High-tone external muscle stimulation in end-stage renal disease: effects on quality of life in patients with peripheral neuropathy

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Abstract. Objective: High-tone external muscle stimulation (HTEM) has been shown to ameliorate painful peripheral neuropathy of dialysis patients. We hypothesized that HTEM could also lead to improved parameters of health-related quality of life (HRQOL). Methods: 25 end-stage renal disease (ESRD) patients (17 men/8 women, mean age 62.2 ± 14.2 years) were enrolled for the study. For evaluation of HRQOL the short form SF-36 was used. In addition, the Hospital Anxiety and Depression Scale (HADS) and the pain severity score were investigated. HTEM was applied intradialytically for 1 hour, 3 times a week. Its effect was evaluated just before the beginning and both 6 and 12 weeks after onset of this study. Results: SF-36 showed a significant effect of time for the subscales of physical role functioning and social functioning. A marginal significant positive trend could be observed for physical functioning. The pain symptom questionnaire sum scores improved significantly after 12 weeks. The HADS did not change significantly. Conclusion: The data indicate that intradialytic HTEM treatment of ESRD patients with peripheral neuropathy ameliorates various components of physical health.

Introduction

Pain is one of the most common symptoms in patients with end-stage renal disease (ESRD) with a prevalence of around 50% [1, 2, 3]. Although in most individuals the pain ranges from moderate to severe, only 1/4 of them is adequately treated [1, 4, 5]. The reason for the insufficient treatment lies in 4 key factors: 1) general lack of recognition of the problem, 2) insufficient knowledge about the nature and origin of various forms of pain in ESRD, 3) enhanced adverse effects of many analgesic drugs in renal failure due to their altered pharmacokinetics and pharmacodynamics, and 4) unwillingness of the patients through daily tablet overload and the fear of drug dependency (as in the case of opiate medication) [5, 6, 7].

Consequences of persistent pain may be mental, physical, and social complications [2, 6, 8, 9]. They include sleep disturbances (in part due to restless legs syndrome) [10, 11], reduced memory and attention [9, 12], manifestations of anxiety and depression [13], impotence [14], impaired interpersonal relationships, and the wish of certain patients to withdraw from dialysis [9, 15]. The subsequently diminished health-related quality of life (HRQOL) is associated with the risk of enhanced morbidity (measured as hospitalizations) and mortality [8, 9, 15, 16, 17].

In the past several years it has been documented that chronic pain affects various brain areas and leads to abnormal brain neurochemistry as well as to a loss of neocortical grey matter [18, 19]. Functional magnetic resonance imaging (fMRI) in patients with persistent pain demonstrated striking differences to healthy subjects [20]. In these individuals the equilibrium between activated brain areas and the subsequent deactivation of others was markedly disturbed [20]. This continuous dysfunction favors the perpetuation of pain and the development of additional central disturbances [20]. Chronic pain may also promote cardiovascular complications, in part due to development of hypertension [21].

Owing to the problems of analgesic drug therapy in ESRD, the use of non-pharmacological strategies is a challenge. In particular, physical exercise has been shown to lower
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However, many dialysis patients are unable or unwilling to perform active exercise training. In these individuals, different forms of electrotherapy provide a promising alternative. In clinical studies and experimental animals the analgesic action of transcutaneous electrical nerve stimulation (TENS) has been demonstrated. Modulation of pain perception is achieved at the spinal cord level and by activation of the descending inhibitory pathway [23]. Recently, application of high tone external muscle stimulation (HTEMS) has been shown to be more effective than TENS in the therapy of diabetic peripheral neuropathy [24]. In ESRD patients our group could demonstrate that HTEMS improves pain and discomfort due to peripheral neuropathy as well as sleep disturbances [25]. These data were recently confirmed and extended [26].

Up to this point in time, there are no investigations examining whether the HTEMS application for pain treatment in ESRD patients is associated with a modulation of parameters of quality of life. For this reason, we performed a multi-center study to assess potential benefits of HTEMS in this patient group.

Methods

The study was approved by the Ethical Committee of the Medical Faculties of the Universities of Würzburg (Germany) and Cluj (Romania). Written informed consent was obtained from all participants.

25 (17 male, 8 female) patients on maintenance hemodialysis between 35 and 89 years (mean 62.2 ± 14.2) from three dialysis centers in Germany (KfH Kidney Centers in Würzburg, Tirschenreuth, and Lohr am Main,) and in Cluj with symptomatic peripheral neuropathy (PN) were enrolled. Their characteristics, biochemistry and co-morbidities are presented in Table 1. They had received hemodialysis for a period of at least 1 year prior to beginning of HTEMS.

Exclusion criteria were: presence of a pacemaker or a cardiac defibrillator, pregnancy, acute thrombosis, a recent myocardial infarction, severe heart congestive heart failure, chronic heart failure, central neurological and psychological disorders as well as bacterial infection. Analgesic drugs were permitted, but reduced to an as-needed basis.

Diagnosis of PN was based on medical history, a neurological examination and one or more of the following neuropathy symptoms in the lower extremities: tingling, burning, pain, numbness, and numbness in painful areas as well as quality of sleep.

HTEMS was performed by a 230V power-supply HiToP 184 and HiToP 191 device (gbo Medizintechnik AG, Rimbach, Germany). In contrast to TENS which uses low frequencies (< 10 Hz) or high frequencies (50 – 100 Hz), the carrier frequencies of HTEMS are continuously scanned from 4,096 to 32,768 Hz, allowing for a much higher power of up to 5,000 mW. The electrodes were placed around the upper leg, and in some patients on the calves as well. Intensity of electric stimulation was individually adjusted, so that neither pain nor discomfort was produced. All patients were treated during the hemodialysis sessions for 1 hour, 3 times a week.

To evaluate the effectiveness of HTEMS, we acquired data just before the beginning (baseline data) and both 6 and 12 weeks after therapy onset. Questionnaires were ap-
plied either in German or in Romanian and were either self (Germany) or interviewer (Romania) administered. The following techniques and parameters were assessed:

– The 36-item Short Form Health Survey (SF-36), which is one of the most used instrument of HRQOL [27]. The questionnaire assesses 8 independent scales to measure physical and mental dimensions of the health states on a 100-point scale (the higher the scale, the better patient’s QOL). The 4 physical domains include physical functioning, physical role functioning, bodily pain and general health perception. The mental domains are mental health, emotional role functioning, social functioning, and vitality. According to Kalantar-Zadeh et al. [28] “physical functioning captures abilities for attending personal needs, walking and flexibility. Role physical evaluates the extent to which physical abilities limit the activities. Bodily pain evaluates the amount of overall pain interfering with normal daily activities. General health evaluates health in terms of personal perceptions. Vitality evaluates energy and fatigue. Social functioning evaluates the extent and amount of time which is interfered with family, friends and social interactions during previous 4 weeks. Role emotional evaluates the extent of emotional factors with the work or other activities. Mental health evaluates feeling of anxiety and depression.” From the 8 scales two composite measures are derived: the physical components summary score (PCS) and the mental components summary (MCS) score.

– The Hospital Anxiety and Depression Scale (HADS), is a 16-item questionnaire to measure anxiety and depression in clinical settings. It is specifically designed to use in somatically ill populations [29]. It scores the severity of symptoms of depression with 7 items (scored 0 – 21). Higher scores on this scale correspond to worse depressive symptoms. In the current literature a HADS value of 7 is frequently chosen as cut-off for significant depressive symptoms [30].

– A pain-symptom questionnaire to assess the severity of tingling, burning, pain, numbness, peripheral neuropathy including tingling in painful areas, and sleep problems. All six symptoms were rated between 0 (“no symptoms”) and 10 (“worst ever felt”) [31].

– The grip strength of both hands, an indicator of muscle strength, was measured with a dynamometer in kg. It is a valuable outcome predictor and a marker of nutritional status in dialysis patients [32].

– Laboratory parameters (hemoglobin, creatinine, albumin, C-reactive protein HbA1c (in diabetics)) were measured by routine assays and use of automatic methods.

Statistical tests were computed by SPSS (Version 18, IBM, Armonk, New York, USA). For all analysis we conducted repeated measure ANOVAs. Alpha was set at 0.05. Effect sizes are reported as partial $\eta^2$ scores. For all ANOVAs, when Mauchley’s test for sphericity was significant, Greenhouse-Geisser corrections of the p-values were applied. Pairwise comparisons were, if conducted, Bonferroni-corrected.

**Results**

For the SF-36, the ANOVA returned significant main effects of time for the physical role functioning subscale ($F_{(2,26)} = 3.97$, $p = 0.031$, $\eta^2 = 0.23$) (Figure 1) (Table 2). Inner subject contrasts revealed a linear increase on that scale ($F_{(1,13)} = 8.66$, $p = 0.011$, $\eta^2 = 0.40$), indicating a continuous decrease of problems with work or other daily activities as a result...
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of physical health. The same pattern could be found in the social functioning subscale (F(2,30) = 5.97, p = 0.015, \( \eta^2 = 0.28 \)). Here a marginally significant linear increase over time could be found (F(1,15) = 4.23, p = 0.057, \( \eta^2 = 0.22 \)). Pairwise comparisons showed an improvement of the ability to perform social activities mainly after 6 weeks of therapy (p = 0.05), an effect that was somehow diminished 12 weeks after therapy onset (p = 0.18). Also, a marginally significant positive trend of physical functioning could be observed (F(2,30) = 2.97, p = 0.091, \( \eta^2 = 0.17 \)), hinting at a linear improvement of the ability to perform physical activities over time (F(1,15) = 3.86, p = 0.068, \( \eta^2 = 0.21 \)). All other SF-36 subscales did not show a significant or marginally significant change over time (all p-values > 0.10).

For the pain symptom questionnaire of the peripheral neuropathy the ANOVA returned a significant effect of time (F(2,26) = 3.89, p = 0.03, \( \eta^2 = 0.23 \)). The overall manifestation of pain symptoms (tingling, burning, pain, numbness, numbness in painful areas) showed a significant linear decrease (F(1,13) = 6.67, p = 0.02, \( \eta^2 = 0.34 \)) (Figure 2). The symptoms of pain decreased within the first 6 weeks from 6.2 ± 2.5 to 5.1 ± 3.3, followed by further decline to 4.8 ± 3.0. The response to HTEMS was less pronounced in the 15 patients with severe pain (score 7 –10).

For the HADS, the ANOVA did not reveal a significant change over time for both the anxiety (F(2,30) = 1.35, p = 0.28, \( \eta^2 = 0.08 \)) and the depression subscale (F(2,30) = 1.21, p = 0.31, \( \eta^2 = 0.08 \)).

Measurement of grip strength of the dominating hand averaged under basal conditions 27.79 ± 12.63 kg. After 6 weeks there was a trend to a higher value (30.24 ± 14.55 kg) which persisted after 12 weeks (29.19 ± 30.55 kg).

Laboratory parameters such as hemoglobin, albumin and C-reactive protein did not change during the study (data not shown).

### Discussion

Consistent to previous investigations [28, 33], our study showed substantial lowering of the domains of SF-36. In comparison to the Dialysis Outcome and Practice Pattern Study (DOPPS) data [33] a similar decline of physical functioning, general health, role emotional functioning and social functioning.
was observed while the scores of physical role functioning were even lower.

Intradialytic application of HTEMS improved various physical components of SF-36. We observed a significant amelioration of physical role functioning and social functioning, while physical functioning showed a marginal positive trend. The mental components of SF-36 remained unchanged.

In the evaluation of the different neuropathic symptoms we found a significant improvement in the sum score (tingling, burning, pain, numbness and numbness in painful areas) after 12-week treatment, while after 6 weeks there was only a trend to improved values. This observation differs from former investigation of our group which showed an earlier amelioration of neuropathic symptoms [25]. We assume that the delayed response to HTEMS in the current study is a consequence of a more severe pain perception of the participants. In fact, in 15 of them the pain score ranged from 7 to 10.

The HADS was not significantly influenced by the HTEMS therapy. Also the hand grip test as a parameter of muscle strength and vitality did not show a significant increase. However, at least in 5 patients a trend to higher values was observed.

Measurements of C-reactive protein and albumin did not change in the study period. Also in the diabetic patients no significant improvement of HbA1c was observed. It is conceivable that a higher dose of HTEMS with its daily application could induce more pronounced effects on the HbA1c and the HRQOL. In fact, in another study with obese diabetic patients daily application of HTEMS was associated with a significant improvement of HbA1c and a lowering of body weight [34].

Up to now we are aware of only one study in ESRD patients in which the effect of intradialytic electro-stimulation of leg extensors on QOL was analyzed [35]. In this prospective randomized study electrical myostimulation (EMS) was performed for 1 hour per dialysis with a frequency of 10 Hz (20-s stimulation, 20-s rest) and compared to a group of patients with active intradialytic exercise (training on a bicycle ergometer) and an untreated group of dialysis patients. After a myostimulation period of 20 weeks (3 times per week) a significant improvement of mental components of SF-36 (vitality, the role emotional, and mental health) was observed [35]. The physical components did not change significantly. These results seem discrepant to our investigation which showed an improvement of some physical domains of SF-36. An explanation may be the fact that low- and high-frequency electrical currents produce different endorphins and neurotransmitters. Thus, low-frequency TENS induces the release of µ-opioids, while high-frequency TENS results in enhanced release of δ-opioids with corresponding activation of their receptors [23]. Furthermore, it should be mentioned that the study of EMS was longer (20 weeks) and the QOL of these patients was less impaired.

An important limitation of our study is the lack of a sham HTEMS-treated group, which is extremely difficult to organize in dialysis patients. Therefore, a placebo effect in our study cannot be excluded with certainty. However, in our study a time-dependent improvement of parameters of well-being was observed which is a strong argument against the role of placebo effect.

In summary, our study shows that HTEMS therapy in ESRD patients with symptomatic peripheral neuropathy also leads to an improvement of parameters of QOL. An important question is whether the effect on QOL could be enhanced by daily application of electrotherapy.

Conflict of interest

A.H. received lecture honoraria from gbo. The other authors declare no conflict of interest.

References

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