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Effect of High-Pressure, Intermittent Pneumatic Compression (HPIPC) for the Treatment of Peripheral Arterial Disease (PAD) and Critical Limb Ischemia (CLI) in Patients without a Surgical Option

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Abstract

Thirty-four subjects with symptomatic PAD or CLI (claudication pain, resting pain, numbness and lower leg/foot ulceration) were randomized into 2 treatment groups. Eighteen received treatment with HPIPC (60 minutes twice daily for 16 weeks) and 16 subjects received standard care consisting of an exercise regimen (walking for 20 minutes twice daily for 16 weeks). The HPIPC device delivers bilateral pressures of 120mmHg. Cycle times provide sequential compression for 4 seconds (+/-0.5 sec.) followed by a 16 second rest period (+/-3.0 sec.), resulting in a 20 second cycle or 3 cycles per minute. The primary endpoint was peak walking time (PWT, time to maximally tolerated claudication pain). Secondary endpoints included: change in resting ABIs, ulcer healing, relief of resting/wound pain, and quality of life index (QOL). Age (73.7 vs. 72.7), baseline PWTs (1-6 minutes) and risk factors were similar in both treatment groups. At 4 weeks the percent change from baseline in PWT, did not vary significantly between treatment groups (17.8% for HPIC and 17% for standard care). After 8 weeks the percent change in PWT for the HPIPC group was 41% compared to 32% for the group receiving standard care (p=0.062). At the week-16 time point the percent change from baseline in PWT was significantly different between treatment arms (35.5% for the standard care group and 54.7% for the group receiving HPIPC [p=0.043]). The mean reduction in wound surface area was 57% and 71% at 12 and 16 weeks respectively for the HPIPC group compared to 45% and 56% for the control group. The HPIPC group reported significantly greater pain relief at the 12 week (p=0.044) and 16 week (p=0.038) time points.

ClinicalTrials.gov ID # NCT01420289

Introduction

An estimated 12-20 million people in the U.S. alone have PAOD (1). The most common presenting symptom of lower extremity PAOD is ambulation-induced muscle pain, or claudication. Normally, a non-surgical, medically treated problem, claudication does not indicate the severity of disease, long-term limitation, or potential limb loss (2). Patients with severe PAOD or critical limb ischemia (CLI) usually require surgical intervention to prevent extremity loss (3). Intermittent claudication may occur in one or both legs and often worsens over time. PAOD symptoms and signs include walking impairment (fatigue, aching, numbness, and pain), ischemic pain at rest, and chronic non-healing wound. PAOD can be improved in many patients with medical treatments (4). Guidelines detail medical and surgical treatment recommendations for lower extremity PAOD patients showing early signs of claudication (4). In the absence of heart failure, cilostazol should be considered in patients with claudication pain (4). In our experience, ischemic ulcers are among the most difficult to treat successfully because they are painful and frequently complicate with infection that can lead to wet or dry gangrene. Arterial ulcers are generally diagnosed clinically and are almost always associated with intermittent claudication, resting pain, pulselessness, and paresthesia. Treatment for ischemic ulcers should be guided by the severity of the PAOD. In patients with mild to moderate PAOD, wounds often improve if the patient is able to ambulate.

High-Pressure, Rapid Sequence, Intermittent Pneumatic Calf and Foot Compression (HPIPC) devices apply compression to the foot, ankle and calf using cuffs attached to the leg. This compression regimen simulates the beneficial effects of brisk walking, without pain or tissue trauma. The foot, ankle and calf veins are almost completely emptied in the sitting position by using pressures that are over twice those typically used in traditional intermittent pneumatic compression (IPC) devices designed for deep venous thrombus (DVT) prevention, CVI or lymphedema. By compressing all the tissues below the knee, a large volume of venous blood is emptied with venous pressure dropping to nearly zero. The increased arterial-venous pressure gradient results in greater arterial flow. Greater arterial flow alters the shear rate and may stimulate endothelial cell function causing the release of nitric oxide along with tissue factor pathway inhibitors that cause dilation and anticoagulation (5). Several studies using HPIPC have shown improvement in perfusion, claudication (resting) pain, and wound healing in patients with PAOD and CLI (6, 7, 8). Reimbursement for AIPC devices has existed since 2004 under HCPCS code E0675. Today reimbursement has now become inconsistent (depending on the decision of DME MAC medical directors) pending the release of a new local coverage determination (LCD).

This randomized prospective controlled study was designed to measure the effects HPIPC therapy compared to Standard Care (consisting of an exercise

program and pharmacological therapy) for the treatment of lower leg ulcers in patients with mild to moderate PAOD.

Study Population and Methodology

From July 2009 to December 2012 we performed a randomized prospective parallel group longitudinal study in an outpatient Wound Care Center setting. In total, 64 patients were evaluated and screened for eligibility and 34 were randomized. All but one (33/34) of the study subjects had been previously diagnosed with type-2 diabetes. All had claudication pain, resting pain, numbness and lower leg/foot ulceration. Eighteen received treatment with HPIPC (60 minutes twice daily for 16 weeks) and 16 subjects received standard care consisting of an exercise regimen (walking for 20 minutes twice daily for 16 weeks). The HPIPC device used in this study was the BioArterial Plus (Figure 1, BioCompression Inc, Moonachie, NJ) This HPIPC device delivers bilateral pressures of 120mmHg. Cycle times provide sequential compression for 4 seconds (+/-0.5 sec.) followed by a 16 second rest period (+/-3.0 sec.), resulting in a 20 second cycle or 3 cycles per minute.

The primary endpoint was peak walking time (PWT, time to maximally tolerated claudication pain). Secondary endpoints included: change in resting ABIs, ulcer healing, relief of resting/wound pain, and quality of life index (QOL). A diagram depicting the study design is presented in Figure 2. The mean age was 72.5 with 45% of the subjects over 75 years. There were 26 males and 8 females and 97% (33/34) had been previously diagnosed with type 2 diabetes. The indication for treatment with HPIPC was nonreconstructable disease (82%) and excessive surgical risk (18%). Patients were excluded from the study if they had gangrene, active infection, had a myocardial infarct within 6mo, were unable to walk, were taking systemic corticosteroids, were receiving treatment with HBO, or had an inflammatory condition that affected healing.

All subjects were followed up weekly for a period of 16 weeks and then once monthly depending on symptom relief. The evaluations at each visit were: PWT, wound surface area, resting ABI, pain, QOL and adverse events. All patients including controls were allowed to continue their pharmacological treatments. Treadmill testing was at a constant load with 10% gradient at 3.5 km/h Peak walking time = maximum time (distance) terminated by pain (PWT = ACD) Treadmill Testing was supervised by an exercise physiologist at The Bronx YMCA but the exercise routine was unsupervised. Wound surface area was measured using photodigital planimetry software (PictZarÊ , BioVisual Technologies, LLC, Elmwood Park, NJ). Resting ABIs were measured using a directional continuous wave hand-held Doppler (ArjoHuntleigh, Inc USA, Addison, IL). And testing was at dorsalis pedis and posterior tibial arteries. The resting ABI was determined by taking the highest of the 3 ankle Doppler readings and dividing it by the average of 3 brachial systolic readings. Pain relief was measured using the faces pain scale and pain index by using the visual

analog scale (VAS). The Short Form-36 Health Survey Questionnaire was used to determine physical and mental QOL parameters (9). The questionnaire was administered at baseline (prior to treatment), at week-8 and week-16.
Percent change from baseline PWTs were compared using Wilcoxon rank sum test. Chi-Square test was used for categorical values and Student's t-Test used for continuous variables. The analysis was by intention to treat. SPSS statistics software Windows version 11.5 was used for all statistical calculations.

Results

Baseline ABIs, PWTs (1-6 minutes), wound surface area, and risk factors were similar in both treatment groups. At 4 weeks the percent change from baseline in PWT, did not vary significantly between treatment groups (17.8% for HPIC and 17% for standard care). After 8 weeks the percent change in PWT for the HPIPC group was 41% compared to 32% for the group receiving standard care (p=0.062). At the week-16 time point the percent change from baseline in PWT was significantly different between treatment arms (35.5% for the standard care group and 54.7% for the group receiving HPIPC [p=0.043]). The mean PWTs for both treatment groups are presented in Figure 3 and the mean change from baseline PWTs for HPIPC and exercise controls are shown in Figure 4.

The mean percent reduction in wound surface area was 57% and 71% at 12 and 16 weeks respectively for the HPIPC group compared to 45% and 56% for the control group (Figure 5).

The HPIPC group reported less pain and significantly greater pain relief at the 12 week (p=0.044) and 16 week (p=0.038) time points (Figure 6).

The mean resting ABIs at baseline and at 4, 8 and 16 weeks are presented in Table 1. There was a slight improvement (not statistically significant) in the ABIs of both treatment groups through time. However, the resting ABIs between the 2 treatment arms were similar throughout the 16 week study period.

The foot to chest skin temperature index (FCSTI) increased in the HPIPC group from 0.73 at baseline to 0.81 after 8 weeks and 0.88 after 16 weeks. Temperatures at the dorsum of the foot did not significantly change in the exercise control group. The FCSTI was 0.71 at baseline and 0.75 after 16 weeks. These differences were statistically significant at both the 8 and 16-week time points ($p<0.05$).

Perceived improvement in QOL from the HPIPC and exercise control group is presented in figure 7. Compared to the control group, the HPIPC group reported improvement in both physical function and bodily pain. These differences were statistically significant at the 4 month evaluation period.

Discussion

In 1917 Sinkowich and Gottlieb (10) were the first to report the benefits of intermittent compression for the treatment of thromboangiitis obliterans (Burger's Disease). In 1934, Herman and Reid (11) demonstrated that pneumatic

compression improved tissue perfusion in patients with PAOD. Since then, several trials on the effects of HPIPC for the treatment of arterial claudication and CLI have been reported. The first prospective, randomized, controlled evidence for an increase in arterial blood flow with HPIPC in patients with intermittent claudication was reported in 1993 (12) and that was followed by 3 additional trials (13, 14, 15). In all of these studies the investigators reported significant beneficial effects on walking distance, symptoms and systolic blood pressure measurements on both upper and lower limbs with therapy. Many published reports on the effects of HPIPC on CLI have been limited to clinical outcomes (16, 17, 18) and case series that for the most part have been retrospective (17, 19, 20). Kavros et al (21) reported their results of a retrospective survey of 24 consecutive patients with CLI that were treated with HPIPC. These findings were compared to a control group consisting of 24 patients who received standard pharmacological therapy and wound care but were not treated with HPIPC. Wound healing and limb salvage were significantly better ($p<0.01$) in the HPIPC group. In addition, when compared to the HPIPC group the odds ratio of limb loss in the control group was 7.0. At the end of the 18 month follow-up period, tissue perfusion measured by resting trans-cutaneous oxygen (TcPO2 levels) was significantly higher in the HPIPC group ($p=0.0038$). Also in 2008 Sultan, Esan and Fahy (22) reported results of a parallel group longitudinal observational study on 35 patients with 39 critically ischemic limbs treated with HPIPC therapy. Their data showed that HPIPC reduced amputations, significantly increased toe pressures and improved popliteal artery blood flow. More recently, Sultan et al (23) reported their assessment of 171 CLI patients who were unsuitable for surgery and received HPIPC therapy as a last resort to amputation. The study consisted of HPIPC therapy for 3 months with a 13 month follow-up. HPIPC resulted in significant increases in mean toe pressure and popliteal flow. The median amputation-free survival was 18 months and limb salvage at 3.5 years was 94%. They concluded that HPIPC therapy was a cost-effective and a clinically efficacious solution in CLI patients with no option of revascularization. Furthermore, it provided adequate limb salvage and improved amputation-free survival while providing relief of rest pain without the use of pain medications.

To our knowledge, this is the first prospective, randomized, exercise-controlled, clinical study to evaluate the safety and efficacy HPIPC. The results reported here are generally consistent with the findings of van Bemmelen et al (20) and others (21, 22, 23, 24, 25, 26) who have reported on a variety of other case series, observational and controlled studies.

In this study, HPIPC therapy was performed using the BioArterial Plus pneumatic compression device. The therapeutic HPIPC regimen was for 1 hour twice daily for a 16 week period. This device has 2 pressure cuff bladders one applied to the foot and ankle and one to the calf. It delivers pressure of 120mmHg (with a time to inflation of 0.6 seconds). Cycle times provide sequential compression (first to the foot) for 4 seconds (+/-0.5 sec.) followed by a 17 second rest period (+/-3.0 sec.), resulting in a 20 second cycle or 3 cycles per minute.

In the Montori et al (17) and Kavros et al studies (21) the requested HPIPC

treatment regimen consisted of three 2-hourly sessions per day using the ArterialFlow System (DJO Global, Vista CA). This compression device consists of a single pressure cuff bladder applied to the calf. The inflation pressure was 85-95 mmHg, delivered for 2 seconds (with a time to inflation of 0.2 seconds) followed by an 18 second rest period at 0 pressure, resulting in a 20 second cycle 3 times per minute.

In the van Bemmelen et al, Sultan, Esan and Fahy and Sultan et al studies (20, 22, 23) the requested HPIPC regimen consisted of two 3-4-hourly sessions per day using the ArtAssist System (ACI Medical Inc, San Marcos CA). This compression device consists of 2 cuff bladders (foot/ankle & calf). It delivers pressure of 120mm Hg (with a time to inflation 0.3 seconds) and an inflation time of 4 seconds followed by a 16 second rest period at 0-pressure, resulting in a 20 second cycle 3 times per minute.

Interestingly, although the specifications of the pneumatic devices used in these studies vary to some extent (maximum pressure, foot and calf compression vs. calf alone, and time to inflation), the measured parameters and clinical effects reported in all studies were all similar. The commonality all HPIPC pneumatic compression devices possess is that all deliver a short burst of high pressure 85-120mmHg) to the calf with a similar rest period and cycle times.

Our protocol of HPIPC of 120 days with 1 hour in the morning and 1 hour in the evening materialized from a feasibility pilot study performed earlier on 12 subjects (21). The 1 hour twice daily regimen produced the most compliance and was generally adhered to by most patients. Also twice daily therapy correlates with the exercise program performed by the control group. Our protocol varies from the treatment regimen used previously in the van Bemmelen et al study (6-8 hours daily, 20) and those of others (22, 23), where HPIPC therapy varied between 3 and 6 hours daily. During our pilot feasibility study we found that more than 4 hours/day treatment regimen was unrealistic for our patient population.

Our findings are also consistent with those of Louridas et al., and Delis et al (16, 27) who noted that HPIPC increases blood flow, relieves resting pain and limits tissue damage. In our experience we found that therapy with HPIPC causes a reactive hyperemia. This finding was first reported by Abu-Own et al (28) that HPIPC lowers vascular resistance with the release of endothelial-derived relaxing factors.

Our study showed no significant differences in resting ABIs between the HPIPC group and the exercise control group at baseline or at any of the evaluation periods (4, 8 and 16 weeks). This finding is in agreement with Kavros et al (21) who also noted no differences in ABIs at baseline or upon completion of their study.

The proposed mechanism of action of HPIPC include an increase in the arteriovenous pressure gradient, suspension of peripheral sympathetic autoregulation, and enhanced release of nitric oxide secondary to augmented flow and greater shear stress (29, 30). The benefits of HPIPC after several

months have been shown to be due to the development of collateral vessels (31).

Conclusion

HPIPC therapy consisting of 2 hours daily for a period of 16 weeks significantly improved peak walking time, reduced resting pain, improved healing rates physical function and bodily pain. There were no device-related complications allowing for long term use. Based on patient treatment diaries, compliance to the recommended treatment regimen was >85% in the HPIPC group and 58% in the exercise control group. This study further supports that HPIPC is safe and effective and is important adjunct to the medical treatment of PAD and CLI.

Acknowledgements

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Disclosures

Dr. Alvarez is a member of the Speakerôs Bureau for BioCompression Systems Inc. Dr. Wendelken is a principal of BioVisual Technologies, LLC the manufacturers of PicZarÊ (the photodigital planimetry software used to measure the wounds). Drs. Markowitz and Comfort have no conflicts to declare.

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Figure 1.
Photograph of study subject undergoing HPIPC therapy. Therapy was prescribed for 60 minutes twice daily for 16 weeks.

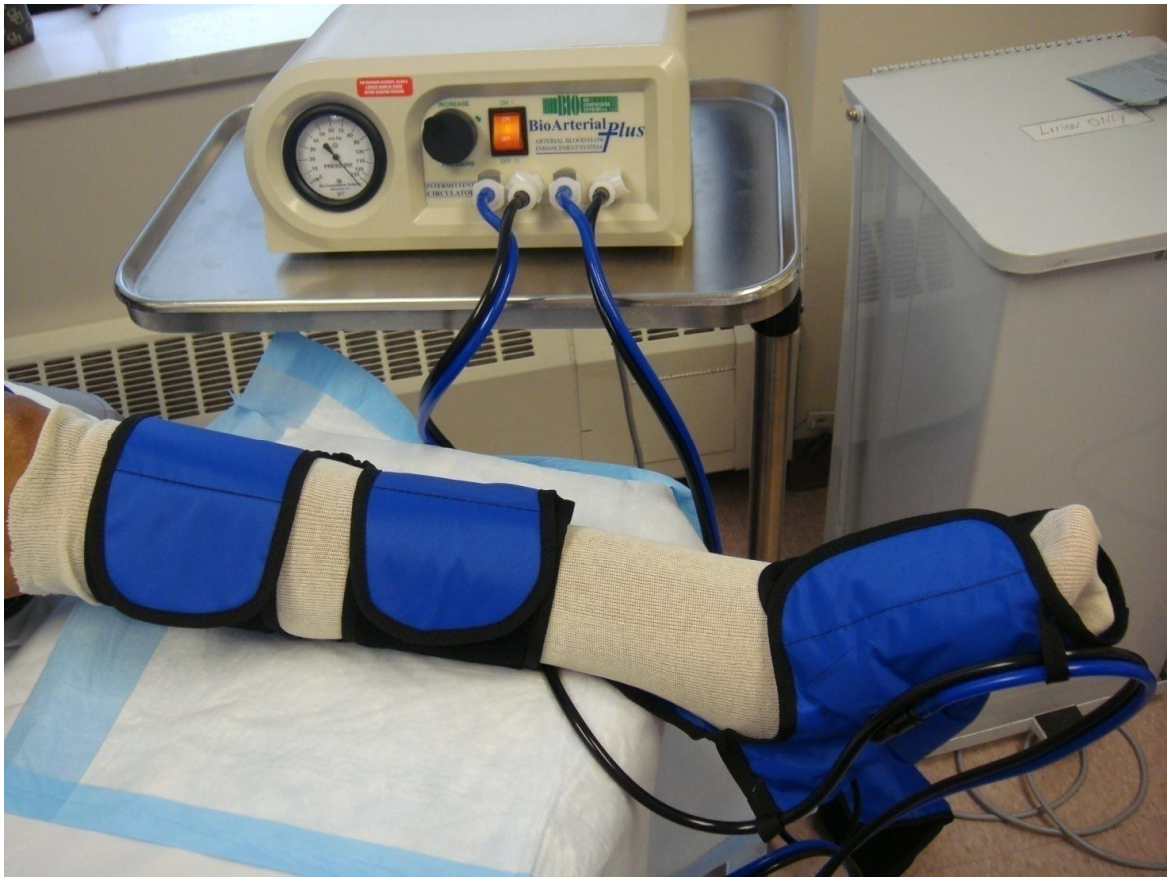


Figure 2.

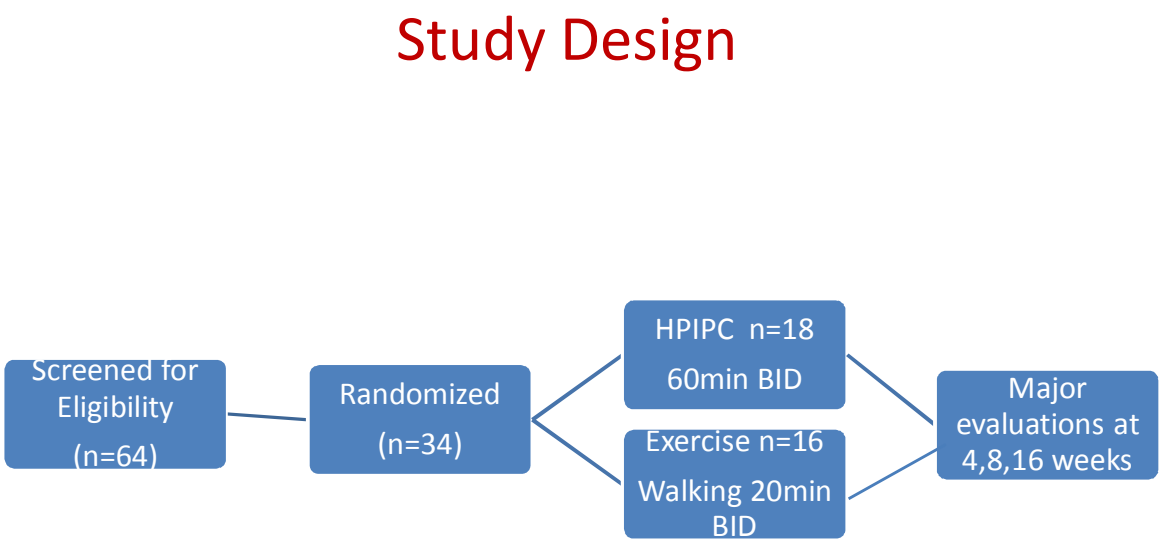

Study Design
Screened for Eligibility (n=64)
Randomized (n=34)
HPIPC n=18 60min BID
Exercise n=16 Walking 20min BID
Major evaluations at 4,8,16 weeks

Figure 3.

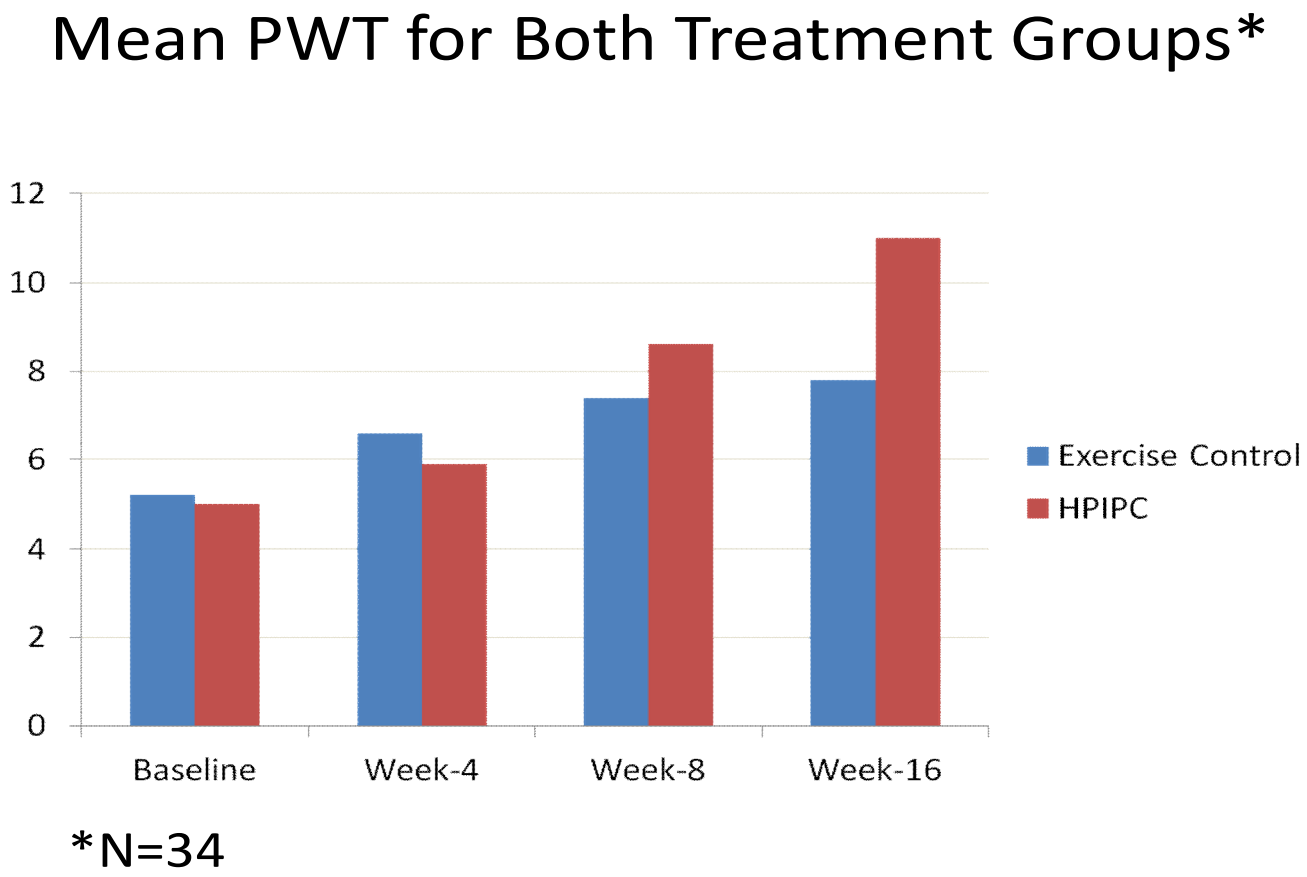
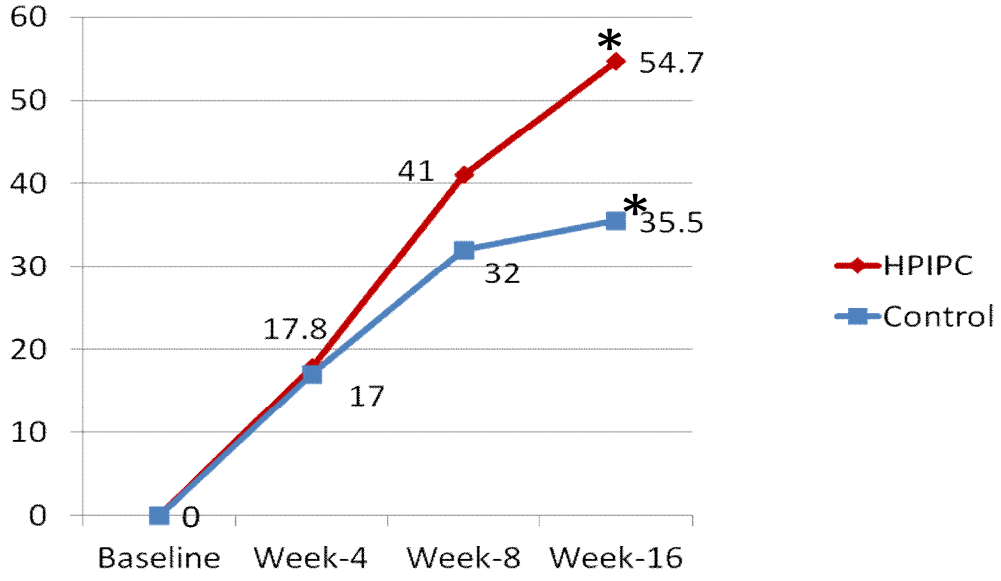

Mean PWT for Both Treatment Groups*
12
10
8
6
4
2
0
Baseline
Week-4
Week-8
Week-16
Exercise Control
HPIPC
*N=34

Figure 4.

Mean Change from Baseline in PWT at 4, 8 and 16 Weeks for HPIPC and Exercise (Control) Groups (N=34)



*P=0.043

Figure 5.

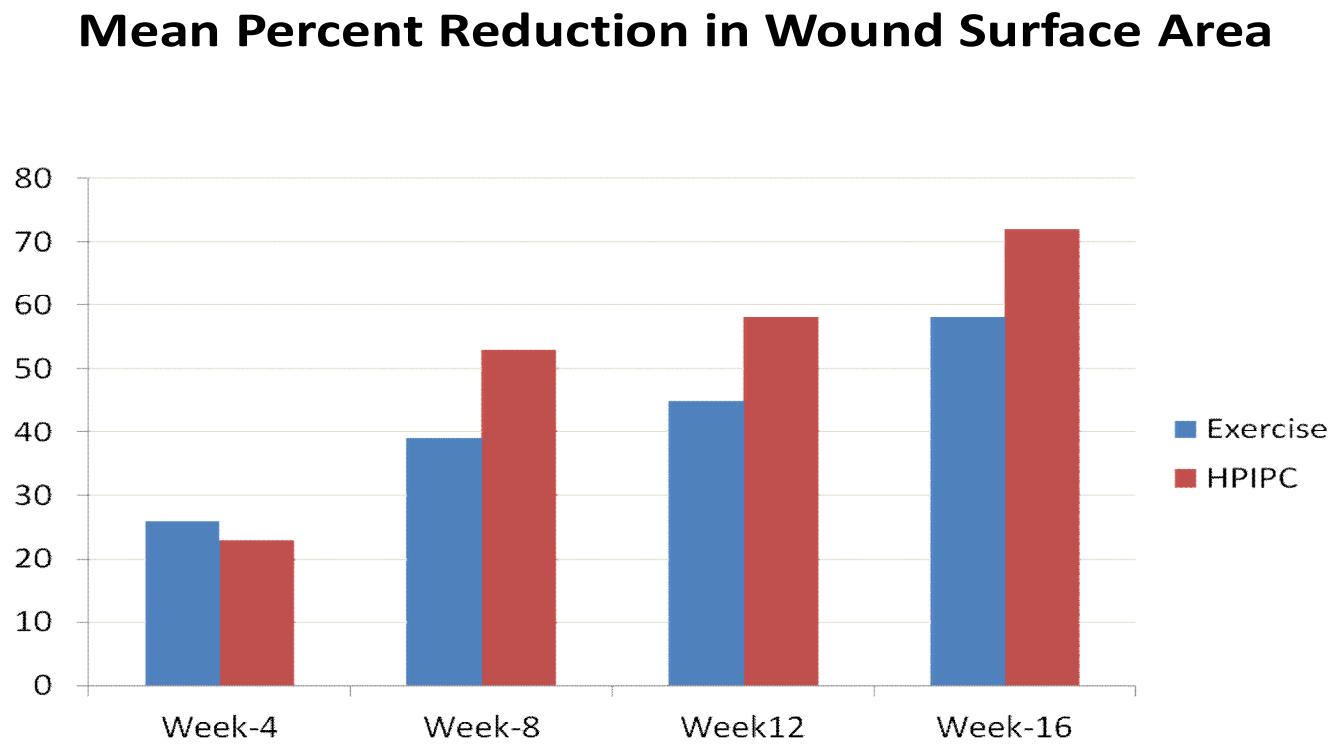

Mean Percent Reduction in Wound Surface Area
80
70
60
50
40
30
20
10
0
Week-4
Week-8
Week12
Week-16
Exercise
HPIPC

Figure 6.

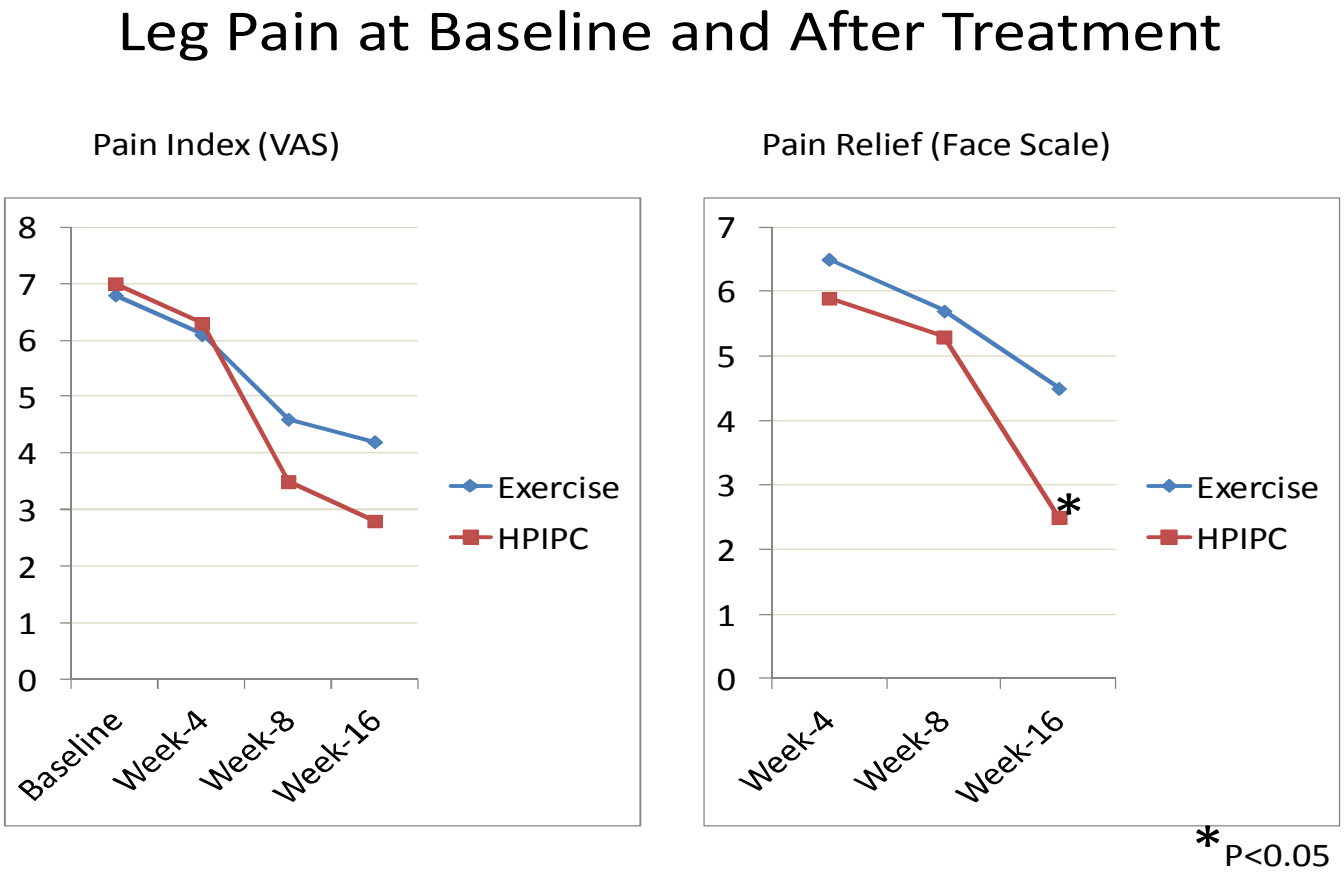

Leg Pain at Baseline and After Treatment
Pain Index (VAS)
8
7
6
5
4
3
2
1
0
Baseline
Week-4
Week-8
Week-16
Exercise
HPIPC
Pain Relief (Face Scale)
7
6
5
4
3
2
1
0
Week-4
Week-8
Week-16
*
Exercise
HPIPC
*P<0.05

Figure 7.

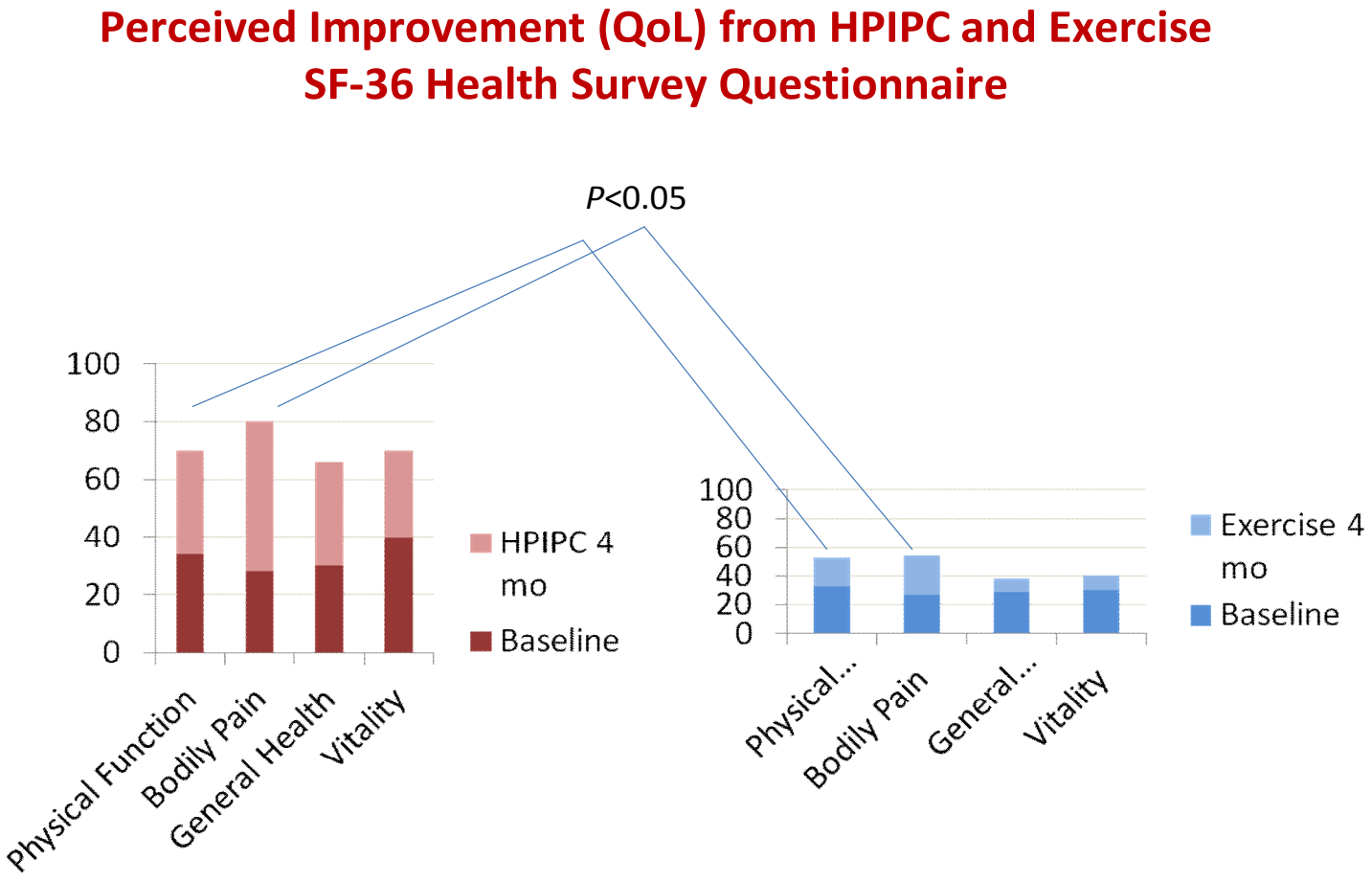

Perceived Improvement (QoL) from HPIPC and Exercise
SF-36 Health Survey Questionnaire
P<0.05
100
80
60
40
20
0
Physical Function
Bodily Pain
General Health
Vitality
HPIPC 4 mo
Baseline
Physical...
Bodily Pain
General...
Vitality
Exercise 4 mo
Baseline

Table 1

Mean r-ABIs at Baseline and at 4,8 and 16 Weeks*

Time	**HPIPC**	**Exercise Control**
Baseline	0.58	0.61
Week-8	0.64	0.69
Week-16	0.63	0.64

*Resting ABI (N=30)

Table 2
Mean Foot to Chest Skin Temperature Index at Baseline, 8 and 16 Weeks

Time	**HPIPC**	**Exercise Control**
Baseline	0.73	0.71
Week-8	0.81*	0.74
Week-16	0.88*	0.75

*P<0.05