

**Does Anodyne Light Therapy Improve Peripheral Neuropathy in Diabetes? A  
Double Blind, Sham Controlled Randomized Trial to Evaluate  
Monochromatic Infrared Photo Energy**

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## **ABSTRACT**

*Objective:* To determine the efficacy of Anodyne Monochromatic Infrared Photo Energy (MIRE) in-home treatments over a 90-day period to improve peripheral sensation and self-reported quality of life in persons with diabetes mellitus.

*Methods:* This was a double blinded randomized, sham controlled clinical trial. We randomized 69 persons with diabetes and vibration perception threshold between 20-45 volts into two treatment groups. Patients were randomly assigned to active or sham treatment groups. Sixty patients (120 limbs) completed the study. Anodyne units were used at home every day for 40 minutes for 90 days. We evaluated nerve conduction velocities, vibration perception threshold, Semmes Weinstein Monofilaments (SWM) (4, 10, 26, and 60 gram monofilaments), the Michigan Neuropathy Screening Instrument (MNSI), 10 cm visual analog pain scale, and the Neuropathy Quality of Life Instrument. We used a nested repeated measures MANOVA design. Two sites (great toe and fifth metatarsal) were tested on both the left and right feet of each patient, so, two feet were nested within each patient, and two sites were nested within each foot. To analyze the ordinal SWM scores, we used a nonparametric factorial analysis for longitudinal data.

*Results:* There were no significant differences in measures for quality of life, Michigan Neuropathy Screening Instrument, VPT, SWM, or NCV's in active or sham treatment groups ( $p>0.05$ ).

*Summary:* Anodyne MIRE therapy was no more effective than sham therapy in the treatment of sensory neuropathy in persons with diabetes.

**M**onochromatic infrared energy (MIRE) has been suggested to improve diabetic sensory neuropathy and even to prevent foot ulcers[1-7]. However, the results of clinical studies are mixed. In a randomized clinical trial (RCT) by Clift and colleagues MIRE did not show improvement in peripheral sensation compared to sham[8]. In contrast, RCTs by Leonard and Arnall report a significant improvement in peripheral sensation with MIRE. All three studies randomized one foot to receive active therapy and one to receive sham therapy. In all three studies Semmes Weinstein monofilament testing was used to evaluate the primary clinical outcomes. Leonard randomized 27 patients' extremities to receive active or sham MIRE in a two week study[4]. Leonard reported a significant improvement in peripheral sensation with Semmes Weinstein Monofilaments (SWM), the Michigan Neuropathy Screening Instrument (MNSI), pain, and in self-reported balance impairment in a subset of patients with "less severe" neuropathy, whereas patients with severe neuropathy did not improve. Arnall used a similar approach and randomized 22 patient's extremities to active or sham therapy for eight weeks[6]. Arnall reported improved sensation with SWMs but not with vibration perception threshold testing.

We planned a randomized clinical study to determine the efficacy of Anodyne MIRE therapy to improve diabetic peripheral sensory neuropathy. Our hypothesis was that MIRE therapy would improve measures of peripheral sensation compared to patients that received sham therapy.

## **METHODS**

This study was conducted as a double blinded, sham controlled randomized clinical trial to determine the efficacy of treatments

using the Anodyne MIRE Therapy. The study was approved by the hospital institutional review board, and informed consent was obtained prior to enrollment. We randomized 69 subjects with 60 (120 limbs) completing the 3 month evaluation period: 33 active therapy patients and 27 sham controls. We collected patient information regarding age, gender, and duration of diabetes and glycated hemoglobin at baseline and at the conclusion of the study.

Inclusion criteria for the study included: subjects with diabetes mellitus that were mentally competent and able to understand and comply with the study, vibration perception threshold  $\geq 20$  volts and  $\leq 45$  volts, and able to complete the required study visits and record treatment activity in the study log book. Subjects were excluded if they met the following criterion: uncontrolled hypertension  $>180$  systolic or  $>110$  diastolic, pregnant or breastfeeding or likely to become pregnant during study, active malignancy on the lower extremities, nerve damage as a results of prior reconstructive or replacement knee surgery, back surgery, spinal stenosis, spinal compression or radiculopathy, non-ambulatory, history of neuromuscular disease, leprosy, chronic alcoholism, or sarcoidosis, foot ulcerations, transmetatarsal or higher amputation.

***Monochromatic Infrared Photo Energy Therapy.*** We used the Anodyne Therapy Professional System 480 (Anodyne Therapy, LLC Tampa, Florida) for application of the near infrared light therapy treatments. The device consists of a base power unit and therapy pads containing 60 near-infrared (890 nm) gallium aluminum arsenide diodes used to increase circulation by dilating arteries and veins. Active units provided  $1.3 \text{ J} \cdot \text{cm}^{-2} \cdot \text{min}^{-1}$  of photo energy. Sham devices were created with the identical appearance of active units

and acquired from the same factory. In the sham units, the diodes were inactivated, so that no near-infrared photo energy was emitted, and heaters were added and preset at 37°C in order to provide local warmth. Neither investigators nor subjects could discriminate active from sham devices either visually or by temperature. Active versus inactive therapy pads were identified by serial number. The serial numbers were provided to the investigators in a sealed package to be open at the conclusion of the study. Active and sham units were sent by the manufacturers and randomly selected from inventory. Four Anodyne therapy pads were placed in the following locations on each lower limb: two on the plantar aspect of the foot in a T formation; and one pad on the medial and lateral side of the calf for 40 minutes daily using a preset and locked power setting. Subjects were instructed to use the device seven days a week for 90 days and to keep a daily treatment log to document the time and length of therapy. Subjects received written and verbal instructions on how to use the Anodyne device at the time of enrollment, and they returned after two weeks of therapy to review the protocol.

**Sensory Evaluation.** Sensory function was evaluated with Semmes Weinstein Monofilaments (Touch-Test™ Sensory Evaluator, North Coast Medical, Inc. Morgan Hill, CA), Vibration Perception Threshold testing (VPT, Xilas Medical San Antonio, Texas), Nerve Conduction Velocity (NC-Stat® NeuroMetrix, Inc., Waltham, MA), Michigan Neuropathy Screening Instrument (MNSI), and 10 cm Visual Analog Scale. We used 4, 10, 26, and 60 gram Semmes-Weinstein Monofilaments (4.56, 5.07, 5.46, and 5.88) to evaluate pressure sensation at 10 sites on each foot. The ten sites tested included the plantar aspect of the first, third and fifth digits, the plantar aspect of the first, third, and fifth metatarsal heads, the medial

and lateral plantar midfoot, the plantar heel, and the dorsal midfoot. The filaments were applied until they began to bend and held in place for approximately 1.5 seconds. Each site was tested randomly during the sensory evaluations. We recorded the lowest monofilament recognized accurately by patients at each anatomic site. The outcomes of the SWM testing were considered to be on an ordinal scale. If the lowest perceived SWM was a 4 gram monofilament the measure at the site was scored a “1,” and if the lowest perceived SWM was a 10 gram monofilament the measure at the site was scored a “2” and so forth (4 g = “1”, 10 g = “2”, 26 g = “3”, 60 g = “4”, and greater than 60 g = “5”). We replaced monofilaments after evaluating every ten patients.

We evaluated Vibratory Perception Threshold (VPT) with the VPT Testing instrument (Xilas Medical San Antonio, Texas) as described by Young and Lavery [9, 10]. Measurements were taken at the distal aspect of the great toe and the fifth metatarsal head. The amplitude of vibration was read as a continuous variable in volts on a 0-100 scale. Both monofilament testing and VPT testing were performed with subjects in a reclined sitting position. Both tests were demonstrated on the upper extremity, and the subjects were allowed to visualize the testing process. The subjects were then asked to close their eyes for the lower extremity testing procedures. The subjects responded by saying “yes” when they felt the monofilament and then were asked to correctly identify the site at which they felt the monofilament. If the patient could not identify the site correctly, the test was recorded as a negative response. We evaluated nerve conduction velocities in the tibial nerve and superficial peroneal nerve of each subject with the NC-Stat nerve conduction system (NC-Stat®, NeuroMetrix, Waltham, MA) on the right foot only.[11] Subjects were not included in the analysis if

they had unobtainable tibial or peroneal nerve responses.

***Neuropathy Quality of Life Instrument.***

Subjects completed the Michigan Neuropathy Screening Instrument (MNSI)[12] and the Neuropathy Quality of Life Instrument (NeuroQoL) at each visit. The NeuroQoL is a neuropathy-specific Quality of Life instrument [13]. It consists of a 35 item survey organized as a hierarchical scale and it assesses patients' subjective evaluation of their ability to function and their quality of life in six domains. Each domain is assessed with questions designed to measure pain and paresthesias, symptoms of loss of sensation, sensory motor symptoms, limitations in daily activities, interpersonal problems and emotional burden. It has been validated and has a high-degree of internal consistence (Cronbach's alpha = 0.94) and robust test-retest reliability ( $r = 0.85$ )[13].

***Statistical Analysis.*** In the statistical analysis of the data, we performed an "efficacy analysis" in which we only included subjects that completed the entire 90 day treatment period. Our rationale for using this approach was to evaluate the efficacy of this therapy under ideal treatment parameters.

Initially, descriptive statistics were generated on all variables. To test if the treatment groups were statistically similar, age and duration of diabetes were compared by treatment, gender and medication regimen using a MANOVA statistical framework. In addition, a cross tabulation of the counts of patients by gender, medication and treatment was analyzed using a log linear model. The VPT scores, continuous variables measured on at least a ratio scale, were analyzed using a nested repeated measures design via the MIXED procedure in SPSS v14. Two sites (great toe and fifth metatarsal) were tested on both the left and right feet of each patient, so

for the experimental design, the two feet were nested within each patient and two sites were nested within each foot. Other variables that were or could be feasibly treated as continuous variables, glycated hemoglobin, nerve conduction velocities (several measures for both peroneal and tibial nerves), visual analog scale pain scores, Michigan Neuropathy Screening Instrument scores and Neuropathy-specific Quality of Life (NeuroQoL) scores were evaluated using repeated measures analysis of variance (ANOVA) via the SPSS GLM procedure. Initially, repeated measures tests were run with treatment group as a factor and also with continuous covariates (age and duration of diabetes) and categorical factors (gender and medication type). However, because none of these added factors were significant, a single-factor repeated measures design was used with just one factor, treatment group. The four monofilaments provided at most a five-level ranking of neuropathy. To analyze the ordinal SWM scores a nonparametric factorial analysis for longitudinal data was used. [14, 15] NeuroQoL survey has pairs of related questions: one on a five-point scale for degree or severity and one on a three-point scale of importance. These five and three-point scale values were multiplied together forming a composite score. These paired questions were grouped into five categories (Table 2), and each category had a question on the overall importance of that category. A composite category score was created by multiplying the sum of individual category scores by the category importance score providing an approximately continuous measure that could be analyzed by repeated measures ANOVA.

In all of the statistical tests, the main focus was to examine if there was a treatment-time interaction. The treatment-time interaction looks at four effect sizes: treatment at baseline, treatment after three months, sham at baseline, and sham after three months. It

tests if there was a change in the effects of the treatment group over time compared to the sham over time. If there was a significant treatment-time interaction, differences in the baseline and ending marginal effects were examined to determine if the sham or anodyne treatments were associated with the result.

## RESULTS

We screened 174 subjects. Sixty-nine subjects met inclusion and exclusion criteria and were randomized into the study. Sixty subjects (120 limbs) completed the 90 day evaluation period. There were 33 completers in the Anodyne MIRE treatment arm and 27 in the sham treatment arm. One study related adverse event was reported. One subject developed a small wound on his lower leg that healed without incident. Of the nine non-completers, one had a myocardial infarction, one could not attend visits because of work, and the remainder withdrew without any additional comment.

Demographics were similar among active and sham groups at baseline (Table 1.). There was no statistically significant changes in SWM, VPT, NCV, MNSI, VAS pain, (Table 1) or NeuroQoL scores (Table 2) for active compared to sham therapy. The ordinal results for the SWM tests were analyzed using a nonparametric factorial design for longitudinal data (Table 3). The effect size is based on an integral of the product of functions derived from empirical distribution functions of the overall or marginal distributions of the ordinal data. [14, 15] Overall, there was no statistical evidence that the Anodyne treatment was effective in improving sensory perception compared to the sham treatment. Not only was there no clear benefit from the treatment, there was a large placebo effect in which sham therapy showed double the number of improvements in effect size compared to the treatment.

We used the NeuroQoL to evaluate self-reported functional status (Table 2). For each category the sham results showed a larger increase than for the Anodyne treatment. There was one statistically significant treatment-time interaction, “Limited Home & Leisure Activities,” but it was significant because the sham group improvement was much greater than the Anodyne group.

To evaluate balance we used two questions from the NeuroQoL, that evaluate unsteadiness when standing and walking (Table 1). There was a significant improvement in self-reported unsteadiness when walking in the sham treatment group ( $p=0.05$ ). To evaluate pain we used a 10 cm visual analog pain scale and the NeuroQoL (Table 2). Neither demonstrated any significant change during the treatment period.

## CONCLUSION

The results of this study demonstrate that Anodyne MIRE therapy provided no more improvement in peripheral sensation, balance, pain, or quality of life than sham therapy. The daily treatment and the 90 day evaluation period in our study were more frequent and longer than previous studies. We used several objective and subjective measures of sensory neuropathy, and none of them showed a significant improvement after 90 days of therapy compared to sham treatment. Our results are similar to the RCT reported by Clift (8).

Evaluating the data from Leonard and Arnall would suggest that there was probably not an overall improvement in sensory neuropathy despite their stated conclusions. There were several classical errors in analysis. First, Leonard did not perform an intent-to-treat analysis. The data from the entire study population were not included in the analysis or reported in the paper. Instead, he separately evaluated subgroups with moderate and

severe neuropathy. It seems very likely that there would not be a significant effect if the entire patient population had been included in the analysis. Second, the analysis used was not appropriate in both Arnall and Leonard's paper. The Semmes Weinstein data are count data and the authors used tests for continuous data in their analysis. Third, both Arnall and Leonard failed to provide analysis comparing the interaction of how patients' conditions changed over time for sham and active therapy. An examination of the data suggests that while there was a significant marginal improvement, there was not a significant change over time between the active and sham treatments. Both studies separately compared means at the beginning and end of the study via a t-test for the active and sham treatments and then compared the p-values from these separate tests. This results in what is called a Simpson's paradox, while one of the marginal results is significant, the comparison of treatment differences over time are not.

**Placebo Effect.** Surprisingly there was a strong placebo effect in our study and in previous RCTs. Clifft, Arnall and Leonard demonstrated improved sensation with Semmes Weinstein monofilaments in the sham group. Arnall was the only study to evaluate vibration perception threshold. No data were provided in the text, but the authors indicated that VPT did not improve. In fact in Leonard's study, there was a significant improvement with the Michigan Neuropathy Screening Instrument questionnaire in both active and sham groups with moderate neuropathy. If these studies had failed to include a sham therapy arm, MIRE would appear to provide a significant improvement in peripheral sensation because of the placebo effect. This may help to explain the observations in uncontrolled studies that MIRE was effective<sup>1-3, 5</sup>. Based on these observations, the majority of the existing

work that supports MIRE therapy for pain, sensory improvement or wound healing is problematic.

One of the main limitations when evaluating neuropathy is the accuracy and reliability of the tools for longitudinal testing. The Semmes-Weinstein monofilament was the primary instrument used to assess neuropathy in Leonard, Arnall and Clifft's RCTs and in several uncontrolled studies. Even new monofilaments have considerable variation in accuracy and durability with significant reduction of loading force after repetitive loading.[16-19] Our study as well as the study by Clifft used several "levels" of Semmes Weinstein monofilaments. In Clifft's RCT, a new set of SWMs from North Coast Medical was used at the beginning of the study[8]. However, in the study by Leonard no information was provided about the manufacturer, previous use or replacement of SWMs[4]. We used 4, 10, 26, and 60 gram monofilaments and replaced them after evaluating every ten patients in an effort to reduce SWM wear and increase its' reproducibility. In addition, our study and Arnall's paper used vibration perception threshold testing. VPT is a well accepted device for quantitative sensory testing<sup>20</sup>; however, several studies have identified large coefficients of variation when testing persons with diabetes and the elderly.<sup>21,22</sup>

In addition, our study may have been underpowered to determine subtle changes in neuropathy with therapy. However, previous studies reported positive results with fewer subjects with shorter evaluation periods that received fewer treatments than in our RCT. We did not see any strong trends that MIRE was different than sham therapy, and in fact there were instances when sham therapy was superior to MIRE therapy.

***Pain and Balance.*** Evaluation of pain and balance were not primary objectives in our study or in other RCTs. We included them because they were outcomes used in a previous study<sup>4</sup>. One of the problems in previous work was that “pain” and “balance” were not separately evaluated in legs treated with sham and active therapy. There was no distinction based on therapy, so it was not possible to determine if the reported “improvement” was due to the effect of MIRE or the strong placebo effect observed in all of the randomized clinical trials with MIRE. We did not enroll subjects based on symptoms of painful neuropathy or balance impairment, so many of our study subjects did not have severe symptoms. Our results did not identify any difference in pain or balance in patients treated with MIRE or sham therapy. However, we probably did not enroll the optimal study population to evaluate these outcomes.

The result of this study should be generalizable to persons with diabetes with “loss of protective sensation.” In normal practice MIRE therapy is initially provided three times a week in a clinical setting. Many patients will subsequently use the device at home, so our daily “dosing” regimen and period of evaluation reflects long term use patterns. At present there is no compelling evidence that MIRE can improve “loss of protective sensation” so that high risk people with diabetes have a decreased risk of foot complications. Our results did not show a change in self-reported balance, pain, quality of life, electrodiagnostic studies, or clinical sensory measures. MIRE is no more effective than placebo or sham therapy to improve peripheral sensation, balance and pain in persons with diabetes mellitus.

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**TABLE 1.** Results for Demographics and Repeated Measures Statistical Analysis

Demographics						
		Anodyne	Sham	P-value		
<b>Number of Patients</b>		<b>33</b>	<b>27</b>			
Age (years)		65.7 (1.9)	64.2 (2.0)	0.59		
Gender % male		35%	0.2			
Duration of Diabetes (years)		13.4 (2.0)	13.4 (2.1)	0.99		
<b>Diabetes Medication (counts of patients)</b>	Oral	22	21	0.34		
	Insulin	7	2			
	Combo	3	4			
	Diet	1	0			
Repeated Measures General Linear Model (GLM) Statistical Results						
		Anodyne		Sham		P-value
		Start	End	Start	End	
<b>Glycated Hemoglobin</b>		7.6 (0.22)	7.6 (0.21)	7.7 (0.26)	7.7 (0.24)	0.70
<b>Vibration Perception Threshold (VPT) Great Toe (Volts)</b>	<b>Right</b>	33.5 (1.1)	34.8 (3.0)	30.4 (1.2)	36.1 (3.3)	0.33
	<b>Left</b>	34.2 (1.2)	36.8 (2.9)	30.5 (1.3)	32.7 (3.1)	0.92
<b>Vibration Perception Threshold (VPT) 5<sup>th</sup> Metatarsal (Volts)</b>	<b>Right</b>	33.1 (1.3)	38.2 (3.1)	29.3 (1.4)	34.2 (3.4)	0.97
	<b>Left</b>	32.7 (1.3)	37.7 (1.3)	32.5 (1.5)	36.2 (1.4)	0.77
<b>Visual Analog Scale Pain Score</b>		62.6 (5.9)	59.6 (6.1)	64.1 (6.6)	55.5 (6.8)	0.85
<b>Michigan Neuropathy Screening Instrument</b>		7.5 (0.42)	7.4 (0.46)	6.8 (0.46)	7.1 (0.51)	0.42
<b>NeuroQoL Unsteadiness Walking</b>		9.4 (1.01)	10.0 (0.96)	8.2 (1.09)	9.6 (1.04)	0.46
<b>NeuroQoL Unsteadiness Standing</b>		8.1 (0.76)	8.5 (0.82)	6.5 (0.85)	8.5 (0.91)	<b>0.05<sup>‡</sup></b>
<b>Difference (Start – End)</b>		0.4		<b>2.0<sup>‡</sup></b>		
<b>Nerve Conduction Velocities (NCV) Distal motor latency Peroneal Nerve</b>		4.1 (0.16)	4.2 (0.24)	4.3 (0.19)	4.5 (0.28)	0.55
<b>NCV Amplitude Peroneal Nerve</b>		2.3 (0.33)	2.1 (0.32)	2.2 (0.38)	1.8 (0.37)	0.15
<b>NCV Mean Peroneal Nerve</b>		61.6 (1.44)	60.6 (1.38)	58.9 (1.70)	58.0 (1.63)	0.90
<b>NCV Distal Motor Latency Tibial Nerve</b>		4.6 (0.20)	4.4 (0.12)	4.5 (0.22)	4.4 (0.13)	0.79
<b>NCV Amplitude Tibial Nerve</b>		1.9 (0.36)	1.7 (0.35)	2.3 (0.41)	2.4 (0.40)	0.12
<b>NCV Mean Tibial Nerve</b>		62.8 (1.41)	60.9 (1.48)	59.2 (1.61)	59.1 (1.69)	0.20

Statistical values represent the mean and standard deviation mean (standard deviation), except for the information on medications. Medication is presented as the counts of subjects under a specific medication regime. The significance or p-value for the demographics data represents the difference by treatment. For the repeated measures analysis the significance (p-value) is for the treatment-time interaction in a repeated measures ANOVA. The symbol <sup>‡</sup> is used to indicate a significant sham result.

**TABLE 2.** Results for Neuropathy Quality of Life Survey.

These data are results for aggregated scores for social-psychological categories evaluated by the survey.

Aggregated Results	Treatment	Time	Mean	Std. Error	95% Confidence Interval	Difference	Treatment-Time Interaction p-value
Painful Symptoms	MIRE	start	222.8	26.6	169.1 - 276.6	70.5	0.67
		end	293.4	32.6	227.5 - 359.3		
	Sham	start	172.3	29.9	111.9 - 232.7	86.9	
		end	259.2	36.7	185.2 - 333.3		
Loss of Feeling	MIRE	start	65.04	11.7	41.6 - 88.5	30.8	0.53
		end	95.8	13.9	67.8 - 123.7		
	Sham	start	80.8	12.6	55.5 - 106.2	41.3	
		end	122.2	15.0	912.0 - 152.4		
Sensory Motor Symptoms	MIRE	start	105.6	13.8	77.8 - 133.4	12.1	0.14
		end	117.7	13.7	90.0 - 145.4		
	Sham	start	85.1	15.3	54.2 - 116.1	32.9	
		end	118.0	15.3	87.2 - 148.9		
Limited Home & Leisure Activities	MIRE	start	59.2	7.0	45.2 - 73.2	4.6	0.05
		end	63.8	7.9	47.9 - 79.7		
	Sham	start	26.3	8.2	9.8 - 42.8	26.4	
		end	52.7	9.3	34.0 - 71.4		
Emotional Burden	MIRE	start	348.4	47.1	252.9 - 444.0	113.6	0.85
		end	462.0	60.7	338.8 - 585.2		
	Sham	start	356.5	47.1	260.9 - 452.0	123.2	
		end	479.6	60.7	356.4 - 602.8		
Overall Rating	MIRE	start	6.0	0.21	5.6 - 6.4	0.03	0.27
		end	6.0	0.22	5.6 - 6.5		
	Sham	start	5.8	0.23	5.3 - 6.2	0.37	
		end	6.1	0.24	5.7 - 6.6		

**TABLE 3.** Results for Nonparametric Factorial Analysis of Semmes Weinstein Monofilament Data

		Treatment Effect Size						Interaction P-value	
		Left Side			Right Side			Left	Right
Site		Start	End	Difference	Start	End	Difference		
Dorsum	MIRE	0.556	0.489	-0.067	0.560	0.477	-0.083	0.056	0.18
Foot	Sham	0.451	0.493	0.042 <sup>†</sup>	0.489	0.576	0.086		
Great Toe	MIRE	0.519	0.473	-0.046	0.526	0.477	-0.048	0.57	0.11
	Sham	0.523	0.468	-0.055	0.489	0.517	0.028		
3rd Toe	MIRE	0.554	0.436	-0.118	0.531	0.488	-0.044	0.004 <sup>†</sup>	0.19
	Sham	0.488	0.523	0.036 <sup>†</sup>	0.492	0.496	0.004		
5th Toe	MIRE	0.508	0.520	0.012	0.562	0.483	-0.079	0.24	0.031 <sup>†</sup>
	Sham	0.458	0.507	0.049	0.458	0.497	0.039 <sup>†</sup>		
5th Metatarsal	MIRE	0.537	0.520	-0.017	0.557	0.520	-0.037	0.40	0.31
	Sham	0.464	0.467	0.003	0.456	0.447	-0.009		
3rd Metatarsal	MIRE	0.496	0.509	0.013	0.519	0.561	0.042 <sup>†</sup>	0.35	0.014 <sup>†</sup>
	Sham	0.479	0.514	0.035	0.497	0.411	-0.086		
Lateral Midfoot	MIRE	0.564	0.477	-0.087	0.490	0.572	0.082 <sup>†</sup>	0.34	0.041 <sup>†</sup>
	Sham	0.503	0.446	-0.056	0.481	0.458	-0.023		
1st Metatarsal	MIRE	0.543	0.504	-0.040	0.526	0.522	-0.003	0.057	0.50
	Sham	0.444	0.498	0.054 <sup>†</sup>	0.473	0.470	-0.003		
Medial Midfoot	MIRE	0.533	0.518	-0.016	0.530	0.517	-0.013	0.42	0.21
	Sham	0.470	0.468	-0.002	0.452	0.486	0.034		
Heel	MIRE	0.484	0.527	0.043	0.494	0.530	0.035	0.20	0.21
	Sham	0.498	0.489	-0.009	0.490	0.477	-0.013		

Treatment effects are shown for the start and end of the study. Seventeen positive differences (shown in bold) indicate improvement over time. Of these, four treatment-time interactions, two for the sham and two for the Anodyne treatment, were significant at 5% level (last two columns). Although the positive differences in effect size are not all statistically significant, eleven out of seventeen times there was an improvement of the sham treatment, while there were only six positive differences for Anodyne treatment. The symbol \* is used to indicate a significant sham result while † indicates a significant Anodyne result.