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Original Article

Comparison between oral pentoxifylline + corticosteroid and oral corticosteroid alone for severe erythema nodosum leprosum

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Abstract

Background: Severe *erythema nodosum leprosum* (ENL) is common but difficult to treat. Long term use of systemic corticosteroid causes side effects. This study compares the use of a combination of pentoxifylline + oral corticosteroids with a single oral corticosteroid in leprosy patients with severe ENL reactions. Parameters measured include skin RSA score, systemic RSA, total corticosteroid dose, resolution time of skin lesions, improvement of pain VAS and treatment side effects.
Methods: 29 subjects with severe ENL reactions are allocated randomly into two groups which receive oral pentoxifylline + methylprednisolone, and oral placebo + methylprednisolone for 12 weeks. The starting dose of pentoxifylline are 400 mg thrice daily for 4 weeks, tapered to 400 mg daily every 4 weeks. Methylprednisolone is based on WHO guideline.
Results: In the end, the median of cutaneous RSA score in pentoxifylline vs placebo group is 4 (0-5) vs 3 (0-5). The median of systemic RSA score in pentoxifylline vs placebo group is 0 (0-6) vs 0 (0-5). The median of total corticosteroid doses in pentoxifylline vs placebo group is 156 (120-200) mg vs 136 (96-200) mg. The median of resolution time in pentoxifylline vs placebo group is 6 (0-12) weeks vs 6 (0-12) weeks. The median of change of pain VAS score in pentoxifylline vs placebo group is 5 (0-6) vs 3 (-3-6). No statistically significant difference (p>0,05) are found in all parameters, including side effects.
Conclusion: Combination of oral pentoxifylline + corticosteroid is not proven to be more effective. Both are safe.

Keywords*: combination, corticosteroid, erythema nodosum leprosum, pentoxifylline*

Background

Leprosy is a worldwide problem. The fear of the leprosy leads to the stigma and discrimination.[1] An individual's susceptibility to contracting leprosy is highly variable and multifactorial. These include: close contact with a recently diagnosed patient, age between 5 to 15 years and >30 years at the time of exposure, immunosuppression, immunodeficiency, and genetic predisposition.[2] World Health Organization (WHO) reported that leprosy prevalence in 160 countries were 177,175 cases by the end of 2019.[3] Based on Indonesia's Health Profile in 2014 there were 17,025 cases, making Indonesia one of the countries with a high number of leprosy cases.[4]
Erythema nodosum leprosum (ENL) is an immune complex reaction in leprosy characterized by painful erythematous nodules that can be accompanied by fever, malaise, and other organ systems involvement. Erythema nodosum leprosum is a borderline lepromatous (BL) or lepromatous leprosy (LL) type of leprosy complication, which is serious and difficult to treat. It can occur before, during, or after multidrug therapy (MDT) treatment, but it was more common in the first year of treatment.[5] ENL may lead to the development of pustules that along with skin lesions can ulcerate and become necrotic.[6,7] Lesions often occur on the face, trunk, and upper and lower extremities.[8,9] The incidence of ENL is increasing with the increasing number of multibacillary cases.[10]

Treatment of ENL has been controversial for many years, because there was no effective and

universal regimen of therapy. Based on the ENL management algorithm set by the Indian Association of Leprologists (IAL), the main therapeutic option is thalidomide, but this drug is banned in many countries because of its teratogenicity.[11] Systemic corticosteroids are the drug of choice for ENL who developed neuritis, but their long-term use will cause side effects such as Cushing's syndrome (moon face, buffalo hump); disturbances of electrolyte, blood sugar, and lipids level; osteoporosis; hypertension; peptic ulcer; increased intraocular pressure; glaucoma; cataracts; increased risk of infection; and wound healing disorders.[11] The management of ENL aims to control acute inflammation and neuritis and prevent the onset of new episodes.[12]

Pentoxifylline is a xanthine derivate which has the potential for therapeutic effects on ENL, by suppressing the transcription of the TNF genes, TNF-α messenger RNA expression, and TNF protein secretion in macrophages and monocytes.[13,14] Pentoxifylline is well tolerated and effective in reducing local and systemic ENL reaction symptoms. Side effects include gastrointestinal symptoms such as dyspepsia, nausea, vomiting, flatus, and central nervous system symptoms such as dizziness, headache, and tremor.[15]

Data reporting the effectiveness of pentoxifylline for severe degree ENL are still limited. Sampaio et al. found that the administration of pentoxifylline alone results in a decrease of the TNF-alpha levels involved in the ENL reaction.[16] Roy et al. found that the combination of pentoxifylline and steroids decreased the severity of ENL faster than the combination of clofazimine and steroids which acted slower.[17] Data reporting the use of pentoxifylline for severe degree ENL patients in Indonesia are still not available until recently. The lack of literature associated with the use of pentoxifylline for ENL encourages the conduct of this study, with the hope that the results can be a reference and strengthen the reasons for using pentoxifylline in ENL management, especially in Indonesia which has a very high number of leprosy patients.

Methods

This study is a double blind randomized controlled trial of a leprosy patient population with severe degree erythema nodosum leprosum. History and physical examination were conducted at the Dermatovenerology Outpatient clinic of the RSUPN dr. Cipto Mangunkusumo (RSCM) and Sitanala Hospital, Infection Dermatology Division, as well as inpatient ward at RSCM and Sitanala Hospital. Additional examinations (scraping skin tissue and laboratories) were carried out at the RSCM and Sitanala Hospital laboratories. The study was conducted from November 2017 to June 2018. Each study subject would receive randomly allocated therapy between a combination of corticosteroids and pentoxifylline, or a combination of corticosteroids with placebo. The Ethical Approval number is 966/UN2.F1/ETIK/2017.

Population and study subject

Subjects selection was conducted by consecutive sampling. The target population is leprosy patients with severe degree ENL. Achievable population is leprosy patients with severe degree ENL who came to the Dermatovenerology Outpatient clinic in the RSCM and Sitanala Hospital Division of Infection Dermatology, as well as inpatients of RSCM and Sitanala Hospital. Severe degrees are characterized by one of the following clinical signs and symptoms: temperature greater than 38.8 °C, myalgia, and other constitutional symptoms, extensive ENL with/without necrotic or pustular lesions, neuritis with/without loss of nerve function, iridocyclitis with/without loss of visual acuity, orchitis, arthritis or marked lymphadenitis.[18,19] Research subjects are achievable populations that meet the criteria of inclusion and exclusion, and willing to sign an informed consent form. Inclusion criteria were patients aged from 18 to 60 years old, diagnosed with leprosy, diagnosed with severe degree ENL, and experiencing a severe degree of ENL reactions in both new and old cases (currently in varied doses of oral corticosteroids administration). New case is the first episode of severe ENL reaction and hasn't used oral corticosteroids. Old cases are the second or more episodes of severe ENL reaction and have used oral corticosteroids. Exclusion criteria were patients with a history of hypersensitivity to the test drug; history of heart, liver, and kidney diseases; bleeding disorders; mental disorders; currently having other diseases that require high dose or long-term corticosteroid treatment or in the treatment of blood diluting drugs; currently get other therapies for ENL treatment (thalidomide and anti-inflammatory clofazimine doses), and had baseline laboratory parameters (SGOT, SGPT, urea, creatinine) with a value of more than 2 times the normal value limit. Determination of the sample size was calculated using an unpaired numerical analytical formula with a limit of 28 subjects as a minimum sample size. During the sampling period, 29 people collected as research subjects.

Basic data recording
Data recorded for the study conducted through history, physical examination, and additional examination. History includes identity, socio demographic data, complaint of red painful lump on the skin, history of leprosy, type of leprosy, history of leprosy treatment and lump therapy, risk factors for ENL reactions, and history of skin tissue scraping. Physical examination includes a clinical assessment of the ENL severity score and a pain VAS score assessment. The location of the lesion will be recorded in dermatologic status. The dose of methylprednisolone and the initial drug dosage given for 2 weeks data were recorded. Additional examination includes basic laboratory tests (peripheral blood, liver function and kidney function), and skin tissue scraping examinations to see acid-fast-bacilli (AFB) of *M. leprae*.

Evaluation of the severity of the ENL reaction
The assessment of ENL severity score was carried out with the reaction severity assessment (RSA) score according to Van Brakel et al.[19] The assessment was determined based on 7 aspects: the evaluation of the number of raised and inflamed lesions, the degree of inflammation of skin lesions or nodules, peripheral edema due to reaction, fever due to reaction, involvement of other organs such as eyes and testes, nerve pain (paresthesia), and nerve tenderness on gentle palpation. Scores have a range of 0-21. The location of skin lesions will be recorded in dermatologic status. This RSA can be used in both type I and type II leprosy reactions, but this scoring system is still not validated for ENL reactions. For the purposes of this study, we adjusted. In the original manuscript, thin plaque is included in the score category 2, but because it is not suitable for ENL lesions, we put thin plaques on a score of 1. This is to anticipate the improvement of ENL nodes that can be palpable as thin plaques.

Method of therapy and evaluation
Each subject will receive a choice of therapy between a combination of methylprednisolone tablets and pentoxifylline caplets, or a combination of methylprednisolone tablets with placebo caplets. The test drug allocation given based on the randomization table that the researcher did not know. The drug given in accordance with the subject number, by the researcher himself. Administration of methylprednisolone therapy with a gradual decrease in dosage according to WHO guidelines (equivalent to prednisone 40 mg/day for 2 weeks, tapered to 30 mg/day, 20 mg/day, 15 mg/day, 10 mg/day and 5 mg/day consecutively every 2 weeks). However, if there is a total increase in the severity score of ENL ≥2, then the dose of methylprednisolone will be increased to 2 levels above it according to WHO guidelines and Schreuder and Naaf recommendations (for example from a dose of 20 mg/day to a dose of 40 mg/day, but not exceeding the dose 1 mg/kg body weight/day).[11] The administration of pentoxifylline 400 mg dose and placebo begins with a dose of 3 caplets per day in the first month, 2 caplets per day in the second month, and 1 caplet per day in the third month, without concerning the increase or decrease in RSA scores. The duration of therapy is three months.

Evaluation of therapeutic outcomes includes evaluation of RSA scores (skin and systemic), total exposure to methylprednisolone dose, pain VAS, time to clinical resolution of skin lesions, and both subjective or objective side effects performed at the initial visit (day-0), and evaluated every 2 weeks for 3 months (1st, 2nd, 3rd, 4th, 5th, re-visit, and end of study visits).

Statistical processing and analysis
All data is recorded in the study status. The collected data will be analyzed and processed with appropriate statistical tests. After recording the results of the study, the blinding code were opened to be analyzed statistically. The entire data analysis process will be carried out by a statistical adviser from the FKUI Community Medicine Department. All subjects who can complete a minimum of 3 visits (1 initial visit and 2 follow up visits) will be included in the analysis. Then an intention to treat analysis were performed. Analysis of the results of the study data was carried out using IBM Statistical Product and Service Product (SPSS) Statistics version 24.0.

Descriptive analysis in the form of basic data and characteristics of subjects will be performed and presented in the form of tables and narratives. Numerical data will be analyzed for normality by the Shappiro Wilks test, and for normal numerical data are presented in the form of mean and standard deviation, meanwhile for the abnormal data are presented in the median and interquartile ranges form.

Comparison of changes in skin RSA scores, systemic RSA, changes in pain VAS, total dose of methylprednisolone administered, as well as the total resolution of skin lesions between the two study groups were analyzed using unpaired Student t test or Mann Whitney rank test if the

distribution was not normal. The significance limit used in this study is alpha of 5%.

Results

Characteristics of study subjects

The characteristics of subjects by groups are presented in Table 1. All characteristics were tested for homogeneity and normality and total p-values were obtained >0.05, so that it can be concluded that subjects in this study and control group was not significantly different.

Comparison of skin RSA scores in both groups

Treatment evaluations were carried out by looking at ENL clinical and systemic improvements assessed from changes in skin RSA scores and systemic RSA every 2 weeks follow-up for 3 months. Total resolution of skin lesions (skin RSA) at the end of the study was obtained in each of the 4 study subjects in the study and control groups (30.7% versus 26.7%). There were no significant differences in the two groups (p = 0.521). Changes in skin RSA scores for each visit in both groups are presented in Table 2.

Comparison of systemic RSA scores in both groups

Total resolution of systemic symptoms (systemic RSA score) at the end of follow-up was obtained in 11 (84.6%) SP in the study group and 9 (60%) subjects in the control group (Table 3). There were no statistically significant differences in the two groups (p = 0.248).

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

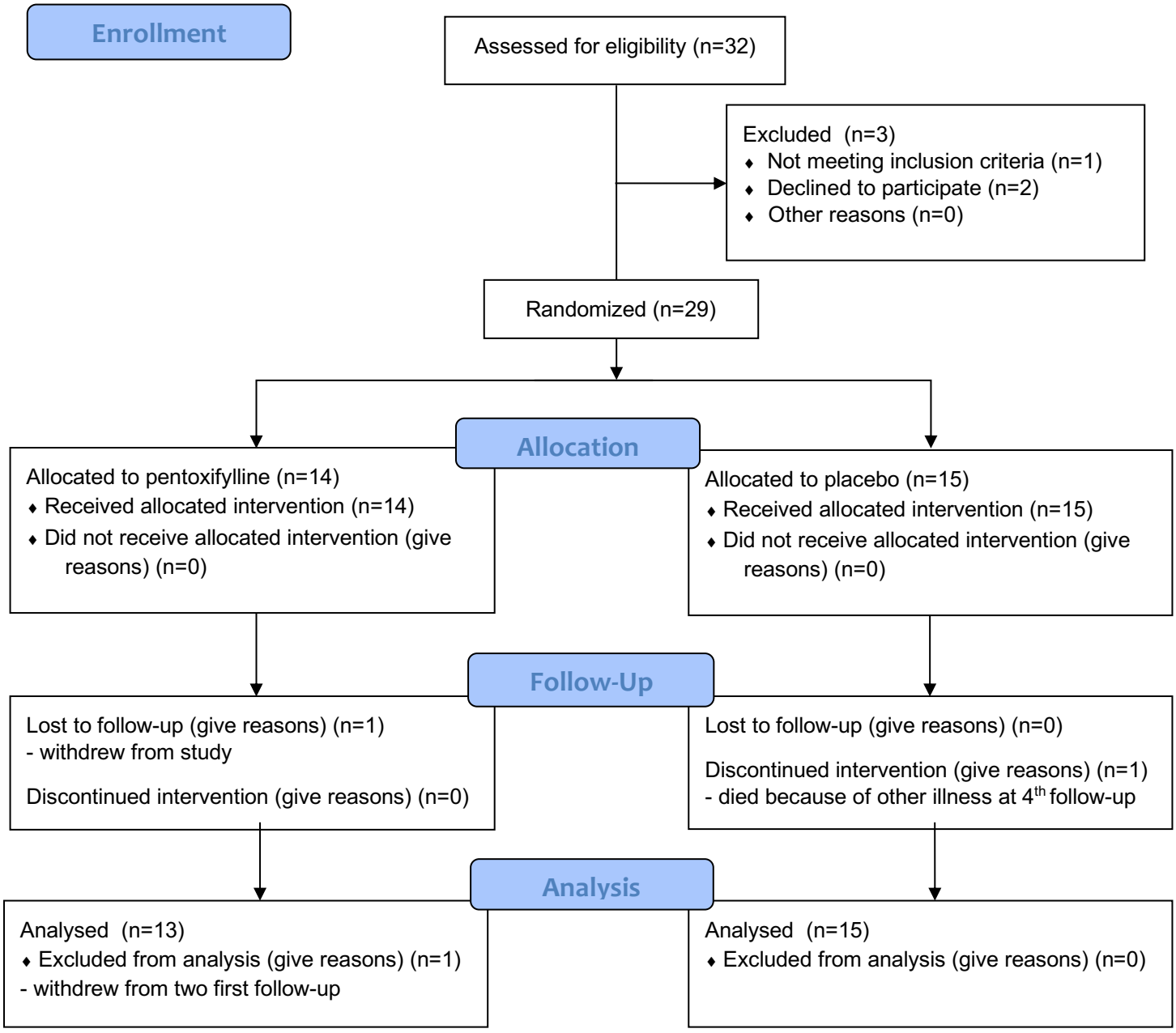

Table 1. Study Subjects Characteristics (N= 28)

Parameter	Pentoxifylline + methylprednisolone (S group) n= 13	Placebo + methylprednisolone (K group) n= 15	P value (between groups)
Age (years)	32.7 ± 8.11	39.8 ±9.74	0.056
Sex (male: female)	9 : 4	13 : 2	0.262
Education			
Not going to school	0	1	0.758
Elementary school	5	4	
Junior high school	3	5	
Senior high school	2	3	
Bachelor	3	2	
Working status			
No	2	6	0.15
Yes	11	9	
Leprosy types			
BL	8	13	0.126
LL	5	2	
Leprosy period (in weeks)	174.76 ± 98.56	158.64 ± 121.96	0.363
Leprosy treatment status			
In MDT therapy	2	5	0.274
Finish MDT therapy	11	10	
ENL status			
Newly diagnosed	0	3	0.088
Chronic/ old cases	13	12	
ENL period (in weeks)	74 ± 54.42	86.9 ± 83.16	0.982
ENL risk factors			
Lepromatous leprosy	4	2	0.262
IB >4+	1	2	0.63
Age > 40 years old	8	7	0.431
Teeth and mouth infection	6	7	0.978
Significant physical and mental stress	1	4	0.191
Anti-leprosy drug (except clofazimin)	2	6	0.15
Baseline skin RSA score	4.92 ± 0.494	4.87 ± 0.516	0.761
Baseline systemic RSA score	1.46 ± 2.436	2.33 ± 2.92	0.402

P value determined by Mann Whitney test for age, leprosy period, ENL period, baseline skin and systemic RSA score. Chi square test was used for sex, education, working status, leprosy types, leprosy treatment status, ENL status, and ENL risk factors.

Table 2. Skin Reaction Severity Assessment (RSA) Scores Changes in Both Groups (N= 28)

Visit	Pentoxifylline + methylprednisolone (S group) n= 13	Placebo + methylprednisolone (K group) n= 15	P value (between groups)
Baseline			
Mean (standard deviation)	4.92 ± 0.494	4.87 ± 0.516	0.761
Median (interquartile range)	5 (4-6)	5 (4-6)	
1st re-visit			
Mean (standard deviation)	0.69 ±1.377	1.33 ±1.718	0.302
Median (interquartile range)	0 (0-4)	0 (0-4)	
2nd re-visit			
Mean (standard deviation)	1.23 ± 1.739	0.8 ± 1.424	0.503
Median (interquartile range)	0 (0-5)	0 (0-4)	
3rd re-visit			
Mean (standard deviation)	2.23 ± 2.242	1.6 ± 2.098	0.435
Median (interquartile range)	3 (0-5)	0 (0-5)	
4th re-visit			
Mean (standard deviation)	2.31 ± 2.323	1.6 ± 2.098	0.377
Median (interquartile range)	3 (0-5)	0 (0-5)	
5th re-visit			
Mean (standard deviation)	2.85 ± 1.676	1.73 ± 1.981	0.135
Median (interquartile range)	4 (0-4)	0 (0-5)	
End of visits			
Mean (standard deviation)	3 ± 2.198	2.8 ± 1.859	0.521
Median (interquartile range)	4 (0-5)	3 (0-5)	
P value	<0.001	<0.001	

P value for comparison between groups was determined by Mann Whitney test (free sample). Significancy levels on P <0.05. P value <0.001 for comparison within group.

Table 3. Systemic Reaction Severity Assessment (RSA) Scores Changes in Both Groups

Visit	Pentoxifylline + methylprednisolone (S group) n= 13	Placebo + methylprednisolone (K group) n= 15	P value (between groups)
Baseline			
Mean (standard deviation)	1.46 ± 2.436	2.33 ± 2.92	0.402
Median (interquartile range)	0 (0-7)	0 (0-9)	
1st re-visit			
Mean (standard deviation)	0.62 ± 1.557	0.93 ± 1.981	0.704
Median (interquartile range)	0 (0-5)	0 (0-6)	
2nd re-visit			
Mean (standard deviation)	0.08 ± 0.277	0.6 ± 1.404	0.307
Median (interquartile range)	0 (0-1)	0 (0-5)	
3rd re-visit			
Mean (standard deviation)	0.46 ± 1.664	0.87 ± 1.356	0.1480
Median (interquartile range)	0 (0-6)	0 (0-4)	
4th re-visit			
Mean (standard deviation)	1 ±1.915	0.53 ± 1.187	0.676
Median (interquartile range)	0 (0-5)	0 (0-4)	
5th re-visit			
Mean (standard deviation)	1 ± 1.915	0.27 ± 0.704	0.388
Median (interquartile range)	0 (0-5)	0 (0-2)	
End of visits			
Mean (standard deviation)	0.69 ± 1.797	1.07 ± 1.624	0.248
Median (interquartile range)	0 (0-6)	0 (0-5)	
P value	0.332	0.094	

P value for comparison between groups was determined by Mann Whitney test (free sample). Significancy levels on P <0.05. P value <0.001 for comparison within group.

Comparison of the mean total dose of corticosteroids in both groups

In this study there were no statistically significant differences in the mean total dose of corticosteroids in both groups (Table 4).

Table 4. Comparison of the Mean Total Dose of Corticosteroids (in Milligram) in Both Treatment Groups (N= 28)

Parameter	Pentoxifylline + methylprednisolone (S group) n= 13	Placebo + methylprednisolone (K group) n= 15	P value (between groups)
Total dose of corticosteroids (milligram)			
Mean (standard deviation)	160.61 ± 25.91	139.73 ± 36.64	0.098
Median (interquartile range)	156 (120-200)	136 (96-200)	

P value for total dose of corticosteroids was determined by student T test.

Comparison of the time of skin lesions resolution in both groups

In this study there were no statistically significant differences in the mean number of times in the skin lesions resolution between the two groups (Table 5).

Table 5. Comparison of the Time of Skin Lesions Resolution (in Weeks) in Both Treatment Groups (N= 28)

Parameter	Pentoxifylline + methylprednisolone (S group) n= 13	Placebo + methylprednisolone (K group) n= 15	P value (between groups)
Total time of skin lesions resolution (weeks)			
Mean (standard deviation)	6 ± 3.559	6.67 ± 4.047	0.421
Median (interquartile range)	6 (0-12)	6 (0-12)	

P value for time of skin lesions resolution was determined by Mann Whitney test.

Comparison of VAS pain difference in both groups

In this study, the mean difference in VAS pain in the study group was higher than in the control group, but did not differ significant statistically (Table 6).

Table 6. Comparison of VAS Pain Difference in Both Treatment Groups (N= 28)

Parameter	Pentoxifylline + methylprednisolone (S group) n= 13	Placebo + methylprednisolone (K group) n= 15	P value (between groups)
Total time of skin lesions resolution (weeks)			
Mean (standard deviation)	4.07 ± 2.06	2.73 ± 2.65	0.167
Median (interquartile range)	5 (0-6)	3 (-3-6)	

P value for VAS pain difference was determined by Mann Whitney test.

Comparison of treatment side effects in both groups

Comparison of treatment side effects in both groups are presented in Table 7.

Table 7. Comparison of Treatment Side Effects in Both Treatment Groups (N= 28)

Parameter	Pentoxifylline + methylprednisolone (S group) n= 13		Placebo + methylprednisolone (K group) n= 15		P value (between groups)
	N	%	N	%	
Subjective					
Dizziness	3	23.1%	4	26.7%	0.827
Headache	2	15.4%	2	13.3%	0.877
Nausea and vomiting	1	7.7%	3	20%	0.353
Stomach pain	2	15.4%	4	26.7%	0.468
Chest pain	0	0%	0	0%	
Palpitation	1	7.7%	1	6.7%	0.916
Objectives					
Erythema	0	0%	0	0%	
Urticarial	0	0%	0	0%	

P value was determined by Chi square test.

Discussion

The results of this study did not show statistically significant differences related to skin RSA scores at each visit or at the end of the visit between the two groups. Observation of changes in skin RSA scores in this study (Table 2) is similar to that of Roy et al.[17] The decrease in skin RSA in the pentoxifylline group lasted only 4 weeks, meanwhile in Roy et al. up to 6 weeks. The RSA score in this study increased when the dose of pentoxifylline was reduced to 2 x 400 mg/day. Roy's study used a fixed dose of pentoxifylline for 3 months, which was 3 x 400 mg/day.[17] This study found that administration of pentoxifylline with a slowly lowered dose at 4-week intervals did not effectively maintain ENL lesion resolution. Pentoxifylline was suggested has the effect of inhibiting TNF-alpha production when given at high doses (1200 mg/day) but when it is reduced, it is unable to inhibit TNF-alpha production totally. Dawlah et al. concluded that pentoxifylline has a minimal effect on the treatment of ENL reactions. TNF alpha induces eicosanoid synthesis which is considered to be the final mediator in cell damage. Pentoxifylline is not seen to affect the inflammatory pathway through eicosanoids because it is an imperfect TNF-alpha inhibitor. In addition, Dawlah et al. found that pentoxifylline was a bad nitric oxide inhibitor. Nitric oxide, eicosanoid, and incomplete TNF-alpha inhibition were hypothesized responsible for the worsening of the ENL reaction.[20] This theory is supported by the results of the study conducted by De Carsalade et al. using pentoxifylline 2400 mg/day (2 patients) and 1200 mg/day (13 patients) in ENL until full remission. Sudden withdrawal of pentoxifylline causes relapse in some patients, but not when the dose of pentoxifylline was reduced slowly (4 months).[15] Other study by Sampaio et al. in 15 ENL patients also found that administration of pentoxifylline at 1200 mg/day reduced TNF-alpha levels in the 3rd to 7th day of therapy significantly, and decreased ENL lesions after 7-14 days of therapy in 13 subjects.[16] In this study, TNF-alpha levels were not measured.

Although study by Roy et al.[17] used doses of pentoxifylline that were not reduced, a consistent increase in RSA scores was found, although not as sharp as in this study. Both in this study and Roy et al.[17], the increase did not return the RSA score to the baseline level. Both of the above observation shows that pentoxifylline had limited potential, in controlling ENL, it may be limited through the inhibition of TNF-alpha. Effective therapy over the long term may require a dose of more than 3x400 mg/day, and with other drugs that are able to control complex inflammatory pathways in the pathogenesis of ENL. In Roy et al.[8] study, the increased dose of corticosteroids was able to reduce skin RSA scores significantly. In this study, an increase in corticosteroid doses did not show an improvement in the mean skin RSA score; indicating that a dose of pentoxifylline less than 1,200 mg/day is not useful in controlling ENL.

This study also found no statistically significant differences in systemic RSA scores in the two groups (Table 3). These results are similar to those of Roy et al. that shows a decrease in the mean of systemic RSA scores on the 1st and 2nd repeat visits, an increase in the mean score on the 3rd visit, a decrease in the average score on the 4th and 5th re-visits, and at the end of the visit there was an increase in the mean score.[17] Pentoxifylline with a dose of less than 1,200 mg/day was thought unable to suppress TNF-alpha completely so that systemic symptoms begin to recur after 1 month of treatment. Another hypothesis was that cytokines that play a role in tissue damage during ENL reactions were not dominantly mediated by TNF-alpha only, but also IL-4, IL-5, and interferon gamma.[19] It was also suggested that there were other inflammatory pathways in ENL (eicosanoid and nitric oxide) reactions that are not/slightly affected by pentoxifylline.[20]

In relation to the average total dose of corticosteroids, in this study there were no statistically significant differences in the two groups. Both groups showed a decrease in dose until the 3rd visit in Table 4. Afterwards, the dose of methylprednisolone increased again in both groups, tends to decrease until the 5th visit, then increasing again at the end of the study. In study from Roy et al., a decrease in corticosteroid doses in the pentoxifylline group remains persisted until the 3rd visit (2 weeks longer than in this study).[17] This was predicted as a result of the administration of pentoxifylline at a fixed dose (3 x 400 mg/day for 3 months) compared to this study, so that the dose of methylprednisolone needed in the study was lower. This also further supported by hypothesis there is a presence of inflammatory pathways other than TNF-alpha in ENL (eicosanoid and nitric oxide) reactions which are not/slightly affected by pentoxifylline.

This study found no statistically significant differences in the mean number of resolution times of skin lesions between the two groups ($p = 0.421$). These results (Table 5) are similar to those of Roy et al. which obtained resolution time

of skin lesions in the pentoxifylline group was not significantly different from the clofazimine group (p = 0.174). Study by Sales et al. in 17 patients who were administered 1,200 mg/day of pentoxifylline and evaluated weekly for 1 month, who received only 75% subjects experienced clinical improvement (both partial and total remission) at 2nd week, and reduced to 62% at the end of 4th week.[21] However, study by Sales et al. did not evaluate the results of the administration of pentoxifylline therapy which was reduced tapered off up to 3 months.

Related to the difference of pain VAS, in this study there were no statistically significant differences in the two groups (Table 6). Until recently, there have been no studies that have assessed the effectiveness of pentoxifylline on the improvement of skin lesions in ENL patients. Roy et al. did not examine the effectiveness of pentoxifylline on pain relief for ENL patients.[17] Beside that, the literature on the mechanism of pentoxifylline in reducing pain in skin lesions of ENL patients were not available.
In this study, side effects were assessed at each follow-up, i.e. 2nd, 4th, 6th, 8th, 10th, 12th weeks. Subjective side effects were obtained through history and objective through physical examination by the examiner. Commonly reported side effects from the use of pentoxifylline were gastrointestinal and central nervous system symptoms. Gastrointestinal symptoms include dyspepsia, nausea, and vomiting (<3%). Meanwhile central nervous system symptoms include dizziness (1.9%), and headache (1.2%).[13,15] No severe side effects were found in both treatment groups, that causes subjects need to be drop out. However, there was one severe unexpected event in the control group, which was mortality on the 4th re-visit (8th week) because of stroke. There were no statistically significant differences in side effects between the two groups (Table 7).

Conclusion

This study suggests that combination of oral pentoxifylline and oral corticosteroid is not more effective than a single oral corticosteroid in treating the clinical symptoms of skin in leprosy patients with severe ENL. The safety of the combination of pentoxifylline and oral corticosteroids is the same as a single oral corticosteroid. The combination of pentoxifylline and oral corticosteroids has not been proven to be more effective in treating systemic symptoms, reducing the need for total corticosteroid doses, extending the total period of skin resolution, and reducing pain VAS
in leprosy patients with severe ENL.

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