2.

Table 2. Relationship between Experience of Sexual Violence and Incidence of Depression

Experience of Sexual Violence	Depression Incidence				Total		OR (95% CI)	P value
	Yes		No					
	n	%	n	%	n	%		
Yes	25	45,5	30	54,5	55	100	4,063 (1,9 – 8,6)	< 0,001
No	16	17,0	78	83,0	94	100		
Total	41	27,5	108	72,5	149	100		

P value <0,05 considered as significant

The description of the relationship between the experience of sexual violence and the four depression scales in students of the Faculty of Medicine, Universitas Pelita Harapan can be seen in Table 3.

Table 3. Relationship between Experiences of Sexual Violence and Four Depression Scales

Experience of Sexual Violence	Depression Scale								Total		*P* value
	Normal		Mild		Moderate		Severe				
	n	%	n	%	n	%	n	%	n	%	
No	78	83,0	10	10,6	5	5,3	1	1,1	94	100	0,003
Yes	30	54,5	14	25,5	9	16,4	2	3,6	55	100	
Total	108	88,6	17	16,1	14	9,4	3	2,0	149	100	

P value <0,05 considered as significant.

The description of the relationship between the experience of sexual violence and the two depression scales in students from the Faculty of Medicine, Universitas Pelita Harapan can be seen in Table 4.

Table 4. Relationship between the Experience of Sexual Violence and the Two Depression Scales

Experience of Sexual Violence	Depression Scale				Total		OR (95% CI)	P value
	Normal - mild		*Moderate - severe*					
	n	%	n	%	n	%		
No	88	93,6	6	6,4	94	100	3,667 (1,2 – 10,5)	0,024
Yes	44	80,0	11	20,0	55	100		
Total	132	88,6	17	11,4	149	100		

P value <0,05 considered as significant

The description of the relationship between the amount of experiences of sexual violence with the incidence of depression in students of the Faculty of Medicine, Pelita Harapan University can be seen in Table 5.

Table 5. The Relationship between the Amount of Sexual Violence Experiences and the Incidence of Depression

Amount of Sexual Violence Experience	Depression Incidence				Total		OR (95% CI)	P value
	Yes		No					
	n	%	n	%	n	%		
>1 type	9	81,8	2	18,2	11	100	7,875 (1,5 – 41,03)	0,018
1 type	16	36,4	28	63,6	44	100		
Total	25	45,5	30	54,5	55	100		

P value <0,05 considered as significant

The description of the relationship between the age of experience of sexual violence and the incidence of depression in students of the Faculty of Medicine, Pelita Harapan University can be seen in Table 6.

Table 6. Relationship between Experience of Sexual Violence and Incidence of Depression

Age of Experience of Sexual Violence	Depression Incidence				Total		P value
	No		Yes				
	n	%	n	%	n	%	
Age <6	4	66,7	2	33,3	6	100	0,897
Age 6 – 12	3	60,0	2	40,0	5	100	
Age >12 – 16	12	54,5	10	45,5	22	100	
Age >16	11	50,0	11	50,0	22	100	
Total	44	80,0	11	20,0	55	100	

P value <0,05 considered as significant

Discussion

This study examines the relationship between sexual violence and the incidence of depression in students of the Faculty of Medicine, Pelita Harapan University which was carried out in the period January 2021 to March 2021. The grouping of respondents who experienced depression was obtained from three categories of depression grouped by researchers, namely mild depression, moderate depression, and depression. major depression. The results obtained from this study indicate that of the 149 respondents involved, as many as 55 people have experienced sexual violence, with the most common form of sexual violence experienced is sexual harassment. Among the 55 people, 45.5% of them were depressed while the other 54.5% were not depressed. A total of 94 people have never experienced sexual violence, and 17% of them are depressed, while 83% are not depressed. The results of the statistical test obtained a p value of < 0.001, which indicated that there was a significant relationship between the experience of sexual violence and the incidence of depression.

This study also saw that there was an increase in depressive symptoms in respondents who experienced sexual violence. The increase in these symptoms can be seen based on a depression scale which is grouped into normal, mild, moderate, and severe categories. To fulfill the requirements of the chi-square test, the authors grouped the categories into two, namely the normal – mild and moderate – severe categories. Of the 55 respondents who had experienced sexual violence, 80% were classified as normal-mild depression, and 20% were classified as moderate-severe depression. Meanwhile, of the 94 respondents who had never experienced sexual violence, 93.6% were classified as normal – mild depression, and 6.4% were classified as moderate – severe depression. The results of the statistical test got a p-value of 0.024, which indicates a significant relationship between sexual violence and depression scale.

The results of this study are in accordance with research conducted by Tarzia which examined the relationship between sexual violence and poor mental health in women in Australia. The results of this study indicate that women who have experienced sexual violence tend to feel depressed compared to women who have not experienced sexual violence.[7] This is also in accordance with the theory which states that if there is an experience that is negative and unexpected, it will increase the occurrence of depression.[9,10] An unexpected experience will also trigger stress, which if it lasts a long time. it will affect a person to be vulnerable to depression. This is also stated in a study conducted by Houle who found that sexual violence was also stated as an unwanted approach that became a trigger for stress, and was associated with an increase in depressive symptoms.[4]

Of the seven types of sexual violence experienced by respondents, as many as 20% of respondents who have experienced sexual violence claim to have experienced more than one type of sexual violence, while the other 80% only experienced one type of sexual violence. The results of the analysis test found that there was a significant relationship between the amount of experiences of sexual violence and the incidence of depression. However, this result can also be influenced by bias, namely the gap between the number of respondents who experienced one type of sexual violence and those who experienced more than one type of sexual violence. However, research conducted by Tarzia suggests that fewer experiences of sexual violence may be related to women's mental well-being at that time. Women who experience at least one type of sexual violence are also said to have a tendency to experience depression.[7] The results of research conducted by Houle also stated that someone who experienced sexual violence more often would have a higher incidence of depression than someone who had never experienced sexual violence.[4]

The cause of the occurrence of depression can be caused by several things, one example is the presence of an experience in early life that is unwanted or negative.[4,9] This is not in accordance with the results of this study, where there was no significant relationship between the time of experience sexual violence with the incidence of depression, which is obtained p value of 0.897. However, this is in accordance with the results of research conducted by Tarzia. The study found a relationship between sexual violence in adulthood with the onset of depression, but the association disappeared after adjusting for childhood sexual abuse.[7] This could be due to the absence of an association between the experience of sexual violence in early life and the occurrence of depression in this sample, the absence of a strong enough effect of the experience of sexual violence to cause depression, or the presence of a group that had protective factors against depression. Vulnerability to depression can be caused by a person's ability to overcome a stressor, such as by having good coping mechanisms, reasons for living, and spirituality.[7,11]

Conclusion

Based on the results of the study, it can be concluded that there is a significant relationship between sexual violence and the incidence of depression in students of the Faculty of Medicine, Pelita Harapan University.

Recommendation

It is hoped that further research will be able to examine the experience of sexual violence more deeply, by looking for further factors that can affect mental health conditions as a result of the experience. Further research is also expected to find out whether there is sexual violence that occurs in the Faculty of Medicine, Pelita Harapan University. It is also hoped that female students who have experienced sexual violence can report and seek help in order to avoid the impact of mental health problems that can occur, such as depression.

References

1. Komnas Perempuan. Bentuk Kekerasan Seksual. 2017

2. Conley AH, Overstreet CM, Hawn SE, Kendler KS, Dick DM, Amstadter AB. Prevalence and predictors of sexual assault among a college sample. Journal of American College Health [Internet]. 2017 Jan 2 [cited 2020 Nov 14];65(1):41–9. https://doi.org/10.1080/07448481.2016.1235578

3. Komnas Perempuan. Catatan Tahunan tentang Kekerasan terhadap Perempuan. Jakarta; 2020.

4. Houle JN, Staff J, Mortimer JT, Uggen C, Blackstone A. The Impact of Sexual Harassment on Depressive Symptoms during the Early Occupational Career. Society and Mental Health. 2011;1(2):89–105. https://doi.org/10.1177%2F2156869311416827

5. Mushtaq M, Sultana S, Imtiaz I. The Trauma of Sexual Harassment and its Mental Health Consequences Among Nurses. Journal of The College of Physicians and Surgeons . 2015;25(9):675-79. https://doi.org/09.2015/jcpsp.675679

6. Yüce M, Karabekıroğlu K, Yildirim Z, Şahın S, Sapmaz D, Babadağı Z, et al. The psychiatric consequences of child and adolescent sexual abuse. Noropsikiyatri Arsivi [Internet]. 2015 Dec 1;52(4):393–9. https://doi.org/10.5152/npa.2015.7472

7. Tarzia L, Maxwell S, Valpied J, Novy K, Quake R, Hegarty K. Sexual violence associated with poor mental health in women attending Australian general practices. Australian and New Zealand Journal of Public Health. 2017 Oct 1 [cited 2020 Dec 6];41(5):518–23. https://doi.org/10.1111/1753-6405.12685

8. Sari IP. KEKERASAN DALAM HUBUNGAN PACARAN DI KALANGAN MAHASISWA : STUDI REFLEKSI PENGALAMAN PEREMPUAN. Vol. 7, DIMENSIA: Jurnal Kajian Sosiologi. 2018 Aug.

9. Marwick K, Birrell S. Crash Course Psychiatry 5th Edition. 5th ed. Elsevier; 2019.

10. Sadock BJ. Synopsis of Psychiatry. 11th ed. Wolters Kluwer; 2015.

11. Breton JJ, Labelle R, Berthiaume C, Royer C, St-Georges M, Ricard D, et al. Protective factors against depression and suicidal behaviour in adolescence. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2015 Feb 1; 60(2):S5–15. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4345848/

Understanding Tsetse Fly (*Glossina morsitans)* Behavior through its *Genome*

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Citation : Marbun Kristin Talia, Nugroho Satya, Jo Juandy. Understanding Tsetse Fly (Glossina morsitans) Behavior through its Genome. Medicinus. 2022 October; 10(3): 122-129.
Keywords: *Glossina morsitans*; African trypanosomiasis; Whole-genome sequence; Symbionts; Vector control
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Online First : October 2022

Abstract

Glossina morsitans (G. morsitans), commonly known as tsetse fly, have caused public health concerns throughout the years. *G. morsitans* is the vector for *Trypanosoma brucei* (*T. brucei*), the parasite responsible for causing the deadly African sleeping disease (African trypanosomiasis). Researchers have searched for ways to contain this disease, but to little avail. Fortunately, new advances in sequencing methods have given researchers a new opportunity to win the war against the disease. The whole-genome sequence of *G. morsitans* provides essential data regarding involved genes that transmits *T. brucei* to humans. Information about those unique genes facilitates researchers to create new methods to prevent *G. morsitans* from becoming the vector of *T. brucei*, enabling the containment of this disease. With this, we review the unique genes in the *G. morsitans* genome, such as those that contribute to blood-feeding ability, establish a relationship with symbionts, and *G. morsitans* unique sensory genes, with an expectation that it would enhance our knowledge of *G. morsitans* as the vector for parasites causing African trypanosomiasis.

Introduction

The tsetse fly (*G. morsitans*) is the vector of *T. brucei*, a parasite that causes human African trypanosomiasis (HAT). HAT can infect humans and animals, impacting the human population, livestock and food supply. As *G. morsitans* is endemic to sub-Saharan Africa, around 70 million people in the region are at risk of contracting HAT.[1] Although treatments are available, they are relatively expensive and are not affordable for most people. Furthermore, there have been several reports of resistance to the available drugs, which calls out for a new drug development. At the moment, vaccine discovery is still an ongoing project.[2]

A way to minimize the disease's spread is by controlling the vector, *G. morsitans*. Whole-genome sequencing (WGS) of *G. morsitans* genome provides new ways to analyze its genetics and opens the door to many possibilities. Attardo and his team were ones of the pioneers who used WGS technology to sequence *G. morsitans* genome. Attardo and his team WGS project resulted in 366 megabases of *G. morsitans* genome, in which there are 12,308 predicted protein-encoding genes. The predicted protein accounts for properties such as a family of lactation-specific proteins, reduced complements of host-pathogen recognition proteins, and genes that are responsible for blood-feeding.[1] Whole-genome sequencing of *G. morsitans* enables us to analyze the unique genes that distinguish this species with other flies, and how its role as *T. brucei* vector. The most notable genes are those related with its ability as a blood feeder, the

ability to enable a symbiotic relationship with pathogens, and unique sensory genes. That genetic information subsequently could be used, controlling *G. morsitans* population to tackle the HAT.

Trypanosoma brucei, *Glossina morsitans* and the present situation

HAT has caused unrest among sub-Saharan Africans since its discovery in 1901 due to the mortality it caused. Once transmitted by the vector *G. morsitans*, this parasite will enter the bloodstream of humans. As depicted in **Figure 1**, after two- or three weeks post-infection, the disease would progress into two clinical stages, i.e., the hemolymphatic and meningoencephalitis stages.[3] The first stage, the hemolymphatic stage, begins after two or three weeks and can be diagnosed by the occurrence of fever episodes, liver problems, and a painful lymph node's swelling. In this first stage, the parasite has successfully invaded the blood and the lymph fluid. However, this stage is often undiagnosed and untreated since people think of it as a simple fever. The second stage is the meningoencephalitis stage. The parasites had crossed the body's blood-brain barrier and invaded the central nervous system (CNS) and the cerebrospinal fluid. This second stage appears slowly, and ranges from months to years.

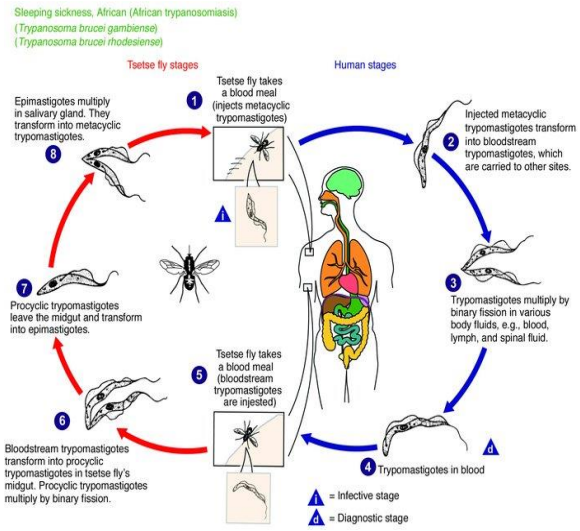

Figure 1. Life cycle of *T. brucei* and stages of infection. Human stages depict the presence of *Trypanosoma brucei* in humans, while *G. morsitans* stages depict the presence of the parasite within the fly (Centers for Disease Control and Prevention, 2022).

When *T. brucei* has successfully invaded the CNS, host immune responses will cause inflammation in the CNS. The inflammation would cause damage to the brain. In the terminal stage, patients will have dementia with incoherence and seizures due to the demyelination of the cells.[5] The most common cause of death is due to heart failure, brain inflammation (encephalitis), as well as weight and muscle loss (cachexia).[6] The term "sleeping disease" is derived from the fact that the parasite infects the hypothalamus that controls the circadian rhythm. Thus, an infection by the parasite will disturb the cycle.

Until now, HAT has been managed by using active or passive detection and treatment programs.[8] Healthcare workers conduct active detection to determine whether an individual contracts HAT by observing their symptoms and running relevant tests. Passive detection is done independently, where individuals decide whether or not they have contracted the disease by comparing their symptoms to the guidelines given by health institutions.[7] However, these methods are inefficient since the current diagnostic procedure used in active detection is costly. Moreover, the procedure used in passive detection is flawed due to the non-specific symptoms presented in the early stages of the disease.[8]

Since a specific vaccine is still unavailable, a fast and accurate diagnosis will be necessary, as poor surveillance may result in a re-emerging epidemic.[9] Scientists are currently developing new rapid serodiagnostic tests for HAT, with an expectation that those tests can be used in a particular region with a high risk of infection and thus, novel rapid serodiagnostic tests will give more countermeasures against HATin that area.[10] In parallel, controlling the vector would be crucial as *G. morsitans* is the sole vector of *T. brucei*. An ability to control *G. morsitans*

would significantly contribute to the eradication of HAT. Therefore, the following parts of this review are dedicated to better understand the vector.

Blood feeding and nutrition uptake by *G. morsitans*

G. morsitans are unique since they consume blood as their primary nutrient, despite coming from the *Diptera* order. Three genes, i.e., *tsal*, putative adenosine deaminases, and insect growth factors (*ADGF*)-related and *aquaporin* genes, play a crucial role in the blood-feeding characteristic of *G. morsitans*. When blood from another organism is transferred to another, the immune system will detect it as foreign, resulting in activation of the complement cascade and the formation of a blood clot.[11] However, in *G. morsitans* case, blood is their meal, and they need to be able to access non-coagulated blood. Thus, a non-coagulation protein is required. This is where the *tsal* gene plays the role (*tsal* stands for "tsetse salivary"), in which there are three distinct contributing genes: *tsal1* (*GMOY012071*), which encodes for tsal1 protein, and *tsal2a* (*GMOY012361*), which encodes for tsal2a protein, and *tsal2b* (*GMOY012360*) which encodes for tsal2b protein.[12] The functions of these genes were deducted through multiple sequence alignment by Caljon et al[10].

The *tsal1*, *tsal2a* and *tsal2b* genes from *G.morsitans* were compared to homologous genes annotated as putative salivary gland nucleases in *Culex quinquefasciatus* (southern house mosquito), *Phlebotomus argentipes* (sand flies) and *Lutzomyia longipalpis* (sand flies), as well as the *Marsupenaeus japonicus* shrimp hepatopancreatic nuclease and the *Serratia marcescens* nuclease. The analysis can be seen in **Figure 2**. The *tsal* gene family encodes high-affinity nucleic acid-binding proteins without strong endonuclease activity.[13] One of the compounds in *G. morsitans* saliva is the product of the tsetse thrombin inhibitor (*TTI*) gene, which plays a huge role in anticoagulation and antithrombotic activity during blood feeding. Not only serves as an anticoagulant agent, but this inhibitor also inhibits thrombin-induced platelet aggregation.[14] Taken together, genes encoding for *G. morsitans* saliva are really essential. Without those genes, *G. morsitans* will not be able to feed blood and survive.

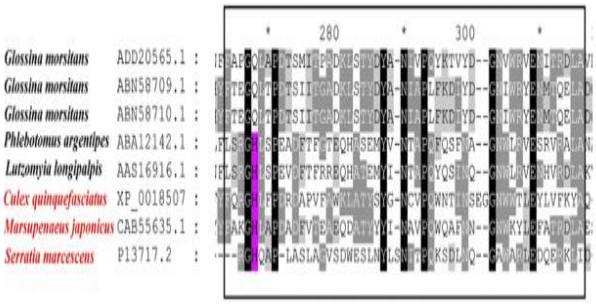

Figure 2. Multiple sequence analysis of *tsal* genes with homologous genes (Franco et al., 2018). Three tsal genes of *Glossina morsitans* were compared to homologous genes from *P. argentipes*, *L. longipalpis*, *C. quinquefasciatus* and *M. japonicus*. The species names in red have a confirmed nuclease activity in their genes. The black box represents the putative nuclease active site region. The black highlight indicates amino acid similarity in all eight species. The purple highlight represents histidine residues that supposedly are important for nuclease catalytic activity.

Other genes that enable blood-feeding are the uncharacterized adenosine deaminases insect growth factors (ADGFs)-related gene and the *aquaporin* gene. The still-yet uncharacterized abundant salivary gland's protein reduces inflammation caused by adenosine and inosine-induced mast cell activation. A mast cell is activated when an antigen is detected by IgE bound to FcεRI on the mast cell surface.[15] Blood contains a variety of antigens. There is a high possibility that one of those antigens will react with IgE and cause inflammation. Since inflammation is not desirable during feeding, the putative ADGF-related protein will suppress mast cell activation. Another essential gene during the blood-feeding by *G. morsitans* is the *aquaporin* gene. *G. morsitans* has ten *aquaporin* genes, in contrast to six and eight respective genes in mosquitoes and *Drosophila* sp., respectively. The presence of *aquaporin* genes ensures water homeostasis following the blood meal.[1] This mechanism is vital

since the ingested blood is equivalent to the *G. morsitans* weight. Hence, excess water needs to be excreted quickly to reduce body density.[1]

The relationship between *G. morsitans* and its symbionts

One of the interesting features of *G. morsitans* biology is how symbionts (i.e., an organism living in symbiosis with another organism, such as gut microbiota and humans) reside and evade *G. morsitans* immune response. Some factors enable this phenomenon, comprising external factors, genetic factors, and the capability of pathogens themselves.[16] Aside from hosting the *T. brucei* parasite, *G. morsitans* also hosts other symbionts, such as *Wigglesworthia glossinidia*, which lives intracellularly in the midgut and extracellularly in lumen milk gland, *Wolbachia* spp. which resides in gonadal tissues, *Sodalis* spp. which resides in digestive and reproductive organs, as well as the salivary gland hypertrophy virus which resides in the salivary glands.[17] *G. morsitans* competence to act as a host for these symbionts depends on multiple factors such as age, sex, and overall health condition. A study was conducted to analyze *G. morsitans* capability to eliminate pathogen invasion to find whether tsetse has an inherited defective immune system or other factors at play.[18] The experiment involved feeding *Trypanosoma*-infected blood to *G. morsitans*. In an optimal condition, less than 50% of the lab-grown tsetse flies that had fed *Trypanosoma*-infected blood became infected with *T. brucei*. This finding suggests that normal tsetse flies with adequate nutrition and *environment* can resist the parasite's infection.

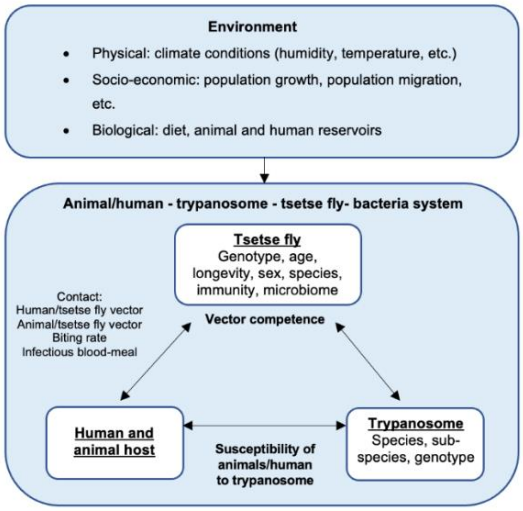

Figure 3. Factors that affect *T. brucei*, *G. morsitans*, and human infections. The interaction between the parasite, the vector and human or animal host dictate the incidence rate of African trypanosomiasis. In addition, the environmental changes will influence this three-party interaction as well.

However, the environmental condition in sub-Saharan Africa differs from the one in the lab. Global climate changes, such as changing temperature, rainfall patterns, urbanization, deforestation, grassland degradation, and overgrazing, will affect the infection rate.[16] The summary of the factors that affect *Trypanosoma* infections can be seen in **Figure 3**. The geographical distribution of *Trypanosoma* reservoirs, nutritional behavior, and development of *Trypanosoma* will be affected. Thus, *G. morsitans* and humans will also be affected. It could be that deforestation and urbanization cause *G. morsitans* to lose their original habitat and therefore move into closer contact with human populations. Furthermore, the constant climate change activity may weaken the *G. morsitans* immune system and impede the infection containment.

Glossina	*Drosophila*	Function
pgrp-la	*pgrp-la*	Toll pathway activation
pgrp-lb	*pgrp-lb*	PGN scavenging
pgrp-lc	*pgrp-lc*	Imd pathway activation
pgrp-ld	*pgrp-ld*	Unknown
	pgrp-le	Imd pathway activation
	pgrp-lf	Negative regulation of the Imd pathway
pgrp-sa	*pgrp-sa*	Toll pathway activation
pgrp-sb	*pgrp-sb1*	Bactericidal
	pgrp-sb2	Unknown
	pgrp-sc1a	PGN scavenging
	pgrp-sc1b	PGN scavenging
	pgrp-sc2	PGN scavenging
	pgrp-sd	Toll pathway activation

Figure 4. List of peptidoglycan recognition proteins (*pgrp*) genes in *Glossina* sp. and *Drosophila* sp. and their respective functions. While *Drosophila* sp. has 13 *pgrp* genes, Glossina sp. only has 6 *pgrp* genes.

G. morsitans genetics also influences the immune response towards its symbionts. A reduced number of genes responsible for microbial detection will simultaneously lower the immune response.[19] Genes responsible for microbial detection are crucial since they signal the body that there is a foreign invader that needs to be neutralized. Pathogen detection is a multistep process that requires contact between host (*G. morsitans*) pattern recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs). Subsequently, a symbiont must be able to withstand the activity of various proteins, such as peptidoglycan (PGN) recognition proteins (PGRPs), antimicrobial effector peptides (AMPs) produced by immune deficiency (IMD) pathway, midgut lectins, and other proteins.[1] **Figure 4** compares PGRP components between *Drosophila* and *Glossina* spp. *Drosophila* sp. has 13 PGRPs that play a role in peptidoglycan (PGN) recognition. While, *G. morsitans* only has six identified *pgrp* genes, four in the long subfamily (*pgrp-la*, *-lb*, *-lc*, and *-ld*) and two in the short subfamily (*pgrp-sa* and *-sb*).[1,15] *Glossina morsitans* lack several PGN receptors (*pgrp-le*, *-lf*, *-sc*, and *-sd*) found in *Drosophila* sp. PGN receptors are important in microbial detection since PGN is the essential component of the cell wall of most bacteria. The absence of PGN-detecting genes causes insensitivity to pathogenic invasion. Hence, an attenuated immune response will be exhibited.[1] Therefore, this is the most probable cause of why symbionts can reside within the *G. morsitans*.

In the case of infection by *T. brucei*, this parasite has evolved. It uses two mechanisms to escape from the *G. morsitans* immune system and simultaneously uses *G. morsitans* attenuated immune system to its advantage.[9] First, *T. brucei* can evade the immune response by overcoming the complement system by recycling its variant surface glycoprotein (VSG). The classical complement pathway, activated by antibodies, can be overcome through a rapid VSG-recycling system that removes IgGs from its surface.[20]

Secondly, *T. brucei* can suppress T-cell proliferation by eliciting suppressive macrophage by activating a parasite membrane protein, Trypanosoma Suppression Immunomodulating Factor (TSIF). As a result, the induced macrophage will produce nitric oxide and prostaglandins responsible for impairing T-cell proliferation during the early infection stage. These macrophages also have a reduced ability to activate specific T cells since macrophages' ability to present peptides via their MHC class II is diminished. Therefore, parasites are free to thrive.[21]

Sensory genes of *G.morsitans*

Population growth of *G. morsitans* needs to be controlled and reduced, if possible. One way is by using traps. Therefore, it is important to determine the traps that attract *G. morsitans*. Scientists currently use one unique feature of *G. morsitans* to lure them more easily to the traps, which is through their sensitivity to color.[22] *G. morsitans* visual systems are similar to other calyptrate *Diptera* (e.g., house flies and blowflies), in which each ommatidium (a cluster of photoreceptors) consists of eight photoreceptors (R1 to R8). The *Rh5* gene encodes those photoreceptors.[1,23]

Photoreceptors R1-R6 are similar across each ommatidium, as they are sensitive to ultraviolet (UV) and blue wavelengths. On the other hand, photoreceptors R7 and R8 are located at the center of each ommatidium. The R7 and R8 have two forms: 'y' is sensitive to green-yellow wavelengths and 'p' is sensitive to blue wavelength.[19] While the R8y form is most sensitive to yellow-green wavelengths, the R7y form is most sensitive to UV wavelength since 'y' has an accessory sensitizing pigment sensitive to UV. The R8p form is most susceptible to blue wavelength, and R7p is most sensitive to lower UV lengths. Since tsetse flies are sensitive to those two types of color (green-yellow or blue-UV), a study by Santer determined which color was preferred by *G. morsitans*.[20] It was discovered that the blue wavelength was preferred over the green-yellow wavelengths. Therefore, blue-colored traps should be used since they will create a higher chance of catching *G. morsitans* in the environment.

Conclusion

WGS of *G. morsitans* are able to give us a better understanding of its role as the vector of *T. brucei*. Five essential genes drive *G. morsitans* to become a prime vector for *T. brucei*. The first three are the *tsal*, *ADGF*-related, and *aquaporin* genes. These unique genes are crucial for the growth and development of *G. morsitans* as a blood-feeder and may be good candidates for vaccine targets. The next gene is the reduced *pgrp* genes which enable parasites and bacteria to evade *G. morsitans* immune response. The final gene is the *Rh5* gene that causes *G. morsitans* to be sensitive to color. This finding is used to develop a control strategy to reduce *G. morsitans* population by setting up traps with blue color. In conclusion, the whole-genome analysis of *G. morsitans* facilitates a better understanding of *G. morsitans* behavior. This information could help to control and even prevent the spread of human African trypanosomiasis

References

1. Attardo G, Abila P, Auma J, Baumann A, Benoit J, Brelsfoard C et al. Genome Sequence of the Tsetse Fly (Glossina morsitans): Vector of African Trypanosomiasis. Science. 2014; 344 (6182): 380-386. https://doi.org/10.1126/science.1249656

2. Fairlamb A, Horn D. Melarsoprol Resistance in African Trypanosomiasis. Trends in Parasitology. 2018; 34(6): 481-492. https://doi.org/10.1016/j.pt.2018.04.002

3. Bouteille B, Buguet A. The detection and treatment of human African trypanosomiasis. Research and Reports in Tropical Medicine. 2012;3: 35-45. https://doi.org/10.2147%2FRRTM.S24751

4. Centers for Disease Control and Prevention. Trypanosomiasis, African. Available on https://www.cdc.gov/dpdx/trypanosomiasisafrican/index.html cited Jan 2022.

5. Kennedy P. Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). The Lancet Neurology. 2013;12(2):186-194. https://doi.org/10.1016/s1474-4422(12)70296-x

6. Ponte-Sucre A. An Overview of Trypanosoma brucei Infections: An Intense Host–Parasite Interaction. Frontiers in Microbiology. 2016;7. https://doi.org/10.3389/fmicb.2016.02126

7. Checchi F, Funk S, Chandramohan D, Chappuis F, Haydon D. The impact of passive case detection on the transmission dynamics of gambiense Human African Trypanosomiasis. PLOS Neglected Tropical Diseases. 2018;12(4): e0006276. https://doi.org/10.1371/journal.pntd.0006276

8. Snijders R, Fukinsia A, Claeys Y, Hasker E, Mpanya A, Miaka E et al. Costs and Outcomes of Integrated Human African Trypanosomiasis Surveillance System Using Rapid Diagnostic Tests, Democratic Republic of the Congo. Emerging Infectious Diseases. 2021;27(8):2144-2153. https://doi.org/10.3201%2Feid2708.202399

2. Franco J, Cecchi G, Priotto G, Paone M, Diarra A, Grout L et al. Monitoring the elimination of human African trypanosomiasis: Update to 2016. PLOS Neglected Tropical Diseases. 2020;14(5):e0008261. https://doi.org/10.1371%2Fjournal.pntd.0008261

3. Jamonneau V, Camara O, Ilboudo H, Peylhard M, Koffi M, Sakande H et al. Accuracy of Individual Rapid Tests for Serodiagnosis of Gambiense Sleeping Sickness in West Africa. PLOS Neglected Tropical Diseases. 2015; 9(2): e0003480. https://doi.org/10.1371/journal.pntd.0003480

4. Ooi C, Haines L, Southern D, Lehane M, Acosta-Serrano A. Tsetse GmmSRPN10 Has Anti-complement Activity and Is Important for Successful Establishment of Trypanosome Infections in the Fly Midgut. PLoS Neglected Tropical Diseases. 2015;9(1):e3448. https://doi.org/10.1371%2Fjournal.pntd.0003448

5. Matetovici I, Caljon G, Van Den Abbeele J. Tsetse fly tolerance to T. brucei infection: transcriptome analysis of trypanosome-associated changes in the tsetse fly salivary gland. BMC Genomics. 2016;17(1). https://doi.org/10.1186%2Fs12864-016-3283-0

6. Caljon G, Ridder K, Stijlemans B, Coosemans M, Magez S, De Baetselier P et al. Tsetse Salivary Gland Proteins 1 and 2 Are High Affinity Nucleic Acid Binding Proteins with Residual Nuclease Activity. PLoS ONE. 2012;7(10):e47233. https://doi.org/10.1371%2Fjournal.pone.0047233

7. Calisto B, Ripoll-Rozada J, Dowman L, Franck C, Agten S, Parker B et al. Sulfotyrosine-Mediated Recognition of Human Thrombin by a Tsetse Fly Anticoagulant Mimics Physiological Substrates. Cell Chemical Biology. 2021; 28(1): 26-33.e8. https://doi.org/10.1016/j.chembiol.2020.10.002

8. Krystel-Whittemore M, Dileepan K, Wood J. Mast Cell: A Multi-Functional Master Cell. Frontiers in Immunology. 2016;6(6): 620. https://doi.org/10.3389/fimmu.2015.00620

9. Nnko H, Ngonyoka A, Salekwa L, Estes A, Hudson P, Gwakisa P et al. Seasonal variation of tsetse fly species abundance and prevalence of trypanosomes in the Maasai Steppe, Tanzania. Journal of Vector Ecology. 2017; 42(1): 24-33. https://doi.org/10.1111/jvec.12236

10. Wang J, Weiss B, Aksoy S. Tsetse fly microbiota: form and function. Frontiers in Cellular and Infection Microbiology. 2013;29(3): 69. https://doi.org/10.3389/fcimb.2013.00069

11. Geiger A, Ponton F, Simo G. Adult blood-feeding tsetse flies, trypanosomes, microbiota and the fluctuating environment in sub-Saharan Africa. The ISME Journal. 2014; 9(7): 1496-1507. https://doi.org/10.1038%2Fismej.2014.236

12. Myllymäki H, Valanne S, Rämet M. The Drosophila Imd Signaling Pathway. The Journal of Immunology. 2014;192(8):3455-3462. https://doi.org/10.4049/jimmunol.1303309

13. Mugnier M, Stebbins C, Papavasiliou F. Masters of Disguise: Antigenic Variation and the VSG Coat in Trypanosoma brucei. PLOS Pathogens. 2016;12(9): e1005784. https://doi.org/10.1371/journal.ppat.1005784

14. Alfituri O, Quintana J, MacLeod A, Garside P, Benson R, Brewer J et al. To the Skin and Beyond: The Immune Response to African Trypanosomes as They Enter and Exit the Vertebrate Host. Frontiers in Immunology. 2020;11. https://doi.org/10.3389%2Ffimmu.2020.01250

15. Lindh J, Goswami P, Blackburn R, Arnold S, Vale G, Lehane M et al. Optimizing the Colour and Fabric of Targets for the Control of the Tsetse Fly Glossina fuscipes fuscipes. PLoS Neglected Tropical Diseases. 2012; 6(5): e1661. https://doi.org/10.1371%2Fjournal.pntd.0001661

16. Santer R. A Colour Opponent Model That Explains Tsetse Fly Attraction to Visual Baits and Can Be Used to Investigate More Efficacious Bait Materials. PLoS Neglected Tropical Diseases. 2014; 8(12): e3360. https://doi.org/10.1371/journal.pntd.0003360

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Future Application of Oncolytic Viruses for Cancer Treatment

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Citation : Lesmana Jevon Aaron, Jo Juandy. Future Application of Oncolytic Viruses for Cancer Treatment. Medicinus. 2022 October; 10(3): 130-140.
Keywords: Cancer; Oncolytic viruses; Immunotherapy
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Online First : October 2022

Abstract

Cancer treatments have developed over the years. A particular improvement is the utilization of oncolytic viruses to treat cancers. Oncolytic viruses are one of the immunotherapeutic tools that potentially could provide good results and benefits to the patients. Oncolytic viruses could mediate antitumor effects. Indeed, the connection between viral infections and cancer treatment have been reported historically. It is known that oncolytic viruses prefer to infect cancer cells rather than normal cells, resulting in the presentation of tumor-associated antigens to the immune system, boosting immunological activity in the tumor microenvironment, as well as assisting in the expression of inflammatory and immunomodulatory cytokines. Oncolytic viruses are a novel regimen in the cancer therapy, in which knowledge and technology of utilizing oncolytic viruses to treat cancer are still evolving. Importantly, clinical trials demonstrated that the viruses were well tolerated by cancer patients. Considering its potency and prospect, oncolytic viral treatments could be a useful additional tool for cancer therapy.

Introduction

Cancer is one of the leading causes of mortality worldwide with nearly 10 million deaths in 2020, in which the most common death-causing cancers in 2020 were lung, colon and rectum, liver, stomach and breast cancers.[1,2] Multiple treatments have been developed in treating cancer, however its prevalence, morbidity and mortality are still high. The conventional treatments, including surgery, chemotherapy, hormonal therapy and radiotherapy, mostly provide a limited durable effect in patients with advanced cancer. The exception presumably applies for hematological and testicular cancer, in which they can be cured with the current therapies if they are detected at the early stage.[3,4] Therefore, the cancer treatments are continuously advanced to create a better, more effective regimen in treating cancers. Oncolytic virus is one, arguably, of such innovations. Surprisingly, the concept of oncolytic viruses is not exactly novel in the medical field. There have been numerous case reports, suggesting that there is a connection between infections by microbes and the spontaneous regression of tumor.[5]

The first evidence might be the writing in the Ebers Papyrus around 1550 BC, stating that the Egyptian physicians used poultice followed by incision to induce infection in order to treat tumor.[6] Another evidence is from the year 1320, when Peregrine Laziozi had suffered from cancer in his tibia, which then needed to be amputated. The cancer had grown through his skin, causing an infection in the area. Something intriguing occurred after the infection, nevertheless, in which the tumor started to disappear and no recurrence observed afterward. The phenomenon was known as 'St. Peregrine tumor'.[7] In the 17th and 18th centuries, a

procedure of creating open surgical wounds to allow infections occurred were considered to be useful. Reports had also shown that several leukemia patients became disease-free after viral infections.[8] A female patient with acute leukemia in 1904 and a female patient with cervical cancer in 1912 reported a reduction of tumor proliferation and demonstrated tumor necrosis after viral infection.[9] However, using viruses as a cancer treatment was unheeded. In addition, the very strict regulation in testing and implementing a new treatment's method have impeded the clinical adoption of this concept. Indeed, it took three decades for this concept to re-emerge with a novel name as 'oncolytic viruses'.[3]

Oncolytic viruses are viruses that able to infect and lyse tumor cells, naturally or artificially. The aim of the artificial modification is to increase efficacy and safety of using oncolytic viruses.[10] Oncolytic viruses have been suggested to be a novel cancer therapy's advancement, as they provided a durable and effective responses in the clinical trials.[5] Oncolytic viruses have also shown to be able to stimulate the immune system against tumor cells, which eventually modulate the development of antitumor response. It is postulated that the immune stimulation occurs due to several mechanisms that happen in the tumor microenvironment, which will be subsequently discussed.[11] There have been numerous clinical trials involving oncolytic viruses with different modifications and in combination with other antitumor therapies thus far. The usage of oncolytic viruses is an attractive concept, hence it could explain why there have been more than 100 clinical trials using those viruses.[12] Most of the reported trials were in phase I and II, while some were already in phase III. Taken together, this would be an exciting period to witness whether those findings would support the clinical implementation of using oncolytic viruses to treat cancers.

Oncolytic viruses and cancers

Certain DNA viruses that might have the potential to be oncolytic are adenovirus (family: Adenoviridae), vaccinia virus (family: Poxviridae), herpesvirus (family: Herpesviridae) and parvovirus H1 (family: Parvoviridae).[13] Adenovirus, vaccinia virus and herpesvirus are double-stranded DNA virus, while parvovirus H1 is single-stranded DNA virus. The replication's site for adenovirus, herpesvirus and parvovirus H1 are in the nucleus and cytoplasm, while vaccinia virus only replicates in the cytoplasm. Unsurprisingly, adenovirus, herpesvirus and parvovirus H1 have the nuclear integration ability, while vaccinia virus does not have it. The cell receptor for adenovirus is coxsackie-adenovirus receptor (CAR); the ones for herpesvirus are herpesvirus entry mediator (HVEM), nectin 1, and nectin 2; while the cell receptor for parvovirus H1 is sialic acid residues. Adenovirus, vaccinia virus and herpesvirus do not show immunogenicity upon re-exposure and penetration across the blood-brain barrier, while parvovirus H1 exhibits the immunogenicity.[13] **Table 1** describes properties of the mentioned DNA viruses.

Table 1. Properties of the mentioned DNA viruses (Kaufman *et al*., 2015).
dsDNA, double-stranded DNA; *ssDNA*, single-stranded DNA; *CAR*, coxsackie-adenovirus receptor; *HVEM*, herpesvirus entry mediator; +, able or shows positive result; -, unable or shows negative result.

Properties	Adenovirus	Vaccinia virus	Herpesvirus	Parvovirus H1
Baltimore classification	Group I: dsDNA	Group I: dsDNA	Group I: dsDNA	Group I: ssDNA
Replication site	Nucleus and cytoplasm	Cytoplasm	Nucleus and cytoplasm	Nucleus and cytoplasm
Cell receptor	CAR	Unknown	HVEM, Nectin 1, Nectin 2	Sialic acid residues
Nuclear integration	+	-	+	+
Immunogenicity	-	-	-	+
Blood-brain barrier penetration	-	-	-	+

Several RNA viruses that could be used as oncolytic virus are reovirus (family: Reoviridae), coxsackievirus (family: Picornaviridae), Seneca Valley virus (family: Picornaviridae), poliovirus (family: Picornaviridae), measles virus (family: Paramoxyviridae), Newcastle disease virus (family: Paramoxyviridae) and vesicular stomatitis virus (family: Rhabdoviridae).[13] Reovirus is double-stranded RNA virus. Coxsackievirus, Seneca Valley virus and poliovirus are positive-sense, single-stranded RNA virus. Measles virus, Newcastle disease virus and vesicular stomatitis virus are negative-sense, single-stranded RNA virus. The replication site for those RNA viruses are in the cytoplasm, hence they do not possess the nuclear integration ability. The cell receptors for coxsackievirus are CAR, intercellular adhesion molecule 1 (ICAM-1) and decay accelerating factor (DAF); the one for poliovirus is CD155; the cell receptors for measles virus are signaling lymphocytic activation molecule (SLAM) and CD46;

While the one for vesicular stomatitis virus is low-density lipoprotein receptor (LDLR). Reovirus, coxsackievirus, measles virus, Newcastle disease virus and vesicular stomatitis virus do not show immunogenicity upon re-exposure. While Seneca Valley virus exhibits the immunogenicity upon re-exposure, poliovirus might show the immunogenicity. Reovirus, Seneca Valley virus, poliovirus and Newcastle disease could penetrate the blood-brain barrier, while coxsackievirus, measles virus and vesicular stomatitis virus cannot penetrate it.[13] **Table 2** describes properties of the mentioned RNA viruses.

Table 2. Properties of the mentioned RNA viruses (Kaufman *et al*., 2015).
dsRNA, double-stranded RNA; *ss(+)RNA*, positive-sense, single-stranded RNA; *ss(-)RNA*, negative-sense, single-stranded RNA*; CAR,* coxsackie- adenovirus receptor; *ICAM-1*, intercellular adhesion molecule 1; *DAF*, decay accelerating factor; *SLAM*, signaling lymphocytic activation molecule; *LDLR*, low-density lipoprotein receptor; +, able or shows positive result; -, unable or shows negative result.

Properties	Reovirus	Coxsackievirus	Seneca Valley virus	Poliovirus	Measles virus	Newcastle disease virus	Vesicular stomatitis virus
Baltimore classification	Group III: dsRNA	Group IV: ss(+) RNA	Group IV: ss(+) RNA	Group IV: ss(+) RNA	Group V: ss(-) RNA	Group V: ss(-) RNA	Group V: ss(-) RNA
Replication site	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm
Cell receptor	Unknown	CAR/ICAM-1/DAF	Unknown	CD155	SLAM and CD46	Unknown	LDLR
Nuclear integration	-	-	-	-	-	-	-
Immunogenicity	-	-	+/-	+	-	-	-
Blood-brain barrier penetration	+	-	+	+	-	+	-

Oncolytic viruses indeed could infect neoplastic cells. A neoplasm comprises cells with an abnormal growth's regulation system, results in cellular abnormalities. Neoplastic cells could expand disproportionately and proliferate in an abnormal way, causing problems to their surroundings. Neoplastic cells could also migrate from their original position via circulatory or lymphatic systems, inducing secondary cancers or metastasis. This characteristic is the hallmark of malignant neoplasms or cancers, in contrast to benign neoplasms that remain to its original location and do not metastases. The metastatic property indeed causes cancers to induce significant morbidity and mortality.[14] In addition, these cancer cells could secrete toxic factors as well, causing systemic illness.[14,15]

The development of cancer cells is based on the clonality of tumor, i.e., the development from a single cell to proliferate abnormally. For a cell to become cancerous, it must develop a series of alterations. This multistep process involves gene mutations (the driver mutations) to activate oncogenes and to select cells that have the properties as a neoplastic cell. The first step is the tumor initiation, in which an alteration in a single cell causing an abnormal proliferation. The second step is the tumor progression, in which additional mutations lead to more cancerous cells. The third step is the clonal selection, in which several mutated cells having selective advantages would become the dominant cancer cells.[15] In addition, cancer cells do not exhibit density-dependent inhibition and contact inhibition, hence they are able to proliferate continuously, eventually migrating over the underneath cells and forming multilayered patterns of cells. Cancer cells display an autocrine growth stimulation, leading to continuous auto-stimulation of cell division without depending on growth factors produced by other cells. Cancer cells could also secrete growth factors promoting new blood vessels' formation (i.e., angiogenesis) to supply nutrients and support the metastasis. Cancer cells have a longer life span as well, compared with normal cells, due to the resistance to apoptosis.[15]

There are several major groups of cancer, including carcinomas, sarcomas, leukemias and lymphomas. Carcinomas are malignant neoplasm of the epithelial tissues, comprising approximately 90% of human cancers. Sarcomas are malignant neoplasm of the connective tissues (muscle, bone, cartilage and fibrous tissue) in humans. Leukemias and lymphomas are cancers of white blood cells and cancers of the gland or nodes of the lymphatic system, respectively, comprising approximately 8% of human cancers.[14,15]

Mechanism of action of oncolytic viruses in treating cancer cells

Oncolytic viruses could be administered to the patient via an injection directly to the tumor (intratumoral), subcutaneous, intraperitoneal, intravenous or intratechal (an injection into the spinal canal).[16] After the administration, the viruses would infect cancer cells by targeting the cell receptors to enter the cells. Within the cancer cells, oncolytic viruses started to create their particles using the host's cell machinery. As major characteristics of cancer cells include immune evasion and abnormal apoptotic regulation, the oncolytic viruses could exploit these properties to obtain an abundant time to complete their life cycle.[13] Furthermore, the innate signaling pathway, including retinoic acid-inducible gene 1 (RIG-1), interferon regulatory factor 7 (IRF-7), interferon regulatory factor 3 (IRF-3) and Janus kinase-signal transducer and activator of transcription (JAK-STAT), of the cells is downregulated, thus minimizing the detection of viral particles by the host's innate immunity (e.g., Toll-like receptors and RIG-1) as well as suppressing the cellular antiviral pathway's mechanism. As a result, the production of type-1 interferon (IFN), inflammatory cytokines and protein kinase R (PKR) are downregulated.[13] Of note, functions of type-1 IFN are to promote immune response, to reduce cellular proliferation, and to activate the pro-apoptotic protein p53. In addition, functions of PKR are to inhibit protein translation and to prevent viral particles' production, which will eventually stop the viral spreading.[17,18]

The viral replication within the cancer cells would eventually induce cell lysis and cell death, such as apoptosis, pyroptosis and necrosis.[13] The viral infection induces dysfunction of cellular organelles and incites the oxidative stress. The oxidative stress is caused by the production of reactive nitrogen species and by the endoplasmic reticulum stress due to an elevated levels of intracellular calcium.[19] Furthermore, the cell lysis would release new viral progeny to

infect other tumor cells and induce the antitumor immunity systematically by releasing several proteins, such as tumor-associated antigens. The released tumor-associated antigens could activate the adaptive immune response, which results in tumor regression, including cancer cells at distant sites (i.e., metastatic cancer).

Furthermore, pathogen-associated molecular patterns (PAMP), danger-associated molecular patters (DAMP) and cytokines are released after cell death, promoting the maturation of antigen-presenting cells, such as dendritic cells. The activated dendritic cells would process tumor-associated antigens and present them to activate $CD4^+$ and $CD8^+$ T cells.[3,13,20] The activated $CD4^+$ and $CD8^+$ T cells would subsequently recognize and destroy the corresponding neoplastic cells. $CD4^+$ T cells would also stimulate B cells to mature into plasma cells to release specific antibodies. Those specific antibodies would facilitate the antibody-dependent cellular cytotoxicity (ADCC) on tumor cells by natural killer (NK) cells as well as the phagocytosis by M1 macrophages. B cells could also be activated by the interaction between B-cell receptors with the oncolytic viruses. In addition, DAMP could also activate NK cells to kill neoplastic cells that downregulated their major histocompatibility complex (MHC) class I expression. $CD8^+$ T cells will target tumor cells that express MHC class I on the cell surface. After the interaction between T-cell receptor and peptide-MHC class I, $CD8^+$ T cells would be activated and release cytotoxic molecules (such as Granzyme B and Perforin) and IFN-gamma. These concerted actions increase the immunological activity within tumor microenvironment.[3,13] The summary of antitumor immunity's induction by oncolytic viruses could be seen in **Figure 1**.

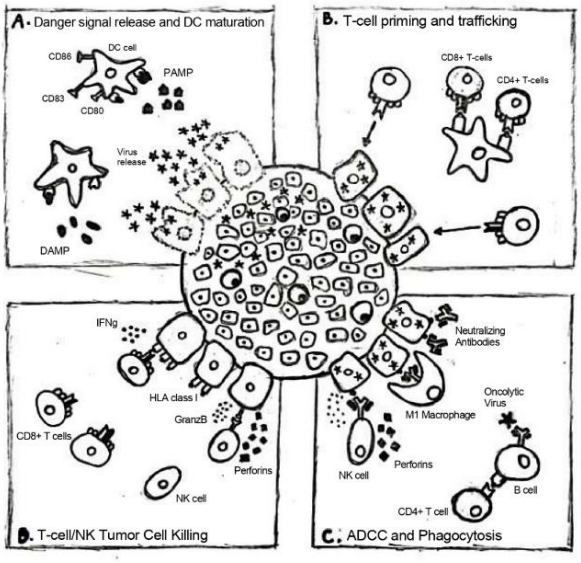

Figure 1. Antitumor immunity of oncolytic Viruses (Hemminki *et al*., 2020).
The tumor microenvironment of advanced cancers naturally inhibits the antitumor immune response. This activity could be enhanced, nonetheless, following lysis of cancer cells (oncolysis) by oncolytic virus. **A.** viral progeny, pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs) and cytokines are released after the oncolysis, which activating dendritic cells (DCs). **B.** Mature DCs activate $CD4^+$ and $CD8^+$ T cells. **C.** B-cells activation, through support of $CD4^+$ T cells, would allow plasma cells (*not shown*) to secrete high-affinity, specific antibodies. **D.** $CD8^+$ T cells and natural killer (NK) cells would subsequently target and destroy the tumor cells.

Limitation and advancement of using oncolytic viruses to treat cancers

Limitations of using oncolytic viruses for cancer treatment are the safety, efficacy and cancer cell's susceptibility to cell death (apoptosis, pyroptosis and necrosis). In terms of safety, wild-type oncolytic virus might able to infect healthy cells as well. In terms of efficacy, the viral ability to infect and methods of administration are the challenges. In terms of susceptibility to cell death, the candidate oncolytic virus must be evaluated whether it is effective in inducing lysis of cancer cells (i.e., oncolysis). Therefore, advancement must be conducted on the oncolytic viruses to tackle those limitations.

Many oncolytic viruses have a natural tropism for cancer cell's surface proteins. For example, while herpesvirus recognizes cancer receptor HVEM and selected nectins, coxsackievirus recognizes ICAM-1 and DAF, as well as poliovirus recognizes CD155 for cell entry.[13] But oncolytic viruses could be engineered to target specific cell receptors, hence increasing their specificity. As an example, the modified adenovirus Ad5/3-Δ24 would bind to integrins that are highly expressed on the surface of ovarian cancer cells.[21–23] Oncolytic virus could also be engineered to enhance tumor tropism for cancers that have a low receptor's expression. For example, the adenovirus DNX-2401 showed a durable response in 20% of glioma patients due to the increase in tumor tropism.[24]

Another purpose of the modification is to exploit the cancer property and its molecular mechanisms (such as immune evasion and apoptotic resistance mechanism), to reduce the pathogenicity, to increase the antitumor immunity, to enhance the lytic activity and to reduce the antiviral immune responses. Normal infected cells would activate PKR, which inhibits protein translation, eventually preventing the production of viral particles. In contrast, cancer cells have an abnormal PKR activation. A modified herpesvirus with gene deletion encoding ICP34.5 and US11 preferably would lyse tumor cells than normal cells. The gene deletion results in the viral inability to inhibit the PKR activation, thus it can only replicate well within cancer cells.[25,26] Next, inserting promoters that are preferentially more active in cancer cells could help oncolytic viruses to exploit the inner mechanism of cancer cells. For example, a modified adenovirus with E1A gene promoter for PSA would facilitate a selective targeting to prostate cancer cells, as normal cells do not express E1A.[27]

Viral genome modification by gene deletion or transgene expression could enhance the antitumor immunity within the tumor microenvironment. The deletion of ICP47 gene in herpesvirus permits transporter associated with antigen processing (TAP) complex to function, thus the infected cells could present antigen to $CD8^+$ T cells.[28] Transgene expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) within genomes of herpesvirus, adenovirus and vaccinia virus could promote the maturation and accumulation of dendritic cells, hence improving the presentation of tumor-associated antigen and the stimulation of T-cell responses.[25,29,30] Transgene expression could also enhance the lytic activity through an inclusion of 'suicide genes', which expressed by tumor-enriched/tissue-specific promoters. For example, transgene expression of cytosine deaminase (CD) and adenovirus death protein (ADP) would increase the lytic efficiency, in which the CD could convert 5-fluorocytosine into 5-fluorouracyl, while the ADP, the nuclear membrane glycoprotein, is used for the efficient cell lysis and the release of viral particles.[31,32]

While the immune activation would mainly eliminate cancer cells, it could also generate the antiviral immunity to eliminate the oncolytic virus. Prevention of the viral neutralization could increase the administrative efficiency. One strategy is to use alternative viral serotypes to limit viral neutralization. Another strategy is to perform viral coat PEGylation and polymer coating to suppress viral neutralization.[33–35] Using cells as a carrier, e.g., mesenchymal stem cells, to protect oncolytic viruses had been tested as well.[36,37] These strategies could circumvent the issue of administration's efficiency. An intratumoral administration would be more efficient as it is directly administered into the cancer mass, hence minimizing the probability of viral neutralization. However, this method could not be used for inaccessible or multifocal cancers, e.g., pancreatic or brain tumors. In these cases, the systemic administration would be required[38–41], as the systemic administration would distribute viruses to the primary and

metastasized cancers. The efficiency could be unsatisfactory, however, as the viruses could be rapidly neutralized before reaching the cancer mass.[42]

Another advancement is to combine oncolytic viruses with other modes of cancer treatment, such as chemotherapy, radiotherapy, adoptive cell therapy or immune checkpoint inhibitors. The most common combination to date is with immune checkpoint inhibitors. Briefly, immune checkpoint is the negative regulation of the immune response.[43] Immune checkpoint inhibitors would attenuate the negative regulation, thus activating the immune response. The current popular targets for immune checkpoint inhibition are CTLA4 and PD-1/PDL1.[13]

Clinical trials of oncolytic viruses for treating cancers

Cook & Chauhan (2020) reported that 86 trials on oncolytic viruses were found in the PubMed clinical trial database.[12] There were 60 trials in phase I, 5 trials in phase I/II, 19 trials in phase II, as well as 2 trials in phase III. They observed the utilization of different types of oncolytic viruses with various modification and of various types of cancer cells as targets. Different outcomes on patient responses were reported from those trials as well. In general, no severe toxicity was observed during the clinical trials and some trials even demonstrated moderate to high responses for oncolytic viruses, as indicated by tumor necrosis.

Chaurasiya *et al*. (2021) summarized several trials utilizing different types of viruses.[44] On each viral category, the authors described the transgene expression, combination with other cancer treatments (conventional and immunotherapy), types of cancers, the clinical trial's phases and their status (recruiting, ongoing, or completed). In general, the treatments were well tolerated at the maximum permitted doses with mild adverse events, such as flu-like syndromes and local reactions (e.g., pain, rash and peripheral edema).

Interestingly, there are several oncolytic viral treatments that have been approved to be used for certain cancer patients. For example, Rigvir®, an oncolytic picornavirus, was approved in 2004 to be used in Latvia for melanoma.[45] Adenovirus H101 (Oncorine®) has been used in China since 2005 for solid tumors in head and neck, such as nasopharyngeal carcinoma.[29,46] Herpesvirus, Talimogene laherparepvec or T-vec (Imlygic®), has been approved by FDA and EMA in 2015 for melanoma patients.[3,47]

Conclusion

Oncolytic viruses have been known for centuries but been only developed in the recent years as one of cancer treatments. The oncolytic viral treatment shows a promising outcome for cancer patients. The oncolytic viral treatment could also be used in a combination with other cancer treatments in order to boost the treatment efficiency. In recent years, advancements and clinical trials using oncolytic viruses for treating various cancers have flourished. The results are expected to support the concept of using oncolytic virus to treat certain cancers.

Acknowledgment

The acknowledgment is a form of appreciation for the contribution of an institution or an individual who is not considered as the writer for example an institution or an individual who provides the research funding of this publication. Individuals with direct involvement in the study but not included in authorship may be acknowledged. The source of financial support and industry affiliations of all those involved must be stated

References

1. International Agency for Research on Cancer. Cancer Today [Internet]. 2020 [cited 2022 May 1]. Available from: https://gco.iarc.fr/today/home

2. World Health Organization. Cancer [Internet]. 2022 [cited 2022 May 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer

3. Hemminki O, dos Santos JM, Hemminki A. Oncolytic viruses for cancer immunotherapy. Journal of Hematology & Oncology. 2020 Dec 29;13(1):84. https://doi.org/10.1186/s13045-020-00922-1

4. Gratwohl A. Hematopoietic Stem Cell Transplantation<subtitle>A Global Perspective</subtitle> JAMA. 2010 Apr 28;303(16):1617. https://doi.org/10.1001/jama.2010.491

5. Hemminki O, Hemminki A. A century of oncolysis evolves into oncolytic immunotherapy. OncoImmunology. 2016 Feb 12;5(2):e1074377. https://doi.org/10.1080/2162402x.2015.1074377

6. Lizée G, Overwijk WW, Radvanyi L, Gao J, Sharma P, Hwu P. Harnessing the Power of the Immune System to Target Cancer. Annual Review of Medicine. 2013 Jan 14;64(1):71–90. https://doi.org/10.1146/annurev-med-112311-083918

7. Jessy T. Immunity over inability: The spontaneous regression of cancer. Journal of Natural Science, Biology and Medicine. 2011;2(1):43. https://doi.org/10.4103%2F0976-9668.82318

8. Kucerova P, Cervinkova M. Spontaneous regression of tumour and the role of microbial infection – possibilities for cancer treatment. Anti-Cancer Drugs. 2016 Apr;27(4):269–77. https://doi.org/10.1097/cad.0000000000000337

9. Larson C, Oronsky B, Scicinski J, Fanger GR, Stirn M, Oronsky A, et al. Going viral: a review of replication-selective oncolytic adenoviruses. Oncotarget. 2015 Aug 21;6(24):19976–89. https://doi.org/10.18632%2Foncotarget.5116

10. Kelly E, Russell SJ. History of Oncolytic Viruses: Genesis to Genetic Engineering. Molecular Therapy. 2007 Apr;15(4):651–9. https://doi.org/10.1038/sj.mt.6300108

11. Desjardins A, Vlahovic G, Friedman HS. Vaccine Therapy, Oncolytic Viruses, and Gliomas. Oncology (Williston Park). 2016 Mar;30(3):211–8.

12. Cook M, Chauhan A. Clinical Application of Oncolytic Viruses: A Systematic Review. International Journal of Molecular Sciences. 2020 Oct 12;21(20):7505. https://doi.org/10.3390/ijms21207505

13. Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nature Reviews Drug Discovery. 2015 Sep 1;14(9):642–62. https://doi.org/10.1038/nrd4663

14. Delves PJ, Martin SJ, Burton DR, Roitt IM. Roitt's essential immunology. Wiley Blackwell; 2017.

15. Cooper GM. The cell: A molecular approach. Sinauer associates, Oxford University Press; 2019.

16. Li L, Liu S, Han D, Tang B, Ma J. Delivery and Biosafety of Oncolytic Virotherapy. Frontiers in Oncology. 2020 Apr 16;10. https://doi.org/10.3389/fonc.2020.00475

17. Bischoff JR, Samuel CE. Mechanism of interferon action activation of the human P1/eIF-2α protein kinase by individual reovirus s-class mRNAs: s1 mRNA is a potent activator relative to s4 mRNA. Virology. 1989 Sep;172(1):106–15. https://doi.org/10.1016/0042-6822(89)90112-8

18. Takaoka A, Hayakawa S, Yanai H, Stoiber D, Negishi H, Kikuchi H, et al. Integration of interferon-α/β signalling to p53 responses in tumour suppression and antiviral defence. Nature. 2003 Jul 16;424(6948):516–23. https://doi.org/10.1038/nature01850

19. Marchini A, Daeffler L, Pozdeev VI, Angelova A, Rommelaere J. Immune Conversion of Tumor Microenvironment by Oncolytic Viruses: The Protoparvovirus H-1PV Case Study. Frontiers in Immunology. 2019 Aug 7;10. https://doi.org/10.3389%2Ffimmu.2019.01848

20. Santos Apolonio J, Lima de Souza Gonçalves V, Cordeiro Santos ML, Silva Luz M, Silva Souza JV, Rocha Pinheiro SL, et al. Oncolytic virus therapy in cancer: A current review. World Journal of Virology. 2021 Sep 25;10(5):229–55. https://doi.org/10.5501%2Fwjv.v10.i5.229

21. Cerullo V, Pesonen S, Diaconu I, Escutenaire S, Arstila PT, Ugolini M, et al. Oncolytic Adenovirus Coding for Granulocyte Macrophage Colony-Stimulating Factor Induces Antitumoral Immunity in Cancer Patients. Cancer Research. 2010 Jun 1;70(11):4297–309. https://doi.org/10.1158/0008-5472.can-09-3567

22. You Z, Fischer DC, Tong X, Hasenburg A, Aguilar-Cordova E, Kieback DG. Coxsackievirus–adenovirus receptor expression in ovarian cancer cell lines is associated with increased adenovirus transduction efficiency and transgene expression. Cancer Gene Therapy. 2001 Mar 1;8(3):168–75. https://doi.org/10.1038/sj.cgt.7700284

23. Liapis H, Adler LM, Wick MR, Rader JS. Expression of αvβ3 integrin is less frequent in ovarian epithelial tumors of low malignant potential in contrast to ovarian carcinomas. Human Pathology. 1997 Apr;28(4):443–9. https://doi.org/10.1016/s0046-8177(97)90033-2

24. Lang FF, Conrad C, Gomez-Manzano C, Yung WKA, Sawaya R, Weinberg JS, et al. Phase I Study of DNX-2401 (Delta-24-RGD) Oncolytic Adenovirus: Replication and Immunotherapeutic Effects in Recurrent Malignant Glioma. Journal of Clinical Oncology. 2018 May 10;36(14):1419–27. https://doi.org/10.1200/jco.2017.75.8219

25. Liu BL, Robinson M, Han ZQ, Branston RH, English C, Reay P, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour

properties. Gene Therapy. 2003 Feb 1;10(4):292–303. https://doi.org/10.1038/sj.gt.3301885

26. Poppers J, Mulvey M, Khoo D, Mohr I. Inhibition of PKR Activation by the Proline-Rich RNA Binding Domain of the Herpes Simplex Virus Type 1 Us11 Protein. Journal of Virology. 2000 Dec;74(23):11215–21. https://doi.org/10.1128%2Fjvi.74.23.11215-11221.2000

27. DeWeese TL, van der Poel H, Li S, Mikhak B, Drew R, Goemann M, et al. A phase I trial of CV706, a replication-competent, PSA selective oncolytic adenovirus, for the treatment of locally recurrent prostate cancer following radiation therapy. Cancer Res. 2001 Oct 15;61(20):7464–72.

28. Tomazin R, van Schoot NEG, Goldsmith K, Jugovic P, Sempé P, Früh K, et al. Herpes Simplex Virus Type 2 ICP47 Inhibits Human TAP but Not Mouse TAP. Journal of Virology. 1998 Mar;72(3):2560–3. https://doi.org/10.1128/jvi.72.3.2560-2563.1998

29. Liang M. Oncorine, the World First Oncolytic Virus Medicine and its Update in China. Current Cancer Drug Targets. 2018 Jan 15;18(2):171–6. https://doi.org/10.2174/1568009618666171129221503

30. Toda M, Martuza RL, Rabkin SD. Tumor Growth Inhibition by Intratumoral Inoculation of Defective Herpes Simplex Virus Vectors Expressing Granulocyte–Macrophage Colony-Stimulating Factor. Molecular Therapy. 2000 Oct;2(4):324–9. https://doi.org/10.1006/mthe.2000.0130

31. Doronin K, Toth K, Kuppuswamy M, Ward P, Tollefson AE, Wold WSM. Tumor-Specific, Replication-Competent Adenovirus Vectors Overexpressing the Adenovirus Death Protein. Journal of Virology. 2000 Jul;74(13):6147–55. https://doi.org/10.1128%2Fjvi.74.13.6147-6155.2000

32. Freytag SO, Stricker H, Pegg J, Paielli D, Pradhan DG, Peabody J, et al. Phase I study of replication-competent adenovirus-mediated double-suicide gene therapy in combination with conventional-dose three-dimensional conformal radiation therapy for the treatment of newly diagnosed, intermediate- to high-risk prostate cancer. Cancer Res. 2003 Nov 1;63(21):7497–506. https://doi.org/10.1038/mt.sj.6300120

33. Morrison J, Briggs SS, Green N, Fisher K, Subr V, Ulbrich K, et al. Virotherapy of Ovarian Cancer With Polymer-cloaked Adenovirus Retargeted to the Epidermal Growth Factor Receptor. Molecular Therapy. 2008 Feb;16(2):244–51. https://doi.org/10.1038/sj.mt.6300363

34. O'Riordan CR, Lachapelle A, Delgado C, Parkes V, Wadsworth SC, Smith AE, et al. PEGylation of Adenovirus with Retention of Infectivity and Protection from Neutralizing Antibody in Vitro and in Vivo. Human Gene Therapy. 1999 May 20;10(8):1349–58. https://doi.org/10.1089/10430349950018021

35. Tesfay MZ, Kirk AC, Hadac EM, Griesmann GE, Federspiel MJ, Barber GN, et al. PEGylation of Vesicular Stomatitis Virus Extends Virus Persistence in Blood Circulation of Passively Immunized Mice. Journal of Virology. 2013 Apr;87(7):3752–9. https://doi.org/10.1128/jvi.02832-12

36. Mader EK, Maeyama Y, Lin Y, Butler GW, Russell HM, Galanis E, et al. Mesenchymal Stem Cell Carriers Protect Oncolytic Measles Viruses from Antibody Neutralization in an Orthotopic Ovarian Cancer Therapy Model. Clinical Cancer Research. 2009 Dec 1;15(23):7246–55. https://doi.org/10.1158/1078-0432.ccr-09-1292

37. Willmon C, Harrington K, Kottke T, Prestwich R, Melcher A, Vile R. Cell Carriers for Oncolytic Viruses: Fed Ex for Cancer Therapy. Molecular Therapy. 2009 Oct;17(10):1667–76. https://doi.org/10.1038%2Fmt.2009.194

38. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: A new era of cancer treatment at dawn. Cancer Science. 2016 Oct 9;107(10):1373–9. https://doi.org/10.1111%2Fcas.13027

39. Hu PY, Fan XM, Zhang YN, Wang SB, Wan WJ, Pan HY, et al. The limiting factors of oncolytic virus immunotherapy and the approaches to overcome them. Applied Microbiology and Biotechnology. 2020 Oct 20;104(19):8231–42. https://doi.org/10.1007/s00253-020-10802-w

40. Reale A, Vitiello A, Conciatori V, Parolin C, Calistri A, Palù G. Perspectives on immunotherapy via oncolytic viruses. Infectious Agents and Cancer. 2019 Dec 11;14(1):5. https://doi.org/10.1186%2Fs13027-018-0218-1

41. Tsun A, Miao XN, Wang CM, Yu DC. Oncolytic Immunotherapy for Treatment of Cancer. In 2016. p. 241–83. https://doi.org/10.1007/978-94-017-7555-7_5

42. Bai Y, Hui P, Du X, Su X. Updates to the antitumor mechanism of oncolytic virus. Thoracic Cancer. 2019 May 22;10(5):1031–5. https://doi.org/10.1111%2F1759-7714.13043

43. Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. Journal of Clinical Oncology. 2015 Jun 10;33(17):1974–82. https://doi.org/10.1200/jco.2014.59.4358

44. Chaurasiya S, Fong Y, Warner SG. Oncolytic Virotherapy for Cancer: Clinical Experience. Biomedicines. 2021 Apr 13;9(4):419. https://doi.org/10.3390/biomedicines9040419

45. Alberts P, Tilgase A, Rasa A, Bandere K, Venskus D. The advent of oncolytic virotherapy in oncology: The Rigvir® story. European Journal of Pharmacology. 2018 Oct;837:117–26. https://doi.org/10.1016/j.ejphar.2018.08.042

46. Wei D, Xu J, Liu XY, Chen ZN, Bian H. Fighting Cancer with Viruses: Oncolytic Virus Therapy in China. Human Gene Therapy. 2018 Feb;29(2):151–9. https://doi.org/10.1089/hum.2017.212

47. Andtbacka RHI, Collichio F, Harrington KJ, Middleton MR, Downey G, Öhrling K, et al. Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III–IV melanoma. Journal for ImmunoTherapy of Cancer. 2019 Dec 6;7(1):145. https://doi.org/10.1186%2Fs40425-019-0623-z

Postoperative Pain Comparison Between Open Hemorrhoidectomy and Stapled Hemorrhoidopexy on Internal Hemorrhoid at Siloam Hospitals Lippo Village

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Citation: Taufik Sudirman, Leonard Wiguna Alvin. Postoperative Pain Comparison Between Open Hemorrhoidectomy and Stapled Hemorrhoidopexy on Internal Hemorrhoid at Siloam Hospitals Lippo Village. Medicinus. 2022 October; 10(3):141-145.
Keywords: Internal Hemorrhoid; Open Hemorrhoidectomy; Stapled Hemorrhoidopexy; Postoperative Pain; Visual Analogue Scale
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Online First: October 2022

Abstract

Background: Hemorrhoids have a prevalence of 4,4%. Surgery is one of the modalities for treating hemorrrhoids. The method accepted as the "golden standard" is open hemorrhoidectomy. Although considered effective, open hemorrhoidectomyis still often associated with a significant rate of morbidity and pain symptoms that are a complaint of most patients. Therefore, another method is an alternative, namely, stapled hemorrhoidopexy. Some studies showed that stapledhemorrhoidopexy has a lower occurrence of postoperative pain, and others offer theopposite.

Methods: This study was conducted at Siloam Hospitals Lippo Village between February and March 2019. Samples were taken as many as 70 patients by taking secondary data from medical records. Patients diagnosed with third or fourth degreehemorrhoids and undergoing open hemorrhoidectomy or stapled hemorrhoidopexy will be taken the pain score from the visual analogue scale. Data is then tabulated using Microsoft Excel and analysed using SPSS.

Result: the occurrence of postoperative pain in the stapled hemorrhoidopexy and open hemorrhoidectomy group, respectively, are 80% and 97%, with a p-value of 0,055. The average visual analogue scale score for open hemorrhoidectomy and stapled hemorrhoidopexy was 3±1,39 and 2±1,39, respectively, with a p-value of 0.003.

Conclusions: the result showed that the occurrence of postoperative pain was notstatistically significant. And the average visual analogue scale score was lower in the stapled hemorrhoidopexy group.

Introduction

Hemorrhoids are a normal structure in the form of a vascular cushion in the anal canal, which can become pathological when the tissue is dilated and prolapsed.[1,2] A studyin the United States showed that hemorrhoids have a prevalence rate of 4.4%.[3] In Indonesia, there are approximately ten million people who experience thisdisease, with a prevalence of about 4%

Surgery is one of the modalities to treat hemorrhoids. The method that is accepted as the "golden standard" is open hemorrhoidectomy.[5,6] Although it is considered effective, open hemorrhoidectomy is still often associated with significant morbidity, as well as pain symptoms that are the complaint of the majority of patients.[7] alternatives, one of which is stapled hemorrhoidopexy.[8]

A prospective study conducted by Sachin,[9] showed postoperative pain after

open hemorrhoidectomy and stapled hemorrhoidopexy, 56% and 30%, respectively. There are still contradictions to the results of these studies. Research conducted by Mattana,[10] showed the opposite results. Pain that occurs in open hemorrhoidectomy and stapled hemorrhoidopexy is 24% and 28%, respectively.

Material And Methods

This study uses an analytical study with a cross-sectional design. The study was conducted on patients who underwent open hemorrhoidectomy or stapled hemorrhoidopexy at Siloam Hospitals Lippo Village. The study was conducted in the period from February to March 2019 using medical record data.

Postoperative pain was determined by the visual analogue scale (VAS) of patients undergoing open hemorrhoidectomy or stapled hemorrhoidopexy. If the VAS value ≠0, it will be included in the pain group and vice versa. The VAS value is the subjective degree of pain felt by the patient. The inclusion criteria in this study included a diagnosis of grade III or IV internal hemorrhoids and undergoing open hemorrhoidectomy or stapled hemorrhoidopexy surgery. Exclusion criteria used were acute hemorrhoids with thrombosis, fistula, fissure, anal stenosis, or a history of previous hemorrhoid surgery. After going through the inclusion and exclusion process, the data were entered into the research database and analysed.

The estimated number of samples required is 60 samples. To anticipate incomplete or missing data, the number of samples was increased by 10% to 66 samples. The samples will be divided into two groups, namely, 33 samples for the open hemorrhoidectomy group and 33 samples for the stapled hemorrhoidopexy group. The number of samples obtained as many as 70 samples.

The data that has been taken is then tabulated using the Microsoft excel 2017 program and analysed using the SPSS version 23 program. Statistical tests in this study were carried out using the Fisher exacttest and Mann U-Whitney.

Result

The samples were divided equally between stapled hemorrhoidopexy and open hemorrhoidectomy group. The average age of the entire sample is 41.92 years, with the lowest age being 19 years and the highest age being 70 years. The median age is at theage of 43 years. The most common agefound is 43 years. The age category shows that the most samples were found in the agerange between 41-50 years, as many as 27 samples. The samples at least are in the age category above 60 years, as many as five people.

In the group that underwent open hemorrhoidectomy, 77.1% of patients had grade III, and the rest had grade IV internal hemorrhoids. Meanwhile, in the stapled hemorrhoidopexy group, 88.6% of patients had grade III, and the remaining had grade IVinternal hemorrhoids.

Of the 70 patients sampled in the study, 35 patients underwent open hemorrhoidectomy, and 35 patients underwent stapled hemorrhoidopexy. 97.1% of the open hemorrhoidectomy group experienced postoperative pain, while only 80% of the stapled hemorrhoidopexy group experienced pain. The significance value (p-value) obtained based on the Fisher exact test is 0.055, which is not statistically significant. Therefore, the OR obtained is not meaningful.

The open hemorrhoidectomy group had an average VAS of 3, with the highest score of 8 and the lowest being 0. The

stapled hemorrhoidopexy group had an average VASof 2, with the highest value of 6 and the lowest value of 0. Based on the Mann- Whitney U test, a significant value was obtained. (p-value) of 0.003, which means significant.

Table 1. Sample demographics

	Stapled Hemorrhoidopexy		*Open hemorrhoidectomy*	
	n	%	n	%
Sex				
Male	20	57,14	15	42,85
Female	15	42,85	20	57,14
Age				
<31	4	11,4	9	25,7
31-40	8	22,9	7	20
41-50	13	37,1	14	40
51-60	7	20	3	8,6
>60	3	8,6	2	5,7
Grading				
Grade III	31	88,6	27	77,1
Grade IV	4	11,4	8	22,9

Table 2. Comparison of the incidence ofpostoperative pain

Surgery technique	Postoperative pain				Total		OR (95%CI)	*P-value*
	No		Yes					
	n	%	n	%	n	%		
Stapled hemorrhoidopexy	7	20	28	80	35	100	8,5 (0,986-73,276)	0,055
Open hemorrhoidectomy	1	2,9	34	97,1	35	100		
Total	8	11,42	62	88,57	70	100		

Table 3. Visual analogue scale averagescore

Surgery technique	n	mean±standard deviation	*P-Value*
Open hemorrhoidectomy	35	3±1,39	0,003
Stapled hemorrhoidopexy	35	2±1,39	

Discussion

A total of seventy patients who underwent surgery and met the inclusion criteria were included in this study. Each of thirty-five patients underwent open hemorrhoidopexy, and thirty-five others underwent stapled hemorrhoidopexy. Visual analogue scale values were taken from eachpatient after undergoing surgery. This value is used to measure postoperative pain. In the open hemorrhoidectomy group, 42.85% of patients were male, while 57.14% were female. For the group that underwent stapled hemorrhoidopexy, most patients (57.14%) were male, and 42.85% were female.

The average age of the sample in this study was 41.92 years. For each group In thestudy conducted by Sachin[9], the mean age of the patients obtained was 40.06 years. Meanwhile, in Mattana's study[10], the mean age for open hemorrhoidectomy and stapled hemorrhoidopexy was 51.6 and 48.1,respectively.

Overall, 82.9% of patients had grade III internal hemorrhoids, and 17.1% had grade IV internal hemorrhoids. In Sachin's study[9], most patients (53%) were diagnosed with grade IV internal hemorrhoids.

Open hemorrhoidectomy is the most radical technique and has the highest morbidity compared to other less invasive procedures.[7] This is because extensive dissection and incisions are made below the dentate line, causing more severe postoperative pain. In contrast, in stapled hemorrhoidopexy, the resulting staple line isabove the dentate line, proximal to the somatic nerve fibres in the anal canal.[11] It makes the patient feel less pain.[12]

The quality of pain felt after open hemorrhoidectomy and stapled hemorrhoidopexy is also different. In an openhemorrhoidectomy, the pain felt has sharp and tearing characteristics. Meanwhile, on stapled hemorrhoidopexy, only vague pain and discomfort are felt by the patient.[13]

The results obtained matched the previous studies,[9,14,] but some differences may affect the results of this study. First,

the research design used was cross-sectional with a retrospective document search. The data collected is secondary data from the medical records of Siloam Hospitals Lippo Village patients for the period 2012-2019. This data collection method had to be done because the prevalence was low and limited research time. Another disadvantage of using medical records is that researcherscannot be sure whether the medical record data is accurate or not. Second, the number of samples taken is less than the research used as a reference. This situation can undoubtedly have an impact on the results of the study. And lastly, this study only focuseson postoperative pain, which is one of the factors taken into account in comparing different surgical techniques, so the results ofthis study cannot provide a complete picture to compare the two surgical procedures.

Conclusion

The comparison of the incidence of postoperative pain in the stapled hemorrhoidopexy group and the open hemorrhoidectomy group was not statistically significant. The average visual analogue scale score in the stapled hemorrhoidopexy group was lower than that in the open hemorrhoidectomy group, and this result wasstatistically significant.

Acknowledgment

The author would like to thank dr. Andry Irawan, M.Si.Med., Sp.B, FINaCS, FICS andall Siloam Hospital Lippo Village for their helpduring the writing of this paper.

References

1. Brunicardi FC, Andersen DK, Billiar TR, et al. *Schwartz's Principles of Surgery*. 10th ed. McGraw-Hill; 2015.

2. Mounsey AL, Halladay J, Sadiq TS. Anne LM, Jacqueline H, Timothy SS. Hemorrhoids. *Am Fam Physician*. 2011;84(2):204-210.

3. Johanson JF, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. *Gastroenterology*. 1990;98(2):380-386. https://doi.org/10.1016/0016-5085(90)90828-o

4. Nugroho SHP. Hubungan aktivitas fisik dan konstipasi hemoroid di URJ bedah RSUD Dr. Soegiri Lamongan. *Surya*. 2014;02(Xviii):41-50.

5. Song S-G, Kim S-H. Optimal treatment of symptomatic hemorrhoids. *J Korean Soc Coloproctol*. 2011;27(6):277-281. https://doi.org/10.3393/jksc.2011.27.6.277

6. Milligan ET, Morgan C, Jones L. Surgical Anatomy of the Anal Canal, and the Operative Treatment of Hemorrhoids. *Lancet*. Published online 1937:1119-1124. https://doi.org/10.1016/S0140-6736(00)88465-2

7. Medina-Gallardo A, Curbelo-Peña Y, De Castro X, Roura-Poch P, Roca-Closa J, De Caralt- Mestres E. Is the severe pain after Milligan-Morgan hemorrhoidectomy still currently remaining a major postoperative problem despite being one of the oldest surgical techniquesdescribed? A case series of 117 consecutive patients. *Int J Surg Case Rep*. 2017;30:73-75. https://doi.org/10.1016/j.ijscr.2016.11.018

8. Longo A. Treatment of haemorrhoidal disease by reduction of mucosa and haemorrhoidal prolapse with circular stapling device: A new procedure. In: *6th World Congress of EndoscopySurgery*. Mundozzi Editore; 1998:777-784.

9. Sachin ID, Muruganathan OP. Stapled hemorrhoidopexy versus open hemorrhoidectomy: a comparative study of short term results. 2017;4(2):472-478. http://dx.doi.org/10.18203/2349-2902.isj20164791

10. Mattana C, Coco C, Manno A, et al. Stapled Hemorrhoidopexy and Milligan Morgan hemorrhoidectomy in the cure of fourth-degree hemorrhoids: Long-term evaluation and clinical results. *Dis Colon Rectum*. 2007;50(11):1770-1775. https://doi.org/10.1007/s10350-007-0294-6

11. Sanchez C, Chinn BT. Hemorrhoids. *Clin Colon Rectal Surg*. 2011;1(212):5-13. https://doi.org/10.1055%2Fs-0031-1272818

12. Sun Z, Migaly J. Review of Hemorrhoid Disease: Presentation and Management. *Clin ColonRectal Surg*. 2016;29(1):22-29. https://doi.org/10.1055/s-0035-1568144

13. Baliga K, Chetty DV. Stapler hemorrhoidectomy versus open hemorrhoidectomy. 2016;3(4):1901-1905. https://doi.org/10.18203/2349-2902.isj20163120

14. Franc J. Stapled Hemorrhoidopexy Versus Milligan-Morgan Hemorrhoidectomy. 2005;242(1):29-35. https://doi.org/10.1097/01.sla.0000169570.64579.31

Transvaginal Ultrasound as an Indicator of Preterm Birth

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Citation: Wibisono Jacobus Jeno, Onasis Serena, Nikendari Sri Mulyani, Andhika Aryasena, Wibisono Maria Georgina. Transvaginal Ultrasound as an Indicator of Preterm Birth. Medicinus. 2022 October; 10(3): 146-148.
Keyword: Premature parturition of preterm birth; Transvaginal ultrasound; Cervical length
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Abstract

Preterm Birth is delivery that occurs when the mother's gestational age is 20-36 weeks starting from the first day of the last menstrual period with a fetal weight still below 2500 grams. In preterm birth there are regular uterine contractions that cause thinning or dilation of the cervix before 36 weeks of gestation is complete. Approximately 50% of sequelae that occur in children are due to preterm birth. It is known that cervical dilatation in pregnant women is associated with preterm birth, so there are several screening methods that are used to predict preterm birth, including cervical length examination. Transvaginal ultrasound examination is a safe method of examination to measure cervical length objectively. Cervical length less than or equal to 25 mm or cervical dilatation 70% to 100% are expected to have preterm birth.

Introduction

Preterm birth is when birth happens prematurely between 20 – 36 weeks of pregnancy. It is thought that preterm birth accounted for about 9,5% of all births worldwide. Preventions that are being done to inhibit the labor are administering tocolytic drugs. It could be subsequently classified based on clinical presentation, including preterm premature rupture of membrane (PPROM), spontaneous preterm birth, or preterm birth due to maternal or fetal reasons. Risk factors of this preterm birth are the history of previous preterm birth, preeclampsia, multiparities, premature rupture of membrane, and length of the cervix.[1] Measurement of cervical length using transvaginal ultrasonography has been proven to predict preterm birth in low risk asymptomatic women and pregnant women with threatened preterm birth.

The annual birth rate in Indonesia reaches 5 million births every year, with a maternal mortality rate of 126 deaths in 100,000 birth, one of the highest in South East Asia in 2017.[2] One of the developmental goals needed to be reached in 2030 could be implementing sustainable development goals (SDGs). One priority program that reflects a country's healthcare developmental level and quality of life is the neonatal mortality rate as one indicator. Based on the Demographic and Health Status Survey in Indonesia in 2017, the neonatal mortality rate was 15 for every 1000 live birth, while the children mortality rate was 24 for every 1000 live birth. The leading cause of this perinatal morbidity and mortality is preterm birth.

Literature Review

Transvaginal Ultrasonography

Transvaginal ultrasonography is a method to assess pregnancy conditions and women's reproduction organs by introducing a probe stick of 5-7,5 cm long into the vagina. The probe will radiate high-frequency sound waves to bring the images of internal organs into the monitor.

Transvaginal ultrasonography itself has a higher resolution of 5-7,5Mhz than abdominal ultrasonography. To increase the picture quality, transvaginal ultrasonography uses a vagina anatomical approach to reduce the distance between probe and pelvic structure.

Preterm birth

As mentioned before, preterm birth is when birth happens prematurely between 20 – 36 weeks of pregnancy with a fetal weight under 2500 grams. A regular and continuous contraction causes the cervix to thin and dilate before 36 weeks.

One of the most significant issues with infant morbidity and mortality is preterm birth.[3] There have been several attempts in the last few decades to increase the survival of low-birth-weight neonates. Some include using a corticosteroid, increasing mechanical ventilation, administering exogen surfactants, and nutritional therapy.

However, the drop in neonatal maternal nutrition is not accompanied by a reduction in the morbidity rate. It is believed that around half of all childhood sequelae are the result of premature delivery.[4]

Transvaginal Ultrasound as a Predictor of Preterm Birth

Cervical dilatation in pregnant women has long been related with premature birth; hence, numerous screening measures, including cervical examination, are employed to predict preterm birth. Several prospective cohort studies have assisted in determining the mean cervical length of pregnant women at risk of preterm birth.[5] Pregnant women with a shorter or dilated cervix have an increased risk of premature delivery. With a cervical length of less than 30 mm or a cervical dilatation of 70 to 100 percent, a premature birth is likely.[6]

In recent decades, ultrasound examination (USG) in pregnant women has been the subject of numerous studies. Changes in cervical length that occur very early in asymptomatic patients are only detectable with transvaginal ultrasonography. Examination using transvaginal ultrasound has a higher image resolution than abdominal ultrasound because the quality of transvaginal ultrasound images is unaffected by air in the intestines, obesity, or scar tissue on the abdominal wall. Transvaginal ultrasound examination is a more secure means of objectively measuring cervical length than digital examination, transabdominal ultrasound, or transperineal ultrasound.[4]

As illustrated in Figure 1, cervical dilatation commences at the internal os. The typical cervical length threshold of 25mm can be used to predict premature birth. In contrast, a cervical length of less than 25 mm before 28 weeks gestation is considered short and may signal premature birth. Pregnant women with a cervical length 25 mm and contractions had a risk of preterm birth that was double that of women with a cervical length 25 mm and no contractions.[7]

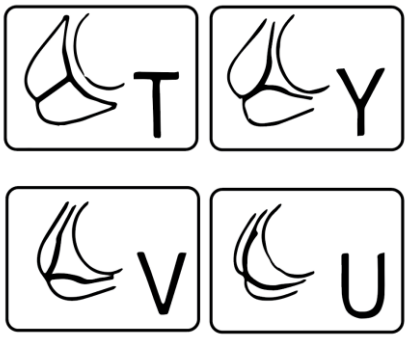

Figure 1. Schematic representation of cervical maturation from closed (T) to open (U) status[8]

Conclusion

Cervical dilatation in pregnant women has long been related with preterm birth. Changes in cervical lenght that occur very early in asymptomatic patients are only detecable with transvaginal ultrasonography. Examination using transvaginal ultrasound is more secure means of objectively measuring cervical length than diginal examination, transabdominal ultrasound, or transperineal ultrasound.

References

1. Dahman HAB. Risk factors associated with preterm birth: a retrospective study in Mukalla Maternity and Childhood Hospital, Hadhramout Coast/Yemen. Sudan J Paediatr. 2020;20(2):99-110. doi: 10.24911/SJP.106-1575722503. PMID: 32817730; PMCID: PMC7423304. https://doi.org/10.24911/sjp.106-1575722503
2. WHO, UNICEF, UNFPA WBG and the UNPD. Trends in maternal mortality 2000 to 2017: estimates [Internet]. Sexual and Reproductive Health. 2019. 12 p. Available from: https://www.who.int/reproductivehealth/publications/maternal-mortality-2000-2017/en/
3. Jones SC, Brost BC, Brehm WT. Should intravenous tocolysis be considered beyond 34 weeks gestation? Am J Obstet Gynecol. 2000; 183: 356-60. https://doi.org/10.1067/mob.2000.107663
4. Kipikasa J. Bolognese RJ. Obsetric management of prematurey In : Fanaroff AA, Martin RJ. Neonatal-perinatal medicine: disease of the fetus and infant. 6 th edition. New York: Mosby-Year Book. 1997; 264-84.
5. Sakala EP. Board review series: obstetrics and gynecology. Baltimore: Williams & Wilkins. 1997; 175-7.
6. Winjosastro G. Kelainan dalam lamanya kehamilan. Dalam: Wiknjosastro G. Saifuddin AB, Rachimhadi T. Ilmu Kebidanan. Jakarta: Yayasan Bina Pustaka. 2000, 312-7.
7. O'Hara S, Zelesco M, Sun Z. Cervical length for predicting preterm birth and a comparison of ultrasonic measurement techniques. Australas J Ultrasound Med. 2013 Aug;16(3):124-134. doi: 10.1002/j.2205-0140.2013.tb00100.x. Epub 2015 Dec 31. Erratum in: Australas J Ultrasound Med. 2013 Nov;16(4):210-211. https://doi.org/10.1002/j.2205-0140.2013.tb00100.x
8. Priv.-Doz. Dr. B. Kuschel, Prof. Dr. K.-Th.M. Schneider. Verschlußoperationen am Muttermund - Maßnahmen zur ... - tum [Internet]. 2012 [cited 2022Oct4]. Available from: https://mediatum.ub.tum.de/doc/1107754/1107754.pdf