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Effect of Clitoria Ternatea as Adjuvant Therapy on Serum Cortisol Levels in Leprosy Reaction

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A B S T R A C T

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Kata kunci:

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A B S T R A K

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INTRODUCTION

Leprosy is an infectious disease caused by the *Mycobacterium leprae* (Wisnu et al., 2019). This is granulomatous disease, with a primary predilection for the peripheral nerves, followed by the skin and upper respiratory tract mucosa (Wisnu et al., 2019). Chronic leprosy with several acute response episodes qualifies as a serious disease because to its impact on multiple organ functions. One of the afflicted organs in the body is the adrenal gland (Nazli et al., 2021). Leprosy is f because ulceration, mutilation, and deformity can occur (Darmawan & Rusmawardiana, 2020). Complications occur due to permanent sensory and motor nerve damage and repeated damage to the anesthetic area accompanied by paralysis and muscle atrophy (MOH, 2018).

Based on WHO in 2019, there were 202.256 new cases of leprosy from 161 countries in the world. Indonesia become the third highest leprosy prevalence in the world after India and Brazil (WHO, 2021). The Indonesian Ministry of Health (2021) reports that the prevalence rate of leprosy in 2020 was 0.49 cases / 10,000. The number of new cases of leprosy is 4.12 cases per 100,000 population, with 11,173 new cases. Of these new cases, 86% of them are multibacillary types (Kemenkes RI, 2021)

Leprosy has a variety of spectrum and clinical scenarios depending on the patient's immune response. The division of clinical spectrum variations is based on Ridley and Jopling's criteria, which consist of *Tuberculoid* (TT) to *Lepromatous* (LL) types (Wisnu et al., 2019). Meanwhile, for therapeutic purposes, two clinical scenarios determine the regimen and duration of therapy, from paucibacillary with several lesions from 1-5 sites to multibacillary with several lesions from more than five sites (Wisnu et al., 2019). The use of *Multi Drug Therapy* (MDT) consisting of a combination of Rifampicin, Clofazimine, and Dapsone for multibacillary cases and a combination of Dapsone and Rifampicin for paucibacillary cases, which is intended to break the chain of transmission, prevent drug resistance and prevent disability (MOH, 2018).

Leprosy reactions are acute episodes in the chronic course of leprosy that can occur before, during, or after treatment, resulting in disability (Arifputra & Arifputra, 2016; Saraswati et al., 2019). Two types of leprosy reactions are distinguished by the type of immunity and clinical manifestation: a reversal reaction or type I and an erythema nodusum leprosum (ENL) or type II reaction. These two reactions can occur separately or together at different times. Reversal reactions are more common in *borderline-type patients.* Although the main trigger is not known with certainty, it is thought to be associated with a type IV hypersensitivity reaction. This reaction is characterized by lesions that suddenly become more active, skin color is reddish, swollen, painful, and hot, and the nerves have neuritis and impaired nerve function. ENL reaction is an immunological complication in BB *(Mid Borderline)* and LL types. It is estimated that 50%-75% of leprosy patients with type LL and 25% of type BL will experience an ENL reaction (Froes et al., 2022). Symptoms that appear are fever, chills, lesions that become more erythematous, bilaterally distributed, and symmetrical nodules that can grow in all body parts except the fuzzy head, axilla, and perineum. In severe cases, it can attack other organs, such as the iris, testes, lymph nodes, and kidneys (MOH, 2018).

Based on WHO guidelines, steroid-class drugs, including Prednisone, are the primary therapy for leprosy reactions (Wisnu et al., 2019). Steroids work to inhibit the inflammatory process in the acute and chronic phases by decreasing neutrophil chemotactic and inhibiting prostaglandin synthesis (Hamzah, 2018). However, the study's results revealed a relapse after steroid therapy 23% (Lambert et al., 2016). Steroids also cause some quite severe side effects such as adrenal crisis, immunosuppression, diabetes, hypertension, mental disorders, erosive gastritis, cataracts, growth disorders in children, *intra-uterine growth retardation* when used in pregnant women (Walker et al., 2011). According to the results of a study in Ethiopia, it showed a mortality rate of 8% in ENL patients due to long-term steroid use (Walker et al., 2014; Nabarro et al., 2016). Exogenous corticosteroids can inhibit the generation of corticotropin and corticotropin-releasing hormones and can cause adrenal atrophy that can remain for months after corticosteroid therapy has been discontinued (Hamzah, 2018).

Cortisol is the glucocorticoid secreted by the adrenal cortex (Sherwood, 2001). Cortisol is released based on diurnal fluctuations in response to corticotropin secreted by the pituitary gland. During the inflammatory phase of leprosy, elevated levels of persistent pro-inflammatory cytokines promote adrenal cortex weariness and resistance to stimulation, resulting in decreased cortisol levels (Marpaung, 2020). According to research by Chaitanya et al. (2013), patients with a reversal reaction had considerably lower serum cortisol levels than those without a reaction. According to another study, leprosy patients with an ENL reaction had lower serum cortisol levels than patients without a reaction (Ayudianti et al., 2014). Another study by Hamzah (2018) explained that leprosy patients with ENL reactions had an average below-normal cortisol level of 6.61 ± 1.99 g/dl.

Clitoria ternatea is an increasingly popular herbal plant that provides many benefits for human health (Marpaung, 2020). This plant has been used in traditional medicine in ancient India and China to treat several diseases, such as dysentery, bronchial asthma, eczema, and pulmonary tuberculosis (Chakraborthy et al., 2018). *Clitoria ternatea* is also easily obtained and cultivated in Indonesia. A study reported that *Clitoria ternatea* contains active flavonoids, saponins, terpenoids, and tannins that are effective as an anti-inflammatory (Cahyaningsih et al., 2019; Al-Snafi, 2016). Researchers Thilavech et al. (2021) found that 2 g/day of *Clitoria ternatea* extract lowered levels of pro-inflammatory cytokines (IL-6 and Tumor Necrosis Factor) in obese male patients who had consumed a high-fat diet. In another study, Nair et al. (2015) reported that *Clitoria ternatea* is beneficial in nutraceutical protection against chronic inflammatory illnesses by inhibiting macrophage cells overproduction of pro-inflammatory mediators. Swathi et al. (2021) found that the ethanolic extract of *Clitoria ternatea* inhibited the release of histamine and prostaglandins, hence exerting an anti-inflammatory action. Another study reported that *Clitoria ternatea* extract has active flavonoid compounds that are effective as an anti-inflammatory to reduce the volume of edema caused by carrageenan (Yanti et al., 2020). Therefore, the researcher wanted to know the effect of *Clitoria ternatea* extract as adjuvant therapy on serum cortisol levels in leprosy reactions.

METHODS

This study is an experimental study with a *randomized single-blinded controlled trial* to compare the control and intervention group. Research began after the ethical clearance issued by the ethics committee University of Diponegoro Semarang. The population in this study were leprosy patients with reversal reactions who visited Donorojo Hospital Jepara, Central Java Province, Indonesia. The samples studied were patients who met the inclusion criteria and exclution criteria. The eligible samples are 22 patients.

Subjects who were enrolled to this study were devide into two groups, which are treatment group and controlled group. Subject in control group were given standard Prednisolone therapy. In the treatment group, given standard Prednisolone therapy and *Clitoria ternatea* extract 2 g / day for one month. The raw material used in this research is *Clitoria ternatea* which comes from plantations in Sleman, Special Region of Jogjakarta, Indonesia. Materials for extraction include food-grade ethanol 96%, Aquadest, Whatman filter paper, and 20 mesh sieves. Materials for testing cortisol levels include the blood of all research samples before and after treatment. Instruments used to test cortisol levels include 3cc disposable syring, pipette, microplate reader, centrifuge, and *Eppendorf* tube, EDTA Tubes and a Human ELISA kit.

RESULTS AND DISCUSSION

Characteristics of the Subjects

The characteristics of the subjects in this study were based on the characteristics of sex, age, and duration of leprosy. As for the characteristics of the subject, it is shown as follows:

Table 1. Characteristics of the Subjects

Characteristics	Control (n = 11)	Treatment (n = 11)	p
Gender, n (%)			
- Man	9 (81.8)	10 (90.9)	1,000*
- Woman	2 (18.2)	1 (9.1)	
Age, n (%)			0.861*
- 20-30 years old	3 (27.3)	5 (45.5)	
- 30-40 years old	4 (36.4)	3 (27.3)	
- 40-50 years	1 (9.1)	1 (9.1)	
- 50-60 years	3 (27.3)	2 (18.2)	
Length of illness (months), median (min-max)	15 (1 – 67)	8 (1 – 31)	0.510^

Note: * = fisher exact, ^ = Mann Whitne

Table 1 shows that the number of male subjects is more than female. The number of male subjects was 9 people (81.8%) in the control group and 10 people (90.9%) in the treatment group with a value (p=1,000). Characteristics of subjects based on age showed that the control group was more in the age range of 31-40 years, which is 4 subjects (36.4%), while in the treatment group, there were more in the 20-30 years old group as many as 5 subjects (45.5%). The average duration of disease for participants in the control group was 15 months, with a range of 1-67 months, whereas for subjects in the therapy group, it was 8 months, with a range of 1-31 months. There was no significant difference in the median lengths of illness (p=0.510). It shows that the patient characteristics in the control and treatment groups were similar.

Statistical Analysis of Average Cortisol Levels

Table 2. The Average Difference Cortisol Levels (ng/ml) Pre and Post Treatment Between Control and Treatment Group

Group	The Average Difference Cortisol Levels (ng/ml) (median, min-max)	*P*
Control	16 (1-58)	0.02[a]
Treatment	51 (14–152)	

Note: *Mann Whitney*, p < 0.05 is significant

From table 2 shows the average difference in pretest-posttest cortisol levels in the control group has a median of 16 ng/ml, while the average difference in pretest-posttest cortisol levels in the treatment group is 51 ng/ml. Where the difference statistically significant (P = 0.02)

Table 3. Results of Analysis of Cortisol Levels (ng/ml) Pretest-Posttest Control Group

	Pretest (median, min-max)	Posttest (median, min-max)	*P*
Control group	43 (13-189)	26 (16-139)	0.008*

Note: *Wilcoxon*, p < 0.05 is significant

The mean levels of cortisol serum after treatment were significantly different (p < 0.008), where the average before treatment 43 ng/ml is higher than after treatment 26 ng/ml.

Table 4. Results of Analysis of Cortisol Levels (ng/ml) Pretest-Posttest Treatment Group

	Pretest (median, min-max)	Posttest (median, min-max)	*P*
Treatment group	47 (14-168)	112 (25-186)	0.026*

Based on table 4.4, the average cortisol level after treatment is 112 ng/ml, that is higher than before treatment 47 ng/ml, where this difference statistically significant (p= 0.026).

DISCUSSION

This study managed 22 subjects who were diagnosed as reversal leprosy reaction. Characteristics of subjects based on gender, majority sex is male 19 subjects (86.37%), while female as many as 3 subjects (13.63%). These results are in line with previous studies which reported the incidence of leprosy in men (64.28%) more than in women (35.72%) (Ayudianti et al., 2014). This is also consistent with the findings of Rosdiana et al. (2021), who found a 75.4% incidence of type 1 leprosy reactions in men in Surabaya. Primasanti et al. (2016) also revealed that 70% of leprosy patients in their study were men.

It was found that the age of most subjects was 20-40 years, that is 15 subjects. This finding is consistent with prior research, which found that the majority of leprosy patients with reversal responses are between the ages of 16 and 35, accounting for 82.4% in the city of Denpasar, Bali (Gusti & Narmada, 2018). Epidemiological studies in RSUD dr. Soetomo in 2017-2019 reported that the frequency of leprosy patients who experienced type 1 reactions was in the productive age, that is 35-55 years (56.9%) (Rosdiana et al., 2021).

Age is an independent risk factor for type 1 reactions, which are more likely to occur in patients above the age of 20, including productive age, which is associated with increasing activity outside the home, putting them at greater risk of exposure to leprosy transmission sources. Transmission of leprosy can occur due to close and prolonged contact with people with leprosy (Wisnu et al., 2019). The risk of leprosy transmission decreases at an older age due to decreased mobility at an older age (Rosdiana et al., 2021).

Subject characteristics based on the length of illness has average 15 months in the control group and 8 months in the treatment group. These results in line with other studies, which state that the most extended duration of patients suffering from leprosy is within one year, which is 79.5% (Antonius et al., 2018). Research by Nazli et al. (2021) reported that the length of leprosy in the group >12 months in their study was 45.7%. Ayudianti et al. (2014) reported that the longest-suffering from leprosy patients in their study was at most > 6-12 months, which was 50%, while > 12 months was only about 28.57%.

The purpose of this study is to demonstrate the effect of *Clitoria ternatea* extracts on blood cortisol levels in individuals with type I leprosy reaction. The average cortisol levels in the treatment group were considerably higher than in the control group. Similarly, there was a substantial increase in post-test cortisol levels between the control and treatment groups. These findings show that 30 days of adjuvant therapy with *Clitoria ternatea* extract at a dose of 2 g/day increase cortisol levels in patients with type I leprosy reaction. These findings are corroborated by studies that show flavonoid chemicals greatly enhance cortisol levels in Addison's disease patients (Methlie et al., 2011). The anti-inflammatory effect of flavonoids is consistent with this study, which found that flavonoids increased serum cortisol levels in patients with type 1 leprosy reactions, as Khas et al. (2019) discovered that giving flavonoids-containing food for for weeks significantly affected cortisol levels in subjects (Tsang et al., 2019).

The mean cortisol levels of the control group who received steroid medication decreased significantly after one month. This is in line with the findings of Gupta et al. (2018), who discovered that leprosy patients with type 1 reactions have lower cortisol levels on average than leprosy patients without reactions. Citrashanty et al. (2014) observed a decrease in mean cortisol in leprosy patients, which was supported by study. Adrenal insufficiency caused by steroid medication or continuous exposure to pro-inflammatory cytokines could be the cause.

The primary glucocorticoid secreted by the human adrenal cortex is cortisol (Sherwood, 2001). Cortisol secretion is regulated by the brain and pituitary gland. When pro-inflammatory cytokines cause an increase in ACTH secretion, ACTH stimulates the release of adrenal glucocorticoids as feedback (Nazli et al., 2021; Gupta et al., 2010). Chronic activation of these cytokines causes adrenal cortex fatigue, which cause lowers blood cortisol. Decrease average cortisol level correlate with the duration and length of time leprosy reaction (Ayudianti et al., 2014). Furthermore, corticosteroid medication can influence the drop in cortisol level serum caused by adrenal insufficiency. Long-term corticosteroid use or chronic pro-inflammatory cytokine exposure can result in secondary adrenal insufficiency (Nazli et al., 2021).

Pro-inflammatory cytokines, particularly TNF-a and IL-6, cause cortisol levels to rise directly by stimulating ACTH from the HPA axis to the adrenal cortex. However, in leprosy patients, this state cannot arise linearly because the degree of exposure to pro-inflammatory cytokines from leprosy induces adrenal insufficiency, which effects reduced cortisol production (Ayudianti et al., 2014). Because of a severe and prolonged inflammatory state, cytokine production is quite abundant. A decrease in glucocorticoid binding to its receptors will occur, causing glucocorticoids to become refractory, particularly in tissue regions that release copious cytokines, resulting in a fall in serum cortisol levels (Ayudianti et al., 2014; Citrashanty et al., 2014).

The anti-inflammatory effect of *Clitoria ternatea* extract was shown by the significant difference in the mean cortisol levels between the treatment groups. Based on phytochemical tests, *Clitoria ternatea* extract contains active phenolic compounds and flavonoids that function as an anti-inflammatory (Marpaung, 2020; Yanti et al., 2020). The active compounds in *Clitoria ternatea* have an anti-inflammatory effect by inhibiting the cyclooxygenation enzyme mechanism so that arachidonic acid metabolism can be inhibited, thereby preventing the inflammatory process. Prohibiting the metabolism of arachidonic acid and the capture of free radicals that play a role, prostaglandin formation will be inhibited so that the inflammatory process in the tissue is reduced (Djunarko et al., 2016). This study is in line with research that reported that the content of *Clitoria ternatea* extracts contained fenolic total of 53 ± 0.34 mg of gallic acid equivalents/g extract and 11.2 ± 0.33 mg equivalents/g extract of total flavonoids. *Clitoria ternatea* extract dose of 2 g / day for 30 days was proven effective in increasing cortisol levels to be used as adjuvant therapy in patients with leprosy reactions.

CONCLUSION

This study provides that the administration of *Clitoria ternatea* 2 g/ day for one month as adjuvant therapy can increase levels of cortisol serum in leprosy reaction.

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