High-Tone External Muscle Stimulation in End-Stage Renal Disease: Effects on Symptomatic Diabetic and Uremic Peripheral Neuropathy

A. Klassen, Dipl-Psych, ⋆ *B. Di Iorio, Dr med,* † *P. Guastaferro, Dr med,* † *U. Bahner, Prof Dr med,* ‡ *A. Heidland, Prof Dr med Dr hc mult,* ⋆‡ *and N. De Santo, Prof Dr med* §

Objective and Design: Pain and peripheral neuropathy are frequent complications of end-stage renal disease (ESRD). Because drug treatment is associated with numerous side effects and is largely ineffective in many maintenance hemodialysis (MHD) patients, nonpharmacologic strategies such as electrotherapy are a potential recourse. Among various forms of electrostimulation, high-tone external muscle stimulation (HTEMS) is a promising alternative treatment for symptomatic diabetic peripheral polyneuropathy (PPN), as demonstrated in a short-term study. Based on these novel findings, we performed a prospective, nonrandomized, pilot trial in MHD patients to determine (1) whether HTEMS is also effective in treating diabetic PPN in the uremic state, and (2) whether uremic PPN is similarly modulated.

Patients and Interventions: In total, 40 MHD patients diagnosed with symptomatic PPN (25 with diabetic and 15 with uremic PPN) were enrolled. Both lower extremities were treated intradialytically with HTEMS for 1 hour, three times a week. Initially, a subgroup of 12 patients was followed for 4 weeks, and a further 28 patients for 12 weeks. The patients' degree of neuropathy was graded at baseline before HTEMS and after 1 and 3 months, respectively. Five neuropathic symptoms (tingling, burning, pain, numbness, and numbness in painful areas) as well as sleep disturbances were measured, using the 10-point Neuropathic Pain Scale of Galer and Jensen (*Neurology* 48:332-338, 1997). A positive response was defined as the improvement of one symptom or more, by at least 3 points. Other parameters included blood pressure, heart rate, dry body weight, and a routine laboratory investigation.

Results: The HTEMS led to a significant improvement in all five neuropathic symptoms, and to a significant reduction in sleep disturbances for both diabetic and uremic PPN. The response was independent of the patient's age, with a responder rate of 73%. The improvement of neuropathy was time-dependent, with the best results achieved after 3 months of treatment. The HTEMS was well-tolerated by nearly all patients.

Conclusions: This pilot study shows for the first time that HTEMS can ameliorate the discomfort and pain associated with both diabetic and uremic PPN in MHD patients, and could be a valuable supplement in the treatment of pain and neuropathic discomfort in patients who do not respond to, or are unable to participate in, exercise programs during hemodialysis treatment.

⋆*Department of Internal Medicine, University of Würzburg, Würzburg, Germany.*

†*Division of Nefrologia, Ospedale A. Landolfi, Solofra, Italy.*

‡*Foundation for Dialysis-Kidney Center, Würzburg, Germany.*

§*Department of Pediatrics, University of Naples, Naples, Italy.*

Address reprint requests to August Heidland, MD, PhD, Department of Internal Medicine, University of Würzburg, and Foundation for Dialysis-Kidney Center Würzburg, Hans-Brandmann-Weg 1, D-97080 Würzburg, Germany. E-mail: August.Heidland@t-online.de

1051-2276/08/1801-0009$34.00/0

doi:10.1053/j.jrn.2007.10.010

PAIN IS A FREQUENT COMPLICATION of end-stage renal disease (ESRD), and has a profoundly negative impact on patients' quality of life. In particular, in peripheral diabetic neuropathy, loss of sensation is a forerunner of neuropathic ulcers and the leading cause of amputation.[1] According to a prospective Canadian study of maintenance hemodialysis (MHD) patients, pain was prevalent in >50% of patients, of whom 83% reported a pain intensity ranging from moderate to severe.[2] Most patients suffered from pain brought on by musculoskeletal disorders. The prevalence of pain because of peripheral

polyneuropathy (PPN) and peripheral vascular disease averaged 13% and 10%, respectively.[2] Moreover, the Pain Management Index was negative in 75% of patients, indicating the inefficacy of many analgetic drug therapies (anticonvulsants, tricyclic antidepressants, and opioids), which are associated with a multitude of side effects, such as sedation, nausea, and dry mouth.[2]

With regard to manifesting fewer side effects, nonpharmacologic strategies are of growing importance. Unfortunately, relaxation techniques, hypnosis, and meditation are of limited value. There is evidence that aerobic exercise training can modify the natural course of diabetic PPN, or even prevent its onset.[3] However, physical exercise (though strongly recommended) is difficult to realize for many (often immobile) MHD patients, who have a low physical functional capacity as a consequence of their multiple comorbidities.

In the management of pain, various forms of electro-medical therapy figure prominently. Most commonly used are transcutaneous electrical nerve stimulation (TENS)[4] and percutaneous electrical nerve stimulation (PENS), which combines TENS and acupuncture.[5] Both treatments were shown to ameliorate painful diabetic neuropathy. Another very effective therapy in patients with painful diabetic PPN is spinal-cord stimulation (SCS), which simultaneously improves exercise tolerance.[6] Spinal-cord stimulation also proved successful in patients with intractable angina pectoris, in whom angioplasty or coronary bypass graft surgery could not be performed.[7,8] This form of electrotherapy was also recommended for pain because of lower-limb ischemia in subjects unsuitable for vascular reconstruction.[9] Recently the effect of SCS was studied in eight MHD patients. Within a treatment period of 6 to 12 months, SCS dramatically lowered pain, improved patient quality of life, and appeared to delay ischemic skin lesions and amputation in patients at Leriche-Fontaine stage 2 or 3.[10] However, SCS therapy may be associated with severe complications, such as life-threatening infections (of 3% to 5% of SCS-treated patients).[11]

Within the new generation of electrotherapy techniques is the so-called "high-tone external muscle stimulation" (HTEMS). Whereas classical electrotherapy uses fixed carrier frequencies of typically 4000 Hz, the frequencies of HTEMS are continuously scanned from 4096 to 31,768 Hz, allowing for a much higher power of up to 5000 mW to be introduced to the muscles treated. In a short-term (3 consecutive days), comparative investigation in subjects with symptomatic diabetic PPN, HTEMS alleviated discomfort and pain more effectively than did TENS. Moreover, this kind of therapy exhibited no harmful side effects.[12]

Based on these novel findings, our objective was to determine (1) whether HTEMS is likewise effective in diabetic ESRD patients with symptomatic PPN, and (2) whether the uremic PPN is similarly modulated. Subsequently, a multicenter pilot study was conducted in MHD patients. The results indicated a significant improvement of pain and discomfort, in symptomatic uremic and diabetic PPN.

Methods

A prospective, nonrandomized, clinical pilot study was performed in MHD patients (with moderate discomfort or pain for at least 3 months) from five dialysis centers in Germany (KfH-Kidney Centers in Aschaffenburg, Frankfurt, Würzburg, the St. Marien Hospital in Duisburg) and Italy (Ospedale A. Landolfi, Solofra). In total, 40 patients, aged between 50 and 93 years (71.8 SD $\pm$ 11.2 years), and who had received hemodialysis for a minimum of 6 months, were enrolled. Patients receiving MHD and with complicating peripheral vascular disease were included in the investigation. Analgetic drugs were permitted, but were reduced to an as-needed basis.

We excluded patients with a pacemaker, a recent myocardial infarction, severe congestive heart failure, central neurologic disorders (e.g., Parkinson's disease, epilepsy, or multiple sclerosis), psychiatric disorders, and bacterial infections. The baseline characteristics of patients are summarized in Table 1.

The diagnosis of symptomatic PPN was based on the medical history, a neurologic investigation, and the presence of the following neuropathic symptoms: tingling, burning, pain, numbness, and numbness in painful areas, as well as sleep disorders.

External muscle stimulation was performed with a HiTop 184 appliance (GBO Medizintechnik, Rimbach, Germany), which is a nonportable 230-V power-supply device.[12] For HTEMS therapy, the electrodes were placed on the femoral muscles, and in some cases on the calves as well (Fig. 1). The intensity of electrical stimulation

Table 1. Characteristics of Forty Maintenance Hemodialysis Patients Who Participated in This Study

Patient Characteristics	All Patients (N = 40)	Diabetic PPN (n = 25)	Uremic PPN (n = 15)
Age (y) (mean ± SD)	71.8 ± 11.2	71.2 ± 11.4	72.8 ± 11.1
Age range (y)	50–93	51–93	50–87
Sex (men/women)	25/15	16/9	9/6
Renal diagnoses			
Diabetic nephropathy	24	24	
Chronic glomerulonephritis	6		6
Ischemic renal failure	5		5
Pyelonephritis	1		1
Wegener's Granulomatosis	2		2
Polycystic kidney disease	2	1	1
Peripheral arterial disease	8	7	1

PPN, peripheral polyneuropathy.

was adjusted to suit the comfort level of each individual patient without producing discomfort or pain. All subjects were treated for 1 hour during the hemodialysis session, three times weekly. Initially, 12 patients were followed for 1 month, and a further 28 patients were followed for a treatment period of 3 months.

The primary outcome measure was the potential modulation of intensity of neuropathic symptoms. For purposes of grading these symptoms, patients were requested to record their baseline levels of pain and discomfort, using a visual 10-point analogue scale, ranging from 0 ("no symptoms") to 10 ("worst ever felt").[13] Improvement was defined as a decline of ≥3 points of at least one symptom.

Other recorded parameters included systolic and diastolic blood pressure, heart rate, and dry body weight. Further, a routine laboratory investigation was performed, including measurements of albumin, C-reactive protein, and Hemoglobin A1c (HbA1c) in diabetics.

All data are expressed as mean ± SD. Changes in the investigated parameters were calculated by paired Student *t* test (two-tailed), with $P < .05$ considered statistically significant. All analyses were performed using Microsoft Excel (Redmond, WA).

Figure 1. High-tone external muscle stimulation of thighs and calves in a maintenance hemodialysis patient with the HiTop 184 device (GBO Medizintechnik, Rimbach, Germany).

Results

In our 40 MHD patients, the neuropathic symptoms of pain and discomfort exhibited significant improvements in terms of tingling, burning, pain, numbness, and numbness in painful areas ($P < .005$). Even the sleep disorders induced by neuropathy were significantly improved during long-term HTEMS therapy ($P < .005$) (Fig. 2). The amelioration of symptoms of peripheral neuropathy was observed after only 4 weeks of HTEMS treatment in a subgroup of 12 patients. Concerning the underlining neuropathy, the response was significant in both uremic and diabetic polyneuropathy, with the exception of the neuropathic symptom "numbness in painful areas." In that case, the improvement in patients with uremic polyneuropathy was not statistically significant. The response was independent of patients' age or sex.

When defining a positive response as the improvement of one symptom or more by at least 3 points, the response rate for all 40 MHD patients averaged 73% (29 out of 40). In the subgroup of patients with uremic PPN, the response rate was higher compared with their counterparts with diabetic PPN (11 out of 15, or 80%, versus 18 out of 25, or 72%).

When comparing the improvement of neuropathic symptoms in the initial subgroup of 12 patients treated with HTEMS for 4 weeks with the 28 patients treated for 12 weeks, the difference

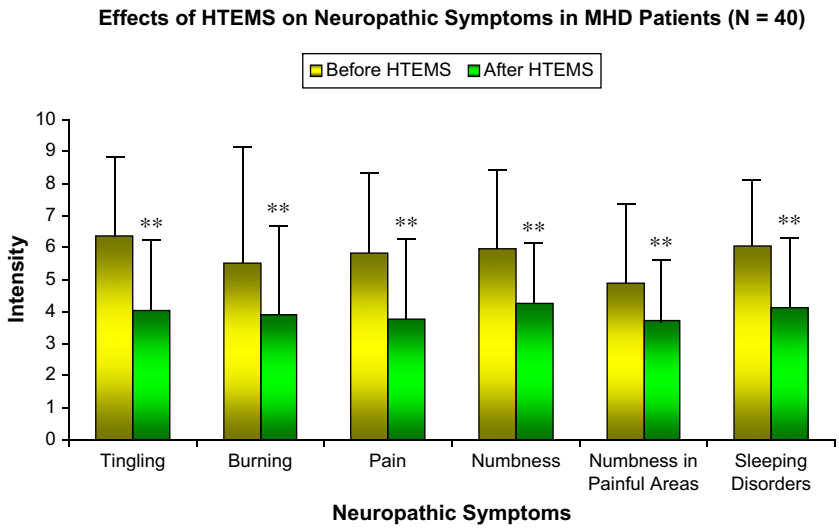

Figure 2. Effects of high-tone external muscle stimulation (HTEMS) on five neuropathic symptoms and on sleeping disorders in maintenance hemodialysis patients. (**$P < .005$).

in response rate was considerable, at 58% (7 out of 12) versus 79% (22 out of 28), respectively. The response rate was clearly dependent on the duration of HTEMS treatment.

The HTEMS was well-tolerated by all subjects in the study, apart from one patient who reported enhanced nervousness and sleeplessness after only three sessions of treatment. She was subsequently excluded from the investigation. After 4 to 6 weeks, some patients reported an increase in overall well-being, accompanied by a rise in muscle strength.

During the treatment period, HTEMS had no significant effect on systolic and diastolic blood pressure or on heart rate. Similarly, there were no significant changes in dry body weight. Concerning blood chemistry, the albumin concentration was followed in 26 MHD patients. Whereas there was no significant change within the first 4 weeks of HTEMS, after 12 weeks of treatment, a clear trend toward a higher albumin concentration was observed. There were no significant changes in C-reactive protein and HbA1C in the diabetic MHD patients.

Discussion

In our prospective, nonrandomized pilot study of MHD patients, we found significant improvement in the neuropathic symptoms of tingling, burning, pain, numbness, and numbness in painful areas. The response was comparable between patients with diabetic PPN and those with uremic PPN. This implies that HTEMS alleviates neuropathic symptoms of different pathogeneses. In addition, patients' quality of sleep was significantly improved, in terms of less frequent nighttime waking on account of pain and discomfort. The treatment effects were clearly dependent on the duration of HTEMS therapy, with the best results observed after >4 weeks.

Our data correspond with, and extend, the earlier investigation of short-term (3 consecutive days) HTEMS treatment.[12] Similarly positive observations were made by Humpert et al.[17] during an 8-week treatment period in 27 patients with painful diabetic neuropathy.

To date, the mechanisms underlying the improvement in neuropathic symptoms after electrotherapy are not well-understood. In various investigations, improved microcirculation after electrotherapy was shown.[17–19] This effect is particularly pronounced when using epidural spinal-cord electrical stimulation in patients with severe limb ischemia.[9] Electrical stimulation was also shown to improve wound-healing in patients with diabetic ulcers.[20] Enhanced microcirculation, as induced by electrical stimulation, could be of therapeutic value with regard to the lowered microcirculation in the peripheral nerves of patients with diabetic neuropathy.

Another possible underlying mechanism of electrotherapy is the activation of dorsal columns. Here, pain input is interrupted via inhibition of

the C fibers.[14] Recently, high-frequency TENS was shown to decrease human motor cortex excitability.[15] Further, it decreased levels of the excitatory amino acids, glutamate and aspartate, in the dorsal horn.[16]

Of particular interest are the metabolic effects of electrotherapy, which was shown to increase muscle oxidative capacity.[21] Electrical stimulation of the lower extremities of healthy humans was shown to enhance energy consumption, carbohydrate oxidation, and whole-body glucose uptake during a euglycemic clamp.[22] Compared with voluntary cycling exercise at an identical intensity, electrostimulation resulted in a higher respiratory gas exchange ratio, indicating higher carbohydrate oxidation. Furthermore, the enhanced glucose removal was not limited to the exercise period, but persisted after the exercise period for at least 90 minutes, in contrast to voluntary exercise.[23] In paraplegic patients, 8 weeks of treatment (3 hours/week) enhanced the glucose transporters 1 and 4, oxidative capacity, and insulin sensitivity.[24]

In line with these observations of enhanced glucose metabolism, HTEMS (1 hour/day) induced a significant improvement in HbA1c (–0.6%) over a treatment period of 6 weeks, associated with a decline in body weight (–1.4 kg).[25] After the discontinuation of therapy, a renewed deterioration of these parameters occurred. In contrast to these findings, we did not observe a significant change in HbA1c in our diabetic MHD patients, which may be a consequence of the lower treatment frequency of HTEMS therapy in our investigation (1 hour, 3 times/week). In fact, in two other patients treated daily with HTEMS (data not shown), an improvement in HbA1c and overweight was observed.

Aerobic and resistance exercise are generally recommended in MHD, particularly to improve the prevalent sarcopenia and physical fitness of these patients.[26] In principle, similar positive effects could be achieved by HTEMS in immobile patients with low physical functional capacity, making electrotherapy a viable, intermediate treatment strategy.

Conclusion

According to our data, long-term treatment with HTEMS in MHD patients can lead to significant improvement of neuropathic symptoms. Many patients also reported a subjective improvement of their general well-being, with greater muscle strength. The greatest shortcoming of our study was the lack of a control group, insofar as no placebo intervention could be implemented. High-tone external muscle stimulation should be considered for patients with symptomatic peripheral neuropathy who do not respond to, or are unable to participate in, exercise programs during hemodialysis treatment.

References

1. Davies M, Brophy S, Williams R, Taylor A: The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care 29:1518-1522, 2006

2. Davison SN: Pain in hemodialysis patients: prevalence, cause, severity, and management. Am J Kidney Dis 42: 1239-1247, 2003

3. Balducci S, Iacobellis G, Parisi L, et al: Exercise training can modify the natural history of diabetic peripheral neuropathy. J Diabetes Complications 20:216-223, 2006

4. Kumar D, Marshall HJ: Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. Diabetes Care 20:1702-1705, 1997

5. Hamza MA, White PF, Craig WF, et al: Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain. Diabetes Care 23:365-370, 2000

6. Tesfaye S, Watt J, Benbow SJ, et al: Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet 348:1698-1701, 1996

7. Mannheimer C, Augustinsson LE, Carlsson CA, et al: Epidural spinal electrical stimulation in severe angina pectoris. Br Heart J 59:56-61, 1988

8. Mannheimer C, Eliasson T, Augustinsson LE, et al: Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris: the ESBY Study. Circulation 97:1157-1163, 1998

9. Jacobs MJ, Jorning PJ, Joshi SR, et al: Epidural spinal cord electrical stimulation improves microvascular blood flow in severe limb ischemia. Ann Surg 207:179-183, 1988

10. Brümmer U, Condini V, Cappelli P, et al: Spinal cord stimulation in hemodialysis patients with critical lower-limb ischemia. Am J Kidney Dis 47:842-847, 2006

11. Torrens JK, Stanley PJ, Ragunathan PL, Bush DJ: Risk of infection with electrical spinal-cord stimulation. Lancet 349: 729, 1997

12. Reichstein L, Labrenz S, Ziegler D, Martin S: Effective treatment of symptomatic diabetic polyneuropathy by high-frequency external muscle stimulation. Diabetologia 48:824-828, 2005

13. Galer BS, Jensen MP: Development and preliminary validation of a pain measure specific to neuropathic pain: the neuropathic pain scale. Neurology 48:332-338, 1997

14. Watkins ES, Koeze TH: Spinal cord stimulation and pain relief. Br Med J [Clin Res] 307:462, 1993

15. Mima T, Oga T, Rothwell J, et al: Short-term high-frequency transcutaneous electrical nerve stimulation decreases human motor cortex excitability. Neurosci Lett 355:85-88, 2004

16. Lundeberg T, Kjartansson J, Samuelsson U: Effect of electrical nerve stimulation on healing of ischaemic skin flaps. Lancet 2:712-714, 1988

17. Humpert PM, Rudofsky G, Morcos M, et al: Hochfrequente Muskelstimulation zur Behandlung schmerzhafter Neuropathie bei Typ 2 Diabetikern verbessert die mikrovaskuläre Endothelzellfunktion. Diab Stoffw 128(Suppl 1):S63, 2006

18. Tesfaye S, Harris ND, Wilson RM, Ward JD: Exercise-induced conduction velocity increment: a marker of impaired peripheral nerve blood flow in diabetic neuropathy. Diabetologia 35:155-159, 1992

19. Tesfaye S, Harris ND, Jakubowski JJ, et al: Impaired blood flow and arterio-venous shunting in human diabetic neuropathy: a novel technique of nerve photography and fluorescein angiography. Diabetologia 36:1266-1274, 1993

20. Baker LL, Chambers R, DeMuth SK, Villar F: Effects of electrical stimulation on wound healing in patients with diabetic ulcers. Diabetes Care 20:405-412, 1997

21. Martin TP, Stein RB, Hoeppner PH, Reid DC: Influence of electrical stimulation on the morphological and metabolic properties of paralyzed muscle. J Appl Physiol 72:1401-1406, 1992

22. Hamada T, Sesaki H, Hayashi T, et al: Enhancement of whole body glucose uptake during and after human skeletal muscle low-frequency electrical stimulation. J App Physiol 94: 2107-2112, 2003

23. Hamada T, Hayashi T, Kimura T, et al: Electrical stimulation of human lower extremities enhances energy consumption, carbohydrate oxidation, and whole body glucose uptake. J Appl Physiol 96:911-916, 2004

24. Chilibeck PD, Bell G, Jeon J, et al: Functional electrical stimulation exercise increases GLUT-1 and GLUT-4 in paralyzed skeletal muscle. Metabolism 48:1409-1413, 1999

25. Rose B, Lankisch M, Herder C, et al: Externe Muskelstimulation beeinflusst die Diabeteseinstellung: eine neuartige Therapieoption für Typ 2 Diabetes. Diabetologie und Stoffwechsel 2(Suppl 1):S107, 2007

26. Johansen KL: Exercise in the end-stage renal disease population. J Am Soc Nephrol 18:1845-1854, 2007