Can an electrical pulsed radio frequency device relieve pain and improve function in patients with pedal diabetic neuropathy? A single blind randomized placebo-controlled trial.

Article type: Randomized single blind placebo-controlled study.

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Abstract

Can an electrical pulsed radio frequency device relieve pain and improve function in patients with pedal diabetic neuropathy? A single blind randomized placebo-controlled trial.

Aim: A randomised single-blind placebo study was conducted on 80 patients with pedal diabetic peripheral neuropathy in 2 cities and their surrounds in South Africa to determine if a pulsed radio frequency current (PRF) can produce changes in the primary outcome of the DN4 Test and possibly in the BPI-short form.

Method: Patients were selected by their physicians at Centres for Diabetes and randomised into 2 groups – 40 patients each in the groups (A=Active, B =Placebo). Inclusion criteria were pedal Diabetic Peripheral Neuropathy and having a score of 4 or 4+/10 in the DN4 Test. Exclusion criteria: previous experience with the pulsed radio frequency current and having: peripheral or spinal cord stimulator, pacemaker, metal implants and pregnancy. The DN4 was the primary objective and BPI-SF (secondary) was also tested at baseline, after 3 treatments and 3 follow ups at 1, 3 and 6 months. Each patient had 3 treatments or placebo once weekly for 10 mins bilaterally at the sciatic nerve in the popliteal fossa.

Results: Data were analysed using the SAS version (9.4 statistical program). Results are expressed as mean and standard deviation by groups (A=Active, B=Placebo). There were differences for age and gender in these 2 groups (Age, p=0.030, gender p=0.01) and adjustments were made where applicable. There were also differences evident regardless of age and gender. The DN4 demonstrated that between baseline and 3 treatments there was a reduction in pain and symptoms greater for the A group: p= 0.010 regardless of age and gender. Between baseline and 1month there was a reduction in pain in both groups, but no significant difference between them p=0.10 but gender and age, nearly significant. There were no differences at 3 and 6 months. In the BPI-SF there were differences between the active and placebo groups in the worst, average and present pain with positive p values some with adjustment for age and gender. For relations with other people there was evidence of significant changes some regardless and some adjusted for age and gender and also relations with other people and without analgesics at baseline. There was no differences even after adjustments for age and gender for work and walking ability. None of the BPI-SF variables showed any differences when adjusting for baseline and or analgesics.

Conclusion: After 3 treatments of PRF current, the DN4 Test demonstrates significant improvements in neuropathic pain and symptoms in certain patients with diabetic peripheral neuropathy.

KEYWORDS: diabetic peripheral neuropathy; pulsed radio frequency current

Trial registry number: M161037

University of the Witwatersrand Human Research Ethics Committee (Medical)

RESEARCH IN CONTEXT:

What is known about this subject?

- Physical therapy modalities may bring some relief to certain patients with diabetic neuropathy
- Evidence for the use of electrical modalities for diabetic neuropathy is presently of low quality, prolonged treatment is usually required over many months and pain relief and symptoms are often unsustainable.
- A recently developed electrical pulsed radio frequency current has demonstrated improvement in pain and symptoms of paraesthesia in other and in pedal diabetic neuropathic conditions.

What are the new findings?

- There are significant differences in pain and symptoms between the active and placebo patients in the DN4 Test after only 3 treatments of the electrical pulsed radio frequency current and these effects are sustained 1 month later.
- There were significant differences between active and placebo patients in pain with the electrical pulsed radio frequency current treatment in the BPI-SF in the VAS worst, average and present pain including age and gender as covariates but none when adjusting for baseline and or analgesic medication however average pain was significantly lower in the active group after 1 month.
- There was significant decrease in pain in the active group in work, walking ability, mood and relations with other people at different time lines with adjustments for age and gender after 3 treatments but none when adjusting for baseline and or analgesic medication except with relations with other people at 1 month and without analgesic at baseline.

How might this impact on clinical practice in the foreseeable future?

- There is a bioelectrical treatment that can reduce pain and paraesthesia in certain patients with pedal diabetic peripheral neuropathy and possibly other neuropathies from different aetiologies.

Can an electrical pulsed radio frequency device relieve pain and improve function in patients with pedal diabetic neuropathy? A single blind randomized placebo-controlled trial.

INTRODUCTION

A newly developed electrical device, a pulsed radio frequency current (known as NMS 460) has demonstrated changes in severe pain (hyperaesthesia and burning sensations) as in neuropathic pain and its possible symptoms such as numbness, paraesthesia and tingling, among others. This device has been used since 2010 [1] to relieve pain and symptoms of various challenging conditions such as complex regional pain, failed back and post-surgical pain syndromes [2], diabetic neuropathy, among many others including expediting improvement in strength and function in neuropraxias including Bell's palsy (observation) [1], long thoracic nerve palsy [3] and those from other aetiologies.

The first report on this device informed on the treatment of patients with pedal diabetic neuropathy. A prototype of the present-day device, was used by the authors, Kothari and Gorozeniuk on a selected group of patients in 2010 at the Pain Clinic at St Thomas' hospital, UK [4]. All of the 34 patients treated had a positive response after only 3 once weekly 5 minute treatments at 15mA current intensity. There was nil blinding and treatment was given bilaterally at the sciatic nerve in the popliteal fossa as this nerve has both motor and sensory components. There were no further follow ups of these patients beyond the initial reporting indicating that 19 patients had 100% relief, 4 patients had 90% relief, 4 patients had 63% and 4 patients had 50% relief – the remaining 3 patients had 25, 20 and 15% relief.

Diabetic peripheral neuropathic pain and symptoms among adults attending private and institutional outpatient diabetic clinics in South Africa is widely prevalent at 30.3% and as in other countries, despite its negative impact on health-related quality of life and sleep, is inadequately treated [5]. It thus appears that despite medication [6] there is an unmet need within various patients with pedal diabetic neuropathy that may be assisted by electrical methods with the possible advantages of relief of pain and sensory symptoms, improvement in function and with the added benefit of nil side effects.

A research project was thus developed on neuropathic pain and symptoms on patients with pedal diabetic neuropathy on the recommendations of the previously mentioned report [4]. The development of this device and the first randomized placebo controlled single blind study was thus conducted in Johannesburg, Gauteng Province, South Africa.

BACKGROUND AND PURPOSE OF THE STUDY

Diabetes mellitus (DM) is a metabolic disorder with heterogeneous aetiologies [7] that is associated with a number of chronic sequelae and around 50% of people develop polyneuropathy. The regional prevalence varies from 3.2% in Africa to 12.9% in North America [8].

Those patients with diabetes either type 1 or 2 that develop peripheral neuropathy are known to be heterogenous in their symptoms, pattern of neurologic involvement, course, risk covariates, pathologic alterations and underlying mechanisms [9]. It has been postulated that the prevalence of neuropathic pain (NP) in the diabetic population is difficult to gauge due to large variations among studies but is estimated at between 3 to 25% of this population [10].

The definition of peripheral NP in diabetes has been adapted from a definition proposed by the International Association for the Study of Pain (IASP) as 'pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes' [11].

The typical DPN is a chronic, symmetrical, length-dependent sensorimotor polyneuropathy and is thought to be the most common variety [11]. The initial inciting event is a 'dying back' axonopathy principally affecting sensory neurons [12]. There are also changes within the central nervous system both at the spinal cord and brain at an anatomical and functional level leading to amplification of nociceptive processing [13]. NP is a multidimensional entity and there are distinct subgroups of patients with particular patterns of sensory symptoms and signs. Certain patients have principally deafferentation with loss of sensory function whereas others have evidence of preserved small fibre function and associated hypersensitivity, a pattern termed the 'irritable nociceptor' [14].

An abnormality of nerve conduction tests, frequently subclinical, is the first objective quantitative indication of the condition [15]. An abnormality in nerve conduction and a symptom or symptoms or a sign or signs of neuropathy confirm diabetic sensory peripheral neuropathy. Painful diabetic peripheral neuropathy relies on the patient's description of pain. The symptoms are distal, symmetrical, often associated with nocturnal exacerbations, and commonly described as pricking, deep aching, sharp like an electric shock and burning [16] with hyperalgesia and frequently allodynia upon examinations [10]. There is limited data on the natural history of painful DPN with some studies suggesting that painful symptoms improve with the worsening of the sensory loss and others reporting no appreciable occurrence of remissions [10].

A number of validated scales and questionnaires including the Neuropathic Pain Symptoms Inventory, Brief Pain Inventory [16], Neuropathic Pain Questionnaire and McGill Pain Questionnaire, may be used. Quality of Life (QoL) improvement may also be assessed using a validated neuropathy specific scale such as the Norfolk Quality of Life Scale (NeuroQoL) [17]. Outcomes must be measured using patient-reported improvement in scales for pain and QoL as measured on validated instruments [17].

According to the Pain in Neuropathy Study [6] and EFNS guidelines on neuropathic pain assessment [16], the DN4 questionnaire is a patient reported symptoms-based approach and is regarded as an effective screening tool for neuropathic pain in DPN and has demonstrated excellent sensitivity (88%) and specificity (93%) in screening for NeuP.

Hebert, Veluchamy, Torrance and Smith; 2017 [18] discovered two non-modifiable factors as in age and sex that have been specifically associated with DPN, in addition to their known roles as risk factors for DM. There is an association of DPN with older age (<50 years) indicating the relative time it takes for nerve damage and painful symptoms to develop after the onset of DM and the decreased ability of the patients to accommodate. Similarly, gender associations may indicate possible subtle differences in biological and psychosocial factors. Four studies have reported greater risk in women and 1 study reported greater risk in men.

TREATMENTS FOR DIABETES

The initial approach to the treatment of a peripheral neuropathy is to address any contributing causes such as infection, toxin exposure, medication related toxicity, vitamin deficiencies, hormonal deficiencies, autoimmune diseases or compression that can lead to neuropathy. Peripheral nerves have the ability to regenerate axons as long as the nerve cell itself has not died and therefore functional recovery over time may be possible. Correcting an underlying condition can often result in the neuropathy resolving on its own as the nerves recover and regenerate [13].

The treatment of painful DPN is almost exclusively pharmacological and consists mainly of symptomatic therapies that improve symptoms of painful DPN without an effect on underlying causes and natural history. Level A evidence exists to support the use of tricyclic antidepressants (e.g. amitriptyline). Others include the anticonvulsants gabapentin and pregabalin; serotonin, norepinephrine reuptake inhibitor, duloxetine [6} with further options that may also include opioids, carbamazepine, lidocaine patches and capsaicin [19].

The pharmacological treatment of painful DPN is not entirely satisfactory; available drugs are often ineffective and their use is complicated by side effects [20] and this may encourage patients to seek alternative measures.

Physical modalities as in physical therapy can be an effective and alternative treatment option for patients. Certain physiotherapy techniques can help alleviate the symptoms of DPN such as deep pain in the feet and legs, tingling or burning sensation in the extremities, muscle cramps, muscle weakness, sexual dysfunction and diabetic foot [21].

These [21] may include gait and posture training, exercise programs of stretching and strengthening and aerobic exercise such as swimming and bicycling. Heat, therapeutic ultrasound, hot wax and short-wave diathermy have also been suggested as treatment options for diabetic neuropathy.

Other complementary approaches [21] may provide additional support such as mechanical aids (foot braces) that help reduce pain and physical disability by compensating for muscle weakness or alleviating nerve compression. Orthopaedic shoes can improve gait disturbances and help prevent foot injuries in people with a loss of sensation. Acupuncture, massage and herbal medications are also considered in the treatment of neuropathic pain [13]. Physical electrical modalities have been investigated and it appears that patients do experience relief, albeit temporary.

Side effects and lack of response to conventional treatment have forced many patients to try alternative therapies such as acupuncture [5], near-infrared phototherapy [22] low-intensity laser therapy [23], magnetic field therapies [24] and Transcutaneous Electrical Nerve Stimulation (TENS) has also been shown in some studies to improve DPN [15]. TENS and interferential current use a painless electrical current and the physiological effects from low frequency electrical stimulation may relieve stiffness, improve mobility, relieve neuropathic pain, reduce oedema and heal resistant foot ulcers [19].

Bosi *et al*. investigated the efficacy of frequency-modulated electromagnetic neural stimulation (FREMS) therapy and reported a significant improvement in pain scores and in some measures of nerve function. Although FREMS induced a significant reduction in day and night pain as measured by a visual analogue scale immediately after each treatment session, this beneficial effect was no longer measurable 3 months after treatment. The effect of this treatment (10 treatments within 3 weeks, 3 months apart) was immediate but length dependent and transient [25], [26].

Reichstein *et al*. indicated in their study of high-frequency external muscle stimulation that these applications have effectiveness in relieving neuropathic pain [27].

The latter studies indicate that stimulation of muscle function may influence night pain, a common complaint in DPN and electrical currents that improve circulation and stimulation of nerve fibres may precipitate improvement in neural conduction and facilitate pain relief with persistent use however the evidence in the above mentioned studies is still weak. Often low quality of evidence however may demonstrate positive changes in future higher quality trials.

Tesfaye and his group have demonstrated that when the pain is persistent and unresponsive to medication, and as a last resort, implantation of an electrical spinal cord stimulator may bring more permanent relief [28].

METHOD

The study was designed with permission from the physicians (Distiller, Landau, Joffe and colleagues) at the CDE, Houghton. A statistician, E Libhaber (University of the Witwatersrand) determined the numbers required for the single blind randomised placebo study. The design of the study was then developed by Berger and application was made, approved and registered (M161037) by the Human Research Ethics Committee (HREC, Medical), University of the Witwatersrand.

The trial entered a sample size of 80 patients – 40 in the active group (Group A) and 40 in the placebo group (Group B) and patients were admitted to the study as they came – there were too many centres and too few participants at each one for stratification. All the patients were enrolled and assigned (strictly according to the randomisation list - 100 numbers to accommodate attrition). The sample size was calculated based on a reduction difference of DN4 between the placebo and the active group (Libhaber). The ethnicity of the participants was derived from Africans, Asians, Caucasians, Coloured and Indian people all from different socio-economic groups. Age, gender and type of diabetes were differentiated. All the investigators were unblinded and all the patients were blinded. Four investigators were selected to record the assessments and treat the patients - E Conradie, J Jacks, K Petersen and L Assad (3 physiotherapists, Witwatersrand University Johannesburg, 1 BSc Exercise and Sports Medicine therapist, Texas State University USA). Information was recorded prior to and after each treatment and follow up as required by the trial design. These investigators assessed and treated patients at different centres – CDE's in Johannesburg and Pretoria – large cities and their surrounding areas. Each assessment was returned to Berger for data capturing after treatments or placebo and the follow ups. No other persons were involved with capturing or being privy to the data collected except Berger and Libhaber, the latter, whose only function was to determine the results.

Prior to commencing the trial each patient was interviewed telephonically to ascertain eligibility and if deemed suitable by Berger, each patient was sent or provided with information to explain the process and requirements regarding the trial. A consent form was to be signed prior to their participation. Inclusion criteria were pedal diabetic peripheral neuropathy, 4 or 4+/10 for the DN4 Test, and naïvete to the electrical pulsed radio frequency current. The exclusion criteria were: pregnancy, pacemaker, peripheral or central nerve stimulator for pain or metal implantation in the knee and or hip.

The information document explains the type of current that patients may or may not receive (placebo). Patients are advised that the current may not have sensation for their particular manifestation of the DPN as many of these patients experience different sensations such as numbness, tingling or paraesthesia and or pain and they may therefore experience non-painful stimulation along the nerve being treated. This enabled blinding of the patients as naieve patients would have no experience of the true current experience. The investigators remained neutral throughout the trial in their treatment or otherwise of these patients. The manifestation of the patients' condition is heterogeneous as well as their reaction to treatment however this does not determine the effect of the treatment. Treatment is not painful nor harmful. There have been no recorded ill effects since its inception in 2010.

The trial commenced December 2016 and was concluded in August 2019.

Treatment or placebo entails: assessment and recording of the DN4 Test prior to the first and after the last treatment. The DN4 test has 7 subjective questions and 3 objective tests for analysis. The questionnaire of the Brief Pain Inventory – Short Form (BPI-SF) is then also administered prior to the first, the second and last treatment and is a completely subjective analysis. These tests are validated assessments that will indicate changes in the DN4 (main outcome) and the BPI-SF (secondary outcome) and the latter demonstrates changes in a visual analogue score of worst, least, average and present pain on a pain scale from 0 to 10 (11 point numerical rating scale) [33], medication use and percentage of pain relief achieved with the medication and the effect on various aspects of life such as: general activities, work, sleep, walking, mood, relations with other people and quality of life using the pain scale from 0 to 10 (11 point numerical rating scale).

Patients are then tested initially with a nerve mapping device to explore the sciatic nerve in the popliteal fossa posteriorly at the knee. This position is then marked. The active treatment or placebo device is applied bilaterally for 10mins. The current may create fasciculation or not at the nerve site with care being taken to ensure that the patient is comfortable at all times. Fasciculation may be poor due to the condition of the patient determined by the severity and duration of the condition. The intensity is recorded at each treatment.

Treatment or placebo is applied once weekly for three weeks only. Follow ups are given one, three and at six months after the last (third) treatment. Measurements are recorded of the DN4 prior to the first and last (third) treatment and before each follow up – one, three and six months after the last treatment. Measurements are recorded of the BPI-SF after the first, second, third treatments and then all three follow ups at one, three and six months.

When the numbers of patients or placebo reached a level for trial evaluation according to the statistician and with agreement of the HREC (Medical) at the six timelines, it was decided to conclude the study. Ninety two patients were eventually randomised due to attrition during this trial.

Interim results were obtained in 2018 of 46 patients with 23 being evaluated in each group (A= active and B=placebo group).

According to the statistician after 3 treatments, the DN4 Test indicates a significant change from baseline to post 3rd treatment between group A and group B with p=value 0.011. These changes were maintained at 1 month follow-up – p-value of 0.047 and at 6 months with p=value of 0.013. In the Brief Pain Inventory Short Form there was most statistical difference in worst pain p=0.002 and some significance of average pain p=0.043 and present pain p=0.018, all at 1 month post treatment. There was no significance for work and walking but mood showed some evidence at 6 months with p=0.041.

The data of the present trial were analysed using the SAS version 9.4 statistical program (SAS, Cary, NC, USA). Results are expressed as mean and standard deviation by groups (A=Active, B=Placebo). To assess baseline (before starting treatment) differences by group, a t-test or a Mann-Whitney test for continuous variables with non-normal distribution and a Chi- square test for categorical variables were used. Generalised linear models for repeated measurements of continuous variables was performed to analyse differences within visits (baseline, 3 treatments, 1 month, 3 months and 6 months) between the two groups and including age and gender as covariates. Analysis of variance of contrast variables between baseline and each of the visits, between placebo versus the active group and adjusted for age and gender and baseline pain measurements as well as analgesic medication were then applied. Assumptions for homogeneity of variances and normality of residuals were met.

Significance was assumed at a both-sided value of $p<0.05$.

RESULTS

Overall there is a reduction of pain and symptoms (DN4 Test) in time in both groups along the 6 months, however there is a difference in age and gender between the groups. Age, p=0.030 and gender p=0.01.

Table A: Baseline characteristics for Active and Placebo Groups

	ACTIVE=A	PLACEBO=B	p-value
N	**46**	**46**	
Age, years	59.1 +/-9.6	63.7 +/-9.4	0.02
Gender (M), n(%)	29 (63)	31 (67)	0.82
Type of diabetes (1/11) (n)	3/43	6/40	0.48
Ethnicity, n (%) African Asian Caucasian Coloured Indian	 6 (13) 0 (0) 29 (63) 2 (4) 9 (20)	 5 (11) 1 (2) 27 (59) 5 (11) 8 (17)	0.57
Medication n(%)			
Analgesics	12 (27)	3 (7)	0.02
NSAID	7 (15)	4 (9)	0.52
Anti-epileptics	14 (30)	11 (24)	0.64
Anti-depressants	8 (17)	6 (13)	0.77
Opioid	3 (7)	8 (17)	0.20
Muscle relaxants	1 (2)	0 (0)	1.00

No differences in the baseline characteristics were found when comparing patients that completed all visits (n=70) to the patients that missed at least one visit or defaulted.

Post hoc analysis showed that:

Table B Patients that completed the 6 month follow-up with all intermediate visits

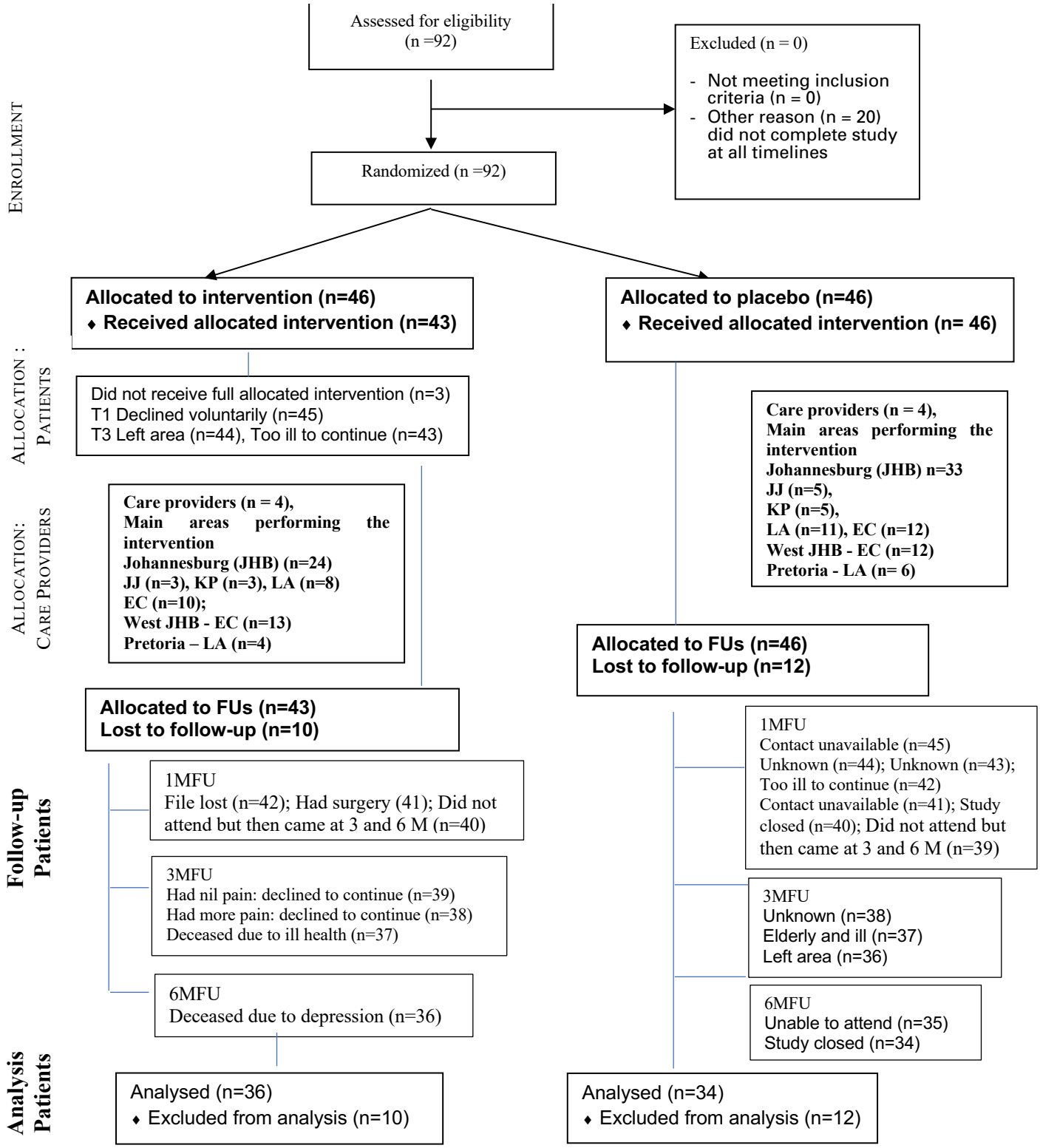
	A	B	p-value
N	**36**	**34**	
Gender M/F (n % M)	20/16 (56%)	23/11 (68%)	0.30 (NS)
Age (years)	65.0 ± 8.8	58.2±9.3	0.0038

COMPARISON BETWEEN A (ACTIVE) AND B (PLACEBO GROUPS IN THE DN4

TEST REGARDLESS AND WITH INCLUSION FOR AGE AND GENDER

1. Between baseline and 3 Treatments there was a reduction in pain and symptoms more pronounced for the active group p= 0.003.

Modified CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments.



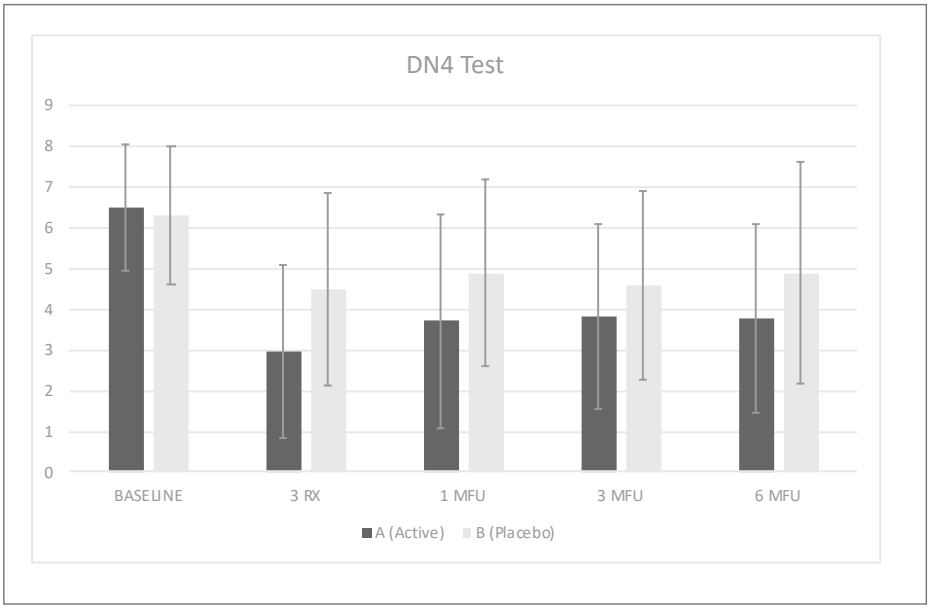
Cited as: Boutron I, Altman DG, Moher D, Schultz KF, Ravaud P. CONSORT statement for Randomised Trials for Nonpharmacologic Treatments: A 2017 Update and a Consort Extension for Nonpharmacologic Trial Abstracts: Annals of Internal Medicine. 2017 Jul 4;167(1):40-7

2. After adjusting for age and gender between baseline and 1 month and at 6 months there was a reduction in pain in both groups.
3. There were no differences at 3 months.

Table C for DN4 Test

DN4 group	Baseline	3 Treatments	1 month	3 months	6 months
ACTIVE (n=36)	6.48+/-1.55	2.97+/-2.12*	3.71+/- 2.62A	3.83+/-2.26	3.78+/-2.31A
PLACEBO (n=34)	6.29 +/- 1.69	4.50+/-2.36	4.88+/-2.29	4.58+/-2.31	4.88+/-2.72
p-value	NS	0.03	<0.01	NS	0.01

Results are presented as mean +/- Standard Error (SE)



BRIEF PAIN INVENTORY SHORT FORM

COMPARISON BETWEEN A (ACTIVE) AND B (PLACEBO GROUPS IN THE BPI-SF TEST REGARDLESS AND WITH INCLUSION FOR AGE AND GENDER

VAS FOR PAIN

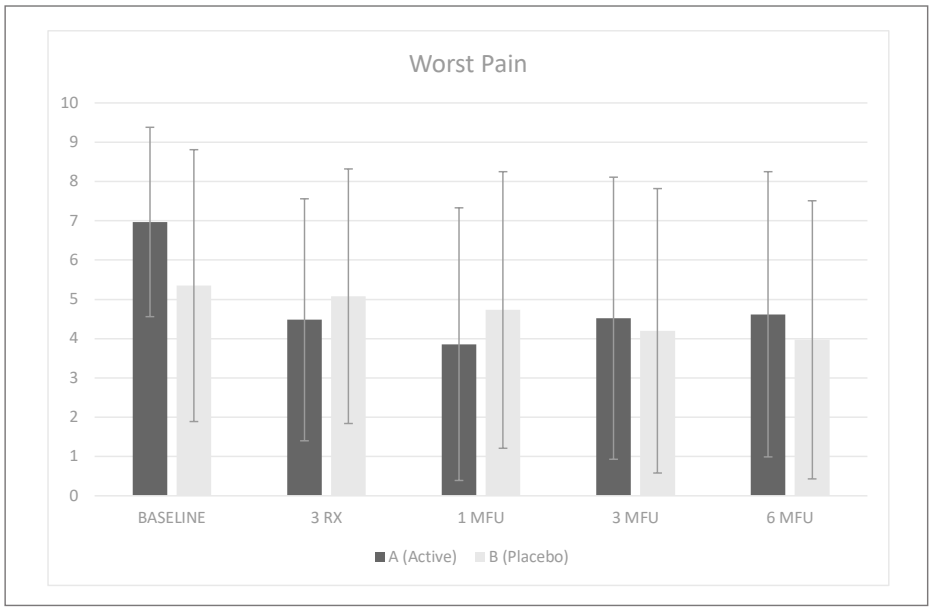
1. WORST PAIN

For Vas W at 3 Treatments differences between A and B, p=0.0126 and at 1 month A vs B p=0.0097 and at 3 months A vs B p=0.0496 after adjusting for age and gender.

When adjustments were made for baseline and /or medication there were no differences.

	A (ACTIVE)	**B (PLACEBO)**	**P- VALUE**
N	**36**	**34**	
BASELINE	6.97 +/- 2.41	5.35 +/- 3.46	0.09
3 RX	4.48 +/- 3.08	5.08 +/- 3.24	0.42
1 MFU	3.86 +/- 3.47	4.73 +/- 3.52	0.26
3 MFU	4.52 +/- 3.59	4.20 +/- 3.62	0.67
6 MFU	4.62 +/- 3.63	3.97 +/- 3.54	0.54

Results are presented as mean +/- SE



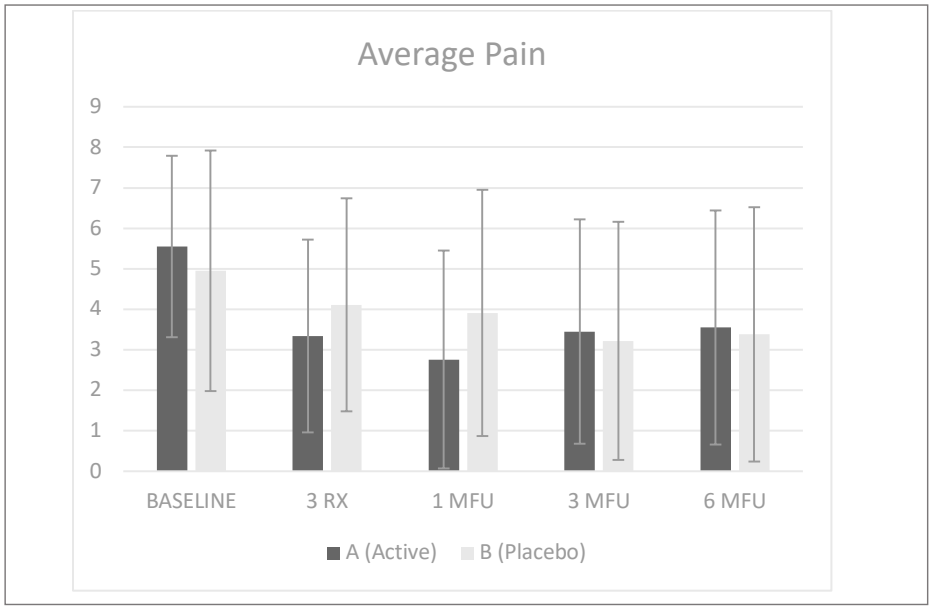
2. AVERAGE PAIN

VAS Average at 3 Treatments A was lower compared to B p=0.0232 regardless of age and gender and at 1 month A vs B p=0.0093 after adjustment for age and gender.

When adjustments were made for baseline VAS Average and /or medication the average pain was significantly reduced compared to the placebo (p=0.016)

	A (ACTIVE)	B (PLACEBO)	P- VALUE
N	**36**	**34**	
BASELINE	5.55 +/- 2.24	4.95 +/- 2.97	0.62
3 RX	3.34 +/- 2.38	4.11 +/- 2.63	0.25
1 MFU	2.76 +/- 2.69	3.91 +/- 3.04	0.08
3 MFU	3.45 +/- 2.77	3.22 +/- 2.94	0.66
6 MFU	3.55 +/- 2.89	3.38 +/- 3.14	0.99

Results are presented as mean +/- SE



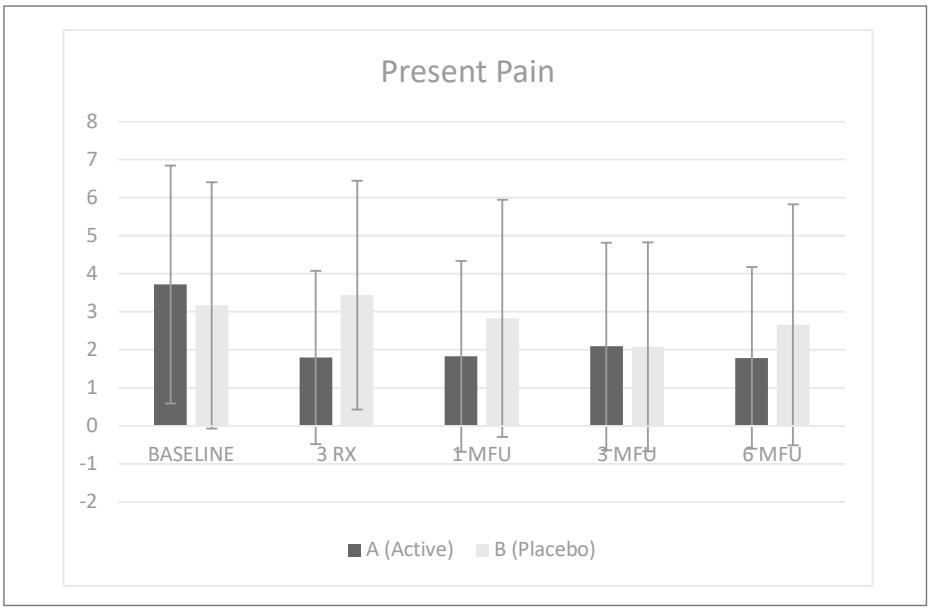
3. PRESENT PAIN

VAS Present at 3 Treatments was lower in the active group p=0.023 and when adjusted for age and gender remained significant A vs B p=0.0167 and also at 1 month p=0.046.

When adjustments were made for baseline VAS P and /or medication there were no differences.

	A (ACTIVE)	B (PLACEBO)	P- VALUE
N	**36**	**34**	
BASELINE	3.72+/- 3.13	3.17 +/- 3.24	0.60
3 RX	1.80 +/- 2.28	3.44 +/- 3.01	0.023
1 MFU	1.83 +/- 2.51	2.83+/- 3.12	0.12
3 MFU	2.09 +/- 2.73	2.08 +/- 2.75	0.98
6 MFU	1.79 +/- 2.39	2.66+/- 3.17	0.21

Results are presented as mean +/- SE



COMPARISON BETWEEN A (ACTIVE) AND B (PLACEBO GROUPS IN THE BPI-SF TEST FOR INTERFERENCE WITH ACTIVITES REGARDLESS AND WITH INCLUSION FOR AGE AND GENDER

4a. WORK

No differences between A vs B for VAS Work were found even after adjustments were made for age and gender.

When adjustments were made for baseline and /or medication there were no differences.

	A (ACTIVE)	B (PLACEBO)	P- VALUE
N	**36**	**34**	
BASELINE	4.83+/- 3.37	3.94 +/- 3.69	0.33
3 RX	2.55 +/- 2.68	2.97 +/- 3.00	0.77
1 MFU	2.00+/- 2.48	2.47 +/- 3.13	0.69
3 MFU	2.11+/- 3.03	3.04 +/- 3.63	0.36
6 MFU	2.29 +/- 2.78	2.47 +/- 3.05	0.75

Results are presented as mean +/- SE

4b MOOD –

After adjustments for age and gender and further for baseline mood and or medication there were no differences between A and B.

	A (ACTIVE)	B (PLACEBO)	P- VALUE
N	**36**	**34**	
BASELINE	4.87 +/- 3.00	4.39 +/- 3.80	0.75
3 RX	3.01 +/- 3.20	2.86 +/- 2.97	0.81
1 MFU	2.41 +/- 3.07	2.83 +/- 3.16	0.32
3 MFU	2.56 +/- 3.04	2.42 +/- 2.96	0.94
6 MFU	2.63 +/- 3.12	2.55 +/- 3.42	0.94

Results are presented as mean +/- SE

4c. WALKING

No differences were found between A vs B even adjusting for gender and age.

When adjustments were made for baseline and /or medication there were no differences.

	A (ACTIVE)	B (PLACEBO)	P- VALUE
N	**36**	**34**	
BASELINE	5.75 +/- 3.17	4.50 +/- 3.79	0.18
3 RX	3.06 +/- 2.99	3.42 +/- 3.22	0.78
1 MFU	2.68 +/- 3.07	3.36 +/- 3.58	0.41
3 MFU	3.51 +/- 3.55	3.26 +/- 3.70	0.74
6 MFU	2.81 +/- 3.29	3.05 +/- 3.35	0.55

Results are presented as mean +/- SE

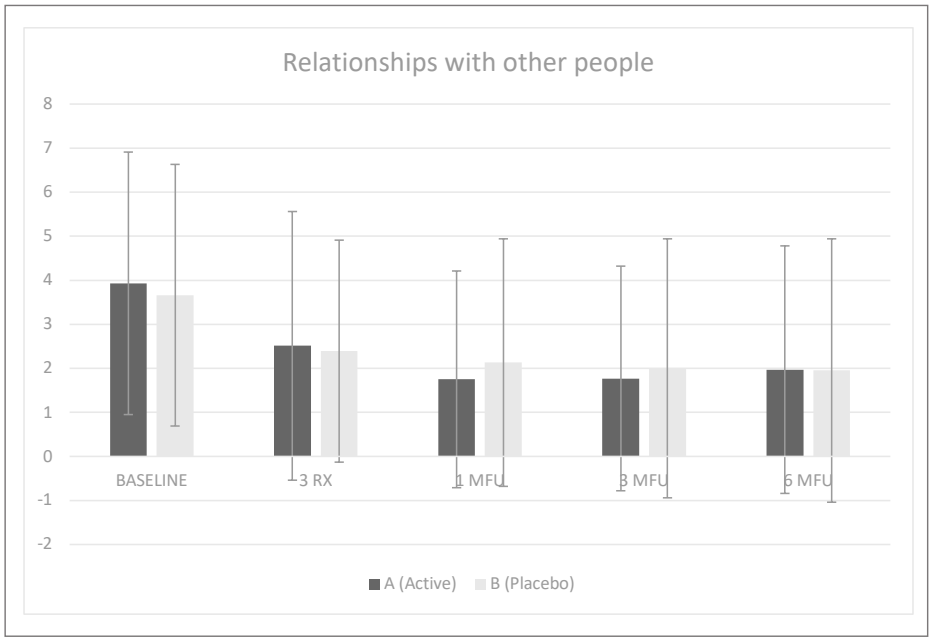
4d. RELATIONS –

After adjusting for gender and age at 3 treatments differences between A and B were nearly significant (p=0.09) and at 1 month A was p=0.10 and at 3 months A vs B was p=0.0138.

After adjustments for baseline relations and /or medication the only difference was with relations with other people but only at 1 month (p=0.023).

	A (ACTIVE)	B (PLACEBO)	P- VALUE
N	**36**	**34**	
BASELINE	3.93 +/- 2.98	2.66 +/- 2.97	0.09
3 RX	2.51 +/- 3.05	2.39 +/- 2.52	0.90
1 MFU	1.75 +/- 2.46	2.13 +/- 2.81	0.66
3 MFU	1.77 +/- 2.55	2.00 +/- 2.94	0.92
6 MFU	1.97 +/- 2.81	1.95 +/- 2.99	0.81

Results are presented as mean +/- SE



Patients on Medications from baseline to 6 month follow up

There was a difference between the active and placebo in the use of analgesics at baseline of p=0.02.

A OR B	Meds_b	Meds_3t	Meds_1m	Meds_3m	Meds_6m
A (ACTIVE)	8	4	8	0	10
B (PLACEBO)	16	8	16	0	20

Patients on different medications at different timelines

Many different medications were used alone and in combination. There were too few participants with each one for stratification.

MEDS	ACTIVE= A	T1	T3	FU6	PLACEBO=B	T1	T3	FU6
ANALGESICS		12	7	6		3	2	2
NSAIDS		10	3	4		9	7	4
ANTI-EPILEPTICS		14	10	10		12	13	5
ANTI-DEPRESSANTS		10	3	4		9	7	4
OPIOIDS		0	1	0		8	8	6
MUSCLE RELAXANTS		1	1	1		0	1	0

DISCUSSION:

The primary investigation of this trial was to determine if 3 once weekly, 10 minute bilateral treatments of pulsed radio frequency current on patients with pedal diabetic neuropathy was able to demonstrate a significant difference in pain and symptoms between the active and the placebo groups in the DN4 Test. These results were visible and continued 1 month later and are comparable with observations when this treatment was administered for various neuropathic and neurogenic states since its development in 2010.

This trial evaluated 92 patients and eventually 70 patients were analysed – 36 in the active and 34 in the placebo group. The goal of the trial was to reach 80 patients, 40 in each group and it was determined that the numbers eventually analysed in the DN4 were sufficient to power this test.

This test evaluates neuropathic pain and has both subjective and objective variables that include both painful and non-painful symptoms. This is important as many of these patients have no pain and only paraesthesia. The basic level of entry for a positive DN4 Test is 4/10 points. If they have pain of burning, painful cold sensations, electric shocks and sensitivity to brushing they will achieve 4/10. If they have tingling, pins and needles, numbness and hypoaesthesia to touch and pinprick they will achieve 5/10

but most patients usually have a combination of both giving them a severity rating of 5+/10. It has been suggested that patient's whose neuropathy have progressed may have less pain but this may indicate worsening of the condition as they may not realise when they have injured their feet with often dire consequences.

The secondary outcome of the BPI-SF Test has 17 variables that include VAS scores, medication usage and many other subjective aspects of quality of life as previously mentioned. There were significant differences in the BPI-SF for VAS worst pain after the 3rd treatment and even at 1 month there was further improvement however when adjustments were made for baseline and/or medication there were no differences. There were also significances in average pain between the A and the B groups p=0.0232 regardless of age and gender and at 1 month p=0.0093 adjusted for age and gender however when adjustments were made for baseline and/or medication there were no differences. There were also significances in present pain at 3 treatments p=0.023 and when adjusted for age and gender, remained significant (p=0.0167). However when adjustments were made for baseline and or medication there were no differences between the groups. In walking and work there were no differences between the groups even after adjustments for age and gender but in mood when adjustments were made for age and gender and then followed by baseline mood and or medication there were no differences. Relations with other people presented differences as after adjusting for age and gender at 3 treatments group A versus group B p=0.09 was nearly significant and at 1 month group A was p=0.010 and at 3 months A vs B was p=0.0138.

Patients were permitted to continue their various medications as required and there was a great variety – 28 different medications that could be assigned to: analgesics, non-steroidal anti-inflammatories, anti-epileptics, anti-depressants, opioids and muscle relaxants. Many patients used a cocktail of different medications as advised by their physicians. Recording these different medications was often problematic due to patients taking their medications intermittently and not remembering when and how often; patients may have only required their medication sporadically yet once medication is mentioned it was recorded in the data and lastly many patients had ceased taking their medications due to the unwanted side effects.

Patients who entered the trial had been taking these combinations of medications previously and often for many years and they may have entered the trial because they sought further pain relief due to an unmet need. It was therefore deemed a fair comparison to evaluate those who were taking medication before the trial with those who took medication during the trial and thereafter.

Evaluations of medications in this cohort of patients presents many difficulties and heterogeneity in patient's requirements and administration in this regard and the adjustments to the data for medication appeared inconsequential due to the minimal numbers being analysed albeit larger studies may present different evidence.

Although some patients had no pain but mainly symptoms, this may have been an altering factor in evaluating and diminishing the strength of VAS scores. Separation of patients with no pain and only symptoms would require a larger group of patients to determine differences.

It may be possible to have had less adjustments required if there was homogeneity in age and gender in the sample size evaluated and this may have revealed greater differences between the active and placebo groups. This may have also applied to work and walking ability.

Relations with other people were also improved and this could impact upon mood (further investigation may be required) and it has importance as NP is known to precipitate depression and even suicidal ideation. Distress may limit interaction with others and a vicious cycle may emerge that leads to withdrawal from socialization.

None of the above variables in the BPI-SF showed any differences when adjusting for baseline and or analgesic medication, except for relations with other people. It is therefore suggested that this Test is insufficiently powered to evaluate these factors and that a Multi-Centred trial would improve evaluation as demonstrated prior to the afore mentioned adjustments.

The weakness of this study is the limited number of participants and treatments given in the trial. Attrition occurred often due to concomitant medical conditions that prevented patients from attending. The complicated other pedal issues that these patients experience (diabetic foot) may impact upon their decision making in evaluating their pain creating difficulty in separating the neuropathic pain from their mechanical symptoms.

Diabetic peripheral neuropathy is a chronic condition that requires at least 6 treatments and as has been observed in previous patients with diabetic neuropathy this may produce sustained results. It would therefore be recommended that clinically between 6 – 12 treatments be provided and as and when progress occurs the treatments can be reduced or curtailed. Patients were only provided with 3 once weekly treatments in this study and it is recommended that in future trials 6 treatments may be given twice weekly over 3 weeks for sustainable results.

Patients without neuropathic pain and with symptoms only, could possibly be separated and evaluated in different groups. Patients who use anti-epileptics and anti-depressants could be singled out for participation in further trials to enable comparison with pulsed radio frequency and without pulsed radio frequency. This may suggest that synergy could be achieved by combining pulsed radio frequency with medication. The age and gender were issues that could reduce deviations within the groups investigated. Double blinding should be considered in further investigations at the treatment time lines that were previously applied in the present study.

CONCLUSION:

The above mentioned pulsed radio frequency current demonstrated significant differences between the active and placebo group in the main outcome of the DN4 test. Certain conditions of neuropathic pain and also in neurogenic pain (observable) may be present that may respond to three treatments but others may require more treatment to attain sustainable relief and further investigations will be required to ascertain these assumptions.

It is important to include physical modalities as an adjunct to pharmacological treatments – it may reduce the quantity of medication required and the side effects and if it is possible to improve nerve conduction then it may provide a valuable bioelectronic contribution to global pain relief and function in this and other population groups.

Ethical considerations and Informed Consent

The Human Research Ethics Committee (Medical) of the University of the Witwatersrand accepted and approved the aforementioned study. The study was allocated the designation - M161037 P Berger.

An information form was presented to each patient and patients were assisted if they required further explanation and a consent form was presented and duly signed by each patient prior to commencing this study.

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Contributor statement

P Berger developed, designed and assigned patients to the trial, collected all the data and wrote the article except for the statistics.

E Libhaber received and assessed all the data from Berger, produced and wrote the statistics for this article.

S Landau gave permission, support and referred many patients for this study in Johannesburg. and has also reviewed the paper for publication in his capacity as Physician at the Centre for Diabetes and Endocrinology

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That is their only involvement in this study.

Conflict of interest

Xavant Pty Ltd has an interest in the outcome of this study to validate their beliefs on the veracity of pulsed radio frequency treatment for diabetic neuropathy. However the only participation of this company was to provide funding for transport for both patients and investigators and payment to each investigator for their treatment of each patient.

There was no other conflict of interest.

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