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Original Article

The effectivity of ultrasound-guided platelet-rich plasma perineural injection in improving leprosy sensory peripheral neuropathy

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Abstract

Background: Sensory nerve damage is the earliest leprosy sign which can lead to disability. Previous studies showed that autologous platelet-rich plasma (PRP) perineural blind injection can stimulate leprosy sensory nerve regeneration. Our study provided a safer and more accurate PRP agent delivery method through ultrasound-guided injection and was the first to compare PRP versus standard neuropathy treatment, the neurotropic vitamin. This study aimed to determine the effectiveness of combination therapy of ultrasound-guided PRP perineural injection and oral vitamin B complex compared to single oral vitamin B complex in sensory peripheral neuropathy of posterior tibial nerve in leprosy patients.
Methods: All 20 subjects were divided into the treatment group, which received combination therapy, and the control group, which received single therapy. Semmes-Weinstein monofilament (SWM) clinical score and Nerve Conduction Study (NCS) latency and amplitude scores were measured at baseline and 14 days.
Results: Both groups were effective in improving SWM and NCS amplitude but not in NCS latency scores. Meanwhile, between the two groups, there was no significant difference in effectiveness in all measurements and in the number of subjects experiencing side effects.
Conclusion: Both therapies are effective in improving leprosy sensory peripheral neuropathy of the posterior tibial nerve, possibly due to axonal regeneration. Although there was no significant difference in effectiveness between the two groups, ultrasound-guided perineural PRP injection did not negatively affect sensory peripheral neuropathy in leprosy patients.

Keywords: *leprosy, perineural injection, peripheral neuropathy, platelet-rich plasma (PRP), ultrasound-guided*

Background

Distal peripheral sensory nerve damage is the earliest sign and most commonly affected in leprosy, especially involving the posterior tibial, ulnar, median, lateral popliteal, and facial nerves. Lower extremities were more frequently and more severely affected than upper extremities.[1] Loss of sensation causes unnoticed injury and secondary infection, which results in tissue damage, deformity, and disability.[2]

Initially, the interaction between *Mycobacterium leprae* and the nerves occurs slowly. The inflammatory process occurs once the immune system recognizes the bacteria. At first, this process affects small nerve fibers, causing impaired autonomic, thermal, and pain sensations. Later, demyelination and axonal damage occur, progressively damaging large nerve fibers, leading to motor damage. At the end of the process, severe nerve damage occurs due to endoneurial fibrosis and irreversible neuropathy.[3] Unfortunately, no

single therapy is effective in restoring impaired nerve function in leprosy patients, especially sensory function.

The administration of neurotropic vitamins is the main recommendation for treating peripheral neuropathy. However, there are limited to no studies on the use of vitamin B in leprosy neuropathy treatment. Neurotropic vitamins or vitamin B complex (B1, B6, and B12) are useful for normalizing nerve function by improving nerve metabolism disorders and stimulating nerve regeneration.[4,5] In contrast, other studies mentioned that only a small proportion of oral B vitamins are absorbed into nerves.[6] This has led to controversy regarding the mechanism of oral B vitamins in treating peripheral neuropathy.

Autologous platelet-rich plasma (PRP) therapy has been developed based on endogenous growth factors, proteins, and biomaterials to stimulate wound healing and tissue regeneration, including neuropathy management.[7] According to a previous study by Anjayani *et al.* (2014), perineural injection of PRP can stimulate sensory nerve regeneration in leprosy patients.[8] However, blind or direct perineural injection has a higher risk of vascular and nerve injury, which can further damage nerve function, compared to injection guided with ultrasound, as demonstrated by Lee *et al.* (2014).[6,9]

This study used ultrasound-guided perineural injection, which provides the advantage of a more accurate and safer application of therapeutic agents around the defective nerve with minimal complications. To date, there are no studies on the effectiveness of PRP injections compared to standard neuropathy therapies (oral B vitamins) in the management of leprosy neuropathy. This study's objective is to compare the effectiveness of the combination therapy of ultrasound-guided perineural PRP injection and oral vitamin B complex compared with single oral vitamin B complex in the management of leprosy sensory neuropathy, especially of the posterior tibial nerve, which is more frequently and severely affected in leprosy patients, as mentioned previously.

Therefore, we hypothesize an improvement in leprosy sensory neuropathy after administration of the combination therapy of ultrasound-guided autologous PRP perineural injection and oral vitamin B complex compared to single oral vitamin B complex therapy (as indicated by improvement SWM clinical score, NCS amplitude, and latency response).

Methods

The sample size was determined based on Federer's formula for experimental research as follows:[10]

$$\{(np-1)-(p-1)\} \geq 15$$
$$\{(n2-1)-(2-1) \geq 15$$
$$n \geq 8.5 \approx 9$$

where: n = sample size
p = number of treatments / interventions

From Federer's formula, the calculated minimum sample size was nine per group, increased by 10% to compensate for any drop-outs, so the minimum sample size was 10 per group. The total number of subjects who participated until the end of the study was 20 subjects. This study was conducted at the Dermatology and Venereology Outpatient Clinic in Dr. Saiful Anwar Regional General Hospital Malang, East Java, Indonesia, from February to November 2019 after obtaining ethical approval. The inclusion criteria were: (1) patients diagnosed with leprosy peripheral neuropathy suffering from hypoesthesia/ anesthesia of the right/ left posterior tibial nerve; (2) > 20 years old; (3) hemoglobin ≥10 mg/dL; (4) platelet of 100,000/mm^3; and (5) willing to be research subjects and signed an informed consent form.

The exclusion criteria in this study were: (1) peripheral neuropathy with other complaints or other underlying disease; (2) consumption of systemic steroid one month before the study procedure; (3) diabetes mellitus; (4) allergy to oral vitamin B complex; and (5) leprosy reaction by the time of the study procedure. All subjects were randomized using the online random block allocation technique; subjects were divided into two groups, ten samples in each group. The treatment group was given a combination of ultrasound-guided perineural PRP injection and oral vitamin B complex, while the control group was given oral vitamin B complex only.

The PRP preparation was carried out at the Central Laboratory of Dr. Saiful Anwar Hospital Malang using the Krasna method.[10] About 20 ml of blood from the cubital vein was taken, put in a tube containing citrate anticoagulant, then centrifuged at 1000 rpm for 20 minutes at room temperature. After the first centrifugation, a precipitate and the top layer of the supernatant containing plasma and a buffy coat were obtained. The supernatant was centrifuged again at a speed of 1890 rpm at 4^0C for 15 minutes.[11] The resulting PRP obtained was about 4 ml.

For the treatment group, ultrasound-guided perineural injection of autologous PRP was performed by an operator who was a neurologist or anesthesiologist at the Neurology Outpatient Clinic or Anesthesiology Outpatient Clinic, respectively, at the Dr. Saiful Anwar Hospital Malang. The injection was performed in the area around the posterior tibial nerve, which is located posteriorly and superior to the medial malleolus, under the guidance of ultrasound to identify the nerve and ensure the injection does not injure other structures.

A hyperechoic image would appear on the ultrasound image, showing nerve tissue. The injection was carried out once with a dose of 1 ml of PRP slowly. After the injection, all treatment subjects were given oral vitamin B complex (brand Neurobion forte®, composition of B1/ thiamine mononitrate 100 mg, B6/ pyridoxal hydrochloride 200 mg, and B12/ cyanocobalamin 5000 mcg) with the dose of 1x1 tablet per day for two weeks. As for the control group, subjects were given oral vitamin B complex (Neurobion forte®) only with a dose of 1x1 tablet per day for two weeks. The SWM clinical scores and sensory NCS of amplitude and latency were taken at baseline and week two evaluation after therapy.

SWM clinical examination was measured by touching monofilament weighing 5.07/10 grams perpendicular to the 10 points on the soles of patients according to WHO recommendations and pressing it to form the letter C for 2 seconds and then immediately withdrawing; the patient was then instructed to close their eyes and asked to point to which part the monofilament touched. The NCS amplitude and latency were performed by Neurologist in Neurology Outpatient Clinic.

The data was analyzed using the following tests: Chi-square and independent T-test for baseline characteristic data; Saphiro Wilk followed by independent T-test for normal distribution variables or Mann-Whitney for rejected normal distribution variables for baseline SWM, NCS latency and amplitude between control and treatment group; Saphiro Wilk followed by paired T-test for normal distribution variables or Wilcoxon test for rejected normal distribution variables between baseline data and evaluation data in each group; independent T-test for normal distribution variables or Mann-Whitney for rejected normal distribution variables between control and treatment group. The significance level is $p < 0.05$.

Results

The number of samples in this study was 24, however, four subjects dropped out, so the total number of subjects until the end of the study was 20. Table 1 showed subject baseline characteristics, all baseline characteristics between the treatment and control groups were not statistically different ($p>0.05$). The maximum age in the control and treatment groups was 44 and 64, respectively. The difference in the leprosy peripheral neuropathy severity index of each sample can be seen in Table 2, which showed no significant difference in clinical SWM, NCS latency, and amplitude examination between the control and treatment groups ($p>0.05$).

There were eight samples (80%) in the treatment group and six samples (60%) in the control group that had improved SWM scores from baseline (Figure 1). Also, five samples (50%) in each group had improved both NCS latency and amplitude scores from baseline, while the rest had fixed scores. Statistically significant differences in either SWM clinical score and NCS amplitude were observed between baseline and evaluation in both the treatment and control groups ($p<0.05$), but not statistically different for NCS latency ($p>0.05$) (Table 3). Meanwhile, between the treatment and control groups, no statistical differences either in SWM clinical score, NCS amplitude, and NCS latency ($p>0.05$) were observed (Table 4). No differences in the number of subjects who experienced side effects between the control and treatment groups ($p>0.05$) were observed (Table 5).

Discussion

This study included participants > 20 years old because adults above 20 were more likely to cooperate during minimally invasive procedures conducted in this study; previous studies also included subjects in this age category. [8] Although statistically, there was no significant difference in age between the control and treatment groups, there was a maximum age difference in the treatment group, which was older than the control group. This may affect therapy response and outcomes because the nerve's regenerative ability decreases with age, indicated by decreased axonal regeneration, terminal and collateral sprouting of regenerated fibers, slowing axonal regeneration rate, and a limit in the compensatory reinnervation capability.[11]

Table 1. Baseline Characteristic Data

Variable	Treatment Group (n=10)	Control Group (n=10)	*p* Value
Gender			
Male	8	6	0.314
Female	2	4	
Age (years old, Mean)	34.1 ± 15.72	33.4 ± 9.32	0.905
Hemoglobin (g/dL, Mean)	14.19 ± 1.90	12.95 ± 1.87	0.160
Platelet (/μL, Mean)	257400 ± 37698	277400 ± 49019	0.320
Blood Glucose (mg/dL, Mean)	88.8 ± 9.04	97.4 ± 15.83	0.153
Leprosy Treatment Status			
On MDT/ROM	5	6	0.500
RFT	5	4	

MDT: Multi-Drug Treatment
ROM: Rifampicin-Ofloxacin-Minocycline
RFT: Release from Treatment

Table 2. Comparison Test Between Baseline in The Control and Treatment Group

Variable	Treatment Group (Mean±St dev)	Control Group (Mean±St dev)	*p* Value
SWM Clinical Score	3.30±2.91	2.70±2.80	0.631
NCS Latency	3.10±5.31	0.81±2.11	0.579
NCS Amplitude	0.98±2.86	0.61± 1.93	0.481

SWM: Semmes-Weinstein Monofilament
NCS: Nerve Conduction Study

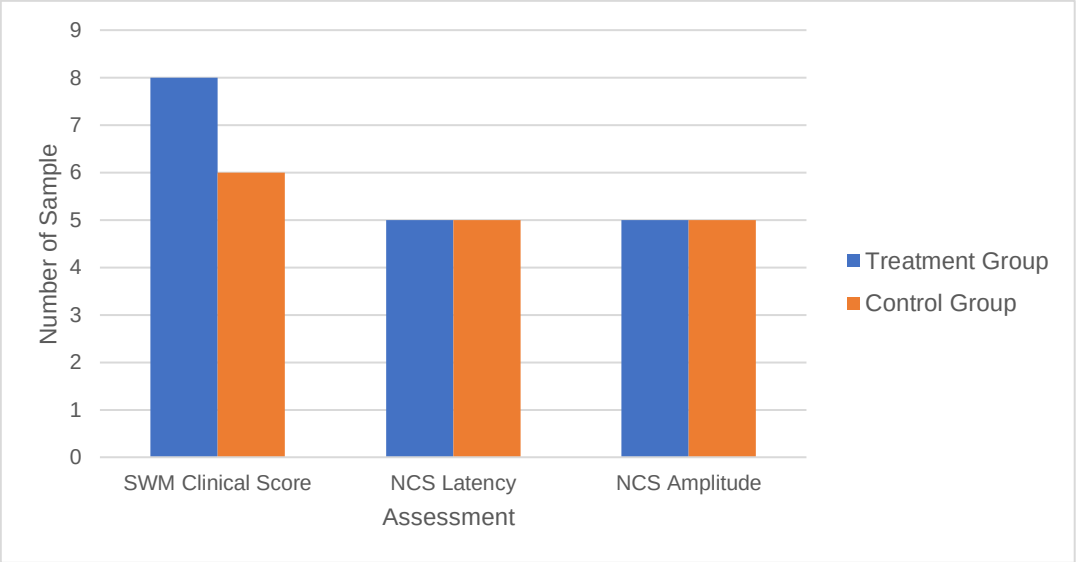

Figure 1. Comparison Graph of Number of Sample that Experienced Score Improvement from Baseline
SWM: Semmes-Weinstein Monofilament; NCS: Nerve Conduction Study

Table 3. Comparison Test Between Baseline and Evaluation in The Control and Treatment Group

Variable	Period	Mean±St dev (Median±IQR)	*p* Value
Control Group			
SWM Clinical Score	Baseline	2.70±2.83 (1.50±5.50)	0.027*
	Evaluation	4.00±4.00 (2.00±8.25)	
NCS Latency	Baseline	0.81±2.11 (0.000±0.350)	0.225
	Evaluation	2.09±2.91 (0.450±4.72)	
NCS Amplitude	Baseline	0.61±1.93 (0.00±0.00)	0.043*
	Evaluation	5.09±6.92 (0.50±10.23)	
Treatment Group			
SWM Clinical Score	Baseline	3.30±2.91 (3.00±4.75)	0.001*
	Evaluation	4.70±3.43 (4.50±6.00)	
NCS Latency	Baseline	3.10± 5.32 (0.00±7.72)	0.345
	Evaluation	1.49± 1.92 (0.65±2.65)	
NCS Amplitude	Baseline	0.98± 2.86 (0.00±0.28)	0.043*
	Evaluation	5.00± 7.97 (0.15±10.5)	

SWM: Semmes-Weinstein Monofilament
NCS: Nerve Conduction Study
* $p<0.05$: statistically significant difference

Table 4. Effectivity Comparison Test Between Control and Treatment Group

Variable	Group	Mean±St dev (Median±IQR)	*p* Value
SWM Clinical Score	Control	1.30±1.42 (1.00±2.25)	0.856
	Treatment	1.40±0.97 (1.50±1.25)	
NCS Latency	Control	1.52±2.59 (30.25±2.50)	0.684
	Treatment	3.01±4.15 (0.65±5.95)	
NCS Amplitude	Control	4.48± 6.85 (0.50±10.23)	0.912
	Treatment	4.02±6.11 (0.15±9.25)	

SWM: Semmes-Weinstein Monofilament
NCS: Nerve Conduction Study

Table 5. Side Effect Comparison Test Between Control and Treatment Group

Group	Did not Experienced Side Effect	Experienced Side Effect	*p* Value
Control	9	1	0.141
Treatment	5	5	
Total	10	10	
OR= 9.00		CI 95%= 0.81-100.14	

OR: Odds Ratio
CI: Confidence Interval

This study used SWM to measure clinical sensory nerve function, with a sensitivity of 81.7% and specificity of 96.1%, and adequate validity as a standard clinical screening tool for diagnosing leprosy neuropathy skin disorders.[12,13] This study also used NCS, the gold standard tool in the examination of neuropathy that can assess nerve damage and regeneration of myelin and axons. A decrease in amplitude response is concurrent with axonal damage. Demyelination results in prolonged latency, and vice versa.[14] In leprosy sensory neuropathy, the NCS abnormalities generally showed prolonged distal latency and low amplitude.[15]

This study used ultrasound guidance in performing the PRP perineural injection technique, carried out by an expert operator. Ultrasound guidance provides the advantage of better visualization of the neural tissue and diffusion of the material that is injected,[6] as well as minimal risk of vascular and nerve injury compared to injection without guidance, as suggested by many studies.[9,16,17] The dose of PRP that was injected perineurally in this study was 1 ml of PRP with two weeks of evaluation, similar to previous studies.[8]

This study showed that both combination therapy of PRP perineural injection and oral vitamin B

complex (treatment group) and oral vitamin B complex alone (control group) were effective in improving leprosy neuropathy, as indicated by a significant improvement in SWM clinical scores and NCS amplitude response after therapy. Thus, it was concluded that PRP and neurotropic vitamins were more effective in inducing axonal regeneration than myelin. This is in line with a previous study that reported vascular endothelial growth factor (VEGF) release from PRP can increase axonal regeneration.[16] Also, vitamins B1 and B12, as part of the vitamin B complex, play important protective roles in axon membranes and increase axon growth. as reported in previous studies.[18] As for myelin regeneration, previous studies reported a positive effect on myelination when PRP in solid or gel forms was used.[19] The PRP used in this study was not solid or gel form; this presumably may have led to no significant NCS latency improvement after therapy in the treatment group.

This study showed that the effectivity between combination therapy of ultrasound-guided autologous PRP perineural injection and oral vitamin B complex was not significantly different from single oral vitamin B complex therapy in improving leprosy neuropathy. However, detailed observation and comparison in SWM clinical scores showed that clinical improvement was observed more in the treatment group (80% of samples) than in the control group (60% of samples). This suggested that ultrasound-guided PRP perineural injection as additional therapy to oral vitamin B complex may increase treatment effectivity, in accordance with previous research.[8,16,17]

Platelet-rich plasma (PRP) is an autologous product with a higher platelet concentration than in the blood that can be activated by thrombin and calcium chloride. In the PRP injection site, degranulation of the granules and the release of growth factors and biomolecules play a role in triggering angiogenesis, extracellular matrix (ECM) remodeling, and recruitment, proliferation, and differentiation of stem cells to accelerate the healing process. These growth factors include the transforming growth factor (TGF)-β1, vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), and basic fibroblasts growth factor (bFGF).[17] TGF-β1 regulates proliferation and differentiation of Schwann cells and can adjust nerve growth factors, such as nerve growth factor (NGF) and bFGF, to participate in peripheral nerve regeneration after injury.[19] *In vitro* studies proved that VEGF, which induces increased vascularity, can increase axonal regeneration and, *in vivo*, is associated with long-term sustained regeneration of nerves.[16] IGF-1 acts as a neurotrophic factor for motor, sensory, and sympathetic neurons to increase growth cone motility and neurite growth and prevent apoptosis, while bFGF has a role in neuroprotection and nerve regeneration. [20]

In this study, no significant differences in effectivity were observed between the treatment and control group; this may have been due to injection only at one site, in this case on the malleolus medial area, while neuropathic events or nerve damage can occur at any point along the proximal or distal peripheral nerves. In addition, due to limited time and equipment, the measurement of the platelet count and growth factor levels in the PRP of each sample was not carried out, so the PRP quality was not assured. Also, the neuropathy type that occurred in each sample was not noted. Neuropathy due to hypersensitivity reactions usually occurs in the extrafascicular, unlike neuropathy due to *M. leprae* invasion, where neuritis occurs intrafascicular.[21] However, the latter possibility was minimized during selection of study subjects, as patients experiencing leprosy reactions were excluded. The baseline neuropathy severity index in both groups was the same (Table 2).

This study is the first to use vitamin B complex in leprosy neuropathy treatment. The vitamin B complex used in this study is a high-dose B complex vitamin with a fixed dose combination, namely the Neurobion Forte® brand, which contains 100 mg of vitamin B1 (thiamine mononitrate), 100 mg of vitamin B6 (pyridoxine hydrochloride), and vitamin B12 (cyanocobalamin) 5000 mcg. It was selected based on previous studies that stated the vitamin B complex was effective and well tolerated in subjects with mild to moderate peripheral neuropathy with various etiologies in Indonesia.[22,23] Although many studies reported the effectivity of vitamin B complex against peripheral neuropathy with various etiologies had been proven,[18,22,23] no studies mentioned neuropathy due to leprosy.

Based on the author's experience so far, vitamin B complex widely used for leprosy in outpatient clinics across Indonesia covered by the national health insurance is a low-dose vitamin B complex containing 2 mg of B1, 2 mg of B2, 20 mg of B3, 10 mg of B5, and 2 mg of B6, that may provide minimal improvement in leprosy neuropathy, compared to this study that found leprosy sensory neuropathy improvement in 2 weeks after giving high-dose vitamin B complex.

Vitamin B1 (thiamine) plays an important role in maintaining cell membrane stability, having a protective role against nerve cells, especially axon membranes.[24] Vitamin B6 has two different functions biologically, as a cofactor in many developmental, physiological, and metabolic processes, including those important in neurotransmitter synthesis, and as an antioxidant.[22] Vitamin B12 can increase neuronal survival and axon growth through activation of the protein kinases Erk1/2 and Akt.[25]

This study showed significant improvements in the SWM clinical score and NCS amplitude after therapy using a single oral vitamin B complex. Significant improvement was not found in the NCS latency, possibly because the neurotropic vitamin has a more positive effect on axonal repair than myelin. However, the exact cause needs further investigation.

Side effects of the therapies in this study are minimal, both in the treatment and control groups. As many as 50% of subjects felt pain during injection, which disappeared immediately after the injection was completed. Previous studies stated that the risk of injection and the risk of immune rejection of PRP is minimal because the source of PRP comes from autologous blood and non-invasive blood collection techniques.[19] In all samples that received oral vitamin B complex, only 5% (one sample) felt the side effects of worsening numbness and paresthesia in palms and soles.

This is in line with previous studies reporting that out of 414 diabetic subjects who were given vitamin B complex once a day for 12 weeks, only three subjects experienced side effects such as abdominal pain and nausea, and one subject experienced skin and subcutaneous tissue disorders.[22] In this study, no significant difference was found in subjects who experienced side effects between the control and treatment groups. This suggests that the ultrasound-guided PRP perineural injection has no negative effect on leprosy sensory peripheral neuropathy of the posterior tibial nerve.

We could not determine whether the treatment group improvement was due to PRP perineural injection or oral vitamin B complex because the PRP platelet and growth factor levels were not measured. As such, this was a limitation of our study. Also, a double-blind method could not be applied to this study because of the different types of therapy between injection and oral therapy. Thus, further studies, including larger sample size, longer observation time, PRP platelet and growth factor levels measurement, and comparing PRP to different doses of vitamin B complex, are required to support this study's conclusion.

Conclusion

This study concluded that both therapies, the combination of ultrasound-guided autologous PRP perineural injection and oral vitamin B complex or single oral vitamin B complex therapy, are effective in improving leprosy sensory peripheral neuropathy of the posterior tibial nerve, possibly due to axonal regeneration. Although no significant difference in effectivity between the two therapies was found, ultrasound-guided PRP perineural injection has no negative effect on leprosy sensory peripheral neuropathy.

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Conflict of Interests

The authors declare that there are no conflicts of interest in this study.

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