The Effect of Mechanical Stochastic Noise on Diabetic Peripheral Neuropathy. A Pilot Study.

Richard H Lee and Maria J Gonzalez. Infratonic Inc. Department of Research and Development. San Juan Capistrano. California.

Summary

Diabetic neuropathy often involves nerve degeneration such that patients can experience pain or, more commonly, lose sensation in their legs and feet, making it very difficult to walk. Neuropathy is closely associated with vascular disease - inhibited peripheral blood circulation - which frequently causes ulceration - skin sores that don't heal. The goal of this study was to investigate whether the application of stochastic resonance (SR) in form of low frequency mechanical vibration alleviates neuropathy symptoms of diabetic patients, improving their quality of life. It was found that the continued use of mechanical SR therapy for 6 months slowed down the progression of the diabetic symptoms and even more surprisingly, slowly improved some of the conditions. After 6 months of treatment the patients reported a decrease in pain, discoloration, ulceration, disability, neuropathy and vascular disease. These results are promising, and we are looking forward to continued research of the use of the stochastic resonance therapy.

Introduction

Diabetic peripheral neuropathies are a group of heterogeneous syndromes with considerable morbidity, increased mortality and impaired quality of life (Turns M. 2012, Tesfaye et al., 2012). The North America and Caribbean regions have the highest comparative prevalence of diabetes with 10.2%, or 37.4 million people with diabetes in the adult population for 2010 (Sicree et el., 2010). The region is expected to continue to have the highest prevalence in 2030 when 12.1% of adults are anticipated to have diabetes (Sicree et al., 2010). About 50% of Americans with diabetes suffer from some form of neuropathy, according to the American Diabetes Association. The peripheral complications associated with diabetic neuropathy such as pain, disability, vascular disease, and nerve degeneration are considered progressive and irreversible (Tesfaye et al., 2012). The prognosis is generally progression of the disease, ongoing pain, amputation of digits or limbs, and increased disability (Tesfaye et al., 2012).

Treatment of peripheral diabetic neuropathy remains a significant clinical challenge, and current treatment options are very limited and marginally effective. Some of the current treatments include the use of multiple drug classes (Chong and Hester, 2007, Vinik A., 2005) that appear to improve symptoms but have variable side effects and uncertain tolerability (Shi et al., 2012). It is very important to investigate other forms of treatments to decrease the consumption of drugs. The most effective approach will probably be a combination of treatments.

It has been found that the use of stochastic resonance (SR) improves neuropathic function in diabetic patients. McDonnell and Abbott (2009) define SR as noise benefit in a signal-processing system where noise can enhance the detection and transmission of weak signals in sensory systems (Hänggi, 2002). SR has been reported in a wide range of systems. In biology specifically, SR has been demonstrated experimentally in various sensory neural systems, including crayfish (Douglas et al., 1993), shark (Braun et al., 1994), cricket (Levin et al., 1996), and human (Collins et al., 1996). In a human study the external application of SR in the form of sub-sensory mechanical noise to the soles of the feet via vibrating insoles enhanced balance in patients with diabetic and stroke impairments (Priplata et al., 2006). In a different study it was found that SR in the form of low level electrical noise applied to neuropathic diabetic patients improves their ability to perceive sensory stimuli (Khaodhiar et al., 2003), reduce the size, and in some cases close completely, hard-to-heal wounds (Ricci and Afaragan, 2010). The use of SR electrical noise had also being found to improve tactile sensation in healthy young adults (Collins et al., 1996), older adults (Dhruv, et al., 2002) and to improve balance in old adults (Priplata et al., 2002).

The Infratonic is an SR device that generates low frequency mechanical noise with an inaudible acoustical energy below 20 Hz and low amplitude (80 dB). The dominant frequency range is about 8 to 14 Hz. One difference between the Infratonic and the apparatus used for wound healing mentioned above is that the Infratonic does not use electrodes and there is no need to apply it with adhesive tape in direct contact to the skin of the patient. In the present study, we investigated the effect of SR treatment using the Infratonic in patients with diabetic neuropathy. Specifically, we hypothesized that the application of Infratonic treatment alleviates a broad spectrum of diabetic neuropathy symptoms.

Research Design and Methods

Patients

A total of 17 diabetic patients participated in this study. They were recruited from doctors on our mailing list who entered the patients into the study based on both the existence of substantial symptoms and the completion of an examination and report from their doctor. The symptoms were measured using a scale of 1 to 5 where level 1 was low symptoms, level 3 was medium and 5 was the most severe symptoms.

Methods

We used an apparatus that generates mechanical stochastic resonance (SR) stimulation in the alpha range, called Infratonic-8, manufactured by Infratonic Inc., San Juan Capistrano, CA, USA. During the treatment the Infratonic is placed on different parts of the body to deliver mechanical stimulation to specific areas. Patients can be seated during the treatment. Without the need of placing the Infratonic directly against the skin, the healing waves easily travel through the clothes or even a blanket. The significance of this is that the treatment can be applied over poor skin conditions without directly touching or disturbing the area. The treatment is to be applied once a day everyday for the duration of this study (6 months) or longer if the patient wishes to continue. After two month of

therapy a small group of patients (5 in total) served as their own control because they voluntarily stopped the Infratonic treatment. The protocol is described below.

Infratonic protocol treatment

During the first two months the protocol involved the treatment on four different points for 10 minutes each, (total 40 min), at the bottom of each foot, at the pancreas area and at the thymus. First, in sitting position the Infratonic is placed at the bottom of each foot for ten minutes (see Figure #1(2) and (3)), resting each foot on the device. Second, the Infratonic is placed at the pancreas area, at the base of the ribcage 3 to 4 inches to the left of the front midline of the body for 10 minutes (See Figure #1(4)). Third, the Infratonic is placed at the thymus area for 10 minutes (See Figure #1(5)).

From the third through the sixth month we added ten minutes of treatment on the occiput at the brainstem (See Figure #1 (1)) at the beginning of each therapy session, increasing the time of treatment from 40 to 50 minutes. The purpose was to treat the nervous system and reduce even further the neuropathy symptoms.

Results

The diabetic neuropathy study was inspired by several anecdotal reports of people who reported improvement attributed to regular Infratonic therapy. This pilot study was started with a total of 17 diabetic patients from doctors on our mailing list, who entered them into the study based on both the existence of substantial symptoms and the completion of an examination and report from their doctor.

Two month Treatment

At 2 months, as shown in Figure #2, we analyzed different physical conditions of each patient obtaining reduction of the symptoms as follows: 33% in ulceration, 27% in vascular disease, 21% in pain, 19% in disability, 17% in discoloration and 9% in neuropathy (Table #1). The exception was one patient who got worse in two of the symptoms. The report received from the medical doctor about this patient described the condition as no change in pain, ulceration and disability, had an improvement in discoloration but got worse in vascular disease and neuropathy. We found that the smallest reported improvement after two month was in neuropathology (9%). At this point we decided to revise the treatment protocol.

Since we wanted to investigate if we could further improve patient well-being, we added one more treatment point in the protocol. This decision was based on previous results obtained from patients with stroke and head injury that showed restored neural functioning. A typical protocol for these patients was to first treat the brainstem or area of brain injury and then treat the extremities like palms of hands and soles of feet. Since the treatment protocol during the first two months did not include treating the brainstem, for the remaining period of this study we decided to add at the beginning of each therapy session ten minutes of treatment on the occiput at the brainstem (See Figure #1 (1)).

Of particular note from the patient feedback is that the treatment helped many of them

with mood, experiencing more relaxation, more optimism and less depression.

Six months treatment

At the six-month point we found out that 3 patients were dropped out of the Infratonic therapy for non-reporting. In the remaining group of 14 participants, only 9 had continued to use the Infratonic therapy protocol as outlined in Figure #1 (steps 1 to 5). Of the 5 participants who indicated they had departed from the protocol, one reported at six-months that he never even used the machine during the last four months, another was being treated for another disease and could not use the Infratonic regularly, and others just chose not to follow the protocol or to curtail the amount of use. Even though these patients chose to discontinue the Infratonic treatment we decided to analyze their results as a control group. It is interesting to observe that those with the more severe symptoms, as reflected by the pre-treatment measurements, were less likely to drop out of the study or to modify the treatment protocol – perhaps indicating that their quality of life had been so greatly affected already that the possibility of finding relief was a powerful motivator for them.

It would be impractical to consider the results of those who chose to alter the protocol in the same statistical grouping as those who continued to rigorously adhere to the treatment plan, so we have presented their results separately. We then re-analyzed the results for 2 and 6 months considering only the 9 patients that continued with the treatment protocol in one group, group A (Figure #3A), and the rest of the patients that discontinued or did not follow the protocol in a second group, group B (Figure #3B). The group B served as the study's controls. As the results indicate, the progress made by these two distinctly separate groups is markedly different.

As shown in Figure #3A those participants who continued to use Infratonic therapy regularly (group A), continued to improve in every category after 6 months. The decrease in symptoms from pre-treatment to 6 months for the group A are as follows: 46% in pain, 33% in vascular disease, 33% in disability, 29% in neuropathy, 15% in discoloration and 11.1 % in ulceration (Table #2, last column). For group A the analysis from pre-treatment to two months therapy shows an increase in ulceration (22%) and discoloration (6.6%), which is different from the results presented in Figure #2. Figure #3A and Table #2 show that group A started with low level of ulceration (0.9 on a scale of 5), while group B started with a level of 1.4. The increase in ulceration was caused by one individual who developed a secondary ulceration site and as a consequence, the measure of ulceration symptoms at 2 months increased, but by 6 months the ulceration category had decreased (Table #2, penult and last column). All symptoms from the group A decreased from 2 to six months (the penult column on Table #2). Those participants from group B who either discontinued or altered the protocol during the study saw their condition continue to deteriorate (Figure #3B, Table #3, penult column), generally beyond the pre-treatment measurement levels.

It is important to note that the physicians examining the participants who continued the protocol (Figure #3A and Table #2) noted a decrease in pain from the pre-treatment to the two-month measurement (33%), and after 6 months the pain dropped further to 45.8%, while the pain level of those in the control group (B) (Figure #3B) who discontinued or

curtailed their therapy had no change in their pain and neuropathy level (0.0%) (Table #3, penult column). More importantly from 2 months to 6 months, the control group showed no change (0.0%) or an increase in nearly every other category – more disability (22%), more discoloration (41%), more ulceration (50.7%) and more vascular disease (34.3%), while the level of neuropathy stayed the same (0.0%) (Table #3, see the penult column).

Discussion

Peripheral diabetic neuropathy therapy includes multiple treatment strategies suggesting that there is no single effective treatment and that a combination of them will be the best answer. Other treatments, besides electrical and mechanical stimulation, include acupuncture and the use of drugs. Drugs have to be used carefully with special attention to patient's susceptibility to side effects, such as hepatic and renal function, and potential drug interactions. We are introducing a new form of therapy for peripheral diabetic neuropathy symptoms, the Infratonic SR treatment in the form of mechanical noise stimulation.

In this pilot study, we have shown that mechanical SR treatment in the range of the alpha rhythm of the nervous system improved diabetic neuropathy symptoms. We have learned two valuable lessons at this point in the study. First, the continued use of Infratonic therapy provided steady progress for the participants. Diabetic neuropathy is a long term, degenerative disease with symptoms that normally continue to worsen (Chong et al., 2007; Tesfaye and Selvarajah, 2012; Turns, 2012). Slowing this downward spiral is a remarkable accomplishment; but to see an improvement, even a slow and steady one, provides tremendous hope for the many who suffer daily. Another important factor is the improvement in mood that most of the patients experienced. They felt less depression, more optimism and improved relaxation. The second lesson is just as significant –a commitment to improvement in the quality of one's life is required, through a continuity of care. It is vitally important that the therapy continue regularly, as the potential for reversal of degeneration is dependent upon it.

The treatment protocol was designed based on the diabetic neuropathy symptoms. The idea was to specifically promote deep relaxation in all parts of the body, increasing blood circulation to the areas affected by this condition and attenuating the disorder in the digestive system and sugar metabolism. During the first two months, in addition to treating the bottoms of the feet, which we felt would engage the nervous system, the protocol involved treating both the pancreas and the thymus. The pancreas was treated at the front of the abdomen with the intention to treat the endocrine system at a point closest to the entry of excess sugars and carbohydrates into the body, at what might be the center of diabetic endocrine dysfunction, the pancreas. The circulatory system was treated by applying stochastic stimulation over the upper sternum, at the thymus. The intention here was to treat the circulatory system at a point where all the blood passes through the body every few minutes, carrying the pressure waves of stochastic resonance throughout the venous system and providing deep relaxation.

We found at two months that, while this initial protocol appeared effective in treating pain and vascular disease, it was less effective in treating disability, discoloration and

neuropathy. We then chose to add stochastic stimulation to a key point in the nervous system, the back of the brain stem at the occipital region of the head in hopes that the central nervous system would get more involved in the local healing of the peripheral neuropathy conditions. This appeared to increase the relative effectiveness of the protocol for these symptoms. For example the conditions of neuropathy, disability and discoloration showed a decrease in symptoms between month 2 and month 6 (29%, 24% and 21% respectively). The low response of neuropathy to conventional therapy is that, when blood sugar goes out of control, nerves, arteries and veins and other cells, particularly in the periphery are damaged. Nerves are among the slowest structures in the body to heal. It currently appears that Infratonic therapy may have arrested the progression of nerve degeneration and brought about a slight reversal. Perhaps a most important question here is whether Infratonic therapy stops the "inevitable" progression of neuropathy in the longer term**.**

While this protocol appears effective in this pilot study, variations in placement or other changes in protocol may increase effectiveness of treatment. For instance, a footrest with two Infratonic transducers is likely to improve effectiveness by making application easier and shorter. One of the advantages with the footrest is that it provides a uniform stimulation and improves the strength of the signal, because putting the Infratonic transducer on the floor and putting the foot on top of it, has the tendency to attenuate the mechanical signal strength. Further, the use of a neck pillow with front vest component that incorporates three transducers to treat the occipital, thymus and pancreas at the same time will improve compliance as well. Then, a more convenient treatment protocol incorporating these modifications could be simply sitting in a chair and putting the feet on a footrest while wearing the vest for 20 minutes instead of moving the device from point to point for 50 minutes. Each foot will receive 20 minutes of treatment per session instead of 10 and during this time the thymus and pancreas can be treated simultaneously for 10 minutes followed by 10 minutes at the occiput. Finally, this setup allows for applying different frequency bands to different points on the body, which has the potential for increasing effectiveness.

Toward this end, we intend to research the effects of specific treatment points and specific SR signals. For instance, one might have a control group, a full treatment group, and three experimental groups which each apply SR to only one point on the body (occiput, thymus, or pancreas) in addition to treating the feet. A crossover protocol might be employed wherein they treat each point for 4 to 8 weeks before changing to another point. All three groups can cycle through the three points in 3 to 6 months. This will determine the therapeutic effects which SR, applied to each point, can provide. A similar study might be employed with different signals, to determine the optimal therapeutic signal to apply to each point.

Whereas the SR therapy using electrical noise showed accelerated wound healing on the feet (Ricci et al., 2010), based on the results of the current study the Infratonic mechanical noise appears to have a much broader application in neuropathic degenerative conditions than just wound healing. One more advantage is that the Infratonic does not use electrodes or need to be in direct contact with the skin, thus does not cause skin

irritation. Other studies using SR mechanical noise in the form of vibrating insoles show an increase in nerve sensation and balance during stimulation (Priplata et al., 2006), which is a similar effect, but was observed only during stimulation, and not a residual improvement in the condition, as in the current study.

The molecular pathways by which SR improves the symptoms of peripheral diabetic neuropathy are not clearly understood, but various mechanisms have been proposed. First, the vibratory noise may add mechanical energy to the vibratory stimulus, thus enhancing the vibration transmission through the dermal tissue (Priplata et al., 2006). Second, the mechanical noise may stimulate the tissue causing fluctuations in the trans-membrane potential through changes in the permeability of ion channels (Charles et al., 1991; Priplata et al., 2006, Shi et al., 2012). Third, other studies have shown that noise stimulation of peripheral receptors can lead to stochastic-resonance-type effects in the central nervous system (Hidaka et al., 2000; Manjarrez et al., 2003). One of the Infratonic mechanisms of action is probably through changes in cell membrane permeability as shown by Rachlin, Moore and Yount (Rachlin et al., 2012). These investigators evaluated cell permeability *in vitro* using the U98 cell line and the fluorophore calcein as a surrogate marker, and analyzed their results by FACS and fluorescent microscope. They found a relative increase of 69% in mean calcein fluorescence intensity in cells receiving Infratonic mechanical noise (Rachlin et al., 2012). It has also been found that the Infratonic does not cause any apparent cytotoxicity as assessed by phase contrast imaging (20x) of morphological characteristics (Rachlin et al., 2012) and does not produce genetic damage (Yount et al., 2004).

Further studies will be required to fully explore the effect of the Infratonic on diabetic neuropathy. In conclusion, we showed that the diabetic neuropathy symptoms could be alleviated by application of mechanical noise through the Infratonic device. This technique may be helpful in improving nerve and venous function, reducing pain, and reducing incidence of ulceration.

References

Braun HA, Wissing H, Schäfer K, Hirsch MC. Oscilllation and noise determine signal transduction in shark multimodal sensory cells. Nature. 367(6460): 270-3, 1994.

Charles A, Merrill JE, Dirksen ER and Sandersont MJ. Intracellular signaling in glial cells: Calcium waves and oscillations in response to mechanical stimulation and glutamate. Neuron. 6(6): 983-992, 1991.

Chong MS, Hester J. Diabetic painful neuropathy: current and future treatment options. Drugs. 67(4): 569-85, 2007.

Collins JJ, Imhoff TT, Grigg P: Noise-enhanced tactile sensation. Nature. 383:770, 1996.

Dhruv NT, Niemi JB, Harry JD, Lipsitz LA, Collins JJ: Enhancing tactile sensation in older adults with electrical noise stimulation. Neuroreport. 13:597-600, 2002.

Douglass JK, Wilkens L, Pantazelou E, Moss F. Nois. Noise enhancement of information transfer in crayfish mechanoreceptors by stochastic resonance. Nature. 365(6444): 337-40, 1993.

Hänggi P. Stochastic resonance in biology. How noise can enhance detection of weak signals and help improve biological information processing. Chemphyschem. 3(3): 285-90, 2002.

Hidaka I, Nozaki D, Yamamoto Y. Functional stochastic resonance in the human brain: noise induced sensitization of baroreflex system. Phys. Rev. Lett. 85: 3740-3743, 2000.

Khaodhiar L, Niemi JB, Earnest R, Lima C, Harry JD, Veves A. Enhancing sensation in diabetic neuropathic foot with mechanical noise. Diabetes Care. 26: 3280-3283, 2003.

Levin JE, Miller JP. Broadband neural encoding in the cricket cercal sensory system enhanced by stochastic resonance. Nature. 380(6570): 165-8, 1996.

Manjarrez E, Rojas-Piloni G, Mendez I, Flores A. Stochastic resonance within the somatosensory system: effects of noise on evoked field potentials elicited by tactile stimuli. J. Neurosci. 23: 1997-2001, 2003.

McDonnell MD, Abbott D. What is stochastic resonance? Definitions, misconceptions, debates, and its relevance to biology. PLoS Comput Biol. 5(5): e1000348. Epub 2009.

Priplata A, Niemi J, Salen M, Harry J, Lipsitz LA, Collins JJ: Noise-enhanced human balance control. Phys Rev Lett 89: 238101-1–238101-4, 2002.

Priplata AA, Patritti BL, Niemi JB, Hughes R, Gravelle DC, Lipsitz LA, Veves A, Stein J, Bonato P, Collins JJ. Noise-enhanced balance control in patients with diabetes and patients with stroke. Annals of Neurology. 59(1): 4-12, 2006.

Rachlin K, Moore DH and Yount G. Infrasound Sensitizes Human Glioblastoma Cells to Cisplatin-Induced Apoptosis. Integr Cancer Ther. Nov.19, 2012

Ricci, E and Afaragan M. The effect of stochastic electrical noise on hard to heal wounds. Journal of Wound Care. 19(3): 96-103, 2010.

Shi L, Zhang HH, Hu J, Jiang XH, Xu GY. Purinergic P2X receptors and diabetic neuropathic pain. Sheng Li Xue Bao. 64(5): 531-42, 2012

Sicree R, Shaw J and Barker PZ. Diabetes and Impaired Glucose Tolerance. IDF Diabetes Atlas. Fourth edition. Pages 1-105, 2010.

Tesfaye S. and Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. Diabetes Metab. Res. Rev. 1: 8-14, 2012.

Turns M. The diabetic foot: an overview for community nurses. Br. J. Community Nurs. 9: 422-433, 2012.

Vinik A. Use of Antiepileptic Drugs in the Treatment of Chronic Painful Diabetic Neuropathy. The Journal of Clinical Endocrinology & Metabolism. 90(8): 4936-4945, 2005.

Yount G, Taft R, West J and Moore D. Possible Influence of Infrasound on Glioma Cell Response to Chemotherapy: A Pilot Study. The Journal of Alternative and Complementary Medicine.10: 247-250, 2004.

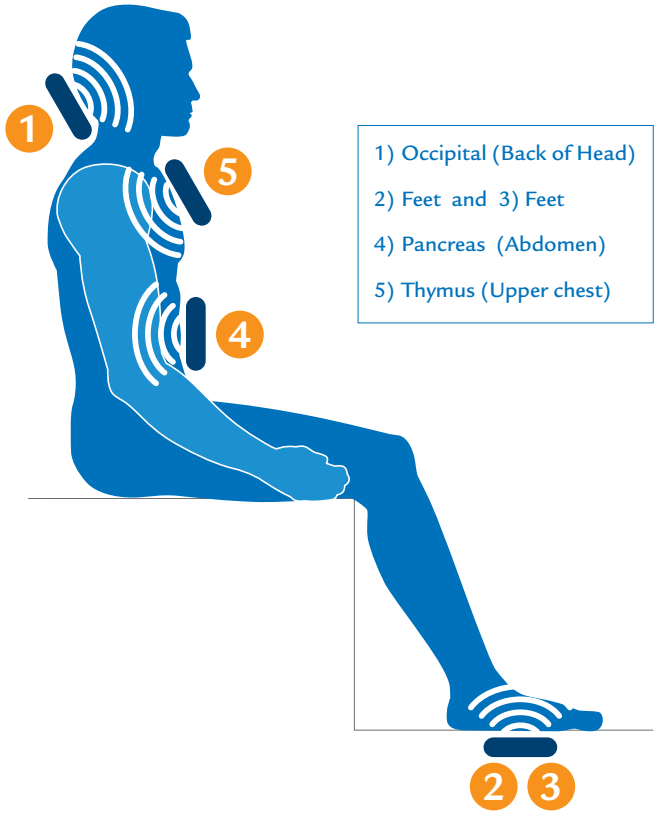

Figure 1. Treatment protocol. The Infratonic is applied first to the occiput at the brainstem (1) for 10 minutes, then, at the bottom of each foot (2 and 3) for 10 minutes. Next, the Infratonic is placed on the pancreas (4) resting at the base of the rib cage about 3 to 4 inches to the left of the front midline of the body for 10 minutes. The protocol ends by placing the Infratonic over the area of the thymus (5) for 10 minutes. During the first two months the protocol did not include treatment at the brainstem on occiput area (1). Total treatment time was 40 minutes. The whole protocol from 1 to 5 was used by the patients from two to six months. Total treatment time was 50 minutes. This figure was designed by John Hopkins (Hopart Inc., Creative Design Services).

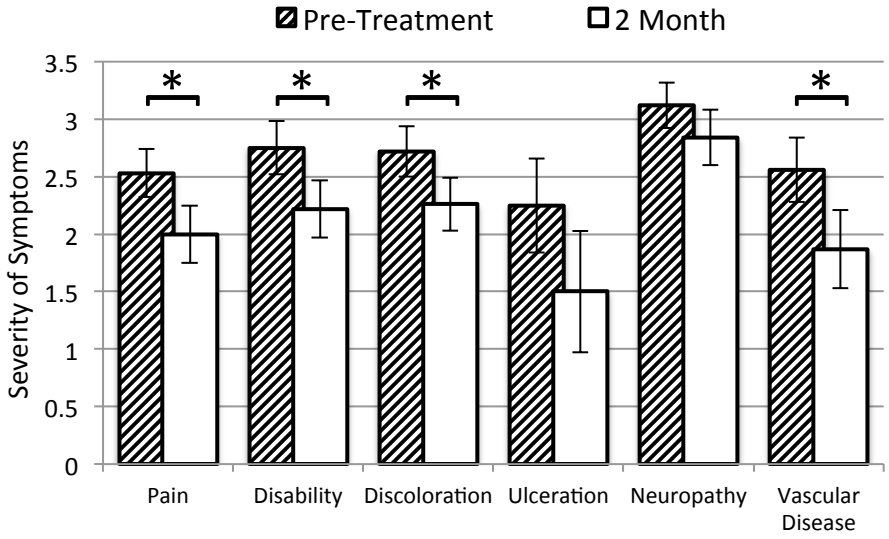

Figure #2. Severity of symptoms in arbitrary units. Symptoms were evaluated in an scale of 1 to 5, where one was low and five the most severe. The columns show the average of symptoms from 17 to 8 patients before therapy (grey) and after two month therapy (white). The (*) symbols indicate that the changes in symptoms before and after two month treatment were statistically significant (see table #1).

Symptoms	Number of patients with symptoms	Severity of Symptoms		Percentage Reduction	T-test
		Pre-Treatment	2 Month		
Pain	17	2.53	2	22.1%	**0.014**
Disability	16	2.75	2.22	21.9%	**0.0018**
Discoloration	16	2.72	2.26	15.1%	**0.0153**
Ulceration	8	2.25	1.5	41.7%	0.0796
Neuropathy	16	3.12	2.84	6.3%	0.2083
Vascular Disease	15	2.56	1.87	25.0%	**0.0217**

Table #1. Severity of symptoms on diabetic patients. A total of 17 patients were evaluated during 2 month Infratonic treatment. The second column shows the number of patients with specific symptoms. The average value from each symptom is presented in columns 3 and 4. The fifth column shows the percentage in reduction of symptoms. The T-test statistical analysis is showed in the last column. The differences in pain, disability, discoloration and vascular disease are statistically significant after two month treatment (P values in bold).

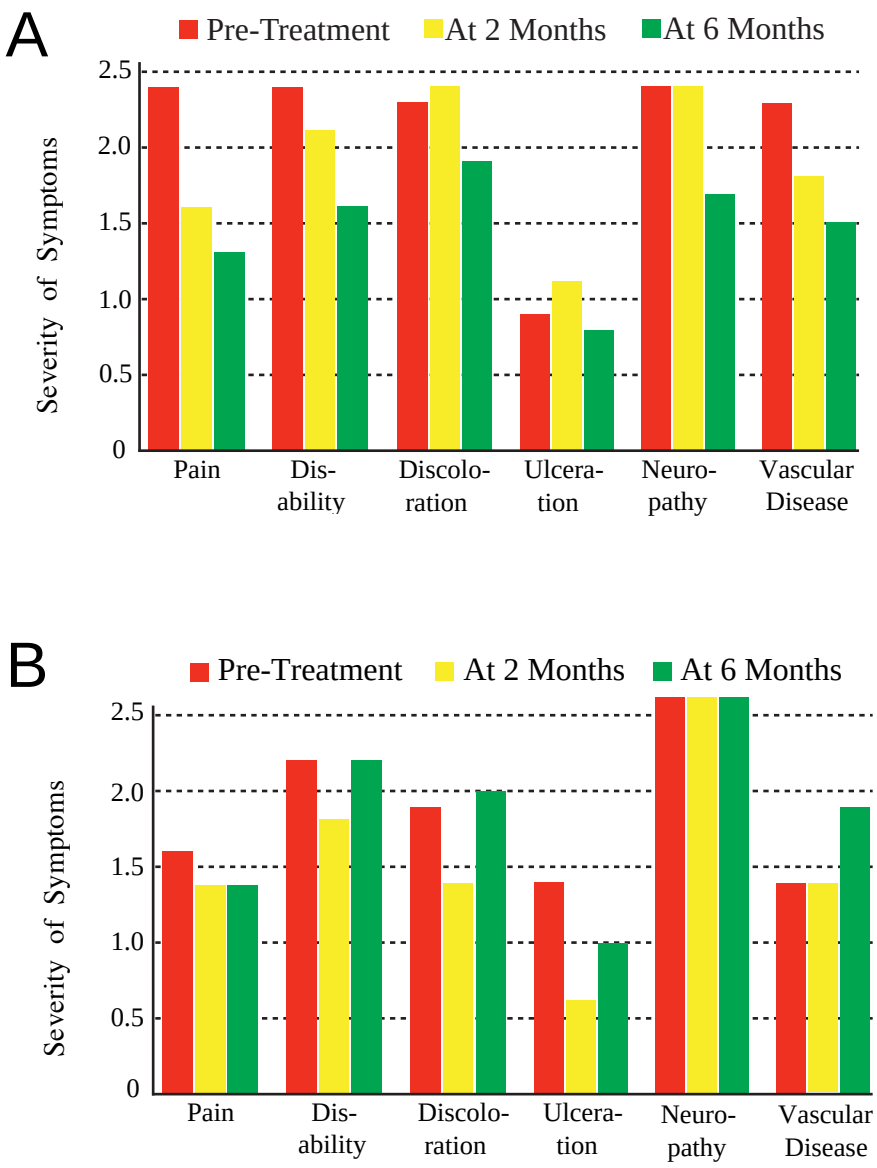

Figure 3. Severity of symptoms in arbitrary units. Symptoms were evaluated on a scale of 1 to 5, where one was low and five the most severe. The columns show the average of symptoms from (A) 9 patients and (B) 5 patients before therapy (Pre-Treatment (red)), two months of therapy (yellow) and six month from the beginning of treatment (green). (A) Patients who continued with the treatment for 6 months without interruption. (B) Patients who discontinued or did not followed the protocol.

Symptoms (Group A)	Severity of Symptoms			% of Change from Pre-treatment to two month	% of Change from Two month to six month	% of Change from Pre-treat to six month
	Pre-treatment	Two-month	Six month			
Pain	2.4	1.6	1.3	-33.33	-18.75	-45.83
Disability	2.4	2.1	1.6	-12.5	-23.81	-33.33
Discoloration	2.25	2.4	1.9	+6.67	-20.83	-15.56
Ulceration	0.9	1.1	0.8	+22.2	-27.28	-11.11
Neuropathy	2.4	2.4	1.7	0.0	-29.17	-29.17
Vascular disease	2.25	1.8	1.5	-20.0	-16.67	-33.33

Table #2. Group of patients that continued with the Infratonic treatment during 6 months (a total of nine patients). Severity of symptoms are quantify in arbitrary units from 1 to 5, where 5 is the most severe. The three first columns show the average of severity of symptoms before (pre-treatment) and after two and six months treatment. The three last columns show changes in the percentage of symptoms severity, where the plus (+) or a minus (-) symbol indicate an increase or a decrease (respectively) in the percentage of severity.

Symptoms (Group B)	Severity of symptoms			% of Change from Pre-treatment to two month	% of Change from Two month to six month	% of Change from Pre-treat to six month
	Pre-treatment	Two month	Six month			
Pain	1.6	1.35	1.35	-15.63	0.0	-15.63
Disability	2.2	1.8	2.2	-18.19	+22.22	0.0
Discoloration	1.9	1.4	1.98	-26.32	+41.42	+4.21
Ulceration	1.4	0.65	0.98	-53.57	+50.77	-30.0
Neuropathy	2.65	2.65	2.65	0.0	0.0	0.0
Vascular disease	1.4	1.4	1.88	0.0	+34.28	+34.28

Table #3. Group of patients that discontinue the Infratonic therapy after two months (total of 5 patients). The first three columns show the average of severity of symptoms at pre-treatment, at two months treatment and at six month after the beginning of the treatment. Severity of symptoms are quantify in arbitrary units from one to five, where 5 is the most severe. The last three columns show changes in the percentage of symptoms, where the plus (+) or a minus (-) symbol indicate an increase or a decrease (respectively) in the percentage of severity.