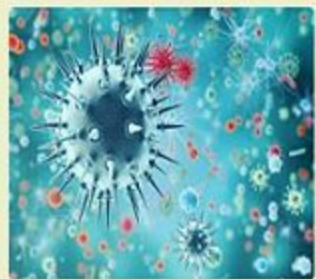


Medical and Health Science Journal



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ORIGINAL ARTICLE

EFFECT OF ASIATIC MANGROVE (*Rhizophora mucronata*) LEAVES EXTRACT AS ANALGESIC IN MALE ALBINO DDW MICE (*Mus musculus L.*) INDUCED BY 0,7% ACETIC ACID**Erika Widianingsih Nanuru, Lestari Dewi*, Prajogo Wibowo**

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ABSTRACT

Background : Pain is an unpleasant emotional experience that illustrates ongoing tissue damage. Excessive use of non-steroidal anti-inflammatory drugs can cause peptic ulcer to gastric mucosal damage and perforation. Indonesia contains the largest area of mangrove forest in the world. There are 45 species of mangrove found and one of them is Asiatic Mangrove (*Rhizophora mucronata*). This type is easy to find and rich of alkaloids and flavonoids which can be used as analgesics.

Method: This study used *post-test only control group design*. The number of mice that used was 25 mice, divided into 5 groups. Which were given different therapies aquadest 10mL/KgBW, acetosal 150 mg/KgBW, extract of *Rhizophora mucronata* 250 mg/KgBW, 500 mg/KgBW, and 1000 mg/kg bw. The pain was induced by 0,7% glacial acetic acid at a dose of 10 mL/KgBW. The writhes of the mice was being calculated with an interval of 10 minutes in 30 minutes.

Result: The results of the analysis showed the decrease in writhes of mice in acetosal group dose 150 mg/kg bw, *Rhizophora mucronata* leaves extract dose 250 mg/kg bw, 500 mg/kg bw, and 1000 mg/kg bw. There was a significant difference in the results of the *Mann-Whitney U* test with $p < 0,05$ in the aquadest group and the acetosal group with the *Rhizophora mucronata* leaves extract group dose 500 mg/kg bw, the difference between the acetosal group and the *Rhizophora mucronata* leaves extract group dose 250 mg/kg bw, and the difference between the *Rhizophora mucronata* leaves extract group dose 500 mg/kg bw and the *Rhizophora mucronata* leaves extract group dose 1000 mg/kg bw. **Conclusion:** *Rhizophora mucronata* leaves extract dose 500 mg/kg bw can provide analgesic effect and can reduce the writhing frequency in mice much better than acetosal group.

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Introduction

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage¹. Almost all disease are accompanied by pain, pain arises because of a disturbance in a tissue so that is used by the body as a sign that an infection is occurring.

Estimated between long-term use of analgesics and anti-inflammatory drugs: 15-40% will experience upper gastrointestinal complaints; 10-25% suffer from gastric ulcers, especially peptic ulcers; and 1-4% will experience life-threatening ulcer complications such as gastric bleeding and perforation². In many countries including Indonesia, non-steroidal anti-inflammatory drugs (NSAIDs) are used for symptoms associated with arthritis and other symptomatic indications including myofascial pain, gout, fever, dysmenorrhea, migraine, perioperative pain, stroke prophylaxis and myocardial infarction³.

Indonesia is an archipelagic country consisting of 17.500 islands with a coastline of about 95.181 km. The total area of Indonesia is about 9 million km² (2 million km² land and 7 million km² sea). Indonesia's area is only about 1,3% of the earth's area, but has a very high biodiversity. For plants, Indonesia is estimated to have 25% of flowering plant species in the world or the seventh largest country with a number of species reaching 20.000 species, 40% of which are endemic or native to Indonesia⁴.

Mangroves are ecosystems located in intertidal areas, where there is a strong interaction between marine, brackish, river and land waters. This interaction makes the mangrove ecosystem has a high diversity of flora and fauna. Mangroves

lives in the tropics and subtropics, especially at latitudes of life 25° North Latitude and 25° South Latitude⁵. Indonesia has the largest mangrove forest in the world, with an area of 42.550 km² and about 45 species of mangroves live in Indonesia⁶.

Rhizophora mucronata or asiatic mangrove is a type of species that is often found and generally this tree has a height of up to 27 m, and rarely exceeds 30 m. stems up to 70 cm in diameter with dark to black bark and horizontal fissures. This plant grows in groups, near or on the bottom of tidal rivers and in river mouths, rarely growing in areas far from the tides. Optimal growth occurs in heavily flooded areas, as well as in humus-rich soil. The wood of this plant can be used for staining, and are sometimes used medicinally in cases of hematuria (bleeding in the urine). It is sometimes planted along ponds to protect the embankments⁷. The phytochemical components of asiatic mangrove include: flavonoids, alkaloids, phenolics, terpenoids and glycoside⁸, proteins, saponins, and tannins⁹. Based on the background, the study was designed to determine the analgesic effect of the leaves extract of asiatic mangrove (*Rhizophora mucronata*) in male albino ddw mice (*Mus musculus L.*) induced by 0,7% acetic acid.

Methods

Place and time of study

This research was conducted in the Biochemistry Laboratory of the Faculty of Medicine, Hang Tuah University, Surabaya for 7 days with the ethical clearance number 724/HRECC.FODM/X/2019.

Plant collection and preparation of the extract

Rhizophora mucronata leaves were collected from Wonorejo Mangrove Forest, Surabaya. Fresh *Rhizophora mucronata* leaves were cleaned, shade dried and crushed to powder by grinder. They were extracted used maceration technique. 1000 grams of dried *Rhizophora mucronata* leaves were macerated with 96% ethanol solvent for 3x24 hours. Then after producing the extract, the resulting extract is concentrated with a water bath to produce a thick blackish green extract. Furthermore, evaporation is carried out and then evaporated at room temperature to produce a thick extract of ethanol.

Animals

25 male albino ddw mice (*Mus musculus L.*) aged 7-9 weeks with an average weight of 20-25 grams were used for these studies. The animals were obtained from the Pusat Veteriner Farma Surabaya (Pusvetma Surabaya). The animals were placed in boxes and given husks. Each box contains 5 mice.

Analgesic activity study

The design of this study was a laboratory experimental study using *post-test only control group design*. Analgesic test of this leaves extract was carried out by induction of 0,7% acetic acid in mice 0,7% acetic acid was injected intraperitoneally for one time to cause pain in mice. Mice were divided into 5 groups with 5 mice in each groups. Group A as the negative control group was given 10 mL/KgBW of aquadest orally,

group B as a positive control group was given acetosal at a dose of 150 mg/KgBW orally, group C as the first treatment group was given *Rhizophora maucronata* leaves extract at a dose of 250 mg/KgBW orally, group D as the second treatment group was given *Rhizophora mucronata* leaves extract at a dose of 500 mg/KgBW orally, group E as the third treatment group was given *Rhizophora mucronata* leaves extract at a dose of 1000 mg/KgBW orally.

After 30 minutes of oral administration, 0,7% acetic acid was injected intraperitoneally in each mice. After 5 minutes, the number of writhing performed by the mice was counted for 30 minutes. Calculations were carried out at 10 minutes intervals. Then determine the percentage of inhibition (%) of analgesic activity with the formula ¹⁰:

$$\% \text{ inhibition} = \frac{(\text{Control} - \text{Sample})}{\text{Control}} \times 100\%$$

Results

In acetic acid induction, *Rhizophora mucronata* extract gave significant analgesic results at a dose of 500 mg/KgBW with percentage of inhibition of 75,15% and a dose of 250 mg/KgBW with a percentage of inhibition of 52,87% compared to the control. And the results of the study in Table 1, shows that there is an analgesic effect asiatic mangrove (*Rhizophora mucronata*) leaves extract in male mice (*Mus musculus L.*) with 0,7% acetic acid induction (Table 1).

Table 1 Writhling Frequency Observation Results

Group	Mean \pm S.D	% inhibition
A	31,4 \pm 27,18	0%
B	29,4 \pm 14,6	6,39%
C	14,8 \pm 11,56	52,87%
D	7,8 \pm 4,65	75,15%
E	20,4 \pm 4,39	35,03%

S.D=standard deviation

The results of the writhing rate per period showed that the leaves extract of the *Rhizophora mucronata* had a significant analgesic effect. At 10 minutes, the highest mean was found in the acetosal group or group B with the value of 12, while the lowest mean was found in the group with *Rhizophora mucronata* leaves extract dose 500 mg/KgBW or group D with the value of 2,4. At 20 minutes, the highest mean was found in the aquadest group or group A with the value of 11,6,

while the lowest mean was found in the group with *Rhizophora mucronata* leaves extract dose 500 mg/KgBW or group D with the value of 3,8. At 30 minutes, the highest mean was found in the aquadest group or group A with the value of 9,6, while the lowest mean was found in the group with *Rhizophora mucronata* leaves extract dose 500 mg/KgBW or group D with the value of 1,6 (Table 2).

Table 2 Average Number of Writhing

Group	Average number of writhing (minutes)		
	10mins \pm S.D	20mins \pm S.D	30mins \pm S.D
A	10,2 \pm 9,41	11,6 \pm 12,30	9,6 \pm 6,94
B	12 \pm 4,06	13,2 \pm 8,58	4,2 \pm 3,11
C	4,2 \pm 3,76	6,4 \pm 4,77	4,2 \pm 3,89
D	2,4 \pm 1,67	3,8 \pm 2,48	1,6 \pm 1,81
E	7,2 \pm 3,83	7,2 \pm 3,27	6 \pm 3,24

S.D=standard deviation

Furthermore, the normality test was carried out using the *Saphiro-Wilks* test. The results of the *Saphiro-Wilks* test, it was found that all groups had significance $p > \alpha$ ($\alpha = 0.05$), except for the

10 minutes of group E and the 30 minutes of group A the significance value was $p < \alpha$ ($\alpha = 0.05$), meaning that the data not normally distributed (Table 3).

Table 3 Saphiro-Wilks Test Results

Group	Significance		
	10'	20'	30'
A	0,169	0,330	0,015
B	0,627	0,639	0,670
C	0,194	0,899	0,093
D	0,314	0,384	0,254
E	0,006	0,914	0,111

Furthermore, a non-parametric test is carried out using the *Kruskal-Wallis* test. The results of the *Kruskal-Wallis* test there is a significant value of $p < \alpha$ ($\alpha = 0.05$), which means that there is a

difference in the analgesic effect of *Rhizophora mucronata* leaves extract in male mice (*Mus musculus L.*) with 0,7% acetic acid induction between groups (Table 4).

Tabel 4 Kruskal Wallis Test Results

	10 Minutes	20 Minutes	30 Minutes
Asymp. Sig. (2-tailed)	0,019	0,388	0,169

To determine whether there was a difference in the mean of the study groups, a post-hoc *Mann-Whitney U* test was performed. There was a significant difference in the results of the *Mann-Whitney U* test with $p < 0,05$ in the aquadest group and the acetosal group with the *Rhizophora mucronata* leaves extract group at

a dose of 500 mg/KgBW, the difference between the acetosal group and the *Rhizophora mucronata* leafves extract group at a dose of 250 mg/KgBW and the *Rhizophora mucronata* leaves extract group at a dose of 1000 mg/KgBW (Table 5).

Table 5 Mann Whitney U Results in the first 10 minute observation period

10 Minutes					
Sig	Group A	Group B	Group C	Group D	Group E
Group A		0,401	0,140	0,044	0,743
Group B			0,027	0,009	0,084
Group C				0,454	0,129
Group D					0,041
Group E					

Discussion

In this study, 25 mice were used which were divided into 5 groups. Each groups consisted of 5 white mice (*Mus musculus L.*) which was induced by pain with 0,7% acetic acid injection. The injection was carried out 30 minutes after being given therapy, such as aquadest, acetosal, and *Rhizophora mucronata* leaves extract.

Group A as a negative control was given 10 mL/KgBW of aquadest, group B as a positive control was given 150 mg/KgBW of acetosal, group C as the first treatment group was given *Rhizophora mucronata* leaves extract at dose of 250 mg/KgBW, group D as the second treatment group was given *Rhizophora mucronata* leaves extract at dose of 500 mg/KgBW, group E as the third treatment group was given *Rhizophora mucronata* leaves extract at dose of 1000 mg/KgBW.

After being given the extract, wait about 30 minutes first, then 0,7% acetic acid injected with a dose of 10 mL/KgBW intraperitoneally and wait for 5 minutes and do the calculations at intervals of every 10 minutes for 30 minutes.

Based on the data of this study, it was found that the *Rhizophora mucronata* leaves extract at a dose of 250 mg/KgBW (group C), a dose of 500 mg/KgBW (group D), a dose of 1000 mg/KgBW (group E) had a significant analgesic effect, as evidenced by the mean of writhing which is smaller than the negative

control group (group A). The percentage of inhibition from group C was 52,87%, group D was 75,2%, and group E was 35,03%, this indicates that the three doses of *Rhizophora mucronata* can inhibit pain process. *Rhizophora mucronata* containing flavonoids, alkaloids, phenolics, terpenoids and glycosides⁹ which some substances can help in inhibiting the pain process¹¹.

Acetic acid induces an inflammatory response in the abdominal cavity with subsequent activation of nociceptors. When animals are injected intraperitoneally with acetic acid, acute pain and an inflammatory reaction appear in the peritoneal area. Constriction caused by acetic acid is considered a nonselective antinociceptive model, because acetic acid acts indirectly by stimulating endogenous mediators that increase nociceptive neurons sensitive to sensitive to nonsteroidal anti-inflammatory drugs, and other active drugs¹². *Rhizophora mucronata* leaves extract contains many flavonoids and alkaloid that are effective in delaying the response time of mice to stimulation, and the researchers identified that this compound is luteolin which interacts strongly with cyclooxygenase and forms a number of specific hydrogen bonds and they identified that the central and peripheral antinociceptive activity of the extract *Rhizophora mucronata* leaves involve opioid receptors¹³.

In the group with high doses of *Rhizophora mucronata* leaves extract

produced more writhing, this can be associated with the administration of too many flavonoids, the higher dose, the more flavonoids are given and can cause opioid receptor binding. If opioid receptors are activated frequently, it can lead to an opioid-induced hyperalgesia response¹⁴. However, luteolin in *Rhizophora mucronata* leaves extract can reduce the intensity of neuropathic pain and can relieve hyperalgesia and nociception and can relieve acute and chronic pain¹⁵.

Conclusion

Asiatic mangrove (*Rhizophora mucronata*) leaves extract at a dose of 250 mg/KgBW, and 1000 mg/KgBW was able to give the effect of decreasing the amount of writhing with 0,7% acetic acid induction method.

Asiatic mangrove (*Rhizophora mucronata*) leaves extract at a dose of 500 mg/KgBW can provide a better analgesic effect than aspirin in reducing the amount of acetic acid by 0,7% acetic acid induction method.

References

1. Raja, S. N. *et al.* The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* (2020) doi:10.1097/j.pain.0000000000001939.
2. V.S, B. & J.G, H. Complications of nonsteroidal antiinflammatory drug gastropathy and use of gastric cytoprotection: Experience at a tertiary care health center. *J. Rheumatol.* doi:26(7):1557-1563.
3. Soleha, M. *et al.* Profil Penggunaan Obat Antiinflamasi Nonsterooid di Indonesia. *J. Kefarmasian Indones.* (2019) doi:10.22435/jki.v8i2.316.
4. Kusmana, C. & Hikmat, A. Keanekaragaman Hayati Flora di Indonesia. *J. Pengelolaan Sumberd. Alam dan Lingkungan.* (2015) doi:10.19081/jpsl.2015.5.2.187.
5. Martuti, N. Keanekaragaman Mangrove di Wilayah Tapak, Tugurejo, Semarang. *J. MIPA* (2012).
6. Spalding, D. & Ravilious, C. *World Atlas of Coral Reefs.* (2011).
7. Noor, Y. R., Khazali, M. & Suryadiputra, I. N. *MANGROVE di Indonesia.* (2012).
8. Nurdiani, R., Firdaus, M. & Prihanto, A. A. Phytochemical Screening and Antibacterial Activity of Methanol Extract of Mangrove Plant (*Rhizophora mucronata*) from Porong River Estuary. *J. Basic Sci. Technol.* (2012).
9. Asha, S. & M .Ruthu, Y.Pradeepkumar, C.Madhusudhana chetty, G.Prasanthi, V. J. S. R. Phytochemical Analysis of Mangrove Derived Crude Plant Extract-*Rhizophora Mucronata*. *J. Glob. Trends Pharm. Sci.* **2**, 55–62 (2017).
10. Unnikrishnan, P., Suthindhiran, K. & Jayasri, M. Alpha-amylase inhibition and antioxidant activity of marine green algae and its possible role in diabetes management. *Pharmacogn. Mag.* (2015) doi:10.4103/0973-1296.172954.

11. Verri, W. A. *et al.* Flavonoids as anti-inflammatory and analgesic drugs: Mechanisms of action and perspectives in the development of pharmaceutical forms. in *Studies in Natural Products Chemistry* (2012). doi:10.1016/B978-0-444-53836-9.00026-8.
12. Dzoyem, J. P., McGaw, L. J., Kuete, V. & Bakowsky, U. Anti-inflammatory and Antinociceptive Activities of African Medicinal Spices and Vegetables. in *Medicinal Spices and Vegetables from Africa: Therapeutic Potential Against Metabolic, Inflammatory, Infectious and Systemic Diseases* (2017). doi:10.1016/B978-0-12-809286-6.00009-1.
13. Gurudeeban, S., Kalamurthi, S., Sheik, H. S. & Thiruganasambandam, R. Molecular docking, isolation and biological evaluation of *Rhizophora mucronata* flavonoids as antinociceptive agents. *Biomed. Prev. Nutr.* (2014) doi:10.1016/j.bionut.2014.08.002.
14. Lee, M., Silverman, S., Hansen, H., Patel, V. & Manchikanti, L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* (2011).
15. Hashemzaei, M. *et al.* Effects of luteolin and luteolin-morphine co-administration on acute and chronic pain and sciatic nerve ligature-induced neuropathy in mice. *J. Complement. Integr. Med.* (2017) doi:10.1515/jcim-2016-0066.

ORIGINAL ARTICLE

AN OVERVIEW SELF-EFFICACY AND SELF-ACCEPTANCE IN TUBERCULOSIS SUFFERERS

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ABSTRACT

Background: Tuberculosis is still a major health problem in Indonesia, especially in the working area of the East Health Center in Surabaya, the long treatment of Tuberculosis (TB) causes sufferers to have low self-efficacy and poor self-acceptance. The purpose of this study is to analyze the relationship between self-efficacy and self-acceptance of patients with Tb.

Methods: The design research is analytic study with cross sectional approach. The study population of 46 patients with active treatment for the last 3 months in the work area of the community Health Center in Surabaya. by 46 patients.

Results: A sample from 41 respondents taken by simple random sampling technique. The independent variable is self-efficacy, the dependent variable is self-acceptance. The instrument uses a questionnaire. Data analysis used Chi Square test with significance value $\alpha = 0.05$. The results showed that of 41 respondents the majority (57.3%) had low self-efficacy, and the majority (57.3%) had poor self-acceptance. Chi Square statistical test results obtained value $p = 0.008 < \alpha = 0.05$ shows there is a relationship of self-efficacy with self-acceptance of patients with TB in the work area of the East Perak Health Center in Surabaya.

Conclusion: Conclusions of the study that the lower the self-efficacy in patients with Tb the worse the self-acceptance and vice versa. Patients with TB should further improve their efficacy by always obeying the advice of health workers, and treatment regularly. The role of nurses in improving self-efficacy by providing education to sufferers and families, working together to care more and motivate patients so that success in treatment.

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Introduction

Tuberculosis is still a major health problem worldwide¹. Indonesia is at the third level (8%) highest incidence of TB cases after India (27%) and China (9%). East Java still occupies the second largest province of cases in Indonesia after West Java². Health Research Data East Java Region³, Surabaya city is at the figure of 0.3 % tuberculosis diagnosis. In 2016 TB cases in Surabaya as many as 2,382 people, with prevalence recovery 42.0%, died 2.5% and failed 0.4%¹.

A preliminary study conducted in November 2019 at the Health Center in Surabaya city obtained 160 cases of tuberculosis consisting of 28 children, tuberculosis with HIV 5 people, pulmonary tuberculosis 124 people, Multi Drug Resistance (MDR) as many as 3 people². Research on tuberculosis in puskesmas in Surabaya has been done by researchers before. But no one has done any research on self efficacy and self acceptance in tuberculosis sufferers.

Based on the data above the prevalence of failure and recovery depends on the efficacy of the patient in receiving the condition of the disease and the disease experienced, because self-efficacy is the belief of the sufferer to organize and implement the treatment program so that success in treatment is realized.

Tuberculosis is a public health problem that causes mental distress for sufferers, because it has to carry out regular treatment and control. The patient's self-acceptance that he suffers from tuberculosis will experience stress, sadness, disappointment and surrender. Perceptions shown by sufferers such as grumpy, withdrawn or even showing self-efficacy are not good³. His lack of

efficacy made him unable to do anything useful due to suffering from tuberculosis⁴.

Patients who have good self-efficacy will choose good behaviors that will improve it, thereby lowering depression and worry, increasing self-esteem and quality of life^{4,5}. Self-efficacy accompanied by the role of motivation is very important for self-acceptance of tuberculosis sufferers in conducting treatment. Some factors that affect the self-acceptance of tuberculosis sufferers in the Health Promotion Model are the benefits of direct action that provides motivation to the behavior of tuberculosis sufferers⁶. Obstacles of action known by sufferers so that tb sufferers have preparedness in doing obstacles or high obstacles are low. Self-efficacy is the ability of tb sufferers in behaving raises action, attitudes related to emotional activities arising in treatment activities and in differentiation of places and behaviors to tb sufferers⁷. The greatest interpersonal influences are the families, groups and influences of health workers, as well as situational influences that are key in the development of affective strategies for tb sufferers to facilitate and maintain health promotion behaviors in the population⁸.

Self-efficacy in behaving is the actions of individuals in carrying out activities in accordance with their expectations, efforts made in performing the desired objectives. the resilience of the individual in strengthening himself when facing failure, resistance to discomfort by assuming the situation faced is not a threat but a challenge to become a better person¹. The mindset of tuberculosis sufferers will usually see everything in their circle narrow when in difficult situations, achievement levels

manifest, and stress or depression becomes a stimulus for sufferers to feel depressed⁹.

The number of tuberculosis sufferers who do not use masks during treatment and the number of patients who do not do regular control is very problematic for someone who has poor self-efficacy that affects the self-acceptance of tuberculosis sufferers⁵. Therefore, efforts to improve the patient's self-efficacy are very important in the patient's self-acceptance, because many sufferers do not believe that they have tuberculosis so not many treatments fail¹⁰. The authors found that a lack of self-efficacy in self-acceptance is one of the causes of such failures, so it is necessary to conduct more research on the relationship of self-efficacy with self-acceptance of tuberculosis sufferers in the work area of a community health center in Surabaya.

Methods

Research design is the study of analysis with a cross sectional approach. The study was conducted in October - December 2020. Inclusion criteria, namely, adult tuberculosis sufferers, tuberculosis sufferers without any accompanying disease, tuberculosis sufferers do routine control for the last 3 months, willing to be respondents. The exclusion criteria are children with tuberculosis, tuberculosis sufferers with Multi Dark Resistance (MDR). Sampling was done in accordance with simple random sampling and sample calculation based on the slovin formula obtained by 46 respondents but at the time of the study there were 2 respondents moved to another city, 3 respondents refused to follow the research. Data collection with questionnaires circulated through google form on whatsapp group created

by researchers with the consent of respondents, considering the condition is a pandemic period where researchers can not directly meet with respondents. Questionnaire contains questions about self efficacy and self acceptance with assessors based on likert scale, 1 strongly disagree, 2 disagree, 3 agree, 4 agree once, 5 strongly agree once. The instrument used a questionnaire that was self-controlled by research and conducted validity tests and reliabilities with Cronbach alpha > 0.5. Analyze the data using the Chi Square test with a value of $\alpha = 0.05$.

Results

The results of this study include the distribution of self-efficacy, self-acceptance and statistical tests of correlation of self-efficacy and self-acceptance. As stated in the following table;

Table 1. Self-efficacy frequency distribution

No.	Self- efficacy	Frequency	(%)
1	High	20	48,8
2	Low	21	51,2
	Total	41	100

Primary data, February 19, 2020

Based on table 1 shows that out of 41 respondents, the majority (51.2%) tuberculosis sufferers have low self-efficacy.

Table 2. Self-Acceptance Frequency
Distribution

No.	Self- acceptance	Frequency	(%)
1	Good	20	48,8
2	Bad	21	51,2
	Total	41	100

Primary data, February 19, 2020

Based on table 2 shows that out of 41 respondents, the majority (51.2%) tuberculosis sufferers have low self-acceptance.

Table 3. Cross Tabulation ff Self-Efficacy with Independent Recipients in Tuberculosis Sufferers

Self-Efficacy	Self-Acceptance				Total		P
	Good		Ugly		N	%	
	N	%	N	%			
High	14	70	6	30	20	100	0,008
Low	6	28,6	15	71,4	21	100	
Total	20	48.8	21	51,2	41	100	

Primary data, February 19, 2020

Based on table 3 shows that out of 41 respondents, the majority (51.2%) Tb sufferers have poor self-acceptance.

Cross tabulation in table 3 shows that of the 21 respondents who had low self-efficacy, the majority (71.4%) poor self-acceptance, and of the 20 respondents who had high self-efficacy most (70%) with good self-receiver. Chi Square test results with *SPSS for Windows* with a meaning level = 0.05 obtained a value of $p=0.008$ ($0.008 < 0.05$) then H_0 rejected which means there is a relationship of Self Efficacy with Self-Acceptance sufferers tuberculosis.

The results of the study in table 1 showed that most (51.2%) have low self-efficacy, tb sufferers in the community health center area in Surabaya have the view that Tb disease is a test in accordance with the statement at number 10, and almost half (48.8%) has high self-efficacy, tb sufferers force themselves to take drugs in

accordance with the provisions of health services in the hope of recovering, this is in accordance with statements number 4 and 11.

Discussion

Tuberculosis sufferers in the work area of a community health center in Surabaya in Surabaya, most have low self-efficacy and most have poor self-acceptance.

The results of this study are in line with the research of ¹¹ which found the majority (57.3%) patients tend to have low self-efficacy because they are not sure to complete tuberculosis treatment. While the results of ¹² found some respondents (66.67%) have sufficient self-efficacy. That self-efficacy is the consideration a person has in carrying out certain behaviors ¹³. Tuberculosis sufferers who are not emotional tend to have high expectations but tuberculosis sufferers with high emotional levels have low expectations ¹⁵.

Tuberculosis sufferers who are not emotional tend to have high expectations but tb sufferers with high emotional levels have low expectations. Patients who have low self-efficacy and high emotional level will feel depressed and have a high restless attitude especially with the habit of having to take medication every day during the treatment process until cured, and the use of masks as personal protection and people around and differentiation of places to eat to bed that cause tb stress and this is in accordance with ¹⁴. Self-efficacy is self-confidence with optimism and hope to be able to solve problems, when the individual is faced with health problems, there will be stress on him and the occurrence of

reactions to the situation he experienced so that he can not condition between his emotions in the face of difficulties ¹⁵.

Identification of Self-Acceptance in Tuberculosis Sufferers

The results of the study in table 2 showed that the majority (51.2%) have bad self-acceptance. The results of the observations of researchers found that tuberculosis sufferers feel minder with themselves and prefer to be alone in the room, this is in accordance with statements 8 and 9, according to one cadre of tuberculosis many tb sufferers do not want to come to the community health center themselves so that cadres educate sufferers, if the sufferer does not want to come to take drugs then it can be taken by the family or assisted by tuberculosis cadres in the community health center area in Surabaya, and almost half (48.8%) have good self-acceptance, the result of the observation of researchers tuberculosis sufferers can adapt to the disease because they routinely take drugs in accordance with statements number 1 and 3, when me and the cadre come to the patient's house, they accept us with joy and explain their grievances in taking drugs and behavior at home, so that cadres always provide motivation for sufferers and families to better supervise the administration of drugs to sufferers. This study is in line with the research of ¹⁵ found that the most self-acceptance is self-acceptance enough, patients who have enough or less self-acceptance caused by most patients have a persistent cough makes it difficult for patients to get along in the community environment, the patient feels minder with the disease experienced and causes

a sense of insecurity can be cured in carrying out treatment. Treatment will be successful depending on the attitude and support of the family, the main source of interpersonal support for tuberculosis sufferers is the family so that the family has an important role in the recovery of tuberculosis sufferers but if the family does not care then there will be other tuberculosis sufferers in one house ⁸.

Comfort to yourself obtained from the closest person will increase self-confidence in overcoming the problems faced, tuberculosis sufferers who can accept themselves will have life satisfaction either directly or indirectly because self-acceptance means having accepted the shortcomings in him ¹⁶.

Research from setyowati ¹⁶ explained from 3 determinant factors tb namely activities, feelings and abilities that strongly affect the occurrence of Tb disease is feelings towards itself. Kurniawati et al, ¹² explained that tb sufferers who have severe emotional feelings will become stressed and gradually depressed because they have not been able to accept the situation that they experience so it is difficult in self-acceptance. Jang et al mentioned that a bad concept of self will result in rejection of oneself, so tb sufferers who have unstable self-concept will refuse to take medication, or still take medication but do not follow the advice of health workers despite always being reminded¹³.

Relationship of Self-Efficacy with Self-Acceptance In Tuberculosis Sufferers

The results of the study in Table 3 Cross tabulation between Self-Efficacy and Self-Acceptance of TB sufferers in the work area of a

community health center in Surabaya using the Chi *Square* test. The research hypothesis obtained the results of $\rho < \alpha$ or $0.008 < 0.05$ which means there is a relationship between Self-Efficacy and Self-Acceptance of TB sufferers in the work area of a community health center in Surabaya.

This can prove that there is a link between Self-Efficacy and Self-Acceptance of tuberculosis sufferers in the working area of the Center for Public Health in Surabaya. This can be seen from the cross-tabulation analysis that of the 21 respondents who had low self-efficacy, most (71.4%) poor self-acceptance, and of the 20 respondents who had high self-efficacy most (70%) have good self-acceptance.

The results of this study are in line with the research conducted ³ the higher the value of self-efficacy the better self-acceptance, and vice versa the lower ¹⁴ the value of self-efficacy the worse self-acceptance. In addition, research conducted by states that self-efficacy is a concept of a person's ability to perform the desired action, self-efficacy becomes an amplifier of the reason a person performs for his or her own good.

From the data obtained, the higher self-efficacy the better self-acceptance. Good self-efficacy occurs because of the belief of tuberculosis sufferers to recover which is accompanied by self-acceptance in tuberculosis sufferers. On the contrary, if the efficacy of him is low then the self-acceptance of tuberculosis sufferers is also bad.

Conclusion

Tuberculosis sufferers in the work area of a community health center in Surabaya in

Surabaya, most have low self-efficacy and most have poor self-acceptance. This is evidence from research stating that there is a relationship of self-efficacy to self-acceptance in people with pulmonary tuberculosis.

Conflict of Interest

The author stated there is no conflict of interest

References

1. Kemenkes RI. Tuberkulosis (TB). Tuberkulosis **1**, 2018 (2018).
2. Andajani, S. Determinant of Latent Pulmonary Tuberculosis Incidence among Health Workers in Community Health Centers in Surabaya, Indonesia. Folia Medica Indones. **55**, 139 (2021).
3. Yang, Y., Dongdong, Y. & Yu, H. Comparative Study on Relationship Between Inconsistent Online-Offline Social Performance and Self-Efficacy of University Students Based on Types of Social Activity. Front. Psychol. **12**, 747 (2021).
4. Setiyowati, E., Hanik, U., Juliasih, N. N. & Wahdi, A. Self-Management Education for the Quality of Life of Patients with Pulmonary Tuberculosis. J. Qual. Public Heal. **4**, 10–19 (2020).
5. Kim, S., Roh, H. J. & Sok, S. Empathy and Self-Efficacy in Elderly Nursing Practice among Korean Nurses. Int. J. Environ. Res. Public Health **18**, (2021).
6. Colvin, C. J. et al. 'It has become everybody's business and nobody's business': Policy actor perspectives on the implementation of TB infection prevention and control (IPC) policies in South African public sector primary care health facilities. Glob. Public Health **0**, 1–14 (2020).

7. Li, J.-B. et al. Chinese public's knowledge, perceived severity, and perceived controllability of COVID-19 and their associations with emotional and behavioural reactions, social participation, and precautionary behaviour: a national survey. *BMC Public Health* **20**, 1589 (2020).
8. Banu, S. et al. Social Enterprise Model (SEM) for private sector tuberculosis screening and care in Bangladesh. *PLoS One* **15**, 1–17 (2020).
9. Recabarren, R. E., Gaillard, C., Guillod, M. & Martin-Soelch, C. Short-Term Effects of a Multidimensional Stress Prevention Program on Quality of Life, Well-Being and Psychological Resources. A Randomized Controlled Trial. *Front. psychiatry* **10**, 88 (2019).
10. Santos, C. D., Santos, A. J., Santos, M., Rodrigues, F. & Bárbara, C. Pulmonary rehabilitation adapted index of self-efficacy (PRAISE) validated to Portuguese respiratory patients. *Pulmonology* **25**, 334–339 (2019).
11. Hallford, D. J., Ricarte, J. J. & Hermans, D. Perceived Autobiographical Coherence Predicts Depressive Symptoms Over Time Through Positive Self-Concept. *Front. Psychol.* **12**, 674 (2021).
12. Kurniawati, A., Padmawati, R. S. & Mahendradhata, Y. Acceptability of mandatory tuberculosis notification among private practitioners in Yogyakarta, Indonesia. *BMC Res. Notes* **12**, 543 (2019).
13. Jang, I., Oh, D. & Kim, Y. S. Factors associated with nursing students' willingness to care for older adults in Korea and the United States. *Int. J. Nurs. Sci.* **6**, 426–431 (2019).
14. Yada, H., Abe, H., Odachi, R. & Adachi, K. Exploration of the factors related to self-efficacy among psychiatric nurses. *PLoS One* **15**, 1–11 (2020).
15. Mata, Á. N. de S. et al. Training in communication skills for self-efficacy of health professionals: a systematic review. *Hum. Resour. Health* **19**, 30 (2021).
16. Setiyowati, E. Determinants of the Quality of Life of Pulmonary Tuberculosis (Ptb) Patients in Surabaya City. *J. Heal. Sci.* **13**, 116–123 (2020).

ORIGINAL ARTICLE

IMPLEMENTATION OF OCCUPATIONAL SAFETY AND HEALTH RISK MANAGEMENT IN ISLAMIC HOSPITAL SURABAYA A. YANI

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ABSTRACT

Background: Risk management is a preventive effort for a company, especially those engaged in the service sector, which is very prone to errors and complaints. For this reason, it is necessary to map the risks that occur in accordance with the work unit in it which is expected to minimize the number of accidents or errors in both patients, visitors and employees in the hospital. In the 2019 patient safety incident report data at the Surabaya A. Yani Islamic Hospital, it was found that there were incidents which included near miss 93%, not injured 4%, unexpected events 3% and Sentinel 0%. The purpose of this study was to identify and identify the application of occupational safety and health risk management at the A. Yani Islamic Hospital in Surabaya.

Methods: This thesis is a qualitative research with a case study method with the aim of fully describing the implementation of K3 risk management at Surabaya A. Yani Hospital based on observation, survey and documentation data on 37 units and hospital workplaces by identifying risks. , analyze and find risk control measures.

Results: The results showed that the implementation of K3 risk management in the Islamic Hospital of Surabaya A. Yani based on the results of risk identification obtained as many as 25 risks in the graha building and the old building which were further analyzed by finding 15 moderate risks and 10 high risks. can be done by repairing damaged infrastructure and improving the existing security system at the A. Yani Islamic Hospital in Surabaya.

Conclusion: The conclusion in this study is the implementation of K3 risk management at the Islamic Hospital of Surabaya A. Yani has 25 potential risks, of which there are 15 moderate risks and 10 high risks that can potentially cause accidents to employees, visitors and patients. In this case, control efforts are made to minimize the number of incidents and accidents.

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Introduction

Occupational Health and Safety (K3) is a preventive effort made for workers or laborers as well as employers to prevent work accidents and diseases due to work relationships in the work environment by recognizing the potential that will cause work accidents and occupational diseases (PAK).¹ RI Law No. I of 1970 concerning work safety states that the workplace is a place where work is carried out for the purposes of a business where there are workers working and the possibility of danger in the workplace. This workspace includes all places of business activity with an economic or social motive.

Regulation of the Minister of Manpower Number PER.05/MEN/1996 states that the Occupational Health and Safety Management System, hereinafter referred to as the OHS Management System, is part of the overall management system which includes organizational structure, planning, responsibilities, implementation, achievement, assessment and maintenance of occupational safety and health policies in the context of controlling risks related to work activities in order to create a safe, efficient and productive workplace. Occupational health is one of the fields of public health that focuses attention on the working community, both in the formal sector and those in the informal sector².

Risk management activities are an important issue for a service based on service quality.³ Risk management is a preventive effort for a company, especially those engaged in the service sector where it is very vulnerable to errors and complaints. For this reason, it is necessary to first map the risks that occur according to the

work units in it. With that, it is hoped that risk management can minimize the number of accidents or errors both for patients, visitors and employees at the hospital. In achieving success in realizing risk control and mitigation in a health service, it is necessary to make rules and procedures and work targets so that they are clearly in accordance with the established agenda. For this reason, risk management makes policies and strategies that will be used in the process. This is intended to avoid errors in identification and monitoring of work programs so that they can focus on carrying out and planning activities in the service unit⁴.

Surabaya Islamic Hospital A. Yani is a hospital under the auspices of the Surabaya Islamic Hospital Foundation (YARSIS). Islamic Hospital Surabaya, which is one of the private hospitals with good service and accredited Plenary (Five Star) by KARS. With this, patients and visitors expect to get good and satisfying service. Based on the patient safety incident report data in 2019 it was found that the number of incident incidents was as follows:

Based on the data table for the 2019 patient safety incident report, it is explained that the percentage of patient safety incident frequency based on the type of incident is KNC 93%, KTC 4%, KTD 3% and Sentinel 0% at Islamic Hospital Surabaya A. Yani. Therefore, to improve service and customer satisfaction, an increase in patient safety services is needed. There is a need for regular monitoring and good risk management to ensure the safety of health workers, patients and visitors at the Surabaya A. Yani Islamic Hospital. Based on this description,

the authors conducted a study on "Application of Occupational Health and Safety Risk Management in Islamic Hospital Surabaya A. Yani".

The general and specific objectives of this study were to determine the application of OSH risk management at the Islamic Hospital of Surabaya A. Yani. Identifying occupational safety and health risks at the Surabaya A. Yani Islamic Hospital. Analyzing and evaluating risk at the Surabaya A. Yani Islamic Hospital, as well as knowing the control of risk at the Surabaya A. Yani Islamic Hospital.

Methods

This research is qualitative research with a case study method that is used to understand a problem or problem by using an event, process, activity and program with the aim of obtaining a complete and in-depth description or picture by collecting data from various sources including observation, , documentation and reports. This study will describe the application of occupational safety and health risk management which includes the stages of risk identification, risk analysis and risk control at the Islamic Hospital of Surabaya A. Yani.

1. The unit of analysis in this study is all workplaces and units in the hospital, totaling 37 hospital units that have the potential to pose a risk of danger at the Islamic Hospital of Surabaya A. Yani.
2. In this study, the techniques used in data collection were divided based on the source of the data obtained, namely primary data and secondary data. Primary data is data obtained

directly from the object of research, namely all units and workplaces at the Surabaya A. Yani Islamic Hospital through observations and surveys using a potential risk identification form. While the secondary data was obtained from the annual data recap which is a report recorded at the Surabaya A. Yani Islamic Hospital. While the data analysis techniques used are observation, survey, and documentation. Observations were made by direct observation of all units and workplaces at the Surabaya A. Yani Islamic Hospital which have the potential to have risks and hazards and to obtain secondary data, namely reports from the PMKP unit.

3. This survey was conducted using a risk identification form to obtain information from the field regarding the potential risks of hazards that cause accidents to health workers, employees and visitors or patients at the Surabaya A. Yani Islamic Hospital. Documentation is carried out with the aim of completing the information obtained so that it is more complete and supports the truth and information provided relating to the identification of potential hazards. From all stages of the process, the researcher inputs the data that has been obtained in the risk identification form and then describes it with photos or documentation in accordance with the conditions in the field and is described in the form of a narrative in the discussion and research results.

After obtaining all the data obtained from the research, it is analyzed to determine the potential hazards or causes of accidents and their sources, and reviewing the control efforts

that have been carried out in accordance with the AS/NZS 4360 standard, in particular by conducting a hazard risk analysis to determine the priority level of risk as a risk control measure so that does not cause work accidents.

4. The unit of analysis in this study is the place or environment in the Surabaya Islamic Hospital
 - a. those who have potential risks that open 37 units
5. This research was conducted at the Islamic Hospital Surabaya A. That is, in 37 units of analysis, namely the Graha building and the old RSI . building

The research was conducted from January to February 2021 with the object of research being all units and workplaces around the Surabaya A. Yani Islamic Hospital. Researchers have used and applied research ethics in this study, the researcher has explained in advance the intent and purpose of carrying out the research to the Surabaya A. Yani Islamic Hospital through an official licensing process from the University with the approval of the location to be studied, the data obtained from the unit and workplace at the Islamic Hospital of Surabaya A. Yani is guaranteed to be kept confidential by providing a report to the researcher, the risk identification form is given from the Hospital with guidance and direction from the General Section and the K3RS Committee, the statement that was studied obtained permission and approval from the Hospital with the output in the form of suggestions and input related to risk control at the Surabaya A. Yani Islamic Hospital.

Results

This research is qualitative research with a case study method that is used to understand a problem or problem by using an event, process, activity and program with the aim of obtaining a complete and in-depth description or picture by collecting data from various sources including observation., documentation and reports. This study will describe the application of occupational safety and health risk management which includes the stages of risk identification, risk analysis and risk control at the Islamic Hospital of Surabaya A. Yani. The unit of analysis in this study is all workplaces and units in the hospital, totaling 37 hospital units that have the potential to pose a risk of danger at the Islamic Hospital of Surabaya A. Yani.

In this study, the techniques used in data collection were divided based on the source of the data obtained, namely primary data and secondary data. Primary data is data obtained directly from the object of research, namely all units and workplaces at the Surabaya A. Yani Islamic Hospital through observations and surveys using a potential risk identification form. While the secondary data was obtained from the annual data recap which is a report recorded at the Surabaya A. Yani Islamic Hospital. While the data analysis techniques used are observation, survey, and documentation. Observations were made by direct observation of all units and workplaces at the Surabaya A. Yani Islamic Hospital which have the potential to have risks and hazards and to obtain secondary data, namely reports from the PMKP unit.

This survey was conducted using a risk identification form to obtain information from the

field regarding the potential risks of hazards that cause accidents to health workers, employees and visitors or patients at the Surabaya A. Yani Islamic Hospital. Documentation is carried out with the aim of completing the information obtained so that it is more complete and supports the truth and information provided relating to the identification of potential hazards. From all stages of the process, the researcher inputs the data that has been obtained in the risk identification form and then describes it with photos or documentation in accordance with the conditions

in the field and is described in the form of a narrative in the discussion and research results. After obtaining all the data obtained from the research, it is analyzed to determine the potential hazards or causes of accidents and their sources, and reviewing the control efforts that have been carried out in accordance with the AS/NZS 4360 standard, in particular by conducting a hazard risk analysis to determine the priority level of risk as a risk control measure so that does not cause work accidents.

Table 2. Data of Risk Control of Graha RSI Surabaya Building A. Yani

No	Possible risks	Root of the problem	Control Recommendations
1	- Stumble - hit by an object - Falls	Excessive placement of items in the workspace	Placed in a safer place such as a warehouse or other storage room.
2	- Get hit by a drugstore - fire extinguisher blocked - Stumbled alkes	Placement of medical equipment around APAR	Placed in a safer place such as a warehouse or other storage room.
3	- Slipped - Falls	Water leaks from the roof that soaks the floor	Repair of the roof and or marking of slippery floors around the floor.
4	- The fire extinguisher cannot be used optimally in the event of a fire	APAR hose that is loose and not maintained	Repair and check fire extinguishers on a regular or scheduled basis
5	- Struck by APAR	Setting the fire extinguisher too high	Place the fire extinguisher in the correct and strategic height position
6	- Stumble - Crashing - Falls	Wheelchair in the hallway	Moving to a safer place and does not hinder activities in the work environment

7	- Noise - Hearing disorders	Machine makes noise	Store it in a soundproof room and wear ear plugs
8	- Slipped - Falls	Cracked and leaking roof	Patching and repairing the roof
9	- Disturbance of electric current - Electrocuted - Can happen fong	Messy cables and close to work activities	Tidy cables and provide cable safety lock
10	- hit by an object - Damage to Facilities - Disturbance of electric current	Putting objects or items on the gallon near the computer	Move objects to a place that has been provided such as a drawer or table

Table 3 Data. of Risk Control of Old Building RSI Surabaya A. Yani

No	Possible risks	Root of the problem	Control Recommendations
1	- Stumble - Slipped - Falls	The stairs are not wide enough and there is no safety, such as rubber on the steps	Renovations and repairs by providing safety rubber on the stair steps
2	- Security system breached - Power failure - Network failure	The electrical installation room is unlocked	Padlocked and locked the room when not in use
3	- Get hit by an item - Falls - Stumble	Putting things and equipment on the stairs	Move items to a safe place
4	- Stumble - Falls - Overturned	Cracked and hollow floor in pharmacy corridor	Floor patching and repair
5	- Insect or vector entry - Smelly water	The water reservoir for oxygen is unlocked and poorly maintained	Periodic checks and monitoring as well as padlocks

6	- Wood cover - Scratched with cracked glass	Sanitary facilities for clinic and spiritual rooms that have been peeled off and cracked glass	Sanitation facility improvement
7	- hit by glass - Stumble	Placement of glass on the road	Move to a safer place
8	- Stumble - Falls - Overturned	Placement of pipes along roads where there is frequent activity	Moving pipes to a safer location or warehouse
9	- Disturbance of electric current - Electrocutted - Can happen fong	Messy cables and close to work activities	Tidy cables and provide cable safety lock
10	- Falls - Stumble - Crashing	Placement of goods in the workspace	Store it in a warehouse or in a safer place
11	- Slipped - Stumble - Falls	Floor rubber starting to peel off	Repair and replace rubber
12	- Slipped - Falls	Water leaks from the roof that soaks the floor	Repair of the roof and or marking of slippery floors around the floor.
13	- Nosy people breaking into - Electrical system shuts down when needed	Unlocked electrical installation	Locking and checking regularly
14	- Falls - Slipped - No Ergonomics	Steep access roads and passages in the ICU hallway and no safety or footing	Added handrails on each side and steps like stairs
15	- Electrocutted - Prone to short circuit when it rains	An open path around the generator and unlocked	Closing the fence and locking it and not being used as an access road

Discussion

In research activities that have been carried out at the Surabaya A. Yani Islamic Hospital, researchers observed and focused on one of the activities, namely the application of OHS risk management which includes risk identification, risk analysis and efforts to control risk. The implementation of the risk management program at the Surabaya A. Yani Islamic Hospital was slightly hampered due to the Covid-19 pandemic which caused monitoring or examination not to be in accordance with the predetermined schedule. The K3 Committee of RSI A. Yani supports and encourages the implementation of risk management in several stages, namely: First, Communicating and showing support for risk management. Second, Trust, report every incident or incident and manage risk. Third, Appreciate and empower good risk management practices. Fourth, Identify and sustainably manage the factors that cause accidents or incidents that occur at the Surabaya A. Yani Islamic Hospital. Fifth, Encouraging organizational learning with established structures and tasks. Sixth, Developing appropriate risk management strategies to reduce the likelihood or recurrence of incident problems, and Seventh, Continuous monitoring and evaluation of the implemented strategies to ensure they are effective or not.

The implementation of OHS risk management is an overall part that includes organizational structure, planning, responsibilities, implementation, procedures, processes and resources needed for the development, implementation, achievement, review and maintenance of OHS⁵ policies in the

context of risk control or prevention of work-related accidents, and occupational diseases in order to create a safe, comfortable and productive workplace³.

According to the Guidelines for Management of Occupational Health and Safety (K3) in Hospitals, K3RS management is an activity process that begins with the planning, organizing, implementing and controlling stages that aim to cultivate OSH in hospitals. The analysis in the implementation of this research refers to the 4 main elements contained in the Ministry of Health, namely Commitment and Policy, Planning, Organizing and implementation^{5,6}.

Based on the results of the study, it can be concluded that the commitment of the Surabaya A. Yani Islamic Hospital related to K3RS is an initial commitment that is expressed verbally, but has not been realized in written form specifically regarding K3. However, policies regarding structure and organization have been formed and several work programs have been running, although slightly hampered in 2020 due to the Covid-19 pandemic. In addition, funding related to K3RS and facilities such as personal protective equipment (PPE) is complete and implemented.

There are some human resources who handle K3RS at the Surabaya Islamic Hospital A. Yani who do not have special expertise in the field of K3, because the training system is carried out in rotation and alternately, existing resources need to be included in K3 training so that the hospital has the resources competent person which is manifested in the form of an organizational container for the K3RS committee⁷. The Islamic Hospital of Surabaya A. Yani also has a policy

that all workers in the hospital must receive counseling about K3.

It is known that several strategies that have been arranged at the Surabaya A. Yani Islamic Hospital, namely the socialization of the K3RS program, the formation of an K3 committee organization even though it has not become an independent organization and is still in the service sector and several human resources in the K3 committee who do not have the basics of K3 but they receive adequate training and work programs that have been arranged.

Risk Analysis is a process to identify and provide a risk assessment that measures the impact, frequency or probability as well as the magnitude of losses to recipients caused by exposure to hazards that result in work accidents or occupational diseases⁸. Based on the risk assessment with the product of the impact, the level of probability and loss to the recipient at the Surabaya Islamic Hospital A. Yani through a survey and observation process using the risk identification form from the OSH Committee of the Surabaya Islamic Hospital A. Yani with the AS/NZS 4360 standard, it was obtained Some of the medium risk and high risk in the graha building and the old building totaling 37 units or sections that are at risk of causing work accidents to health workers, employees, patients and visitors.

Moderate risks were found, such as the placement of excessive items in the workspace that narrowed the workspace area, placement of medical devices along the road and around the stairs, water leaks from the roof that wet the floor which was at risk of slipping, the rubber floor was peeling off and there were bumps on the surface

of the floor that can cause health workers and visitors and patients to fall or stumble when accidentally passing the location point, other risks such as computer installation cables or dispensers in the workspace are messy and close to risky work activities that can cause electrical disturbances, electric shock and can cause fong, then reservoirs or water pumps that are not locked which are at risk of entering insects or vectors that can cause smelly or polluted water and placing excess goods in the workspace which poses a risk to workers when carrying out work activities falling or tripping over objects. However this result was found to be similar with previous study⁹.

High risks include such as an unlocked electrical installation system and water tendons which can result in being broken into by irresponsible and irresponsible people and causing the hospital's electrical system to be disrupted and problematic, placing the fire extinguisher in a position that is too high and close to work activities that are at risk of falling and happened to people who were close to the location, then checked the unscheduled fire extinguisher so that the condition of the fire extinguisher was not good, such as rubber or hoses that had peeled and expired so that the use of the fire extinguisher when needed and a fire could be hampered . Another risk is the roof of the meeting room in the old building peeling off and almost collapsing which risks falling on people who are in the room and causing a detrimental impact and scattered and messy cables that are near work activities and computer equipment, this can be at risk of current disturbances. electricity

and fongs and can cause a fire. Previous study in Japan also found similar result that¹⁰.

Control measures that can be taken from the risks found are such as the condition of runnah walls at several points that have cracked and leaky roofs as well as cracked and perforated floors and some rubber floors that are starting to peel as well as the placement of items scattered around the streets and spaces^{11,12}. work, scattered cables, wet and slippery floor surfaces at several locations, some of which can cause work accidents for health workers, employees and patients or visitors at the Surabaya A. Yani Islamic Hospital.

Conclusion

Based on research on the application of occupational safety and health risk management at the Surabaya A. Yani Islamic Hospital, it was concluded that the implementation of K3 risk management in the risk management program at the Surabaya A. Yani Islamic Hospital was running well but not optimal because it was caused by the Covid-19 pandemic that causing monitoring or inspection not according to a predetermined schedule. Risk identification obtained 25 potential risks contained in 37 units which include the graha building and the old building at the Surabaya A. Yani Islamic Hospital, while the existing risks include the risk of falling, tripping, slipping, electrocution, breaking the security system and noise risk. Risk analysis at the Surabaya Islamic Hospital there are 25 potential risks in the graha building and the old building, Among them there are 15 moderate risks and 10 high risks. The graha building has 7 moderate risks and 3 high risks, while the old

building has 8 moderate risks and 7 high risks. Risk control that can be done is by repairing infrastructure that has started to break down, providing a special place or space for storing medical items and equipment and improving the security system to avoid breaking into electrical installations and water tendons by irresponsible people and checking and monitoring regularly scheduled.

Conflict of Interest

The author stated there is no conflict of interest

References

1. Portmann, L. & Giusti, V. [Obesity and hypothyroidism: myth or reality?]. *Rev. Med. Suisse* **3**, 859–62 (2007).
2. Asian Development Bank & BPS-Statistic. *The Informal Sector and Informal Employment in Indonesia: Country Report 2010*. (2011).
3. Boateng, J. K. & Arthur, Y. A. Influence of Risk Management Practices on Service Quality in Health Care Delivery. **5**, 176–186 (2014).
4. Youngberg, B. J. *Principles of risk management and patient safety*. (2011).
5. Hastuti, D. D., Setyaningsih, Y. & Adi, K. Design of Occupational Health and Safety Management Information System at Telogorejo Semarang Hospital. *Unnes J. Public Heal.* **9**, 20–27 (2020).
6. Purnomo, D. H., Indasah, I. & Melda, B. Analysis of Implementation Safety and Health Occupational Management System in Kertosono General Hospital. *J. Qual. Public Heal.* **1**, 78–85 (2018).

7. Nasution, A. D. & Mahyuni, E. L. Hospital Occupational Safety and Health Management System based on Internet of Things (IoT). 495–499 (2020) doi:10.5220/0010076004950499.
8. Alayyannur, P. A. Correlation of Management Commitment and K3 Training With Knowledge in Hospital 'X'. *J. Ind. Hyg. Occup. Heal.* **2**, 102 (2018).
9. Kim, Y.-J. & Kang, S.-W. The Quality of Life, Psychological Health, and Occupational Calling of Korean Workers: Differences by the New Classes of Occupation Emerging Amid the COVID-19 Pandemic. *Int. J. Environ. Res. Public Health* **17**, 5689 (2020).
10. Tanaka, R. et al. Dietary Differences in Male Workers among Smaller Occupational Groups within Large Occupational Categories: Findings from the Japan Environment and Children's Study (JECS). *Int. J. Environ. Res. Public Health* **15**, 961 (2018).
11. Zare, S. et al. Occupational stress assessment of health care workers (HCWs) facing COVID-19 patients in Kerman province hospitals in Iran. *Heliyon* **7**, e07035–e07035 (2021).
12. Brighenti-Zogg, S. et al. Physical Workload and Work Capacity across Occupational Groups. *PLoS One* **11**, e0154073–e0154073 (2016).

ORIGINAL ARTICLE

NEUROPROTECTIVE ACTIVITY of EXTRACT of CELERY (*APIUM GRAVEOLENS*) IN INSILICO STUDY

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ABSTRACT

Background: Celery (*Apium graveolens* L., *Apiaceae*) is one of the medicinal plants with secondary metabolite components that have pharmacological effects such as vitamin (choline) content. This study aims to evaluate the mechanism and interaction of choline contained in celery on its effectiveness as a neuroprotective.

Methods: This research is an experimental research using the in silico study.

Results: The insilico search found that the choline content in celery binds to Slc5a7, Chat and Ache. Which has a function in the process of neurotransmitter biosynthesis, neurotransmitter metabolic processes and neurotransmitter secretion processes

Conclusion: The celery (*Apium graveolens* L., *Apiaceae*) have pharmacological activity as neuroprotective through the interaction of Slc5a7, Chat and Ache.

Medical and Health Science Journal

Introduction

The use of herbal plants in medicine has been used for centuries and until now, herbal medicine has shown pharmacological activity which is quite effective in various diseases^{1,2}.

One of the herbal plants that are often used in medicine is celery. *Apium graveolens* or celery belongs to the Apiaceae family. Celery plants grow throughout the continent of Asia, Europe, and parts of Africa that have a tropical climate, but until now celery has been consumed and cultivated throughout the world³.

Previous pharmacological studies have shown that celery has antimicrobial activity, antiparasitic, cardioprotective, gastroprotective, neuroprotective, hypolipidemic, cytotoxic, antioxidant, anti-inflammatory, and antiinfertility⁴⁻⁶. Until now, the public's knowledge in using celery is still limited as a flavor enhancer for food and vegetable commodities.

The methanol extract of the celery seeds contains several chemical compounds of flavonoids, steroids, glycosides, and alkaloids Celery also contains furocoumarins, phenols, sesquiterpenes alcohol, and essential oils^{7,8}.

Recent research has also shown that celery contains vitamins (choline and riboflavin), and pigments (safflomin A)⁹.

There are so many benefits of celery, but very little has been explained about the benefits of celery on the nervous system. Although previous studies have found the effect of celery as a neuroprotective, but its mechanism is still not widely known. So, the study aims to determine the mechanism of the vitamin content, namely choline in celery leaves on the function of the nervous system, especially neurotransmitters in-silico.

Methods

This type of research is experimental research in silico. Components of secondary metabolites in celery based on previous research⁹.

The secondary metabolite in celery used in the insilico search is vitamin (choline). Then the search for choline interactions with proteins is carried out in the following way:

1. Search for secondary metabolites (choline) by accessing <https://pubchem.ncbi.nlm.nih.gov/>
 2. Searching for choline interactions with proteins in the body by accessing <http://stitch.embl.de> and continued by looking at the structure of each protein from the Protein data bank (PDB) <http://rcsb.org>
 3. Then search for specific functions based on the interaction of each protein by accessing <https://string-db.org/>.
-

Results

From the results of an insilico search for the metabolite content of celery, namely choline, a 3D structure was obtained through a search on Pubchem as shown in Figure 1.

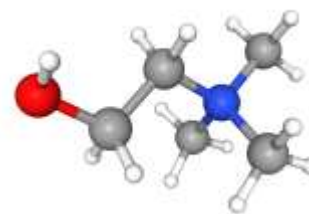


Figure.1 The 3D picture of Coline structure

After determining the chemical structure of colin based on the canonical smile, the search for colin interactions in the body was carried out using the stitch.embl.de database. The search found strong interactions of choline on Slc5a7, Chat, and Ache proteins where these three proteins function at cholinergic synapses (neurotransmitters) (figure.2)

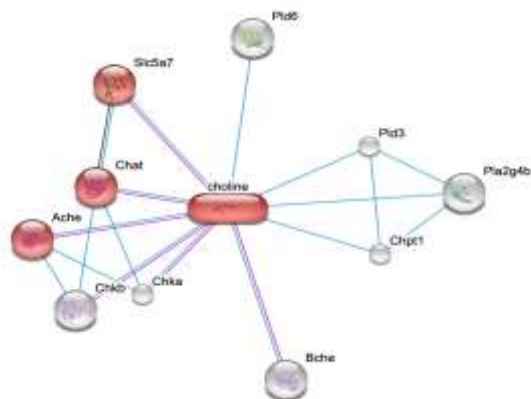


Figure.2 Prediction of coline interactions on proteins in the body

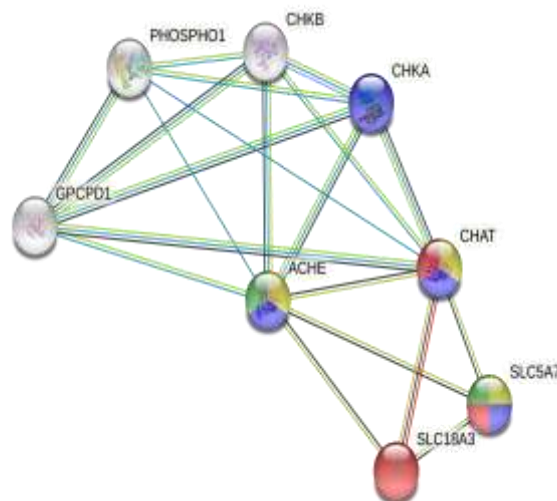


Figure.4 Interaction function of Chat, ACHE, SLC5A7

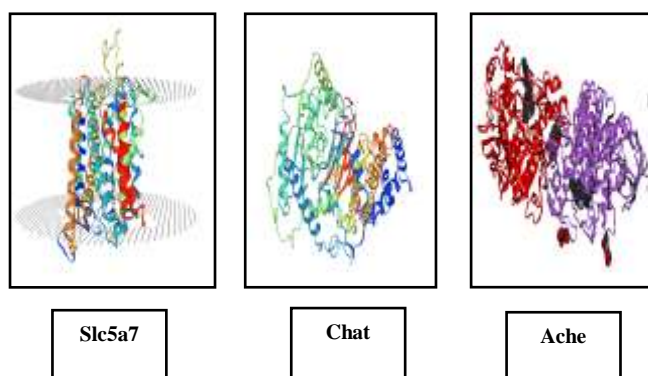


Figure.3 The 3D picture of each protein

To find out the specific function of each protein, a search was carried out through the data base accessed at <https://string-db.org/>. From the search results, it was found that the three proteins have more than one function, namely the process of neurotransmitter biosynthesis, metabolic neurotransmitter processes, neurotransmitter secretion processes and metabolic hormone processes (Figure.4)

Table.1 The function of protein in nervous systems

Function	Protein	Indication
Neurotransmitter biosintetic process	1. Chat	Yellow
	2. ACHE	
	3. SLC5A7	
Neurotransmitter metabolic process	1. CHKA	Purple
	2. CHAT	
	3. ACHE	
	4. SLC5A7	
Secretion neurotransmitter	1. CHAT	Red
	2. SLC18A3	
	3. SLC5A7	
Hormon metabolic process	1. ACHE	Green
	2. SLC5A7	

Discussion

This study evaluates the content of secondary compounds from celery extract, namely choline as a neuroprotective with an in silico approach. The approach was taken by looking at the interaction of Colin from celery extract on proteins in the body. Based on the results of this study, it was found that there are three proteins that have strong interaction

with choline which is a secondary metabolite component of celery, namely Slc5a7, Chat, and Ache, which work specifically on neurotransmitters in the nervous system. These results are in line with previous studies, which found that celery extract has a neuroprotective effect, although the mechanism has not yet been clearly explained¹.

The results of this study can be one of the initial data for interactions related to the mechanism of celery in providing a neuroprotective effect.

This study was found that Slc5a7, Chat, and Ache have interactions in the process of neurotransmitter biosynthesis, neurotransmitter metabolic process, secretion of neurotransmitter, and hormone metabolic process. These three proteins assist in the transmembrane transporter that imports choline from the extracellular space into high-affinity neurons. Choline absorption is the rate-limiting step in acetylcholine synthesis¹⁰.

Previous studies have found that mutations in Slc5a7 are found in a rare group of genetically heterogeneous neuromuscular junction (NMJ) disorders associated with variable skeletal muscle fatigue and weakness, generally classified under the term 'congenital myasthenic syndrome' (CMS)¹¹. Other studies have found that Slc5a7 also has a role in the process of Alzheimer's disease (AZ)¹².

It is well known that the enzyme choline acetyltransferase (Chat) catalyzes the transfer of an acetyl group from acetyl-coenzyme A (acetyl-CoA) to choline to produce ACh in the axoplasm of neurons. After its biosynthesis, ACh is packaged into synaptic vesicles by the vesicular ACh transporter (VAChT) and released into the synaptic cleft upon neuronal depolarization. This ACh then

binds to nicotinic and muscarinic receptors to activate downstream signaling pathways, then the transmitter is broken down by the enzyme acetylcholinesterase (AChE) into acetate and choline to limit its binding to the receptor. these two proteins are essential in the process of signaling via neurotransmitters in a variety of biological processes, including cognition, movement, and attention processing¹³.

The interactions obtained in the insilico can be used as a reference in knowing the mechanism of the secondary metabolite of celery extract, namely choline and it can be suggested to use celery as a medicinal plant that has a neuroprotective effect.

Conclusion

Apium graveolens or celery belongs to the Apiaceae family. Based on the results of an insilico search for the content of secondary metabolites, namely choline, that celery leaves have pharmacological activity as neuroprotective through the interaction of SLC5a7, ChAt, and Ache and suggested as a very potential medicinal plant. However, a number of studies are still needed to validate the effectiveness of celery as a treatment.

Conflict Of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Khairullah, A. R. *et al*. Review on the pharmacological and health aspects of apium graveolens or celery: An update. *Syst. Rev. Pharm.* **12**, 606–612 (2021).

2. Solikhah, T. I., Setiawan, B. & Ismukada, D. R. Antidiabetic activity of papaya leaf extract (*Carica Papaya* L.) isolated with maceration method in alloxan-induced diabetic mice. *Syst. Rev. Pharm.* **11**, 774–778 (2020).
3. Kooti, W. & Daraei, N. A Review of the Antioxidant Activity of Celery (*Apium graveolens* L.). *J. Evid. Based. Complementary Altern. Med.* **22**, 1029–1034 (2017).
4. Jittiwat, J., Chonpathompikunlert, P. & Sukketsiri, W. Neuroprotective effects of *Apium graveolens* against focal cerebral ischemia occur partly via antioxidant, anti-inflammatory, and anti-apoptotic pathways. *J. Sci. Food Agric.* **101**, 2256–2263 (2021).
5. Al-Howiriny, T. *et al.* Gastric antiulcer, antisecretory and cytoprotective properties of celery (*Apium graveolens*) in rats. *Pharm. Biol.* **48**, 786–793 (2010).
6. Sameh, B., Ibtissem, B., Mahmoud, A., Boukef, K. & Boughattas, N. A. Antioxidant Activity of *Apium graveolens* Extracts. *J. Biol. Act. Prod. from Nat.* **1**, 340–343 (2011).
7. Brahma Srinivasa Rao Desu and Sivaramakrishna K. Anti-Depressant Activity of Methanolic Extract of *Apium Graveolens* Seeds. *Int. J. Res. Pharm. Chem.* **2**, 1124–1127 (2012).
8. Baananou, S. *et al.* Antiulcerogenic and antibacterial activities of *Apium graveolens* essential oil and extract. *Nat. Prod. Res.* **27**, 1075–1083 (2013).
9. Liu, D. K. *et al.* Evaluation of bioactive components and antioxidant capacity of four celery (*Apium graveolens* L.) leaves and petioles. *Int. J. Food Prop.* **23**, 1097–1109 (2020).
10. Choudhary, P. *et al.* Discovery of Compounds that Positively Modulate the High Affinity Choline Transporter. *Front. Mol. Neurosci.* **10**, 40 (2017).
11. Wang, H. *et al.* Choline transporter mutations in severe congenital myasthenic syndrome disrupt transporter localization. *Brain* **140**, 2838–2850 (2017).
12. Tönnies, E. & Trushina, E. Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. *J. Alzheimers. Dis.* **57**, 1105–1121 (2017).
13. Obermayer, J., Verhoog, M. B., Luchicchi, A. & Mansvelder, H. D. Cholinergic Modulation of Cortical Microcircuits Is Layer-Specific: Evidence from Rodent, Monkey and Human Brain. *Front. Neural Circuits* **11**, 100 (2017).

ORIGINAL ARTICLE

THE PROFILE AND PATIENT ACUTE HEPATITIS CHILDREN OUTPUT IN DR SOEBANDI JEMBER HOSPITAL

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ABSTRACT

Background: Indonesia is an endemic area for Hepatitis akut. District of Jember determines the status of extraordinary event Hepatitis akut at the end of 2019. The purpose of this study was the profile and patient acute hepatitis children output in dr Soebandi Jember Hospital in December 2019 until January 2020.

Methods: This study was *retrospective descriptive*. The material was taken of the medical records Hepatitis akut patient at the pediatric department of the dr. Soebandi Hospital in Jember.

Results: In this study, patients most often occurred in male, age ranged between 7 – 14 years, and lived on the villages. The most common of clinical manifestation are anorexia, jaundice, fever, hepatomegaly, dark urine, vomiting and abdominal pain. The result of laboratory examination showed that Hepatitis acute patients had elevated of SGOT , SGPT, *direct* and *total bilirubin*. The combination of curcuma with SNMC (*Stronger Neo-Minophagen C*) reductly significant SGOT and SGPT serum levels ($p < 0,001$).

Conclusion: The combination of curcuma with SNMC (*Stronger Neo-Minophagen C*) reductly SGOT and SGPT serum levels in hepatitis patients.

Medical and Health Science Journal

Introduction

Indonesia is an endemic area of acute hepatitis. Acute viral hepatitis (HAV) is the most common type of viral hepatitis that is transmitted by the fecal-oral route. In developing countries, HAV generally occurs in children with age.¹ The main signs and symptoms include anorexia, nausea, vomiting, abdominal pain, jaundice, and hepatomegaly. Elevated liver enzymes SGOT and SGPT are the main laboratory findings in HAV-infected children.^{1,2} The diagnosis is confirmed by the presence of anti-HAV IgM in the patient's blood.³ Giving curcuma tablets is used as an additional supplement that functions to improve liver function and improve appetite.² SNMC (Stronger Neo Minophagen C) is an injection preparation with the main content of glycyrrhizin derived from herbal plants which is used to treat liver disorders.^{3,4}

At the end of 2019, there was an increase in reports of cases of diseases caused by the acute hepatitis virus. The Jember Regency Government has determined the status of an Acute Hepatitis Extraordinary Event (KLB). The purpose of this study was to see the profile and outcomes of acute hepatitis patients in children at Dr Soebandi Hospital Jember in December 2019-January 2020.⁹

Method

This study is a descriptive retrospective. The research materials and subjects used were data taken from the medical records of patients diagnosed with acute hepatitis at the Children's Section of Dr. Soebandi Hospital, Jember. The affordable population of this study were all pediatric patients with new cases diagnosed with

acute hepatitis in December 2019-January 2020. The inclusion criteria for the study were age 14 years, diagnosed with acute hepatitis with increased levels of SGOT and SGPT..

The variables collected were: Demographic Characteristics (gender, age and place of residence), Clinical Features (vomiting, abdominal pain, fever, jaundice, hepatomegaly, dark urine and anorexia). Laboratory tests include SGOT, SGPT, direct bilirubin, total bilirubin, anti-HAV Igm and HBsAg. The output seen is the recovery of acute hepatitis patients at Dr. Soebandi Hospital based on an assessment of the decrease in SGOT and SGPT, as well as the length of stay of patients on curcuma administration compared to curcuma + SNMC administration.

Results

In this study, patients with acute hepatitis most often occurred in boys (68%) compared to girls (32%). Characteristics for the age of the 25 patients with acute hepatitis in children, most of whom were school age, namely 7-14 years, amounted to 17 people (68%). Characteristics for the place of residence of the 25 patients with acute hepatitis in children, most of whom lived in the village, which amounted to 13 people (52%). adalah usia sekolah yakni 7 –14 tahun berjumlah 17

The most common clinical symptoms in this study were anorexia (52%), jaundice (48%), fever (44%), hepatomegaly (40%), dark urine (36%), vomiting (32%) and abdominal pain (32%). .

In this study, all patients were checked for SGOT and SGPT (100%), there were 12 patients who were checked for direct bilirubin and total bilirubin based on clinical symptoms of jaundice. There were 6 patients who were checked for IgM anti-HAV and there were 10 patients who were checked for

Table 2. Clinical Symptoms & Laboratory Examination at the beginning of diagnosis

VARIABEL		n	Persentase (%)
Clinical Symptoms	Vomited	8	32
	Abdominal pain	8	32
	Fever	11	44
	Jaundice	12	48
	Hepatomegali	10	40
	Dark urine	9	36
	Anorexia	13	52
Laboratory examination	SGOT	25	100
	SGPT	25	100
	Bilirubin direct	12	48
	Bilirubin total	12	48
	IgM anti HAV	6	24
	HBsAg	10	50

HBsAg.

The SGOT level of patients at Dr. Soebandi Hospital Jember was taken at an average value of

Table 1. Characteristics of patients with acute hepatitis in children

VARIABEL		n	%
Gender	Men	17	68
	Women	8	32
Age	0-6 th	8	32
	7-14 th	17	68
Residence	Desa	13	52
	Kota	12	48

1272 U/L at the beginning of the patient's admission, the results of the evaluation after the patient was given treatment showed a decrease in the average SGOT value of 315 U/L.

While the average value of the initial evaluation of SGPT was 1079 U/L and experienced a decrease in the value of SGPT to 448 U/L.

Table 3. SGOT and SGPT levels in acute hepatitis patients at the beginning of diagnosis and evaluation

Pemeriksaan Lab	Awal	Evaluasi
SGOT	1272 U/L	315 U/L
SGPT	1079 U/L	448 U/L

The administration of curcuma reduced the SGOT value by 65%, while the administration of curcuma together with SNMC reduced the SGOT value by 72%. The Saphiro-Wilk normality test resulted in $p > 0.05$, meaning that the data was normally distributed. Paired T-test results p value < 0.001 means that there is a significant difference between the administration of Curcuma xanthorrhiza extract, and Curcuma xanthorrhiza extract + SNMC on the initial SGOT value and the evaluation SGOT after 4 days.

The administration of curcuma reduced the SGPT value by 44%, the administration of curcuma together with SNMC reduced the SGPT value by 59%. The Saphiro-Wilk normality test resulted in $p > 0.05$, meaning that the data was normally distributed. Paired T-test results p value < 0.001 means that there is a significant difference between the administration of Curcuma xanthorrhiza extract, and Curcuma xanthorrhiza extract + SNMC on the initial SGOT value and the evaluation SGOT after 4 days.

In the administration of curcuma and curcuma + SNMC in this study, patients had an average hospitalization period of 4 days.

Tabel 4. Outcome of Acute Hepatitis Patients

SGOT value comparison					
Treatm ent	n	Perbandingan Lab			Masa Raw at
		SGOT Before	SGOT After	%	
Cur*	1 2	929	325	65	4
Cur + S ⁰	1 0	1080	302	72	4

SGPT Value Comparison					
Treatme nt	n	Perbandingan Lab			Masa Raw at
		SGP T Befor e	SGPT After	% Penuruna n	
Cur*	1 2	636	355	44	4

Cur + S ⁰	1	1337	542	59	4
	0				

Ket :

Cur* = Curcuma xanthorrhiza extract

Cur+ S⁰ = Curcuma xanthorrhiza extract + SNMC

This study is a retrospective study based on data in medical records so that researchers only process data based on data that has occurred in the past.

This study is in line with research conducted by Rewatkar et al, that acute hepatitis occurs more often in boys than girls with a ratio of 1.45:1. This is associated with the activity of boys who are more active than the activities of girls.¹¹

Extraordinary incidence of acute hepatitis in Thailand in schools with 269 students aged 7-12 years. There were 70 of 89 subjects who were examined serologically with positive anti-HAV, 16 of them with positive IgM anti-HAV.5 Acute hepatitis virus infection that occurs in childhood is generally asymptomatic or with mild symptoms.5,6 Infections that occur in childhood Subsequent age can only be determined by laboratory examination of liver function.¹¹

The initial clinical picture is a prodromal phase of viral infection with nonspecific symptoms including nausea, vomiting, anorexia, weakness, weight loss, subfebrile fever, myalgia, arthralgia, and headache.⁷ Patients had an anicteric phase on average of 7 days. Output becomes icteric phase with dark urine due to the excretion of bilirubin, and pale stools may be followed.^{8,10} Jaundice only occurs in 10% of children aged less than 6 years, 40% of children between the ages of 6 and 14 years, and 70% in children over 14 years of age. The risk of transmission decreases 1 week after the onset of jaundice.¹⁰ Additional symptoms include

abdominal pain, pruritus, arthralgia, itching, fever and hepatomegaly. Duration of symptoms in weeks averaged 4 weeks, and correlated with HAV viral load. Spontaneous resolution with minimal sequelae.^{1,2}

Elevated SGOT and SGPT values are a sign of hepatocellular inflammation and liver damage.²

In this study, there were 6 patients who were checked for anti-HAV IgM due to limited reagents in the hospital. Anti-HAV IgM can be detected 5-10 days before the onset of symptoms and can persist for up to 6 months after infection.^{1,2}

The administration of Curcuma tablets according to the recommended dosage is used as an additional supplement that functions to improve liver function and improve appetite. According to research conducted by Hartono using a dose of 5-10 mg/kgBW/day has been shown to be able to repair damaged liver cells and is hepatoprotective.²

Curcuma has protective and therapeutic effects on oxidative-associated hepatitis through suppression of proinflammatory cytokines, lipid peroxidation products, PI3K/Akt and hepatic stellate cell activation, as well as avoiding cellular responses to oxidative stress such as Nrf2, SOD, CAT, GSH, GPx and GR expression. Curcuma itself acts as a free radical scavenger on the activity of various types of ROS through phenolic, -diketone and narcotic groups. Further clinical studies are still needed to identify the structure-activity relationship and molecular mechanism of curcuma in oxidative-related liver disease.²

Stronger Neo-Minophagen C is a drug used to correct abnormal liver function in chronic liver disease.³ Stronger Neo-Minophagen C contains Monoammonium glycyrrhizinate (like

glycyrrhizin), amino acetic acid, and L-cysteine HCl.⁴ The SNMC dose is 40-60 mL by intravenous injection or once-daily intravenous infusion. The maximum daily dose is 100 mL. Side effects that may occur during the use of Stronger Neo-Minophagen C include shock, pseudoaldosteronism, severe hypopotassemia, hypertension, Na retention, swelling, and weight gain.

Contraindications should not be used by patients with known allergies to the content of Stronger Neo-Minophagen C and patients with a history of aldosteronism, myopathy and hypopotassemia.

SNMC may interact with thiazides, ethiazide and trichlormethiazide, ethacrynic acid and furosemide.^{3,4}

In Japan, SNMC has been used as a treatment for hepatitis for more than 30 years. Suzuki et al. reported that the levels of SGOT, SGPT and -GTP can be significantly reduced by administration of SNMC. In a double-blind multicenter study, serum SGOT levels have been shown to be significantly decreased in patients given 40 ml/day of SNMC for four weeks ($P < 0.001$). Furthermore, giving 100 ml/day of SNMC for eight weeks, reduced the SGOT value, and improved liver histology in patients with chronic hepatitis and liver cirrhosis so that the risk of developing liver carcinoma could be reduced.^{3,4}

Conclusion

Based on the results of the study, it was found that acute hepatitis patients most often occurred in boys, aged between 7-14 years and resided in the village. The most common clinical manifestations are anorexia, jaundice, and fever. The administration of

curcuma in combination with SNMC (Stronger Neo-Minophagen C) was able to significantly reduce the SGOT and SGPT values ($p < 0.001$).

Conflict Of Interest

The author stated there is no conflict of interest

References

1. Bilge C, Hasan T, Aslinur. Evaluation of Pediatric patients with Hepatitis akut. *J Infect Dev Ctries*. 2014; 8(3): 326-330
2. Hartono. 2005. Pengaruh ekstrak curcuma terhadap peningkatan kadar SGOT, SGPT akibat pemberian asetaminoven, Tesis. Solo. FK UNS.
3. Ismi, N.F. dan Rina, H (2013) 'Evaluasi penggunaan stronger minophagen c (SNMC) injeksi pada gangguan fungsi hati di beberapa rumah sakit di Yogyakarta', *repository ugm*, [Online]. Available at: http://etd.repository.ugm.ac.id/home/detail_pencarian/63315 (Accessed: 6 Maret 2021).
4. Kumada H. Long-term treatment of chronic hepatitis C with glycyrrhizin [stronger neo-minophagen C (SNMC)] for preventing liver cirrhosis and hepatocellular carcinoma. *Onco logy* 2002;62 Suppl 1:94-100.
5. Michelle Rook. *Viral Hepatitis in Children*. 1st ed. London. Humana Press; 2010
6. Mohammad H.F., Mahdi Z., Fatemeh P. dkk (2018) 'Curcumin in Liver Diseases: A Systematic Review of the Cellular Mechanisms of Oxidative Stress and Clinical Perspective', *N*, 10(7), pp. 855.
7. Nenden HL, Mahkota R, Elvieda. Faktor Risiko Terjadinya Kejadian Luar Biasa (KLB) Hepatitis akut di Kabupaten Tangerang tahun 2016. *Jurnal epidemiologi kesehatan indonesia*. 2018; 2(1): 1-6
8. Oswari H, Rahayu T. Kejadian Luar Biasa Hepatitis akut di SMPN 259 Jakarta Timur. *Sari Pediatri*. 2005; 6(4): 172-175
9. Pemerintah Kabupaten Jember. *Hepatitis Merebak, Tetapkan Status Kejadian Luar Biasa*. <http://www.jemberkab.go.id/hepatitis-merebak-tetapkan-status-kejadian-luar-biasa/> (diakses 2 Februari 2020).
10. Poonawagul U, Warinrawat S, Snitbhan R, Kitisriwarapoj S, Chaiyakun V, Foy HM. Outbreak of Hepatitis akut in a college traced to contaminated water reservoir in cafeteria. *Southeast Asian J Trop Med Public Health* 1995; 26:705-8.
11. Rewatkar SS. Etiology of hepatitis in children. *International Journal of Contemporary Pediatrics*. 2017; 6(4): 2130-2135
12. Suzuki H, Ohta Y, Takino T, Fujisawa K, Hirayama C. The therapeutic effects of Stronger Neo Minophagen C for chronic hepatitis. *Igaku no Ayumi*. 1977;102:562-8.

CASE REPORT

CASE REPORT: BLEPHAROCONJUNCTIVITIS AS MANIFESTATION OF STEVENS-JOHNSON SYNDROME

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ABSTRACT

Background: Stevens Johnson syndrome (SJS) is a collection of acute and life threatening skin symptoms caused by an allergic drug reaction. SJS also attacks the other mucous membranes, one of which is the eye. SJS is a rare case. The initial complaint of SJS is the eruption on the skin in the form of redness followed by blisters and attacking other mucous membranes. The ocular manifestations of SJS are conjunctivitis, corneal erosion, corneal ulcers, and blepharitis.

Methods: Treatment of SJS's ocular manifestation is administration of drugs and surgical intervention. Administration of drugs that often done in the acute phase is antibiotic eye drops with steroids to prevent complications. Complications that can occur include symblepharon, distichiasis, and keratitis. This complication can cause a sharp decrease in vision.

Results: This case report discusses a 68 year old male patient with blisters all over his body accompanied by swelling in both eyes, redness in both eyes, and difficult to open eyes. Patients with history of taking the new drug a month ago. No history of drug allergy. The patient suffered from hypertension, non-hemorrhagic stroke, and epilepsy with irregular treatment. Patient was performed a fluorescein test. In this case, the patient is given antibiotic ointment and artificial tears with steroids. In this case there were no complications.

Conclusion: The ocular manifestations of SJS if handled quickly and properly can prevent long-term complications.

Medical and Health Science Journal

Introduction

Stevens Johnson Syndrome (SJS) is life threatening condition and rarely happened. Incidence of SJS in Western countries 0,1-1 in 100.000 population¹. SJS in Indonesia happened at least 12 cases on a year. Mortality rate for SJS can reached 5-15% in total cases². In other study, SJS mortality rate usually on elderly patient. Pediatric patient have a lower mortality rate than geriatric patient, but pediatric patient more likely experienced long term complication³. Patient with SJS tend to have ocular manifestation and the acute phase of ocular manifestation occur in 50-88% cases. The acute sign of ocular involvement which result from long term sequelae are cornea and conjunctiva epithelial defect, dry eye, symblepharon, cornea scar, and cornea limbal stem cell deficiency⁴. The authors are interested in discussing SJS case because of frequently seen ocular cases in SJS.

Case

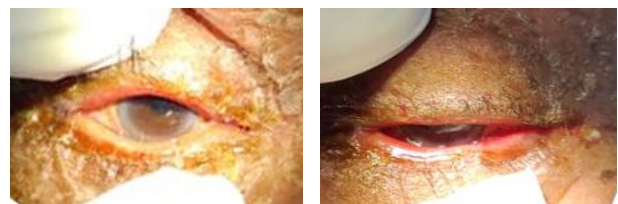
A 68 years old male, married, Balinese, Hindu, had been work as a teacher was referral patient from the Aricanti Hospital, Ubud, Gianyar, Bali.

Medical History

The patient came complaining of full body blisters since 3 days ago. Initially, the patient had fever for 4 days ago. The patient also complained of reddening of the whole body and received therapy in the form of azithromycin, paracetamol and vitamins since 3 days ago. After that, the patient complained of blisters all over his body. The whole body is reddish and turns white scaly and sloughing. Other complaints include swelling and redness of the patient's eyes. Redness of eye

appeared when the body full of blisters. It began when the patient complained of swelling in both eyes followed by redness of the eyes. The patient's eyes were also difficult to open and accompanied by pain. The patient also complained of white eye discharge, sometimes yellowish white eye discharge. Patient was not complaining blurred vision, photophobia, and watering. Patients also had hypertension, epilepsy, and non-hemorrhagic stroke with treatment of atorvastatin, amlodipine, and phenytoin. This disease has been suffered since 2019. The patient rarely used his medicine and began to reuse the drugs on January 6, 2021. There is no history of wearing glasses or eye disease on this patient. Previously, the patient had no drug allergy. The patient's family history is the patient's parents suffering from parkinson's disease, hypertension, and stroke. The patient's sister was suffering from hypertension. Ocular family history was not found.

Figure 1. The patient's eye condition on the first



day of hospitalization. Crusted on the right and left eyelids. The right and left eyes looked difficult to open.

Physical Examination

On physical examination, found uncorrected visual acuity for both eyes are $>3/60$. On bed side external examination, found swollen of superior and inferior palpebra with crusting of the eyelid, sloughing of skin, and erythematous macules. On examination of the anterior segment of the eye, it was found conjunctiva vascular injection. The

conjunctiva palpebra was difficult to evaluate. The cornea is clear. The anterior chamber, iris and lens are normal. The patient also underwent an additional examination of a fluorescein test and the result was there were no defects in the cornea and conjunctiva epithelium. Patient diagnosed with blepharoconjunctivitis.

Treatment

Blepharoconjunctivitis was treated with eye drops containing dextran-70 1 mg and hypromellose 3 mg given 6 times a day to both eyes and eye ointment containing gentamycin which was given 2 times a day to both eyes.

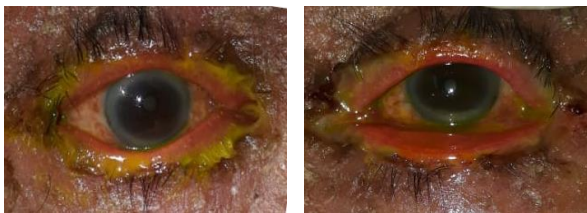


Figure 2. Fluorescein test negative

Follow Up and Outcomes

In the patient's daily follow-up, the patient showing improvement of visual problems from day to day. The patient said complaints of swelling and redness in both eyes improved. Then, the complaints of eye discharge are said to have started to decrease. Complaints of pain in both eyes were also said to have decreased. This patient did not experience complications such as defects in the cornea and conjunctiva, and a sharp decrease in vision. There are no adverse and unanticipated events that have not been handled properly in this case. The prognosis in this patient is *dubia ad bonam*. The patient and the patient's family already understand about the disease and how to prevent complications from this disease. The patient's and patient's family really maintains eye cleanliness and is assiduous in using the drugs

used, gentamycin eye cream and dextran-70 1 mg and hypromellose 3 mg eye drop.

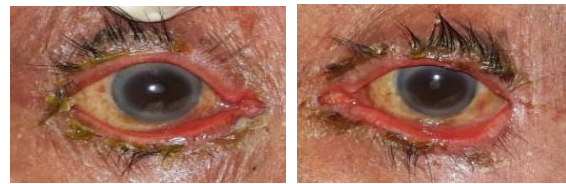


Figure 3. The patient's eyes on the third day of treatment. The eyelids did not appear swollen and the redness in both eyes improved.

Discussion

SJS is an acute and life-threatening skin drug reaction that affects the skin and other mucous membranes⁵. SJS is more common in young adults, but can affect other age groups. Acute symptoms of SJS in the eye include redness of the eye, sensation to having a particle of sand in the eye, photophobia, watering, and blurring⁶. Jenkins's study explained eye symptoms in the acute stage often occur with 15% -75% bilateral conjunctivitis and 25% conjunctiva or corneal ulceration⁵. This case is a 68 year old man with complaints of swelling in both eyes since 3 days ago. This complaint began with the blister on whole body of the patient after experiencing fever for 4 days. Swelling in both eyes accompanied by redness of the eyes. The patient also has white discharge in the eye. The patient also said it was difficult to open both eyes and felt pain. The patient did not complain of blurring of the eyes, photophobia, and watering. Several types of drugs that can cause Stevens Johnson Syndrome, namely antibiotics such as sulfonamides and trimethoprim, analgesics such as paracetamol and NSAIDs, HIV treatment with combination therapy using nevirapine, barbituates, allopurinol,

and anticonvulsants such as carbamazepine, phenytoin, and lamotrigine^{5,6,7}.

In this case, patients took medication of azithromycin, atorvastatin, amlodipine, and phenytoin. The patient started taking medication again during the past month due to patient non-compliance in taking regular medications such as atorvastatin and amlodipine and vitamins. The drug he recently drank in the form of phenytoin was due to complaints of seizures that he had just suffered in the past month.

Based on other literature, symptoms of SJS in the eye are frequent and can cause visual impairment, so patients with SJS should be evaluated immediately⁷. Initial symptoms of SJS occurred in the prodromal phase, namely malaise and fever followed by soft skin eruptions and generally consisted of macules, papules, vesicles, and bullae. Another symptom is that at least two other mucosal surfaces are affected such as erosions and crusting of the mouth, conjunctivitis, and urogenital manifestations such as urinary retention and urethritis which may accompany skin manifestations in 90% of cases⁸. On a slit-lamp examination, the severity of eye manifestations in SJS can be determined as mild, moderate, and severe^{8,9}. Mild eye manifestations consist of desquamated and bald skin of the eyelids, edema of the eyelids, mild conjunctival injection, mucus discharge or chemosis. Moderate eye manifestations may include membranous conjunctivitis, epithelial defects with more than 30%, corneal ulceration, or corneal infiltrates. Severe ocular manifestations consist of acquired eyelid malposition, symblepharon, non-healing corneal epithelial defect, partial or complete loss of vision, or

narrowing of the conjunctival fornix. Chronic ocular sequelae due to SJS occurs in 21-29% of pediatric cases and 27-59% of adult cases⁸.

Additional investigations such as fluorescein stain should be performed to evaluate for corneal and conjunctival epithelial defects⁷. Patients have symptoms such as persistent ulceration, dry eyes, and scarring of the eye as much as 35% due to chronic eye damage⁵. Patient in this case was in the acute phase. Patient was carried out several physical examinations as well as a supporting examination in the form of a fluorescein test on the patient. The uncorrected visual acuity for both eyes are $>3/60$. On bed side external examination, found swollen of superior and inferior palpebra with crusting of the eyelid, sloughing of skin, and erythematous macules. On examination of the anterior segment of the eye, it was found conjunctiva vascular injection. The conjunctiva palpebra was difficult to evaluate. The cornea is clear. The anterior chamber, iris and lens are normal. The patient also underwent an additional examination of a fluorescein test and the result was there were no defects in the cornea and conjunctiva epithelium.

Ocular treatment in SJS is divided into 2. There are drugs and surgical management. Management of Stevens-Johnson's acute ocular manifestations is administration of topical antibiotics, steroids, calcineurin inhibitors, and lubricants⁸. Use of topical steroids at the onset of symptoms can result in better eye visuals. In severe cases, early surgical intervention can involve transplanting the amniotic membrane, which can increase epithelialization and reduce inflammation and scarring on the surface of the eye¹⁰. One of the amniotic membrane transplant methods is called

cryopreserved amniotic membrane, which is a biological device made by cutting the amniotic membrane between two symblepharon rings and a human amniotic membrane graft. There have been several studies conducted to evaluate amniotic membrane transplantation in the eye in SJS and it appears to be showing significant results. The cryopreserved amniotic membrane produces maximum results when applied early in the disease by reducing the risk of long-term eye damage and producing sequelae after 6 days⁵. On the other study, treatment for the chronic phase aims to prevent worse eye surface damage, treat eye sequelae, and visual rehabilitation. If there are structural abnormalities of the eye, surgical interventions such as keratoprosthesis and keratolimbus allografting (KLAL) are required to help restore the visual eye. In the final stages with severe corneal blindness and dry eye, limbal stem cell transplantation (LSCT) and cultivated oral mucosal epithelial transplantation (COMET) are recommended. Providing prompt diagnosis and treatment is the key to good eye prevention and recovery in SJS cases^{8,10}.

On the Pandiaraj case series, eye management with SJS was carried out with a frequent topical lubricant, carboxymethyl cellulose, in all patients. Then, given a topical antibiotic in the form of tobramycin if secondary infection is suspected. Fluorometholone can be added for patients with excessive eye inflammation. In patients with symblepharon, membranolysis with glass rod passing is performed 2-3 times a day. All patients were asked to move their eyes and frequently asked to separate their eyelids to prevent symblepharon. Eye hygiene must be maintained properly. Patients with corneal epithelial defects

are given bandaged contact lenses. All patients were given systemic steroids while paying attention to the administration of fluids and electrolytes according to the patient's condition. This therapy is done once or twice a day for each patient until the patient goes home. No deaths were found and all were discharged within 2 weeks to 2 months¹⁰. In present case, patient was treated with eye drops containing dextran-70 1 mg and hypromellose 3 mg given 6 times a day to both eyes and eye ointment containing gentamycin which was given 2 times a day to both eyes. Currently, there are no complications in this case. Wang's study explained among those who survive, there are long-term eye complications that can become serious, which occur in about 60% of patients. Corneal and conjunctival damage in the form of scar tissue can lead to further visual disturbances⁷.

In Abrol's study, several complications were found in the form of complications on the eyelids, conjunctiva, and cornea. Complications on the eyelids include eyelid edema, discharge of eye discharge, distichiasis, ulceration of the edge of the eyelids and crusting, wrinkled eyelashes, meibomitis, blepharitis, and peeling of the skin above the eyelids. Conjunctiva complications include subconjunctiva bleeding, conjunctivitis, and symblepharon. Corneal complications include superficial epithelial keratitis, corneal ulceration, and erosion of the epithelium⁸. In the present study patient's daily follow-up, the patient showing improvement of visual problems from day to day. This patient did not experience complications such as defects in the cornea and conjunctiva, and a sharp decrease in vision. There are no adverse and unanticipated events that have

not been handled properly in this case. The prognosis in this patient is *dubia ad bonam*. The Abrol's study also found 8 patients who had chronic sequelae from the eye manifestations of SJS. Of the 8 patients, 3 patients had severe dry eye disease, 2 patients had trichiasis, 2 patients had decreased visual acuity, and 1 patient had severe photophobia. Complications are often not seen at first in conditions of severe eye manifestations. Damage to the mucous membranes of the skin and mouth was more associated with the incidence of ocular manifestations in SJS^{8,10}.

This case report discussed a case of Stevens Johnson Syndrome which is handled at the district level hospital and can be used as a reference for other research on eye cases in Stevens Johnson's syndrome and informs the hospital about things that need to be improved in handling rare cases like this. The limitation of this case report are that it does not include follow-up of patients after being discharged from the hospital and does not use snellen charts for visual examination due to limited facilities and infrastructure.

Conclusion

We discussed eye involvement in the case of Stevens Johnson syndrome with a 68 year old male patient who complained of swelling of the eyelids and redness of both eyes with blister all over his body after taking the new drug he had just taken for the past 1 month. The patient was also investigated with a fluorescein test and the result was that there were no defects in the cornea and conjunctiva. The patient was given antibiotic eye ointment and artificial tears with steroids to reduce inflammation in both eyes. The patient did

not experience complications, namely a sharp decrease in vision and defects in the cornea and conjunctiva and the formation of symblepharon. From this case, the author is more aware of a disease that is rare in cases but can be life threatening condition and produce long-term complications if not treated quickly and appropriately.

Conflict of Interest

The author stated there is no conflict of interest

References

1. Schwering, S. M., Kayange, P. & Rothe, C. Ocular manifestations in patients with Stevens–Johnson syndrome in Malawi—review of the literature illustrated by clinical cases. *Graefe's Archive for Clinical and Experimental Ophthalmology* vol. 257 2343–2348 (2019).
2. Putri, N. D., Mutiara, H., Sibero, H. T. & Sukohar, A. Steven-Johnson Syndrom et causa Paracetamol. *Med. Prof. J. Lampung Univ.* 6, (2016).
3. Fitriana, A., Endaryanto, A. & Hidayati, A. N. *Gambaran Klinis Steven Johnson Syndrome dan Toxic Epidermal Necrolysis pada Pasien Anak.* *Berk. Ilmu Kesehat. Kulit dan Kelamin - Period. Dermatology Venereol.* 30, (2018).
4. Chow, L. L. W., Shih, K. C., Chan, J. C. Y., Lai, J. S. M. & Ng, A. L. K. Comparison of the acute ocular manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis in Chinese eyes: a 15-year retrospective study. *BMC Ophthalmol.* 17, (2017).

5. Jenkins, P., Enurah, A. & Scherbak, D. A case report of ocular Stevens-Johnson syndrome: An important condition for the internist to see. *Int. J. Acad. Med.* 6, 33–5 (2020).
6. Salmon, J. F. Conjunctivitis In Blistering Mucocutaneous Disease. in *Kanski's clinical ophthalmology: a systematic approach* 189–193 (Elsevier, 2020).
7. Wang, J., Rixen, J., Goins, K. & Kitzmann, A. Ocular Manifestations of Stevens-Johnson Syndrome: 13-year-old female with mucosal and dermatologic eruptions. *EyeRounds* <http://eyerounds.org/cases/192-Stevens-Johnson.htm> (2014).
8. Abrol, A., Gulanikar, A., Thakre, S. & Patel, A. Study of Ocular Manifestations of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. *Indian Dermatol. Online J.* 11, 570–574 (2020).
9. Saeed, H. & Rashad, R. Ocular Disease in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. in *Foundations of Corneal Disease* (eds. Colby, K. & Dana, R.) 97–108 (Springer Nature Switzerland AG, 2020).
10. PANDIARAJ, S. S. V. Vigilant Treatment and Early Intervention Of Ocular Manifestations Of Steven Johnson Syndrome. *Univ. J. Surg. Surg. Spec.* 3, (2017).

REVIEW ARTICLE

COMPARISON OF LAPAROSCOPIC AND ABDOMINAL SACROCOLPOPEXY FOR POST HYSTERECTOMY VAGINAL VAULT PROLAPSE REPAIR: META ANALYSIS

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ABSTRACT

Background: Comparing the clinical outcomes of laparoscopic and abdominal sacrocolpopexy in vaginal vault prolapse post-hysterectomy patients.

Method: Systematic search data is performed on a medical database (PUBMED, Cochrane Database) using keywords:(1) vault prolapse [title] AND (2) laparoscopic[title] AND sacrocolpopexy[title]. Inclusion criteria:(1) randomized controlled trial and observational studies, (2) women with vaginal vault prolapse post hysterectomy, (3) intervention studied: laparoscopic (LSC) and abdominal sacrocolpopexy (ASC), (4) the entire fully accessible papers can be accessed and data can be accurately analyzed. Comparison about clinical outcomes of LSC and ASC was performed using narrative analysis and meta-analysis (RevMan).

Results: Three studies compared clinical outcomes of LSC and ASC with a total of 243 samples (118 in LSC and 125 in ASC group). There was no significant difference in the incidence of complications between LSC and ASC (OR 1.10;95% CI 0.58-2.08). LSC was associated with less blood loss (MD 111.64 mL,95%CI-166.13 - -57.15 mL) and shorter length of hospital stay (MD -1.82 days;95%CI -2.52- -1.12 days) but requires a longer operating time (MD 22.82 minutes,95%CI 0.43-45.22 minutes). There was no statistically significant difference to anatomical outcomes (measurement of point C on POP-Q), subjective outcomes measured by PGI-I and reoperation numbers (repeat surgical interventions) for prolapse recurrence between LSC and ASC groups after one year of follow-up.

Conclusions: LSC showed similar anatomic results compared to ASC with less blood loss and shorter length of hospital stay in management patient with vaginal vault prolapse.

Medical and Health Science Journal

Introduction

Pelvic organ prolapses (POP) is a condition commonly encountered by women, and incidence increases after menopause¹. This prolapse condition is not a life-threatening condition but women with POP often experience uncomfortable symptoms such as urinary incontinence, sexual dysfunction and overall, it decreases the quality of life². Definition of vaginal vault prolapse according to The International Continence Society is decreasing the vaginal peak or vaginal cuff below 2 cm below the total vaginal length above the hymen³. The vaginal peaks correspond to point C on the determination according to Pelvic Organ Prolapse Quantification (POP-Q). The main risk factor for vaginal vault prolapse is if there was pre-existing pelvic organ prolapse during hysterectomy³. The prevalence of vaginal vault prolapse was 11.4% when hysterectomy was performed on an indication of uterine prolapse, and by 1.8% when indications of hysterectomy due to benign disease³.

There are two main routes in pelvic reconstructive surgery: abdominal approach (Laparotomy or laparoscopy) and vaginal. Abdominal Sacrocolpopexy via laparotomy route (ASC) is considered the gold standard in the management of apical prolapse surgery with long-term success rate of 78-100% and satisfaction rate of 75-100%⁴. Laparoscopic Sacrocolpopexy (LSC) was first introduced in the early 1990s, which rapidly became a routine gynaecological procedure.

According to a Barber study in 2013⁷, LSC is as effective as ASC with decreased blood loss and length of stay in the hospital. The objective of this study was to compare the clinical outcomes of LSC and ASC that performed in patients with vaginal vault prolapse post hysterectomy.

Methods

Data Search Strategy

Systematic literature searches have been conducted using PubMed and Cochrane Database using the keywords: "Vaginal vault prolapse, Laparoscopic Sacrocolpopexy and Abdominal Sacrocolpopexy". Duplicate titles are omitted. Abstracts of each journal are assessed according to the inclusion criteria.

Inclusion Criteria

Inclusion criteria in this study were: (1) randomized controlled trial (RCT) and observational studies, (2) women with vaginal vault prolapse (apical compartment prolapse post hysterectomy), (3) interventions studied: LSC and ASC, (4) the entire fully accessible papers can be accessed and analyzed accurately.

Study Quality Assessment

The validity of each study was assessed by criteria listed on the Cochrane Handbook for Systematic Reviews of Interventions⁸. Each study was grouped and assessed according to the quality category: low, high, or, unclear risk of bias. It can be seen in Figure 2 and 3.

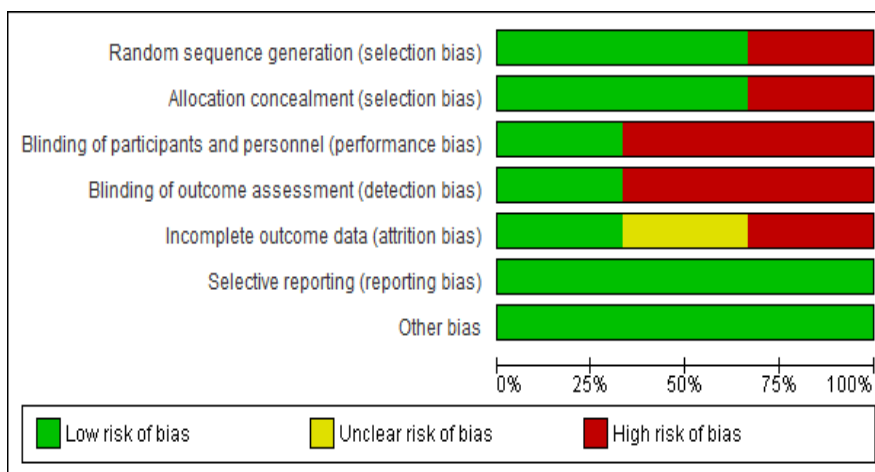


Figure 1. The conclusion of the risk stratification of bias for each study

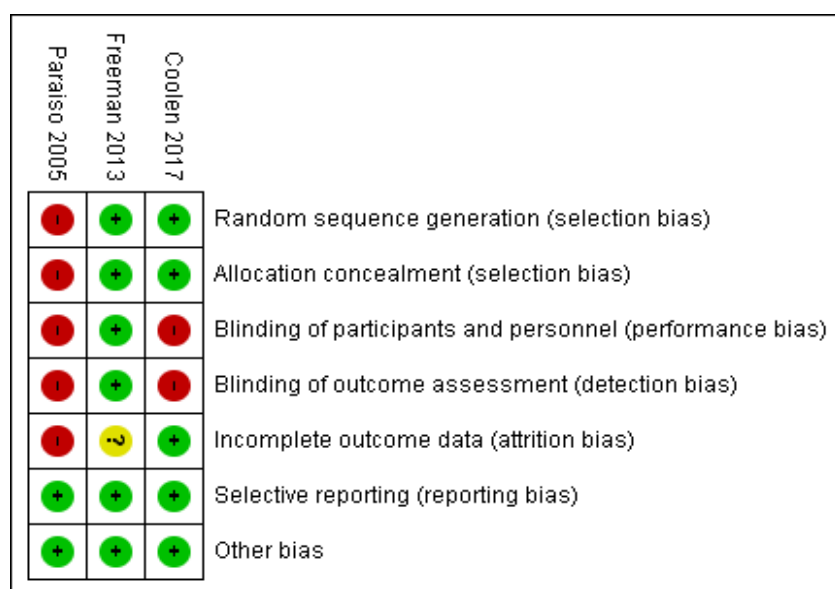


Figure 2. Assessment of the author's risk of bias for each study included.

Statistical Analytic and Meta-Analysis

The clinical outcomes that compared in this study were: duration of surgery, LOS (length of stay), EBL (Estimated Blood Loss), effectiveness as a vaginal vault prolapse management (objectively by point C measurements in POP-Q and re-surgery or repeat surgical intervention, subjectively by presence of symptoms of prolapse and prolapse recurrence rates during follow-up period). Surgery complications were also noted to assess the safety of procedures.

Meta-analysis was arranged using Review Manager (RevMan) version 5.3. For categorical outcomes, Odds Ratio (OR) was calculated using the Mantel-Haenszel method. For continuous variables, the mean difference (MD) was derived from the mean and standard deviation and used when the reported results had an identical scale. The confidence interval used was 95% and the p value <0.05 (two-tailed) was statistically significant.

Results

Study Selection

Data search in PubMed and Cochrane library resulted in 314 articles. There were 196 duplicated articles that were omitted. Screening based on inclusion criteria, obtained a total of three articles inclusion for meta-analysis^{5,6}. Illustration of screening and selection process using a PRISMA flowchart can be seen in Figure 3.

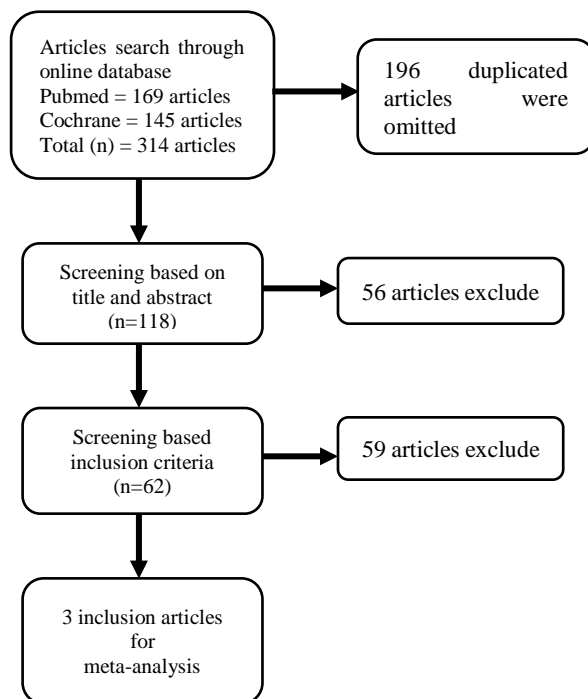


Figure 3. Flowchart of the study selection process using PRISMA flowchart

Our study included three articles with a total of 243 samples who underwent post hysterectomy vaginal peak prolapse with or without cystocele or rectocele. A total of 118 LSC samples and 125 others underwent ASC. Two studies^{5,7} were randomized controlled trials that had a follow-up time of one year. The other 11 were retrospective cohort studies with a follow-up range of 13.5 months for LSC and 15.7 months for ASC. The success criteria of two studies^{5,6} for surgery were different. One study did not mention the success criteria⁸. The characteristics of three inclusive studies are summarized in Table 1.

Table 1. The Characteristic of Included Articles

Article	Country	Study Design	Population (LSC/ASC)	Prolapse Grading	Primary Outcome	Success Criteria	Success Rate (LSC/ASC)	Subjective Outcome Measurement	Subjective Outcome Result	Reintervention	Surgeon experience
Coolen et al ⁹	Netherlands	RCT	36/37	POP-Q	Disease-specific quality of life	No prolapse beyond hymen, no bothersome bulge symptom, and no repeat surgery or pessary use for recurrent prolapse within 12 months	83.8%/89.2%	UDI, DDI, IIQ, PGI-I	No different	4 LSC/1 ASC	Experienced

Freeman et al¹⁰	UK	RCT	26/27	POP-Q	Test the clinical equivalence of open (ASCP) and laparoscopic (LSCP) sacrocolpopexy using objective and subjective outcomes	Point C on the POP-Q and subjective complaint	No Significant different	PGI-I,P-QOL, SF36	Not mentioned	1 LSC	Experienced
Paraiso et al¹¹	US	Comparative cohort	56/61	unclear	Compare laparoscopic and open sacral colpopexies for efficacy and safety	Not mentioned	Not mentioned	Not mentioned	Not mentioned	6 LSC/3 ASC	Some in learning curve

Duration of Operation

This analysis was carried out on three inclusive studies involving a total of 118 women who underwent LSC and 125 underwent ASC. The estimated mean difference (MD) for operating time was 22.82 minutes and the 95% CI was 0.43 - 45.22 minutes ($p = 0.05$) (Figure 4a). The results of this analysis indicate that the duration of surgery in the LSC group was longer than the ASC.

Blood Loss during Surgery

The analysis from three studies with a total of 243 samples found that the average difference estimation (MD) for blood loss during surgery was 111.64 mL with 95% CI -166.13 to -57.15 mL ($p < 0.00001$) (Figure 4b). These results suggest that surgical blood loss in the LSC group was significantly lower than that in the ASC group.

Length of Stay (LOS)

Based on the three included studies, LSC was associated with a lower LOS in hospital compared to ASC. The estimated mean difference (MD) was -1.82 days with 95% CI -2.52 to -1.12 days ($p < 0.00001$) (Figure 4c).

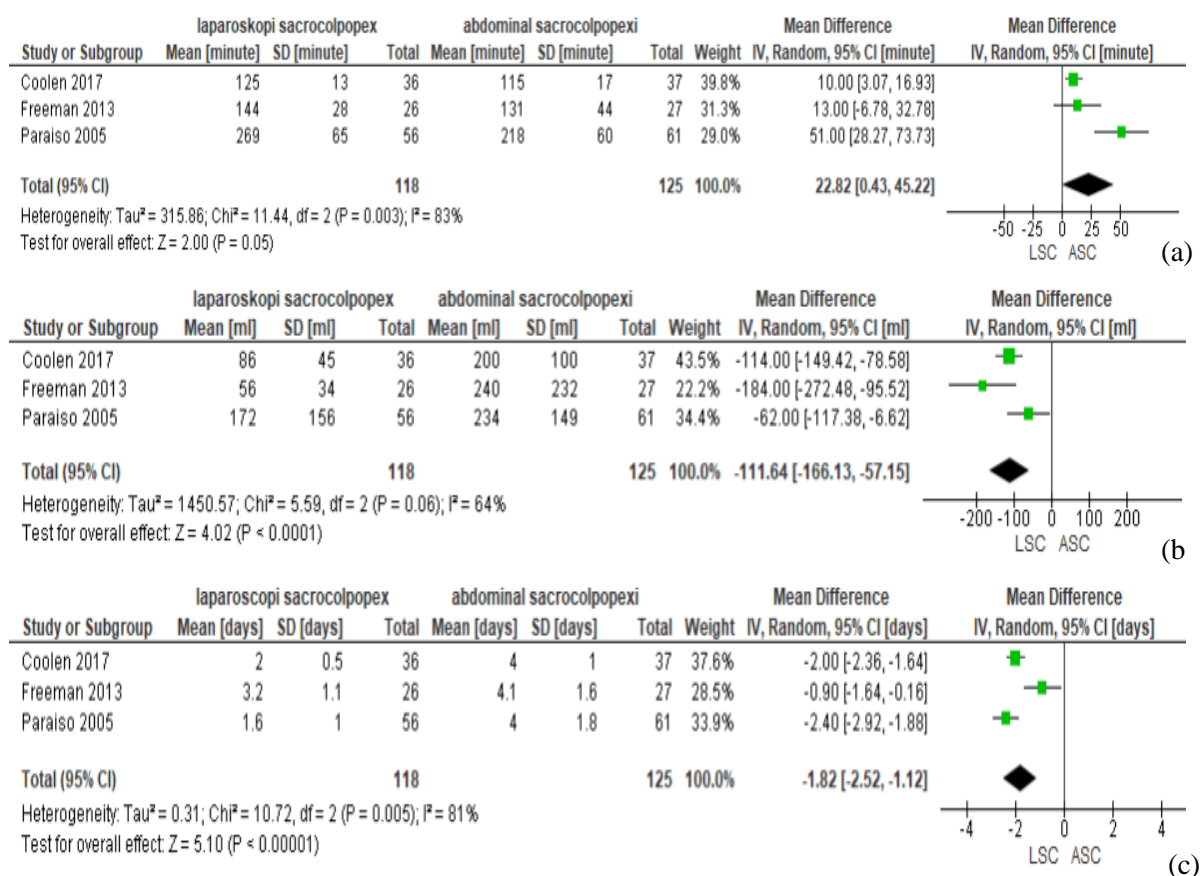


Figure 4. The Forest Plot of (a) Operating Time, (b) Blood Loss During Surgery, (c) Length of Stay in Hospital between LSC and ASC Group. SD, standard deviation; CI, confidence interval; df, degrees of freedom

Complications Incidence of Surgery

We analysed the intra and postoperative complications incidence between LSC and ASC group. From the three studies analysed, it was found that the incidence of total complications was the same between LSC and ASC group (26 cases in each group). There was no significant difference in the number of total incidence of complications between the LSC and ASC groups (OR 1.10; 95% CI 0.58-2.08; p = 0.77) (Figure 5a). Table 2 describes the details of complications

in the LSC and ASC groups. In the study of Freeman et al⁹, there were no cases of LSC that experienced conversion to the abdominal surgery. There was one case of LSC group in Paraiso et al's 11 study that converted to abdominal due to excessive bleeding during surgery. In Coolen et al's study⁷, there were found two cases of LSC that converted to abdominal surgery (one case was due to bladder lesions and the other was due to bleeding).

Table 2. Comparison Details of LSC and ASC Complications

Complications		Coolen et al ⁹		Freeman et al ¹⁰		Paraiso et al ¹¹	
		LSC (n=36)	ASC (n=37)	LSC (n=26)	ASC (n=27)	LSC (n=56)	ASC (n=61)
Intraoperative	Bladder injury	1	0	1	0	6	2
		(conversion to abdominal)					
	Bowel injury	1	1	0	1	1	2
		(conversion to abdominal)					
	Bleeding		0	0	1	1	0
						(conversion to abdominal)	
	Opening of vaginal			1	0		
Postoperative	Wound dehiscence	0	2				
	Lung emboli	0	1				
	Ileus	0	3			0	2
	SBO*					1	2
	Surgery Site Infection	1	0			6	2
	Pyelonephritis	1	0				
	DVT**					1	1
	Needed for transfusion					1	1
	Cardiac complication					0	2
	Ventralis Hernia					1	2
Mesh Erosion					2	1	

*Small Bowel obstruction; **Deep Vein Thrombosis

Incidence of postoperative ileus and simple bowel obstruction (SBO)

The incidence of postoperative ileus and SBO was higher in the ASC group, but not statistically significant (OR 0.21; 95% CI 0.03 - 1.23; $p = 0.08$) (Figure 5b). In the study of Paraiso et al⁹, there was one case of postoperative SBO in the LSC group and two cases in the ASC group. In two studies^{7,9}, there were a total of five cases of ileus in the ASC group and no incidence of ileus in the LSC group.

The study by Freeman et al¹⁰ did not report specifically on the incidence of ileus and SBO.

Bowel injury

There was no significant difference in the number of bowel injury cases between women who underwent LSC and ASC (OR 0.4; 95% CI 0.08-2.17, $p = 0.30$) (Figure 5c). In Coolen et al's study, one patient in the ASC group died postoperatively from multiorgan failure due to sepsis after bowel perforation.

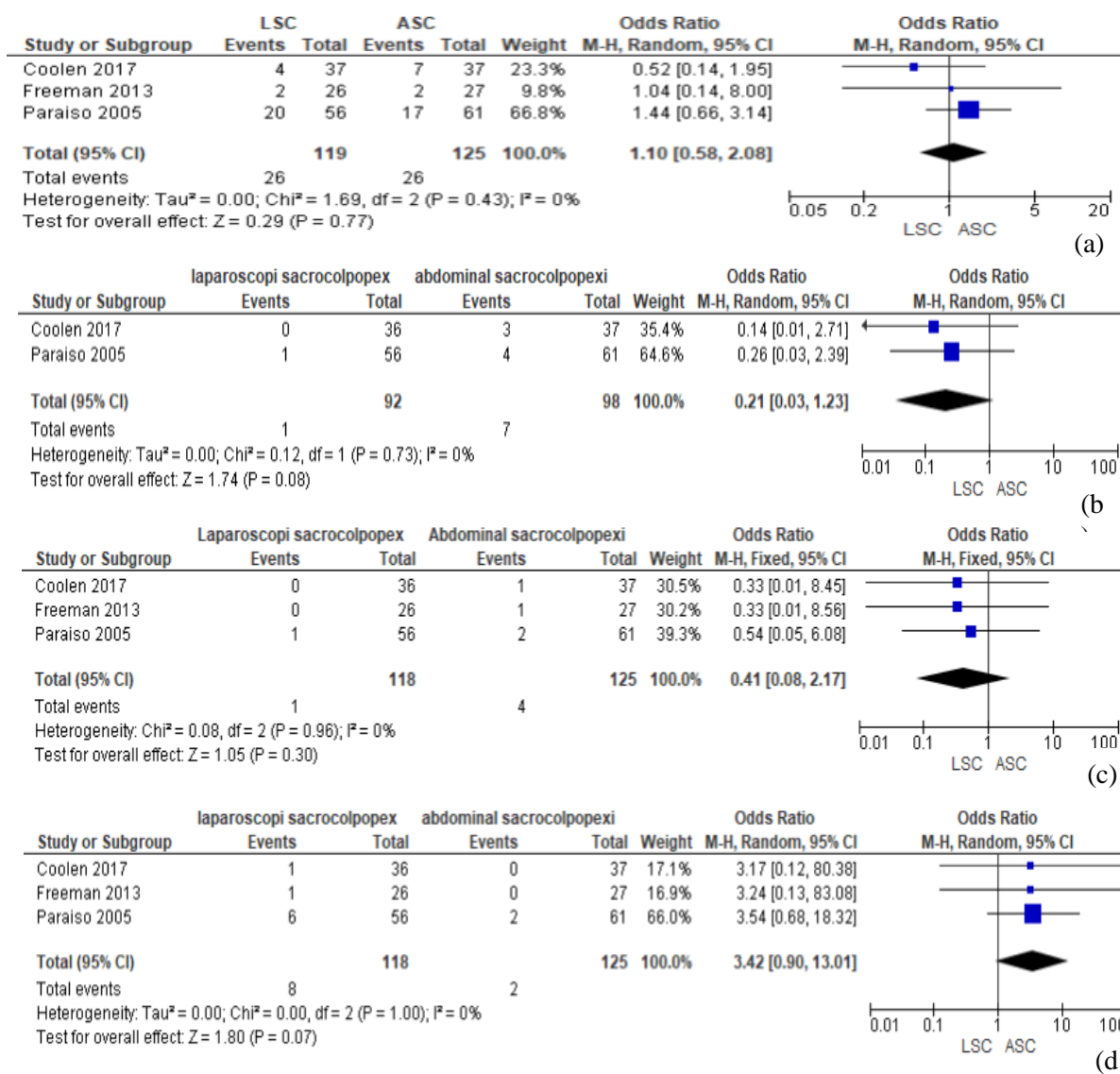


Figure 5. The Forest Plot of (a) Total Complication Incidence, (b) Ileus and SBO Incidence, (c) Bowel Injury Incidence, (d) Bladder Injury Incidence. SD, standard deviation; CI, confidence interval; df, degrees of freedom.

Bladder injury

There were no significant differences in the incidence of bladder injury between women who underwent LSC and ASC (OR 3.42; 95% CI 0.90-13.01, p = 0.07) (Figure 5d). In all studies, it was found that the number of bladder injuries was higher in the LSC group than in ASC.

Surgery Outcomes

PGI-I (within 1 year)

There was no significant difference in the measurement of the PGI-I questionnaire (the sample gave a “very much better” score) within one year after surgery between the LSC and ASC groups (OR 0.90; 95% CI 0.35 - 1.85; p = 0.61) (Figure 6a).

Measurement point C on POP-Q

Only two studies compared POP-Q measurement after surgery as an objective measure. Freeman et al⁸ found no significant difference in point C measurements for POP-Q after 1 year of doing LSC or ASC. Coolen et al⁸ also reported no significant difference between the two groups in the anatomical results based on POP-Q within 12 months after surgery. When included in the analysis as shown in Figure 6b, there was no significant difference at point C POP-Q after one

year of LSC or ASC (MD 0.06 cm, 95% CI -0.49 to 0.61, $p = 0.83$).

Reoperation for POP

There was no statistically significant difference regarding reoperation (repeat surgical intervention) for pelvic organ prolapse between the LSC and ASC groups (MD 2.92; 95% CI 0.95-8.98; $p = 0.06$). The results of this analysis based on three studies found 11 cases in the LSC group and 4 cases in the ASC group requiring re-surgical intervention for POP recurrence (Figure 6c).

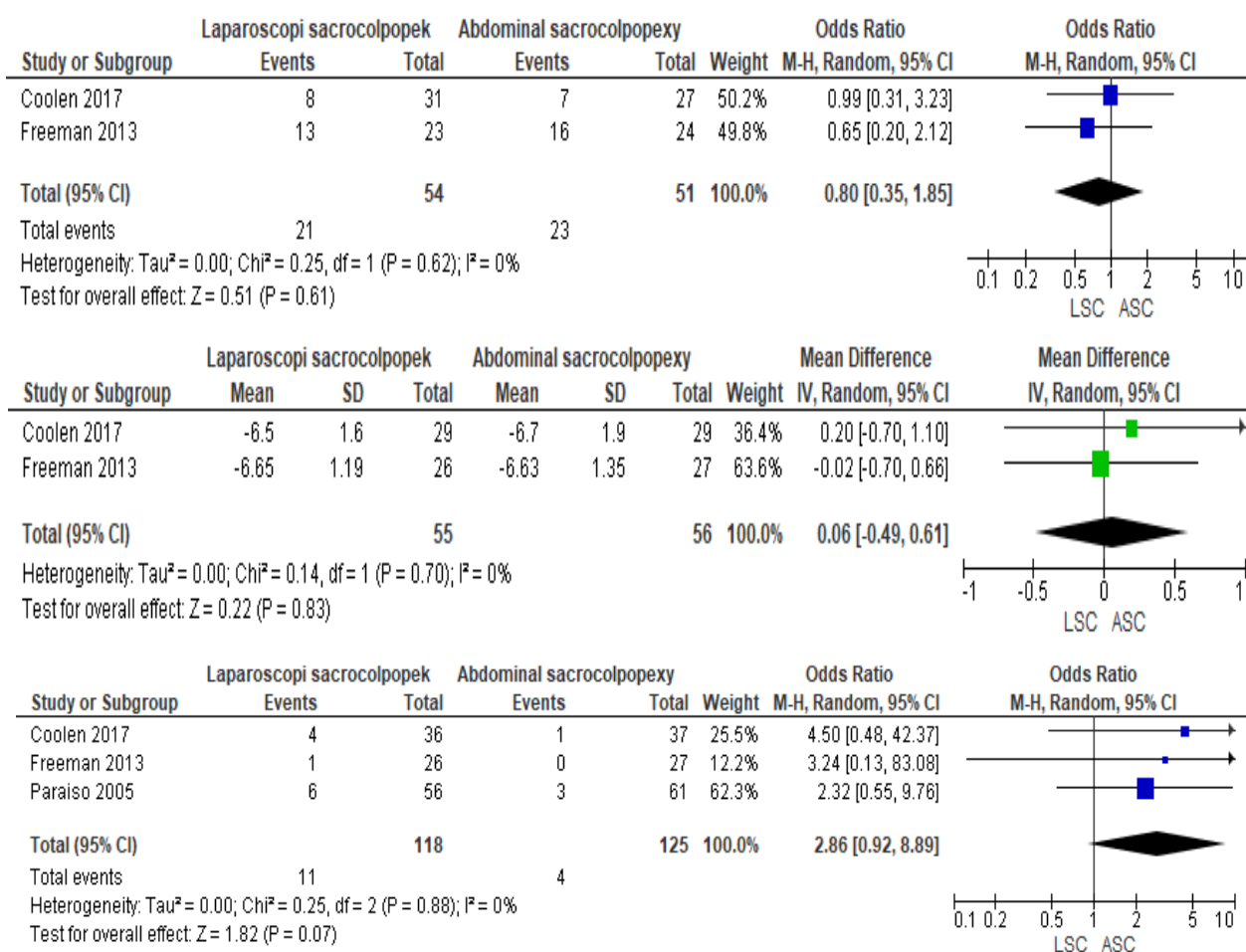


Figure 6. The Forest Plot of (a) PGI-I Questionnaire, (b) Point C Measurement in POP-Q Within 1 Year After Surgery, (c) Reoperation for POP between LSC and ASC Group. SD, standard deviation; CI, confidence interval; df, degrees of freedom.

Discussion

Hysterectomy is one of the most common gynecological surgery procedures worldwide in women of reproductive age. As life expectancy increases, the incidence of vaginal vault prolapse post-hysterectomy increases with an average of 60 years¹⁰. Sacrocolpopexy is the gold standard to overcome the vaginal vault prolapse with the success rate of 78-100%¹¹. Abdominal approach of sacrocolpopexy (ASC) is superior to the vaginal approach with fewer recurrent prolapse numbers, but vaginal access is faster with better cosmetic results and shorter LOS. The development of laparoscopic surgery presents the advantage of better pelvic anatomical vision due to the magnification of endoscopic video, better cosmetic results and lower LOS¹². Several research studies have demonstrated the effectiveness and safety of laparoscopic approaches to the treatment of vaginal vault prolapse that provide good outcomes in long-term anatomy and functional and high levels of satisfaction^{6,12}. The LSC bridges these gaps and is expected to produce outcomes like ASC with advantages such as the vaginal approach. From the results of our meta-analysis, we found that LSC was significantly associated with longer duration of surgery but fewer duration of blood loss during surgery and shorter LOS than ASC group. This is in accordance with the meta-analyses performed by Coolen *et al*¹⁸ and Campbell *et al*¹². The risk of complications such as bladder injury, bowel injury and ileus did not differ significantly between LSC and ASC. However, the incidence of ileus was higher in ASC group (five cases) while in the LSC group there was no ileus incidence. When viewed from

overall complications, there were more complications in the LSC group than ASC but statistically did not differ significantly. This contrasts with the meta-analysis performed by Coolen *et al*¹⁸ where the rate of complications was higher in the ASC group although it also did not differ significantly statistically. From the results of our study, LSC complications are most prevalent in Paraiso *et al*⁸ study, this is because some laparoscopies are performed by operators in the learning process. It is said in his journal that the expertise, experience and learning process of the surgeon plays a role in the occurrence of a bladder injury in the LSC group.

The Effectiveness of Surgical Treatment of Vaginal Vault Prolapses

The effectiveness of surgical treatment of vaginal vault prolapse is assessed through subjective and objective outcomes. The objective outcomes are anatomical outcome (the measurement of point C in POP-Q more than 1 cm above the hymen) and the prolapse recurrence rate requiring reoperation during the follow-up period. Subjective outcome is the absence of symptoms or complaints after the procedures that assessed through the PGI-I (Patient Global Impression of Improvement) questionnaire¹². Only two studies have measured the point C on POP-Q as the objective outcome of vaginal vault prolapse surgery. Both studies are RCT studies. Paraiso *et al*¹¹ in the study did not include POP-Q measurements as a comparison because it was a retrospective cohort study in which POP-Q pre and postoperative data were incomplete (only in 60% of laparoscopic groups). From two RCT studies^{5,12,13}, showed no statistically significant differences in anatomical outcomes and reoperation (repeat surgical

intervention) for recurrence of pelvic organ prolapse between LSC and ASC groups after one year of follow-up. Our meta-analysis also found no statistically significant difference in subjective outcomes during the one-year follow-up between LSC and ASC groups assessed through the PGI-I questionnaire.

Conclusion

Meta-analysis in this study concludes that LSC compared to ASC has a longer duration of surgery but is associated with less duration of bleeding during surgery, shorter length of stay in hospital. LSC and ASC have similar objective and subjective outcomes for vaginal vault prolapse management. The effectiveness of LSC and ASC as vaginal vault prolapse management cannot be concluded in this meta-analysis because the number of inclusion studies has not been adequate as the preparation of clinical recommendations. Therefore, the authors suggest a further investigation of large-scale studies in this patient population.

Conflict of Interest

The author stated there is no conflict of interest

References

1. Masenga, G. G., Shayo, B. C. & Rasch, V. Prevalence and risk factors for pelvic organ prolapse in Kilimanjaro, Tanzania: A population based study in Tanzanian rural community. *PLoS One* **13**, e0195910 (2018).
2. Zheng, Y., Zhou, H., Dunstan, C. R., Sutherland, R. L. & Seibel, M. J. The role of the bone microenvironment in skeletal metastasis. *J. Bone Oncol.* **2**, 47–57 (2013).
3. Austin, P. F. et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the international children's continence society. *J. Urol.* **191**, 1863-1865.e13 (2014).
4. Mearini, L., Nunzi, E., Di Biase, M. & Costantini, E. Laparoscopic Management of Vaginal Vault Prolapse Recurring after Pelvic Organ Prolapse Surgery. *Urol. Int.* **97**, 158–164 (2016).
5. Paraiso, M. F. R., Jelovsek, J. E., Frick, A., Chen, C. C. G. & Barber, M. D. Laparoscopic compared with robotic sacrocolpopexy for vaginal prolapse: A randomized controlled trial. *Obstet. Gynecol.* **118**, 1005–1013 (2011).
6. Coolen, A. L. W. M. et al. The treatment of post-hysterectomy vaginal vault prolapse: a systematic review and meta-analysis. *Int. Urogynecol. J.* **28**, 1767–1783 (2017).
7. Coolen, A.-L. W. M. et al. Laparoscopic sacrocolpopexy compared with open abdominal sacrocolpopexy for vault prolapse repair: a randomised controlled trial. *Int. Urogynecol. J.* **28**, 1469–1479 (2017).
8. Paraiso, M. F. R., Jelovsek, J. E., Frick, A., Chen, C. C. G. & Barber, M. D. Laparoscopic Compared With Robotic Sacrocolpopexy for Vaginal Prolapse: A Randomized Controlled Trial. *Obstet. Gynecol.* **118**, (2011).
9. Freeman, R. M. et al. A randomised controlled trial of abdominal versus laparoscopic sacrocolpopexy for the treatment of post-hysterectomy vaginal vault prolapse: LAS study. *Int. Urogynecol. J.* **24**, 377–384 (2013).
10. van der Ploeg, J. M., van der Steen, A., Zwolsman, S., van der Vaart, C. H. & Roovers, J. P. W. R. Prolapse surgery with or without incontinence procedure: a systematic review

-
- and meta-analysis. *BJOG An Int. J. Obstet. Gynaecol.* **125**, 289–297 (2018).
11. Parkes, I. L. & Shveiky, D. Sacrocolpopexy for Treatment of Vaginal Apical Prolapse: Evidence-Based Surgery. *J. Minim. Invasive Gynecol.* **21**, 546–557 (2014).
12. Bacle, J. et al. Laparoscopic promontofixation for pelvic organ prolapse: A 10-year single center experience in a series of 501 patients. *Int. J. Urol.* **18**, 821–826 (2011).
13. Campbell, P., Cloney, L. & Jha, S. Abdominal Versus Laparoscopic Sacrocolpopexy: A Systematic Review and Meta-analysis. *Obstet. Gynecol. Surv.* **71**, (2016).

REVIEW ARTICLE

MAKING PREGNANCY A MISSED OPPORTUNITY FOR TREATMENT OF TUBERCULOSIS INFECTION : A SYSTEMATIC REVIEW

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ABSTRACT

Background : Eleven million Americans, representing 4% of the U.S. general population, are estimated to have latent tuberculosis infection (LTBI). In countries with low TB incidence, immigrant from higher incidence countries form the major pool of infected individuals. To understand the prevalence, screening and management of TBI in pregnancy.

Methods : A systematic review of 4 databases (Embase, Embase Classic, Medline, Cochrane Library) covering articles published from January 1st 2010 to April 30th 2018. Articles in English with relevant information on prevalence, screening strategies and treatment of TBI during pregnancy were eligible for inclusion.

Results : Of 193 titles initially identified, 108 abstracts were eligible for review. Of these, 86 articles qualified for full text review and 22 were retained: 3 cohort studies, 2 case-control studies, and 17 cross-sectional studies. In the USA, the estimated prevalence of TBI ranged from 14 to 48% in women tested, and tuberculin skin test (TST) positivity was associated with ethnicity. The proportion of women who attended follow-up visits after positive tuberculin tests varied from 14 to 69%, while 5 to 42% of those who attended follow-up visits completed a minimum of 6 months of isoniazid treatment. One study raised the possibility of an association of pregnancy/post-partum state with INH hepatitis (risk ratio 2.5, 95% CI 0.8–8.2) and fatal hepatotoxicity (rate ratio 4.0, 95% CI 0.2–258). One study deemed INH safe during breastfeeding based on peak concentrations in plasma and breast milk after INH administration.

Conclusion : Pregnancy is an opportunity to screen for TBI. Interferon-gamma release assays are likely comparable to tuberculin skin tests and may be used during pregnancy. Efforts should be made to improve adherence with follow-up and treatment post-partum. Further data are needed with respect to safety and feasibility of antepartum INH therapy, and with respect to alternative treatment regimens.

Medical and Health Science Journal

Introduction

In 2013, tuberculosis (TB) was responsible for a half a million deaths amongst women world-wide, making TB one of the top killers of women of reproductive age, most being HIV negative. Eleven million Americans, representing 4% of the U.S. general population, are estimated to have latent tuberculosis infection (LTBI). In countries with low TB incidence, immigrant from higher incidence countries form the major pool of infected individuals. In the United States, the reduction in active TB incidence has in part reflected improvements to screening and treatment of latent infection. Immigrant women face financial, educational and cultural barriers, which can limit health status and health-seeking behaviors. The antenatal period represents an opportunity for them to access the medical system. For this reason, the *American College of Obstetricians and Gynecologists* and the *Center for Disease Control and Prevention* recommends screening all pregnant women at high risk for TB when beginning prenatal care. While treating active disease during pregnancy offers clear benefits, the treatment of LTBI during pregnancy remains controversial and current CDC and ACOG guidelines favor deferring treatment to the post-partum period in most cases¹.

In order to further understand the prevalence, natural history, screening and management of LTBI in pregnancy, we conducted a systematic literature review addressing the screening and treatment of LTBI, in women without known HIV infection². We did not review treatment of latent TB infection in pregnant women with concomitant HIV infection, as the indication for urgent treatment is stronger.

Methods

Information Source and Search Strategy

A librarian from the McGill University Health Center aided in the development of a comprehensive search strategy. Databases searched were Embase, Embase Classic, Medline via PubMed and the Cochrane Library. Articles published from January 1, 1980 to April 30, 2014 were eligible. Search terms used were: pregnancy, or pregnancies, or pregnant, or puerperium, or postpartum, or antepartum, or obstetric, or obstetrical, and mycobacterium tuberculosis, or tuberculosis, or latent tuberculosis.

Inclusion Criteria

Articles eligible for review were original research publications available online or through inter-library loan. Articles had to be written in English, French or Spanish, the languages spoken by the investigators. Studies included were randomized controlled trials, cohort studies, case-control studies and cross-sectional studies. Articles from any country, with relevant information on prevalence, natural history, screening tools, screening strategies and treatment of LTBI during pregnancy were eligible for full review. Articles were excluded if (1) full text was not available (2) articles were written in a language not understood by reviewers (3) they were case series or case studies, meaning case descriptions of pregnant women with latent or active TB, without a comparison group for purposes of analysis; pharmacokinetic studies were considered acceptable. (4) they focused exclusively on prevalence, diagnosis and treatment of active TB (5) the study population was exclusively HIV-infected.

Two independent reviewers (IM, MC) reviewed titles, abstracts, and articles. Titles were screened for relevance to the subject of TB. Any articles reporting original studies with information on LTBI in pregnancy, which did not meet one or more of the exclusion criteria, were retained for full-text review. The investigators independently read full-text versions of eligible articles. Disagreements were resolved by consensus between the two reviewers; where they did not reach consensus, input from a third investigator (KS) was obtained. References from included articles were manually reviewed for additional, potentially eligible articles.

Data Collection Process

Data abstracted included (1) year of publication; (2) country of study; (3) setting; (4) study design; (5) participant numbers; (6) participant characteristics; (7) recruitment and follow-up period and methods; (8) intervention or exposure; (9) main outcomes or events observed; (10) confounding variables and other covariates considered; (11) main findings.

Participant characteristics described the study population by summarizing eligibility criteria for the study, the method of selection of participants, and their demographic characteristics; when the study design involved matching, the criteria for matching were recorded. Depending on the study question, "Intervention or exposure" represented pregnancy status, treatment administered, testing methods used, TB status, ethnicity, or trimester of pregnancy. Similarly, depending on the study question for each article, main outcomes or events included development of latent or active TB, rates of

adherence to testing or to treatment, identification of predictors of active disease, identification of predictors of adherence, and/or correlation of results from different testing modalities. Confounding variables and covariates included age, socioeconomic status, Medicaid coverage, marital status, education, occupation, ethnicity, country of birth, immigration status, language spoken, prior TB screening and treatment, BCG vaccination history, number of antenatal visits, gestational age at first antenatal visit, parity, HIV status, known substance abuse, travel to endemic area, location of residence, exposure to individuals with known TB, and chronic medical conditions.

We included a 3-point quality score (2 = well described, 1 = poorly described, 0 = not described) for the following 8 attributes extracted from the STROBE Statement [6] with an emphasis on methods: (1) description of the study setting; (2) description of study participants; (3) definitions of all variables; (4) description of the data sources and measurement tools; (5)

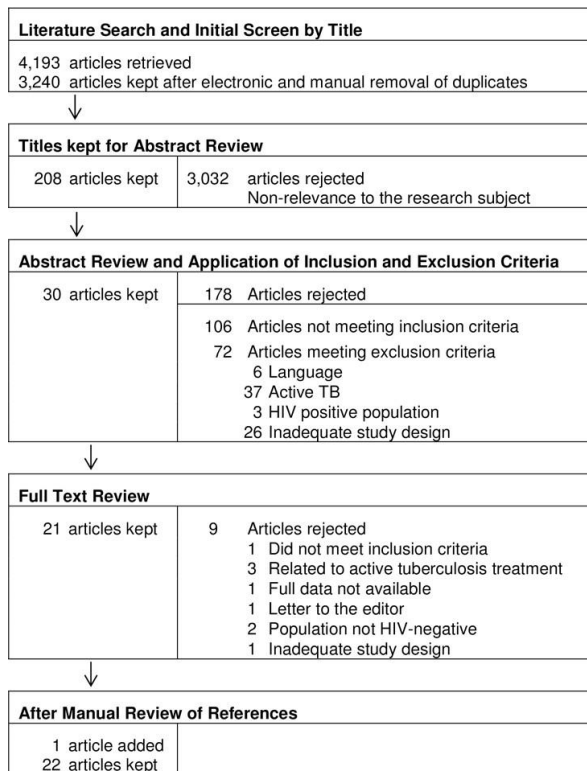


Fig 1. Summary of retrieval and review of articles on tuberculosis and pregnancy, 1980–2014.

justification of sample size; (6) description of statistical methods; (7) description of results; (8) discussion and interpretation of results. The maximum quality score was therefore 16.

Results

The initial search yielded 3,240 titles, of which 208 titles were retained for abstract review. Of the 208 abstracts reviewed, 30 met inclusion criteria and were eligible. After full text review and manual review of references, 22 articles were retained (Fig 1). Three cohort studies, 2 case-control studies and 17 cross-sectional studies were included. Quality scores ranged from 8 to 15 with a mean quality rating of 12.4 (S1 Appendix). Of these studies, 13 reported prevalence of LTBI during pregnancy; 7 addressed treatment of LTBI pregnancy; 3 addressed the risk of TB reactivation during pregnancy; 5 examined the performance of interferon-gamma release assays during pregnancy, and 6 addressed adherence with TB screening during pregnancy. Some studies investigated more than one of these subjects.

1) Prevalence of LTBI

Thirteen studies reported the prevalence of LTBI in cohorts of pregnant women based on tuberculin skin testing (Table 1). In cohorts of pregnant women tested in the USA, the prevalence of latent infection varied from 14 to 48%³. Skin test positivity was related to the ethnicity of cohort members: In one study 31.3% of Asian-American women, 23.9% of

Table 1. Prevalence of LTBI During Pregnancy Measured by Tuberculin Skin Test.

Reference	Country	Study period (y)	Participant (n)	US-born (%) ^{*1}	Non US-born (%)	Mean (range)	ageInterval testing reading (h)	between Indurations and cutoff	PPD + (%)
Cruz	USA	2000	1331	n/s ^{*2}	n/s	n/s	n/s	n/s	32%
Metersky	USA	1990–1991	1412	n/s	n/s	n/s	before 48	5 mm	18%
Magann	USA	n/s	1000	58.5	41.5	25.3 (13–42)	48–72	10 mm 5–8 mm ^{*3}	4%
								8–12 mm ^{*4}	
								12 mm ^{*5}	
Jackson	USA	2000	30	47	53	27.5	48–72	10 mm	0%
Meints	USA	2003–2006	382	0	100	n/s		n/s	22%
Medchill	USA	1993–1997	1763	38.2	61.8	n/s	48–72	5 mm	15%
Schwartz	USA	2001–2006	4049	11.1	88.9	27.0 (13.0–46)	n/s	10 mm previously	48%
Sackoff	USA	1999–2000	558	0	100	26.0 (22–31)	n/s	10 mm previously	37%
Lighter-Fisher	USA	n/s	140	59	41	18.5 (13.5–36.5)	48–72	10 mm	20%
Worjolah	USA	2009–2010	220	35	65	25 (17–41)	48–72	10 mm ^{*6}	21%
								15 mm	
Chehab	USA		102	10	90	25.9			
Mathad	India	2011–2012	401			n/s	48–72	10 mm	14%
Sheriff	Tanzania	2008	286			25.0 (16–40)	n/s	5 mm ^{*7}	30%
								10 mm ^{*8}	
Sepulveda	Chile	n/a	840			n/s	72	10 mm	51–57%

^{*1} When not explicitly detailed, Non-Hispanic Caucasian women were considered US born, whereas women from all other ethnicities were considered non US-born

^{*2} Not specified in article

^{*3} If suspected of having HIV, or close contact with known case

^{*4} If from endemic area, medically underserved low income populations, residents of long term care facility, migrant workers, homeless

^{*5} If no known risk factors

^{*6} Recent immigrants (<5 years), from high prevalence country, injection drug user, residents or employees of high risk congregate settings

^{*7} HIV positive

^{*8} HIV negative

Hispanic women, 9.3% of African-American women and 4.1% of Caucasian women had positive skin tests. Hispanics had a risk ratio of 5.9 (95% CI 3.9 to 8.8) and Asian-American women had a risk ratio of 7.6 (95% CI 3.4 to 17.5) compared with Caucasian women. Of note, 223 of the 1634 skin tests initially placed had to be repeated 2 to 5 times because of failure to return for initial reading. A cross-sectional study conducted in a New York City ambulatory care facility also focused on ethnicity; Asian-American women were again most likely to have a positive tuberculin test with an odds ratio of 3.15 (95% CI 1.62–6.14) relative to white women and 1.55 (95% CI 1.35–1.8) compared to Hispanic women. On multivariate analysis, U.S. born women were substantially less likely to have a positive tuberculin test than were foreign-born women (odds ratio 0.08 95% CI 0.05–0.13)^{4,5}.

A study from an antenatal care clinic in Northern Tanzania identified members of two tribes as having a lower prevalence of LTBI compared to other clinic patients; these tribes were thought to have better socio-economic status as a result of more fertile lands, and a better knowledge of agricultural techniques.

1) NATURAL HISTORY: RISK OF TB REACTIVATION WITH PREGNANCY

In order to examine the epidemiology of TB in pregnancy and to establish whether pregnancy is an independent risk factor for active TB, Zenner and colleagues conducted a primary care-based retrospective cohort study, using the General Practitioner Research Database. They considered all women in the UK with known pregnancy start and end dates between 1996 and 2008. The

diagnosis of TB was attributed based on culture confirmation, clinical or radiological signs compatible with active TB, or receipt of treatment for active disease. The overall crude incidence rate of active TB diagnosis was 10.1/100,000 (95% CI 8.7–11.8) person-years. The incidence rate for TB during pregnancy was 12.8/100,000 (95% CI 8–19.4) person-years. The incidence in the same cohort when women were not pregnant was 9.1/100,000 (95% CI 7.6–10.8) person-years. During the 180-day postpartum period the crude incidence rate was 19.2/100,000 (95% CI 12–29) person-years. TB occurred significantly more frequently during pregnancy and the 180 days post-partum combined, i.e. 15.4/100,000 (95% CI 11.2–20.6) person-years (crude incidence rate ratio, 1.68 (95% CI 1.17–2.38). After adjustment for age, socioeconomic status, region of residence, and BCG vaccination status, TB incidence was significantly higher during the 180 days postpartum (IRR, 1.95 (95% CI 1.24–3.07) but not during pregnancy itself^{6–8}. However, given the usual time frame over which TB disease evolves, diagnosis post-partum may well reflect the onset of active disease antepartum⁹.

A case-control study from the Dominican Republic did not identify any association between recent pregnancy and TB reactivation. Cases were women with a new diagnosis of active TB, treated at four facilities in Santo Domingo; controls were women who sought HIV screening at the Santo Domingo National Laboratory of Public Health. Case and control subjects had comparable reproductive histories. Among HIV-negative women, those with active TB were no more likely to have been pregnant within the preceding six

months than the control subjects (OR 1.1, 95% CI 0.4–2.4). On the other hand, it is not clear whether cases and controls were comparable with respect to other risk factors for active TB, e.g. antecedent smoking and substance use, or what the relative frequency of latent TB infection was in the two groups.

A matched case-control study conducted in a northern province of Malawi, where TB is differentially distributed between men and women depending on age, examined risk factors

for active TB among men and women, after adjustment for socioeconomic status and HIV infection. In this study, neither pregnancy nor the post-partum period (defined as 9 months after delivery) was associated with active TB. It is possible that in this and other settings, women with incipient active TB, or with associated risk factors, were in fact less likely to become pregnant.

Table 2. Adherence to Antepartum Screening Programs for Latent Tuberculosis.

Reference of origin	Country	Study period (y)	Participants eligible for PPD	PPD placed n (%)	PPD available n (%)	Adherence to Chest X-Ray (%)	Participants eligible for treatment evaluation	Adherence follow-up appointment n (%)	Completion of to >6 months INH n (%)
Cruz	USA	2000	1331	n/s	1195 (90)	n/s	393	167 (42)	71 (42)
Metersky	USA	1990–1991	1412	1405 (99.9)	1405 (100)	254 (98)	272	39 (14)	2 (5)
Medchill	USA	1993–1997	1763	1634 (93)	1497 (92)	211 (93)			
Schwartz	USA	2001–2006	4049	n/s	3847 (95)	1841 (95)			
Sackoff	USA	1999–2000	730	521 (77)	678 (93)		291	202 (69)	27 (13)
Worjolah	USA	2009–2010	220	220 (100)	199 (95)				
Mathad	India	2011–2012	154	154 (100)	109 (71)				
Sheriff	Tanzania	2008	396	n/s	286 (72)	87 (100)			

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2) SCREENING

a) Programs.

Studies assessing antenatal screening programs for LTBI and/or active TB revealed a high level of adherence with both skin testing and chest radiography (Table 2). In the USA, reported adherence with antenatal tuberculin skin testing was between 90–100% while with chest radiography it was 93–100%. In a study of 4049 pregnant women considered eligible for screening in New York City, Asian-American women were more likely to adhere to testing than Hispanic and Caucasian women. U.S.-born patients were the least adherent with both tests. Of note, this particular screening program did not identify any cases of active TB disease. In higher incidence countries, 71–72% of patients returned for skin test reading, while 100% of pregnant Tanzanian women underwent CXR after it was recommended to them.

b) Tools.

Four studies compared TST with the Quantiferon GOLD In-Tube test in pregnant women. In three studies from low incidence settings, concordance between TST and the IGRA was 77, 88 and 91%, with Kappa values of 0.26 (95% CI 0.12–0.40), 0.45 (95% CI 0.26–0.64) and 0.36 respectively. In those studies, the prevalence of TST positivity ranged from 10 to 23%, and IGRA positivity from 5 to 14%. Discordance mostly often reflected TST positive/ IGRA negative results although no specific predictors of discordance were identified. Prior BCG

vaccination was a significant predictor of TST positivity. There was no significant difference between stimulated IFN- γ levels measured during each trimester of pregnancy. There was no significant difference observed in the IFN- γ mitogen response between pregnant and non-pregnant controls of similar age and socio-economic status in an adequately powered analysis. In low incidence settings an IGRA may therefore be more specific and less sensitive than TST in pregnancy, and results do not appear to be altered by pregnancy^{10,11}.

In a study conducted among pregnant women in India, 37% had a positive IGRA in comparison with 14% with a positive TST. Overall agreement was 76% with a kappa of 0.37. The highest frequency of discordance (37%) was observed during the post-partum period, and mainly reflected TST negative/ IGRA positive results. On multivariate analysis, being employed and postpartum enrollment were associated with discordance. Education below the 4th grade was associated with a positive TST. Living in an urban setting and being postpartum was associated with a positive IGRA. The median concentration of stimulated interferon-gamma changed significantly with period of pregnancy, with the highest concentration observed in the postpartum period. In a high burden setting, IGRA may be more sensitive than TST. Immune changes during pregnancy, as well as potential repeated exposure, may contribute to the discordance observed, as well as to the

increase in the concentration of interferon gamma in the postpartum period ¹⁰.

One study found an association between indeterminate IGRA results and concomitant helminthes infection in pregnant women, raising the possibility that helminthic infection may lead to immune alterations that can hamper IGRA testing.

3) TREATMENT

Three studies reported adherence with follow-up of positive tuberculin skin test results, and completion of treatment for LTBI. The proportion of women who attended follow-up after positive tuberculin tests varied from 14 to 69%, while 5 to 42% of those seen after positive skin tests completed at least 6 months of isoniazid treatment. One study found that less than 10% of women potentially eligible for treatment of LTBI completed INH prophylaxis. Attrition was found at every step of the process e.g. lack of referral for evaluation after positive tests, gaps in adherence with follow-up appointments, limited adherence to treatment once prescribed. Another study identified that Asian ethnicity and continuity of care with the same physician in the antepartum and postpartum period were significantly associated with more frequent follow-up and treatment completion rates, while age below 25 was associated with poorer attendance at follow-up appointments.

One study examined predictors of INH treatment completion, in Rhode Island; planned treatment initiation during the postpartum period was negatively associated

with treatment completion. Indeed, 52% of pregnant women referred for postpartum therapy did not return to initiate it. A cross sectional study highlighted that pregnancy was a missed opportunity for screening. Indeed, in a cohort of patients who developed active TB, 22% of missed opportunities for screening in the community arose during pregnancy. Conversely, 40% of patients who were known to have LTBI had been screened during pregnancy¹²⁻¹⁴. Similarly, the highest proportion of patients with active TB despite previous screening for LTBI were those who failed to initiate INH therapy after testing during pregnancy.

After the death of two pregnant women receiving isoniazid treatment in 1982, local health officials requested an analysis of isoniazid hepatitis morbidity and mortality among patients attending a U.S. prenatal clinic, which served a predominantly Hispanic population. A retrospective cohort study compared 3,681 pregnant and postpartum women enrolled in the 1981 INH preventive therapy program until its termination in 1982, with an unmatched comparison group of 3,948 women aged 15 to 44 years old involved in the 1971 Public Health Service (PHS) multicenter INH hepatitis surveillance study. Two panels of experts determined possible cases of INH hepatitis. Five cases were identified in the prenatal group and 10 cases were identified in the non-pregnant group. Two Hispanic women aged 24 and 27 years old died in the preventive therapy program group at 3 and 5 months postpartum. One death occurred in a 38 year-old non-pregnant black woman in

the PHS group. This analysis raised the possibility of associations of pregnancy/post-partum state with INH hepatitis (risk ratio of 2.5, 95% CI 0.8–8.2) and fatal hepatotoxicity (rate ratio 4, 95% CI 0.2–258). However, these groups were unmatched, were followed a decade apart, and the analysis was underpowered because of the rarity of these events.

Finally, one cross-sectional study examined the presence of INH in breast milk among lactating women during treatment for LTBI. Peak INH concentrations in plasma and breast milk were measured one hour after administration. Although some isoniazid did penetrate into breast milk, there was considerable inter-individual variability; the calculated mean relative infant dose of 1.2% of weight-adjusted maternal dose was deemed safe. The authors further suggested that lactating women wait at least one-hour interval to breastfeed, after ingesting INH.

DISCUSSION

LTBI was estimated to be present in up to nearly one half of foreign-born pregnant women tested in the USA. Moreover, the post-partum period may be associated with an increased risk of TB reactivation. In low incidence settings, an IGRA may be more specific and less sensitive than TST, and results do not appear to be altered by pregnancy. Screening programs in pregnant populations revealed excellent adherence with both tuberculin skin testing and CXR. However, adherence with post-partum follow-up of positive screening tests was poor, and a minority of women completed treatment. Pregnancy may

therefore represent a missed opportunity for treatment of latent infection. There remains some concern about higher incidence of INH-associated hepatitis in pregnancy and the post-partum period. Based on measurements of plasma and breast milk concentration of isoniazid, it is likely safe to administer during lactation¹⁴.

This study is the first systematic review focusing on LTBI in pregnancy. Using available information from both low and high incidence countries, we addressed several aspects of its management, including prevalence, adherence with screening and treatment, new diagnostic tests, and potential treatment toxicity. Most studies were of reasonable quality, with quality rating scores above 10 out of a maximum of 16 points.

Our study was limited by the absence of randomized controlled trials on the treatment of LTBI in pregnancy; we therefore could not draw any firm conclusions about the safety of INH therapy antepartum. There may have been some selection bias with respect to the articles included: we limited our review to studies published after 1980 because we felt that earlier studies would not reflect current practice. Secondly, we excluded 6 articles that were published in languages other than English, French or Spanish. Abstracts were available online for three of those rejected articles: there was one cohort study identifying pregnancy as a risk factor for TB reactivation, one case report and one case series of women with postpartum TB. The titles for each of the other three articles referred to active disease. Finally, we did not review the grey literature. Another limitation was the lack of information concerning the

potential use of newer LTBI treatment regimens during pregnancy, e.g. rifampin, combined isoniazid and rifampin, or combined isoniazid and rifapentine.

Prevalence of LTBI in HIV seropositive and seronegative pregnant women has been addressed in previous reviews, as has adherence to post partum follow-up of LTBI. However, we were able to retrieve studies not included in those earlier reviews. Hence, while not all authors have concluded that pregnancy affects the evolution of latent TB infection, we believe that pregnancy may be a minor risk factor for disease reactivation whether it is through the immune changes of pregnancy itself, or the immune reconstitution that follows delivery. In addition, post partum TB may involve more severe disease, including immune reconstitution inflammatory syndrome (IRIS) and a high mortality rate. A case-series of 29 cases of postpartum TB published in 2013 described 93% of women with extra-pulmonary disease, and 69% with CNS disease, although this series may have reflected publication bias. In those cases, treatment was initiated at a median 27 days after the onset of symptoms, and the mortality rate was 38%¹⁵.

A Markov decision analysis model estimated the cost effectiveness of ante partum or post- partum treatment of LTBI with 6 months of INH therapy. With an assumed 90% adherence to post-partum follow-up of a positive tuberculin test, and an assumed mortality rate of 0.001% related to INH-induced hepatitis, treatment initiated at 20 weeks of gestation was estimated to result in the fewest cases of TB. It was predicted to be less costly than postpartum treatment or no treatment. Our

review suggests substantially lower adherence to post-partum follow-up for latent TB infection, which may favor ante partum treatment with regards to cost-effectiveness.

The frequently cited study suggesting pregnancy as a risk factor for INH induced hepatitis and associated mortality had wide confidence intervals which crossed the null value of 1. It used unmatched historical controls for comparison, while assessment of risk factors for INH induced hepatitis (e.g. alcohol consumption, baseline elevation of transaminases and viral hepatitis screen) was not consistent¹⁶. Close monitoring of liver function tests during ante partum therapy with isoniazid could decrease the rate of clinically significant hepatitis. In view of these findings, it appears clinically relevant to consider further investigation of ante partum treatment for LTBI, particularly in the setting of other risk factors for reactivation e.g. diabetes. It would also be highly relevant to collate and publish outcomes of such treatment, e.g. through cooperative registries or networks such as the Tuberculosis Epidemiologic Studies Consortium (TBESC). An ongoing clinical trial on treatment of LTBI during pregnancy in HIV infected women, may allow for new insight into the previously described potential increased risk of hepatitis⁹.

In addition, since current practice continues to emphasize deferring treatment of LTBI until after pregnancy, it would be important to examine strategies to enhance adherence among women who are treatment candidates.

Conclusion

For women at risk, pregnancy provides an important opportunity to screen for latent TB infection. As women are already in care, adherence with tuberculin testing and chest radiography is high when these tests are recommended. However, adherence to post-partum follow-up and treatment is much lower, making pregnancy a missed opportunity for treatment of latent infection. Interferon-gamma release assays may be considered as useful alternatives to the tuberculin skin test. The evidence base documenting treatment toxicity during pregnancy is limited, making further research in this area highly relevant

References

1. World Health Organisation. Warning: This report is out-of-date. In particular, entire time-series of TB disease burden estimates are updated every year. For the latest data and analysis, please see the most recent edition of the global TB report. *Glob. Tuberc. Control* (2014).
2. Control, D., National, P., Aids, H. I. V, Hepatitis, V. & Prevention, T. B. Latent Tuberculosis Treatment Guidelines: 2020 Update. 7 (2020).
3. von Elm, E. *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Int. J. Surg.* **12**, 1495–9 (2014).
4. Lewinsohn, D. M. *et al*. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin. Infect. Dis.* **64**, e1–e33 (2017).
5. Force, U. S. P. S. T. Screening for Latent Tuberculosis Infection in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* **316**, 962–969 (2016).
6. Malhamé, I., Cormier, M., Sugarman, J. & Schwartzman, K. Latent Tuberculosis in Pregnancy: A Systematic Review. *PLoS One* **11**, 1–12 (2016).
7. Mathad, J. S. *et al*. Pregnancy differentially impacts performance of latent tuberculosis diagnostics in a high-burden setting. *PLoS One* **9**, (2014).
8. Mayer, K. H., Mathad, J. S. & Gupta, A. Tuberculosis in pregnant and postpartum women: Epidemiology, management, and research gaps. *Clin. Infect. Dis.* **55**, 1532–49 (2012).
9. Nguyen, H. T., Pandolfini, C., Chiodini, P. & Bonati, M. Tuberculosis care for pregnant women: A systematic review. *BMC Infect. Dis.* **14**, 1–10 (2014).
10. Lighter-Fisher, J. Performance of an Interferon-Gamma Release Assay to Diagnose Latent Tuberculosis Infection During Pregnancy. *Obstetrics and Gynecology* vol. 120 398 (2012).
11. Worjolah, A. *et al*. Interferon gamma release assay compared with the tuberculin skin test for latent tuberculosis detection in pregnancy. *Obstet. Gynecol.* **118**, (2011).
12. Parooei, F., Mahmoodi, Z., Keikhaie, K. R. & Salarzaei, M. Breast tuberculosis in pregnancy (A review and report). *J. Pharm. Sci. Res.* **9**, 1701–1702 (2017).
13. Fisher D, E. K. *Canadian Tuberculosis Standards 7th Edition: 2014 - Canada.ca*. 2017 (2014).
14. Jackson, T. D. & Murtha, A. P. Anergy during pregnancy. *Am. J. Obstet. Gynecol.* **184**, 1090–2 (2011).

15. Jonsson, J., Kühlmann-Berenzon, S., Berggren, I. & Bruchfeld, J. Increased risk of active tuberculosis during pregnancy and postpartum: a register-based cohort study in Sweden. *Eur. Respir. J.* **55**, (2020).
16. Dhar, G. C. Treatment of latent tuberculosis infection. *Ann. Intern. Med.* **162**, 394 (2015).