ORIGINAL ARTICLE

A Randomized Controlled Study to Evaluate the Efficacy of Noninvasive Limb Cover for Chronic Phantom Limb Pain Among Veteran Amputees

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ABSTRACT. Hsiao A-F, York R, Hsiao I, Hansen E, Hays RD, Ives J, Coulter ID. A randomized controlled study to evaluate the efficacy of noninvasive limb cover for chronic phantom limb pain among veteran amputees. Arch Phys Med Rehabil 2012;93:617-22.

Objective: To assess the efficacy of a noninvasive limb cover for treating chronic phantom limb pain (PLP).

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Outpatient clinic.

Participants: We randomly assigned 57 subjects to 2 groups: true noninvasive limb cover (n=30) and sham noninvasive limb cover (n=27). Inclusion criteria included age of 18 years or greater, upper or lower extremity amputation with healed residual limb, and 3 or more episodes of PLP during the previous 6 weeks.

Interventions: Subjects received 2 true or sham noninvasive limb covers to be worn over the prosthesis and residual limbs 24 hours a day for 12 weeks.

Main Outcome Measures: Primary outcome measure was the numerical pain rating scale of PLP level (0–10). Secondary outcomes included overall pain level (0–10), PLP frequency per week, and the Veterans RAND 12-Item Health Survey (VR-12). We collected data at baseline and at 6- and 12-week follow-up visits.

Results: Demographic and clinical characteristics were not significantly different between groups. The true noninvasive limb cover group reported nonsignificant reductions in PLP from 5.9±1.9 at baseline to 3.9±1.7 at the 12-week follow-up. The sham noninvasive limb cover group also had nonsignificant reductions in PLP from 6.5±1.8 to 4.2±2.3. PLP did not differ significantly between the 2 groups at 6 weeks (mean difference, 0.8; 95% confidence interval [CI], −1.4 to 3) or at 12 weeks (mean difference, 0.2; 95% CI, −1.9 to 2.3). Similarly, overall pain level, PLP episodes per week, and VR-12 physical and mental health component scores did not differ between the 2 groups at 6 and 12 weeks.

Conclusions: A true noninvasive limb cover did not significantly decrease PLP levels or the frequency of PLP episodes per week, overall bodily pain levels, or VR-12 physical and mental health component scores compared with a sham noninvasive limb cover in our veteran amputee sample.

Key Words: Phantom limb pain; Rehabilitation.

PHANTOM LIMB PAIN (PLP) is a painful sensation perceived in the missing limb after amputation and may be triggered by episodes of residual limb pain.[1] A growing body of literature indicates that 50% to 80% of amputees may have PLP.[2-5] More than 1.2 million individuals in the United States have a limb loss each year[6,7] primarily the result of vascular disease, traumatic injury, diabetes mellitus, congenital defects, or malignancy.[8] In the United States, the highest prevalence of limb loss (19.4/1000) occurs in the elderly (aged ≥65y), and most new amputations are caused by peripheral vascular disease.[7] In the U.S. military, amputations commonly occur in younger individuals[9,10] who have sustained blast injuries caused by high-velocity weapons. Soldiers with amputations who were involved in previous military conflicts had higher mortality, underwent more surgery,[11] and were hospitalized twice as long as nonamputees.[12] Therefore, PLP is a major cause of morbidity for the civilian, military, and veteran populations, and its cost of care represents a major burden on the health care system.

Most amputees (50%–80%) have PLP,[13] yet causes of PLP have not been specifically determined, and a clear definition is lacking. PLP has been described as a painful sensation felt in the missing portion of a limb after amputation, although burning, tingling, and electric shock sensations are also experienced. These sensations are purported to decrease over time in frequency and duration, although prevalence remains constant.[14] Residual limb pain (pain in the residual limb) and PLP are associated and may be difficult to differentiate.[5,15] In 1 study,[4] subjects experiencing residual pain were twice as likely to have PLP, and subjects having phantom sensations (any feelings experienced other than pain in the missing limb) were 11 times more at risk of having phantom pain. This evidence

List of Abbreviations

CI	confidence interval
NPRS	numerical pain rating scale
PLP	phantom limb pain
VA	Veterans Affairs
VR-12	Veterans RAND 12-Item Health Survey

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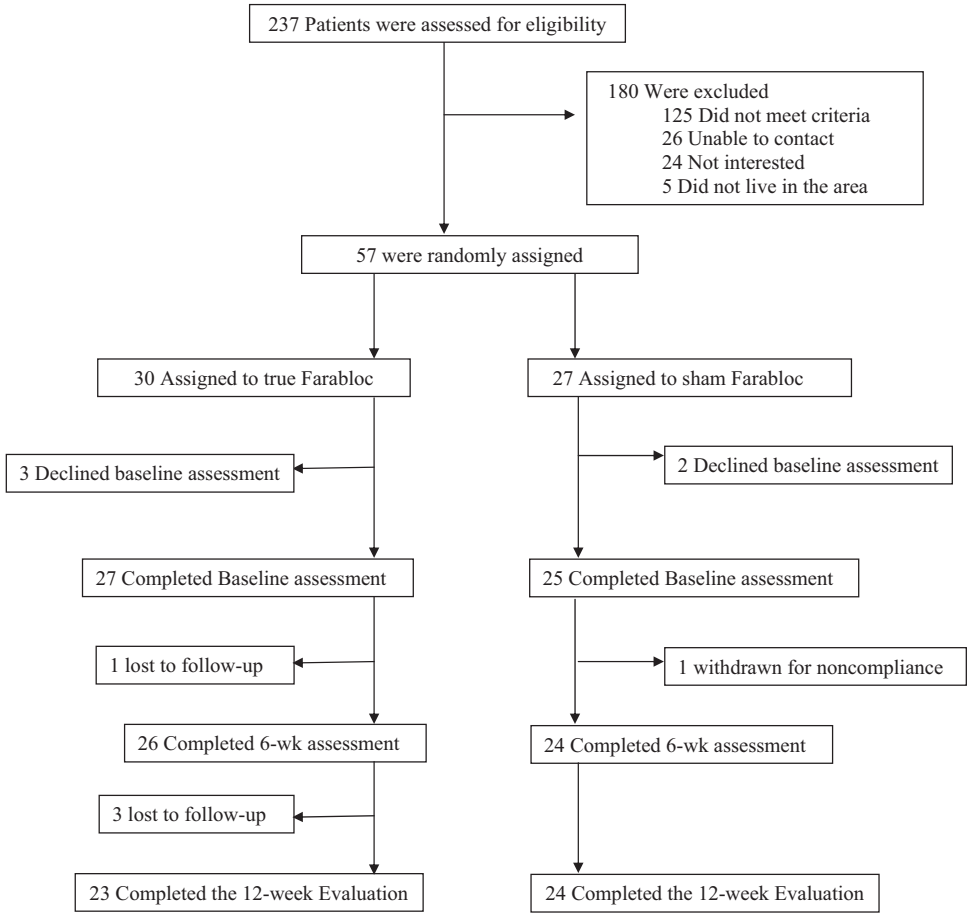

Fig 1. Participant flowchart.

underscores the importance of residual limb pain and phantom sensations when characterizing PLP.

The etiology and pathophysiology of PLP are poorly understood. Peripheral and central nervous system mechanisms have been suggested, yet underlying etiologies continue to elude researchers. Some studies[13,14,16] suggest that PLP may be associated with amputation cause, prosthetic use, time since amputation, sex, and age. Others suggest that peripheral mechanisms such as spontaneously firing neuromas[17] and reorganization of the primary somatosensory cortex, subcortex, and thalamus[2,18,19] may be to blame. Recent research[2] has postulated that the central nervous system plays an important role in PLP. For instance, sensitization of neurons may occur at the spinal cord level as a result of upregulation of *N*-methyl-D-aspartate receptors.[20] Increased sodium conductance may play an important role, as gallamine injection has been shown to produce PLP while lidocaine blocks it.[21] These theories, however, do not completely explain the pathophysiology of PLP because it may also be caused by congenital defects.

Many amputees who have PLP are underdiagnosed and suboptimally treated by their physiatrists, prosthetists, podiatrists, and other providers. For instance, 72% of clinicians believed that less than one fifth of amputees have severe PLP, whereas the prevalence of PLP is as high as 50% to 80%.[22] While many patients with PLP are treated with pain medications and epidural injections, fewer than 50% of patients report lasting pain relief from conventional medical treatment.[23] Unfortunately, many amputees with PLP are disabled by their chronic pain.

Table 1: Study Population Demographic and Clinical Characteristics

Characteristic	True Farabloc (n=30)	Sham Farabloc (n=27)
Age (y)	61.8±12.3	65.8±13.4
Sex		
Men	97	100
Women	3	0
Cause of amputation		
Diabetes/PVD/infection/ osteomyelitis	73	70
Trauma	17	26
Other	10	4
Type of amputation		
Below knee	53	59
Above knee	47	41
Time since amputation (y)	10.5±15.3	15.6±19.5
Baseline PLP level	4.7±2.4	4.7±2.6
Baseline overall pain levels	5.9±1.9	4.5±2.2

NOTE. Values are mean ± SD or percentages.
Abbreviation: PVD, peripheral vascular disease.

Table 2: Comparison of True Farabloc and Sham Farabloc Groups on Pain and Health-Related Quality of Life

Variable	True Farabloc (n=30)			Sham Farabloc (n=27)		
	Baseline	6wk	12wk	Baseline	6wk	12wk
PLP level	5.9±1.9	4.5±2.0	3.9±1.7	6.5±1.8	4.3±2.1	4.2±2.3
Overall pain level	4.7±2.4	4.6±2.5	3.4±2.0	4.8±2.6	4.0±2.6	4.7±2.2
PLP frequency/wk	10.7±15.4	6.1±12.4	4.3±9.8	20.0±27.0	11.5±23.0	11.9±23.4
PLP frequency/mo	48.7±68.9	24.1±49.5	17.5±39.3	62.3±84.2	21.2±37.4	21.1±39.2
VR-12 physical component score	31.5±8.3	32.1±8.4	31.8±7.8	33.9±9.0	34.2±9.5	33.7±7.9
VR-12 mental health component score	50.0±12.0	49.1±11.7	48.0±10.7	47.4±13.8	49.0±12.5	49.2±12.0

NOTE. Values are mean ± SD.

Because conventional medical treatment has had limited success in treating phantom pain, many patients and clinicians are looking for alternative therapies that may offer better or longer lasting pain relief. It appears that modest, immediate pain relief may be achieved with the use of low-frequency, high-intensity auricular transcutaneous electrical nerve stimulation, although the duration of this relief is uncertain.[24] Mirror therapy has also been shown to reduce episodes, the duration, and the level of PLP in lower limb amputees.[25] Furthermore, many amputees with PLP have turned to noninvasive limb covers to treat their PLP. A noninvasive limb cover made using proprietary technology has been shown to block out high-frequency electromagnetic fields.[26] Previous studies[26-28] have suggested that this limb cover is efficacious in treating chronic PLP, fibromyalgia, and pain related to delayed-onset muscle soreness. However, the prior PLP study[28] was limited by its small sample and short intervention time.

The purpose of this study was to assess the efficacy of the noninvasive limb cover for treating chronic PLP in a larger sample of a veteran amputee population and during a longer intervention time. In a double-blind, randomized, sham-controlled trial, we evaluated the impact of the noninvasive limb cover on PLP pain and frequency and on general health-related quality of life.

METHODS

This study was approved by the VA Long Beach Healthcare System Institutional Review Board and the Office of Research Protections for the U.S. Army Medical Research and Material Command. All subjects provided written informed consent before any study-related procedures were performed. Fifty-seven patients (56 men, 1 woman) routinely treated in the prosthetics/amputee clinic at the VA Long Beach Healthcare System participated in this study. Inclusion criteria included subjects presenting with an upper or lower extremity amputation with a healed residual limb who experienced intermittent PLP, had 3 or more episodes of PLP during the previous 6 weeks, and had not used Farabloc[a] within the last 6 months. Subjects were excluded from the study if they had residual limb complications (eg, cellulitis and residual limb pain caused by a new bone spur within the past 12mo), previously used Farabloc within 6 months, or were pregnant. Randomization of subjects was performed by Farabloc Corporation (manufacturer for noninvasive limb cover), and both investigators and subjects were blinded to their assignment. The Farabloc Corporation revealed the true assignment of subjects after the completion of data collection.

Table 3: Mean Changes in Primary and Secondary Outcomes

Variable	Mean Change From Baseline (95% CI)		Between-Group Difference (95% CI)	
	True Farabloc	Sham Farabloc	True vs Sham	*P*
PLP				
Week 6	−1.4 (−6.4 to 3.6)	−2.2 (−6.2 to 1.8)	0.8 (−3.6 to 5.2)	.78
Week 12	−2.2 (−6.4 to 2.0)	−2.4 (−6.8 to 2.0)	0.2 (−4.0 to 4.4)	.38
Overall pain				
Week 6	−0.2 (−5.2 to 4.8)	−0.7 (−4.7 to 3.3)	0.5 (−4.1 to 5.1)	.55
Week 12	−1.4 (−5.2 to 2.4)	−0.2 (−5.2 to 4.8)	−1.2 (−5.6 to 3.2)	.22
PLP frequency/wk				
Week 6	−4.7 (−30.7 to 21.3)	−9.2 (−43.3 to 25.0)	4.5 (−25.7 to 34.7)	.08
Week 12	−6.6 (−31.6 to 18.4)	−9.5 (−52.3 to 33.3)	2.9 (−31.1 to 36.9)	.06
PLP frequency/mo				
Week 6	−24.8 (−139 to 89)	−39.9 (−74 to −5.7)	15.1 (−59.1 to 89.3)	.10
Week 12	−31.7 (−165 to 102)	−40.1 (−211.9 to 131.7)	8.4 (−144.2 to 161)	.09
VR-12 PCS				
Week 6	0.6 (−10.0 to 11.2)	0.3 (−12.9 to 13.5)	0.3 (−9.5 to 10.1)	.19
Week 12	0.3 (−9.7 to 10.3)	−0.2 (−13.2 to 12.8)	0.5 (−11.1 to 12.1)	.14
VR-12 MCS				
Week 6	−1.0 (−8.0 to 6.0)	1.6 (−13.0 to 16.2)	−2.6 (−13.4 to 8.2)	.58
Week 12	−2.1 (−10.5 to 6.3)	1.8 (−14.0 to 17.6)	−3.9 (−16.1 to 8.3)	.78

Abbreviations: MCS, mental health component score; PCS, physical component score.

All subjects were measured for individual fit of the Farabloc limb cover at screening, and received 2 covers 4 weeks later at the baseline visit. Subjects were asked to wear the cover 24 hours per day, 7 days per week, for the duration of the study. We decided that patients should wear the cover continuously based on our discussion with the manufacturer of Farabloc, in addition to the results of a prior study.[28] A few subjects reported the cover repeatedly falling off their limb. We attempted to remedy this by using medical tape to tighten the limb cover so that it could be worn more snugly. Surveys were administered and data collected at baseline, and at 6- and 12-week follow-ups. Subjects received a $50 honorarium for participating. Our primary outcome was the severity of PLP and overall bodily pain measured using the numerical pain rating scale (NPRS). The NPRS consists of a 10-cm line with numbers ranging from 0 (no pain) to 10 (worst pain possible). Subjects were asked to indicate the point on the line that represented their pain during an episode of PLP.[29,30] The secondary outcomes included PLP frequency per week, PLP frequency per month, and the Veterans RAND 12-Item Health Survey (VR-12) general health-related quality of life measure.[31]

The Student *t* test was used to calculate the statistical significance of pain improvement and frequency reduction, and VR-12 physical and mental health component scores between the true and sham Farabloc groups. Effects were evaluated on an intent-to-treat basis, and participants who did not complete the follow-up visits were considered not to have had any changes in scores. A 2-sided *P* value of less than .05 indicated statistical significance, and results were presented as between-group differences with 95% confidence intervals (CIs). The sample size was calculated to ensure that we would have enough statistical power to conduct analyses for the primary outcome of NPRS. Effective sample size calculations for this study are based on a prior study[28] that evaluated the use of Farabloc in patients with PLP by using a 2-period crossover design. The effect size from the first period was Õ equal to .637, while the effect size from the second period of the crossover was Õ equal to .820. Assuming that the overall effect of the treatment is at least the average of the 2 effect sizes (Õ=.729), with n equal to 30 in each group (N=60), we will have at least 80% power to detect a difference between the 2 groups with a 2-sided α equal to .05.

RESULTS

Between January 2009 and April 2010, we screened 237 patients by telephone. We excluded 180 patients for the following reasons: 125 did not meet inclusion criteria, 26 could not be contacted, 24 declined, and 5 lived outside Long Beach and could not come for follow-up visits. Fifty-seven eligible

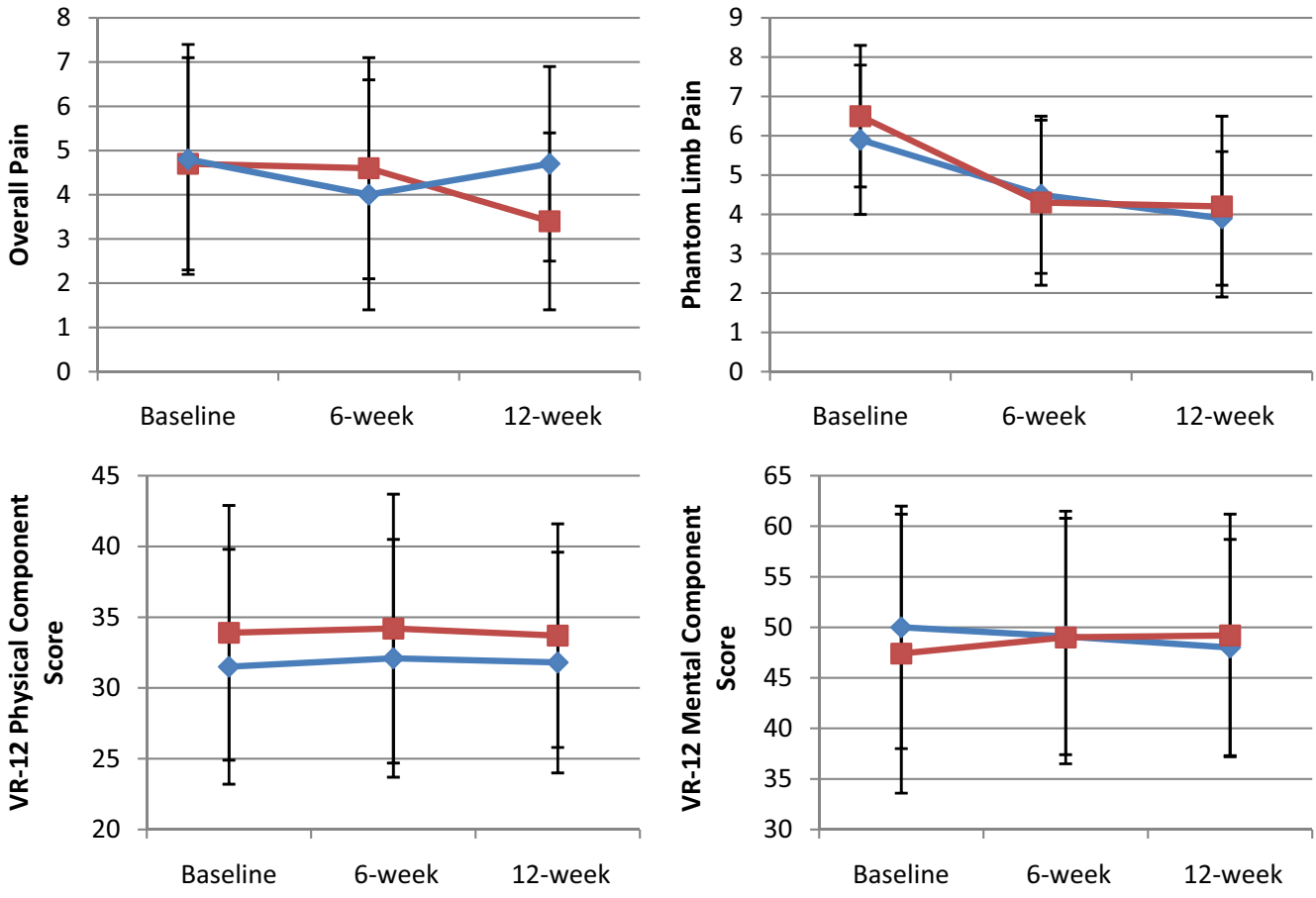

Fig 2. Mean changes in 4 outcomes at 6 and 12 weeks, according to treatment groups. Outcome scores are shown for the true Farabloc group (blue diamonds) and sham Farabloc group (red squares). The values shown are unadjusted means; I bars indicate 95% CIs. Measurements were obtained at baseline, 6 weeks, and 12 weeks. Overall pain and PLP assessments were made on a visual analog scale from 0 (no pain) to 10 (excruciating pain). Summary scores on the physical and mental components of the VR-12 are scored on a T-score metric (mean ± SD: 50±10), with higher scores indicating better health status.

participants were randomly assigned to either the true Farabloc (n=30) or sham Farabloc (n=27) group (fig 1).

Baseline Study Population Demographic and Clinical Characteristics

The demographic and clinical characteristics of the sham and true Farabloc groups were not significantly different (table 1). Table 2 compares baseline, 6-week, and 12-week outcomes between the true and sham Farabloc groups. The true and sham Farabloc groups had similar levels of PLP (5.9±1.9 vs 6.5±1.8) and overall bodily pain (4.7±2.4 vs 4.8±2.6). At 6 weeks, the sham Farabloc group had lower PLP levels than did the true Farabloc group (4.3±2.1 vs 4.5±2.0), whereas the true Farabloc group had lower PLP levels than did the sham Farabloc group at 12 weeks (3.9±1.7 vs 4.2±2.3). The similar trends are observed in overall pain levels, PLP frequency per week, and PLP frequency per month.

Table 3 shows changes from baseline to 6 and 12 weeks for all outcomes. Figure 2 shows changes from baseline to 6 and 12 weeks for overall pain, PLP, VR-12 physical health component score, and VR-12 mental health component score. At 6 weeks, the sham Farabloc group had a greater reduction in PLP than did the true Farabloc group (−2.2 points [95% CI, −6.2 to 1.8] vs −1.4 points [95% CI, −6.4 to 3.6]). The mean between-group difference was 0.8 points (95% CI, −3.6 to 5.2; P=.78), but the difference was not significant. Similarly, at 12 weeks, the sham Farabloc group had a greater reduction in PLP than did the true Farabloc group (−2.4 points [95% CI, −6.8 to 2.0] vs −2.2 points [95% CI, −6.4 to 2.0]). The mean between-group difference was 0.2 points (95% CI, −4.0 to 4.4; P=.38), but the difference was not significant.

At 6 weeks, the sham Farabloc group had a greater decrease in overall pain than did the true Farabloc group (−0.7 points [95% CI, −4.7 to 3.3] vs −0.2 points [95% CI, −5.2 to 4.8]). The mean between-group difference was 0.5 points (95% CI, −4.1 to 5.1; P=.55), but the difference was not significant. At 12 weeks, the true Farabloc group had a greater decrease in overall pain than did the sham Farabloc group. The mean between-group difference was −1.2 points (95% CI, −5.6 to 3.2; P=.22), but the difference was not significant. The similar trends are also seen in PLP frequency per week, PLP frequency per month, and VR-12 mental health component score.

DISCUSSION

This randomized controlled trial shows that true and sham Farabloc did not differ significantly in change over 6 weeks and 12 weeks in PLP, overall pain, PLP frequency, or general physical and mental health. Our results contradict the findings of a prior study,[28] which showed that Farabloc was efficacious in reducing PLP levels. Although the previous study was a randomized, double-blind trial, it used a crossover design with a "washout" or no-treatment period to control for a possible carryover effect of treatment. However, it was unclear how long the washout period was, which may potentially confound the efficacy of the true Farabloc interventions. In addition, the researchers enrolled 52 subjects, but conducted analysis on 34 subjects who completed the trial. Because these investigators chose not to use intent-to-treat analysis, the effect of the true Farabloc group may have been biased. Our study had a much longer follow-up period of 12 weeks compared with the prior study, which better evaluated the true efficacy of Farabloc and its long-term efficacy.

The proposed mechanisms by which Farabloc might affect PLP lie within its ability to shield high-frequency electromagnetic fields or to act like a "Faraday cage." It is hypothesized that high-frequency electromagnetic fields may cause cellular damage and trigger PLP, and the blockade of such stimulus will decrease and prevent PLP. However, the results of this study demonstrate that Farabloc is not an effective adjunctive treatment for chronic PLP, possibly because of PLP having a more central nervous system than peripheral nervous system cause. It may be more beneficial for those seeking alternative treatments to focus on modalities that affect the central nervous system, such as mirror therapy, which has demonstrated reduced PLP pain, duration, and number of episodes.[25]

The sham Farabloc used in our study was an adequate placebo control because it used the same nylon fabric and is indistinguishable from the true Farabloc material. Our study provides additional support for the importance of including a placebo control group in conducting clinical trials to control for potential biases of regression to mean and selection bias. Although clinical trials involving medications commonly use a placebo control group, this occurs less commonly in clinical trials focusing on device intervention or surgical procedures because it is much more difficult to design an adequate placebo control. If we had selected "usual care" as a control group instead of sham Farabloc, we probably would have falsely concluded that the Farabloc material was more efficacious in reducing PLP compared with usual care. To evaluate the true efficacy of Farabloc, it was essential that we included a sham (placebo) control group.

Study Limitations

Our study had some limitations. Our study population had a high proportion of amputations attributable to diabetes and peripheral vascular disease, in contrast to trauma as the main cause of amputation in prior studies. It is possible that Farabloc may be efficacious in treating chronic PLP caused by trauma, but not diabetes, which may be explained by the idea that PLP is not peripheral in nature. Since only 22% of our population reported trauma as the cause of their amputation, we are unable to perform a subgroup analysis to evaluate the efficacy of Farabloc on this subgroup. To appropriately address whether Farabloc is efficacious in treating chronic PLP caused by trauma, one needs to conduct a new study focusing on the amputee population with trauma as the cause of amputation. Another potential limitation is that our subjects used Farabloc as an insert instead of laminating it into the prosthesis. It is possible that using Farabloc as an insert may have resulted in more discomfort and suboptimal fitting and caused more subjects to drop out in the true Farabloc group. However, the randomization and double-blind design of our study should have minimized this potential bias, and subjects in both the true and sham Farabloc groups reported comparable, high levels of compliance and minimal levels of discomfort.

CONCLUSIONS

True Farabloc and sham Farbloc did not significantly decrease PLP levels, overall pain levels, and frequency of PLP episodes per week in our veteran amputee sample. Farabloc does not appear to be an efficacious, adjunctive thrapy for chronic PLP in veteran amputees whose main cause of amputation is diabetes or peripheral vascular disease.

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Supplier

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