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Treatment of Peripheral Neuropathy: Combination Therapy Using LED Light, Extracorporeal Shockwave Therapy, Platelet Rich Plasma, and an Oral Dietary Supplement

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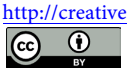

Abstract

Objectives: Peripheral neuropathy (PN) is a significant contributor to disability in the elderly. It is also one of the most prevalent complications of type 2 diabetes, prediabetes and metabolic syndrome. PN is commonly associated with pain, numbness, tingling, burning, and cramping in the feet and legs. Current treatment options are limited to controlling pain, seizures and use of antidepressant medications. These treatments have undesirable side effects and don't stop PN progression. Here we utilized a combination of individual-specific modalities to improve local circulation and relieve PN symptoms. **Methods:** We conducted an open-label, multicenter pilot trial with 34 subjects (19 males and 15 females ranging from 40 - 85 years of age). All of the participants were diagnosed with peripheral neuropathy and had bilateral symptoms in their feet, and many reported the same symptoms (pain, numbness, tingling, burning, and cramping) in their lower legs. The duration of symptoms ranged from four months to over six years. On Day 0, subjects were given a 90-day supply of the oral supplement with dosing instructions and a LED light therapy device. They also received three platelet-rich plasma (PRP) injections in their lower extremities. Subjects also received an extracorporeal shockwave therapy (ESWT) treatment for each foot and subsequently twice per week for the first six weeks, then once weekly for the duration of the study. Subjects filled out the Brief Pain Index (BPI) at weekly intervals. On Day 90, subjects completed the Patient Global Impression of Change (PGIC) survey. **Results:** There were significant responses to pain, as evidenced by BPI scores at weeks 8, 9, 10 and 11 ($p = 0.02$, 0.01, 0.02, and

0.003, respectively). Analysis of the final day PGIC survey showed a favorable outcome for 73% of participants (p = 0.003), with the majority reporting Very Much Improved. **Conclusions:** By utilizing a multi-modality treatment protocol that includes PRP, LED light therapy, ESWT and an oral dietary supplement, we observed significant reductions in BPI scores. Quality of life and their overall impression of change (PGIC) were significantly improved, and there were no significant side effects.

Keywords

Peripheral Neuropathy, LED Light Therapy Device, Extracorporeal Shockwave Therapy, PRP Injections, Oral Supplement, Multi-Modality Treatment, Pain

1. Introduction

Peripheral neuropathy (PN) is a significant contributor to disability in the elderly and is one of the most prevalent complications associated with type 2 diabetes (T2D), prediabetes, and metabolic syndrome [1]. PN usually affects the feet and legs first, but can also affect the fingers and hands. It is commonly associated with pain, numbness, tingling, burning, and cramping. Although the most prevalent causes of PN are T2D, prediabetes and metabolic syndrome, the exact cause of peripheral neuropathy remains unknown. It has often been postulated that poor circulation, which can be secondary to the weakening of the walls of capillaries caused by elevated blood sugar, plays an important role in the pathogenesis of PN [2].

One approach to PN treatment has involved the use of infrared and red light LED therapy, and such devices are FDA approved and are used to increase local circulation and decrease pain [3]. This effect is believed to be accomplished by dilating vessels to increase local blood circulation and reducing pain by decreasing inflammation.

Platelet-rich plasma (PRP) injections have been shown to promote nerve regeneration [4]. PRP injections act as fillers of nerve conduits or vein-muscle grafts to bridge the nerve gaps after the nerves have been severed by trauma. PRP infiltrates the stumps of the nerve perineurally as well as intraneurally. Moreover, PRP can also act as a scaffold to bridge or wrap nerve stumps [4]. In T2D patients PRP treatments for neuropathy have been shown to decrease neuropathic pain and numbness while increasing nerve function [5]. A recent study also showed promising results by presenting evidence of nerve regeneration of damaged peripheral nerves [6].

Extracorporeal shockwave therapy (ESWT) has also been used to protect nerves against PN development. A study by Seabaugh showed that ESWT, when applied after PRP injections, caused the release of growth factors from platelets and showed beneficial responses. The biological effects of ESWT include: improved vascularization, the local release of growth factors, and local anti-inflam-

matory effects. ESWT has been shown to promote axonal regeneration [7].

Finally, there is evidence that nutritional supplementation can help support damaged peripheral nerves [8]. The oral supplement used in this study consisted of alpha lipoic acid (ALA), methyl B-12, folate, and other components. ALA has been shown to ease the numbness, burning, and pain associated with peripheral neuropathy [9]. It is a powerful antioxidant that improves blood flow and glutathione levels. Methyl B-12 is one of the most critical nutrients for proper nerve function. This B vitamin helps repair and maintain healthy myelin and is associated with decreased PN [10]. Folate has been shown to significantly improve endothelial cell function and normalize blood flow to nerves. Improved nerve conduction velocities are beneficial in treating diabetic polyneuropathy [11]. However, no studies have assessed the efficacy of specific multi-modality treatment of PN. The effects of different individual treatments have been studied for PN, but have not been used together. Our pilot study sought evidence of the benefit from using a combination of modalities to treat PN.

2. Subjects and Methods

We conducted an independent IRB-approved, open-label, multicenter pilot trial with a total enrollment of 39 subjects with a diagnosis (dx) of PN. The clinics that participated in this study were all located in California (cities of Corona, Placentia, and Gardenia). The study recruitment began on August 8, 2021 and final subject finished treatment on July 16, 2022. Before entering the trial each participant signed an Informed Consent document. Five of these subjects were disqualified for failure to comply with home and office treatment schedules. Thirty-four subjects (average age = 67, range 40 - 85 years) completed the study. Both males (n = 20) and females (n = 14) were included in the study. Thirty-one of the participants were diagnosed with T2D with diabetic neuropathy. Three participants presented with prediabetes (total patients, n = 34).

Participants were excluded from the study if they were taking immunosuppressive drugs, they were pregnant or lactating, were outside the age range, had cognitive impairment, or were allergic to any ingredient used in the study supplement. Also excluded were subjects with active cancer(s), HIV, foot ulceration(s), thrombocytopenia, hemodynamic instability, septicemia, septic arthritis, overlying cellulitis, or adjacent osteomyelitis, platelet dysfunction syndrome, high blood pressure (greater than 180/100), fractures or were taking NSAIDS drugs or steroids. This study was conducted per all applicable regulations, including the current U.S. Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, and 56, and Title 45, Part 164. Regulations and guidelines were also observed within the ethical principles described in the current revision of the Declaration of Helsinki.

After the subjects were recruited according to the inclusionary criteria, participants underwent a physical and neurological exam to confirm the diagnosis of PN. The neurological exam included: a pinprick sensation test to the dorsal

and plantar surface of the feet, a 128-Hz tuning fork placement at the base of the great toenail, a Semmes-Weinstein 5.07g monofilament test to the dorsal and plantar surface of the feet, heat perception, deep tendon reflexes tests, muscle strength grading, and gait tests. Participants were scheduled to meet with the study monitor at each clinic location to review and sign the Informed Consent Document.

On Day 0, subjects were given a 90-day supply of the Bedrock Bioscience Nerve Support supplement with dosing instructions and one Bedrock Bioscience LED Light Therapy Device. The Bedrock Bioscience Nerve Support supplement is a vitamin supplement containing ALA, B-12, B-1, B-6, and folate. Bedrock Bioscience LED Light Therapy Device has 60 red light LEDs (660 nm wavelength) and 60 infrared LEDs (880 nm wavelength). Participants were instructed to take two capsules of the Bedrock Bioscience Nerve Support supplement twice daily and use the Bedrock Bioscience LED Light Therapy for twenty minutes in the morning and twenty minutes in the evening throughout the study. Participants were monitored for compliance at home with phone calls, emails, and during office visits. They were also directed to fill out the medical intake form, including the Brief Pain Inventory (BPI) survey on Day 0 and once weekly for 90 days. They also received three PRP injections in both lower extremities on Day 0. Subjects also started receiving an ESWT treatment to each foot on Day 0 and twice per week for the first six weeks, then once weekly for the 90 days. On Day 90, participants were asked to answer questions on an Exit Survey, the Patient Global Impression of Change (PGIC). The subjects were also assessed for side effects and monitored for compliance via phone calls (**Table 1**). The primary endpoints were assessment of the Brief Pain Inventory survey [12], the PGIC survey and their statistical analyses [13] [14]. At the end of the study participants who completed the study were offered compensation.

3. Statistical Analysis

The BPI survey provided most of the data that were analyzed. Descriptive statistics were calculated for each variable, and the frequency was calculated for the categorical variables. The BPI survey was completed throughout the study (12 times), and the pairwise comparisons in BPI scores at each survey were assessed against Baseline. Thirty-four subjects completed the exit survey. The proportion of participants who responded "Moderately Better" and "Very Much Better" was obtained, and a 95% Confidence Limit (95% CL) was calculated.

4. Results

All 34 participants read, understood, and signed the Informed Consent document and completed the BPI and PGIC surveys. Temporary discomfort during ESWT and minor pain during PRP injections were the only minor side effects reported. There were no significant side effects reported. We found a decreasing trend starting at the survey taken on weeks 8 through 11 compared to the BPI

Table 1. Study flow chart summary.

STUDY	Day 0	Week											
		1	2	3	4	5	6	7	8	9	10	11	12
Physical Exam	X												
Medical Intake	X												
Diagnosis	X												
Informed Cons.	X												
LED light therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral supplement	X	X	X	X	X	X	X	X	X	X	X	X	X
TREATMENT													
PRP Injections	X												
TREATMENT													
LED light therapy	2X/day	X	X	X	X	X	X	X	X	X	X	X	X
TREATMENT													
Oral Supplement	2X/day	X	X	X	X	X	X	X	X	X	X	X	X
TREATMENT													
ESWT Wave	X	X	X	X	X	X	X	X	X	X	X	X	X
SURVEYS													
BPI	X	X	X	X	X	X	X	X	X	X	X	X	X
FINAL EXIT													
PGIC													X
Compensation													X

score at the baseline using the Bonferroni-Holm multiple comparison adjustment methods (an unadjusted p-value of 0.003) (Table 2). The estimated means and 95% confidence limits of BPI scores at each survey taken time were obtained and used to construct a figure (Figure 1).

Of the 34 participants, all thirty-four completed the PGIC Exit survey. Figure 2 shows the proportions of patients in each response category of the PGIC Exit survey. Based on the data, the observed proportion of participants who stated "moderately better" and "very much improved" at the end of the study was 73% (95% CL 0.5564, 0.8712). This was statistically significantly higher than the theoretical threshold of 0.5, with a p-value of 0.003.

5. Discussion

The study's objective was to assess whether a multi-modality treatment protocol effectively reduced the pain and other symptoms of PN. The authors postulated from previous clinical observations that a multi-modality approach could have a synergistic effect that would be more beneficial in reducing PN symptoms than

Table 2. The estimated mean differences, p-values and 95% CLs of the BPI score in pairwise comparisons between each time point and at the baseline.

Pairwise Comparison (Time point vs. Baseline)	Time point (week)	The estimated mean difference & 95% CL	The Unadjusted p-value
1 vs. 0	1	−3.79, (−8.17, 0.59)	0.09
2 vs. 0	2	−2.5, (−8.2, 3.2)	0.39
3 vs. 0	3	−1.88, (−8.47, 4.71)	0.57
4 vs. 0	4	−3.05, (−9.41, 3.3)	0.34
5 vs. 0	5	−4.09, (−10.04, 1.85)	0.17
6 vs. 0	6	−1.92, (−8.32, 4.47)	0.55
7 vs. 0	7	−3.7, (−9.75, 2.36)	0.23
8 vs. 0	8	−7.36, (−13.68, −1.03)	0.02
9 vs. 0	9	−7.46, (−13.7, −1.22)	0.01
10 vs. 0	10	−7.92, (−14.33, −1.5)	0.01
11 vs. 0	11	−9.13, (−15.17, −3.09)	0.003

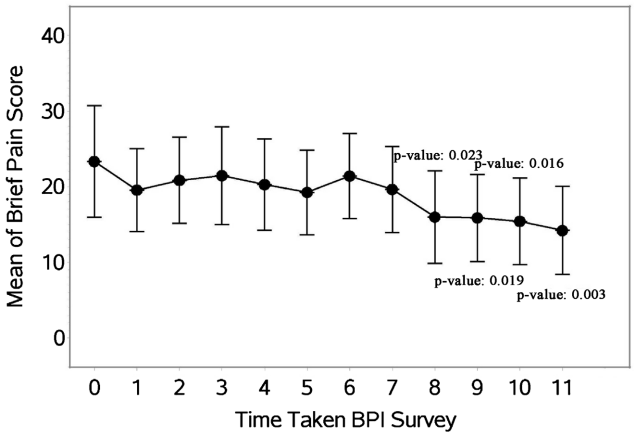

Figure 1. The estimated mean and 95% Confidence limit (95% CL) of the BPI score each time (weeks) the survey was taken.

the use of any one modality alone. The Bedrock Bioscience LED Light Therapy device has been used for over four years in various clinics (over 60,000 treatments). This treatment has been well tolerated. LEDs do not contain ultraviolet rays and have been proven safe for regular use [15]. ESWT has also been proven safe and effective for multiple musculoskeletal conditions. Various clinics have provided over 30,000 ESWT treatments with only transient mild discomfort reported. Other research reported similar results (Wang *et al.* [16]), showing that ESWT effectively reduced foot ulcers and painful diabetic neuropathy. Snyder *et al.* [17] suggested that the ESWT should be used in combination therapies where other therapies alone were not sufficient enough to control diabetic NP. It was shown in their studies that combination therapies with ESWT resulted in a marked reduction in PN pain.

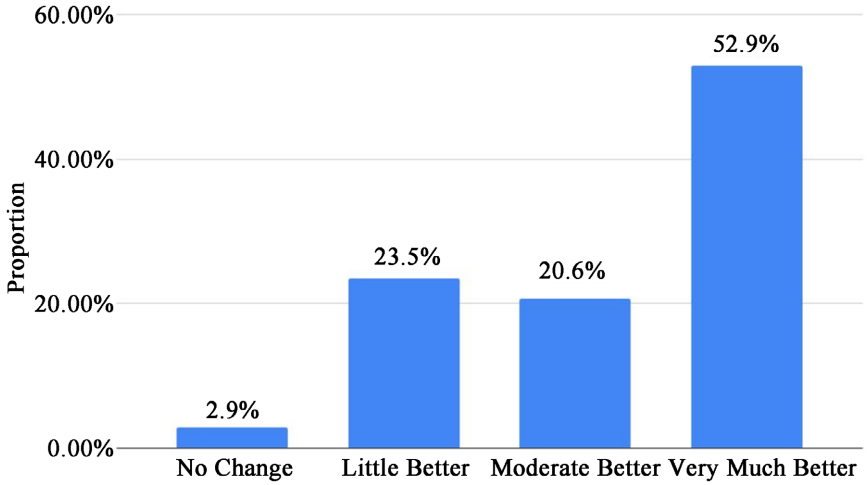

Figure 2. The proportions of patients in each response category of the PGIC Exit survey (n = 34, p < 0.003).

The Bedrock Bioscience Nerve Support supplement has been utilized in over 2 million doses and contains alpha lipoic acid, B-12, B-1, B-6, and folate. In these patients adverse reactions (ARs) have occurred in less than fifty patients (<0.00003%), and reported ARs were limited to upset stomachs and acid reflux. This is supported by the fact that a recent RCT study showed that a decrease in pain could be achieved safely and effectively compared to other analgesics by supplementing with ALA. There were no side effects reported in the same RCT study [18]. Another study by Boghdadi *et al.* [19] suggested that when combined, ALA and Vitamin B complex are more effective than simple vitamin b12 complex for treating PN. In contrast to these results, we found that although vitamin B12 deficiency has been demonstrated in polyneuropathy, supplementation with B12 has not been effective in controlling NP [20]. However, we added B12 as a component in our combination oral supplement.

PRP injections have also been shown to be an effective treatment for NP. The main ARs include local infection (<1%) and pain at the injection site. Recent studies reported the promising effects of PRP on nerve regeneration [21]. However, the lack of standardization in the PRP preparation makes its evaluation difficult. In addition, there is a lack of well-designed, randomized, placebo-controlled clinical trials (RCT) in this subject area [22].

Our combination therapy was successful for PN, and all the modalities used were effective and safe. We found a significant decreasing trend of NP assessed by BPI starting at the survey taken at weeks 8 through 11. We also found a statistically significant decrease in the mean of BPI scores compared to the Baseline at Day 0.

6. Conclusion

By using a multi-modality treatment therapy protocol for PN patients we demonstrated that the combination of PRP, LED light therapy device, ESWT, and an oral supplement lowered pain scores and significantly improved subjects' im-

pression of change. Seventy-three percent of participants reported either Very Much Improved or Moderately Better at the end of the trial. Twenty-three percent of participants reported Little Improvement, and one reported No Improvement from the treatments. Temporary discomfort during ESWT and minor pain during PRP injections were the only minor side effects reported. There were no significant side effects in the study. Although the results were promising, there were some limitations of the study. A larger number of subjects would be recommended with pre- and post-neurological evaluations. Also, it would be interesting to see if a longer treatment schedule would improve outcomes even more than the results reported here. In this multi-modality study protocol we could not compare the results to individual treatments alone. Most importantly, this study should be eventually repeated with a larger placebo-controlled RCT trial.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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