

External Electric Muscle Stimulation Improves Burning Sensations and Sleeping Disturbances in Patients with Type 2 Diabetes and Symptomatic Neuropathy

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ABSTRACT

Objective. External muscle stimulation (EMS) of the thighs was previously shown to have beneficial effects in a pilot study on painful diabetic neuropathy. However, differential effects on specific symptoms of neuropathy as well as determinants of treatment response have not been described.

Design. Ninety-two type 2 diabetes patients with different neuropathic symptoms were included in a prospective uncontrolled trial. Patients were treated twice a week for 4 weeks. Symptoms were graded on numeric scales at baseline, before the second and the eighth visit.

Results. Seventy-three percent of the participants reported marked improvement of symptoms. Subjective treatment response was positively and independently associated with symptom intensity but independent of disease extent, metabolic factors, age, or gender. Total symptoms graded by patients on numerical scales decreased significantly after 4 weeks of treatment. Patients in the upper tertile of symptom intensity showed significant improvement of paresthesia, pain, numbness and most pronounced for burning sensations and sleeping disturbances.

Conclusions. In an uncontrolled setting, EMS seems to be an effective treatment for symptomatic neuropathy in patients with type 2 diabetes, especially in patients with strong symptoms.

Key Words. Type 2 Diabetes; Diabetic Neuropathy; Electric Muscle Stimulation; Treatment

Introduction

It was recently shown in a pilot study that external electric muscle stimulation (EMS) of the thigh causing isometric muscle contraction might be an effective treatment for painful diabetic neuropathy [1]. Type 1 and 2 diabetes patients were treated with EMS and compared with patients treated with transcutaneous electric nerve stimulation (TENS) [1,2]. Both EMS and TENS reduced the total symptom score significantly, while EMS resulted in a significantly higher response rate [1]. So far, there is no information

regarding the influences of EMS on neuronal function and mechanisms underlying the observed treatment effects. Previous studies suggested that electrical stimulation activates the dorsal columns, inhibits C-fibers, and consequently leads to a decrease in pain perception [3]. EMS, which can stimulate a large number of nerves in the thigh, might therefore lead to a spinal stimulation that in turn decreases excitability of small nerve fibers.

It is not known which specific symptoms of diabetic neuropathy can be treated using EMS and which factors determine the treatment responses. Hence, we conducted this study in a large group of type 2 diabetes patients with neuropathic symptoms to identify subjects benefiting from this intervention and studied effects on different aspects of symptomatic neuropathy.

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Table 1 Baseline characteristics of the treated patients (N = 92)

| | |
|--|-----------|
| Age (years) | 66 ± 8 |
| Gender (m/f) | 64/28 |
| Diabetes duration (years) | 13 ± 9 |
| BMI (kg/m ²) | 31 ± 5 |
| HbA1c (%) | 6.8 ± 8 |
| Total cholesterol (mg/dL) | 190 ± 37 |
| Creatinine (mg/dL) | 1.0 ± 0.3 |
| Urea (mg/dL) | 42 ± 15 |
| GPT (U/l) | 26 ± 14 |
| GOT (U/l) | 34 ± 21 |
| Neuropathy symptom scores | 7.6 ± 1.3 |
| Neuropathy disability scores | 6.1 ± 2.3 |
| Insulin therapy (%) | 49 |
| Oral medication (%) | 67 |
| Previous or current pain medication (%) | 59 |
| Anticonvulsants | 34 |
| Antidepressants | 4 |
| Opioids | 7 |
| Antioxidants | 17 |
| Others | 9 |
| Treatment response individual judgment (%) | |
| ≥30% reduction in mean | 73 |
| Symptom score (N = 81) | 47 |

GPT = glutamat-pyruvat-transaminase;
transaminase.

GOT = glutamat-oxalazetat-

Methods

Participants

One hundred type 2 diabetes patients with symptomatic diabetic neuropathy were included in this study after giving written informed consent. As a consequence of a lack in suitable placebo treatments, the study was performed in a prospective uncontrolled design. The study protocol was approved by the University of Heidelberg Ethics Committee. Patients were eligible if they reported any symptoms of diabetic neuropathy (i.e., pain, paresthesia, burning sensations, numbness, sleeping disturbance). Patients with implanted pacemakers or defibrillators were excluded from the study. Eight patients were excluded from the analyses as other causes of neuropathy or symptoms could not be excluded (i.e., excessive alcohol consumption, peripheral artery disease and ischemia, chemotherapy, amyloidosis). The detailed characteristics of the patients included are shown in Table 1.

Grading of Symptoms

At baseline, diabetic neuropathy was graded using the established neuropathy disability scores (NDS) and neuropathy symptom scores (NSS) [4]. In addition, patients had to grade their symptoms on 10-point numeric scales (1 = no symptoms, 10 = worst possible) as previously reported [1] at

baseline, before the second and eighth treatment session. The duration of treatment effects was estimated by the participants before the eighth session. Eighty-one participants completed the 4-week protocol while 11 patients were lost to follow-up after the fourth session.

External Electric Muscle Stimulation

Patients were treated with EMS for 60 minutes, twice a week, and for 4 weeks (eight treatment sessions). EMS was performed using the HiToP® 184 device (gbo Medizintechnik, Rimbach, Germany). As previously described [1], a 20-Hz frequency scan of carrier frequencies between 4,096 Hz and 32,768 Hz was used to generate a deep and comfortable muscle contraction. This application was repetitively modulated with 3 seconds rest time, 3 seconds rise time, and 3 seconds contraction time. The intensity of the electrical stimulation was adjusted to a tolerable level causing muscle contraction and avoiding pain or discomfort.

Statistical Procedures

Logistic regression models were calculated to detect possible influence factors on treatment response. In these models, patients were divided into responders and non-responders according to self-report of improvement of symptoms and in patients completing the 8-week protocol according to a minimum of 30% mean decrease in symptoms according to the graded symptom scores before the eighth session.

A total symptom score (TSS) was calculated by addition of the individual scores on the numeric scales, leading to a maximum score of 50. To study influences of EMS on the specific symptoms, patients were divided into tertiles of the TSS and the respective symptoms (i.e., paresthesia, pain, burning sensation, numbness, sleeping disturbance). Tertiles of patients and the respective symptom scores for equally powered groups were as follows: paresthesia (1–4/5/6–10), pain (1–3/4–6/7–10), burning sensation (1–3/4–6/7–10), sleeping disturbance (1–3/4–5/6–10), and numbness (1–3/4–6/7–10). Treatment effects were studied in the entire group and in patients in the highest tertile of the respective score. Significant differences in symptom scores between the follow-up measurements were determined using two-tailed paired *t*-tests compared with the baseline. All statistical analyses were performed using SPSS (Version 15.0).

Results

Sixty-seven (~73%) of the 92 participants reported subjective improvement of neuropathic symptoms. Eighty-one patients completed the protocol, while 11 patients did not continue after the fourth treatment session; all of these patients reported no treatment response. Forty-seven percent of the participants completing the protocol had an improvement of the mean symptom score by $\geq 30\%$ on the graded symptom scales. Although patients were not remunerated for participation or travel expenses, adherence to the protocol was 100% in the patients reporting improvement of symptoms. The mean duration of symptomatic relief was 31 ± 21 hours; the maximum duration reported was 80 hours. Fifty-four patients (~59%) were previously or currently treated with medication for neuropathic symptoms and participants currently treated continued medication; the number of patients with an improvement of the mean symptom score by $\geq 30\%$ was similar in these patients compared with previously untreated participants (41% vs 51%, $P = \text{ns}$). The only side effect of EMS reported was mild muscle soreness in the thighs on the day after treatment.

Differences between responders and non-responders were studied at baseline to identify possible influence factors on treatment responses. Responders according to self-judgment had more intense symptoms as given by the NSS scores (7.8 ± 1.2 vs 7.2 ± 1.5 , $P = 0.04$), and there was a trend toward older age in non-responders (65 ± 8 vs 69 ± 8 , $P = 0.07$). When patients were divided into responders and non-responders by a minimum of 30% decrease in mean symptom score as was previously suggested [5], there were no significant differences in the baseline characteristics (not shown). Logistic multivariate models including biometrical data and the classical risk factors revealed the NSS to be the only variable independently associated with subjective treatment response ($\beta = -0.47$, $P = 0.02$, Table 2). In participants with a minimum decrease of 30% in mean symptom score after 4 weeks of treatment, there was only a trend for an association with the NSS (Table 2).

When all participants in this study were analyzed, the TSS significantly improved on visit 8 (25.7 ± 10.5 vs 19.2 ± 10.4 , $P < 0.001$), while the change in TSS on visit 2 was not significant (26.0 ± 10.3 vs 24.8 ± 10.6 , $P = \text{ns}$). In the self-reported responders, TSS improved marginally significant on visit 2 (25.9 ± 10.4 vs 24.4 ± 10.7 ,

Table 2 Logistic multivariate analyses of variables influencing response to treatment

| | Regression Coefficient β (SE) | Regression Coefficient β (SE) |
|------------------------------|-------------------------------------|-------------------------------------|
| Age | -0.05 (0.04) | -0.02 (0.03) |
| Gender | -0.52 (0.59) | -0.12 (0.63) |
| Diabetes duration | -0.03 (0.03) | 0.04 (0.03) |
| BMI | -0.05 (0.06) | -0.01 (0.05) |
| HbA1c | 0.44 (0.20) | -0.45 (0.32) |
| Neuropathy symptom scores | 0.47 (0.20)* | 0.37 (0.21)** |
| Neuropathy disability scores | -0.18 (0.12) | 0.69 (1.46) |
| Creatinine | 0.33 (1.02) | -0.25 (0.91) |

* $P = 0.02$; ** $P = 0.08$.

Response to treatment is judged as reported by the individual patient (left column) and in patients with a $\geq 30\%$ reduction of mean symptoms on the feet after 4 weeks of treatment (right column, $N = 81$).

Treatment response is the dependent variable and coded numerically as 1 = non-responder and 2 = responder.

$P = 0.05$) and highly significant on visit 8 (26.0 ± 10.4 vs 18.2 ± 10.4 , $P < 0.001$). In self-reported non-responders, TSS did not change significantly on visit 2 (26.3 ± 10.3 vs 26.0 ± 10 , $P = \text{ns}$) and visit 8 (24.2 ± 11.2 vs 23.5 ± 9.7 , $P = \text{ns}$). When all patients were divided into tertiles of TSS, the second and third tertiles showed improvements of TSS on visits 2 and 8, while the lower tertile showed significant improvement of TSS on visit 8 only (Figure 1a). In self-reported responders, all three tertiles of TSS showed significant improvements of TSS on visit 8 only (Figure 2b).

Changes in specific symptoms were studied in all participants followed up to the eighth visit and patients in the upper tertile of the respective symptom score on visits 2 and 8 (Figure 2, Table 3). The mean score of all symptoms (Figure 2a), paresthesia (Figure 2b), pain (Figure 2c), burning sensations (Figure 2d), sleeping disturbances (Figure 2e), and even numbness (Figure 2f) improved significantly on visit 2 and visit 8. The treatment effects were strongest on visit 8 for burning sensations (8.5 ± 1.2 vs 4.9 ± 2.5 , $P < 0.001$, Table 3) and sleeping disturbances (7.9 ± 1.4 vs 4.6 ± 2.8 , $P < 0.001$, Table 3) as documented on the 10-point scale. The relative decrease in severity of symptoms for these scores was approximately -42%.

Discussion

This is the first study on treatment effects of EMS in a large group of type 2 diabetes patients. The data show significant improvement of total symptoms and each specific quality of symptoms. Sig-

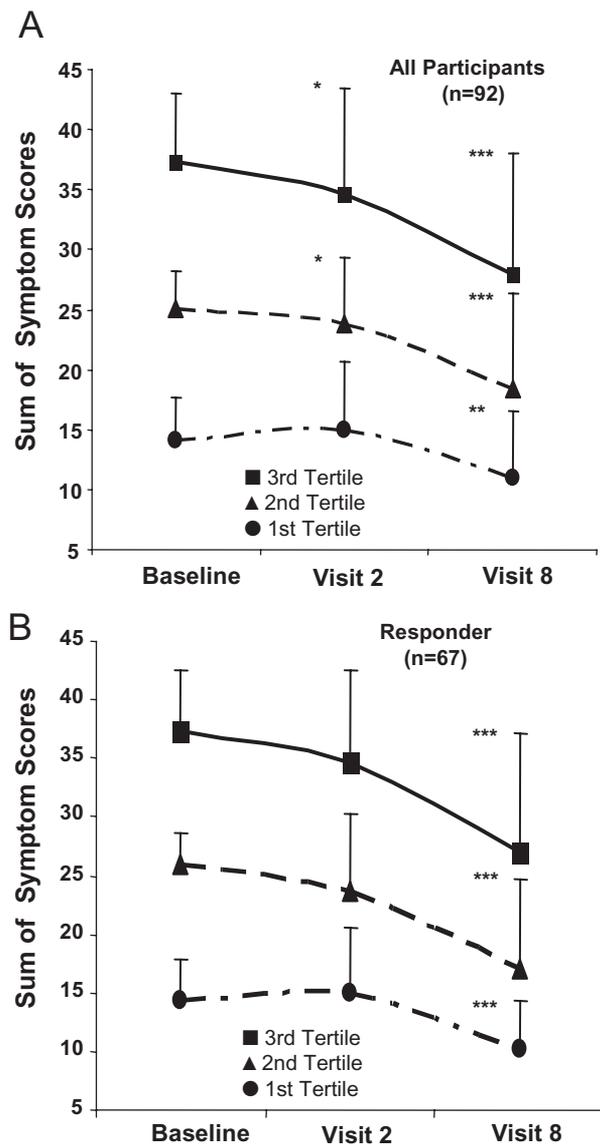


Figure 1 (A) Total symptom score (TSS) in all participants of the study by tertile of TSS. Patients in the upper and middle tertile of TSS showed significant reductions of symptoms on the second and the eighth visit. Patients in the lower tertile showed significant reductions on visit 8 only. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs TSS at baseline. (B) When responders were analyzed separately, highly significant reductions in total symptoms were observed on visit 8 only. This was true for type 2 diabetes patients in all three tertiles of the TSS.

nificant improvement was found in all tertiles of the TSS; however, the treatment effects were most pronounced in the upper tertile of patients affected by burning sensations and sleeping disturbances after 4 weeks of treatment. In these patients, symptoms were reduced by ~42%. This reduction in symptoms can be considered a strong and clinically

relevant improvement, which was previously shown in a meta-analysis of studies comparing placebo-controlled data on pain reduction detected using numerical scales and in patients with different causes of neuropathic pain [6].

Multivariate analyses revealed that response to treatment was independently and positively associated with the NSS, but not with the NDS. This suggests, that type 2 diabetes patients at all ages and stages of disease might benefit from EMS. Additional metabolic factors such as BMI or even HbA1c, as a marker of long-term glucose control, did not influence the response rate significantly (Table 2). There were no significant differences in response rates between patients previously treated with pharmacological interventions and treatment-naïve participants. This indicates that EMS might even be effective in patients that are not sufficiently treated using conventional medications such as anticonvulsants and antidepressants.

Pain and paresthesia in our study were reduced by ~31% and ~35%, respectively, effects that can also be considered clinically relevant [6]. It is likely that a significant part of the treatment effects can be attributed to placebo effects; the reduction of numbness was calculated at ~24% and is likely to represent the placebo effect in our study. Yet definite differentiation of placebo and treatment effects need to be clarified in future placebo-controlled trials.

Our data support the previously published high response rates of EMS in pilot studies and patients with symptomatic diabetic and uremic neuropathy [1,7] and further define the duration of treatment effects as well as specific symptoms that can be treated efficiently. The mean duration of the treatment effect was limited to 31 hours and varied strongly between participants. The underlying reasons for this large variation remain unclear, and it seems important to decipher the physiological changes induced by EMS to understand this finding. Although not an endpoint of this study, it seems likely that for example the significant reduction of sleeping disorders reported by the participants leads to a major improvement in quality of life. This improvement and the lack of severe adverse events seem to be reflected by the strong adherence to the study protocol (100% in self-reported responders) over a period of 4 weeks and eight treatment sessions. Future controlled studies will be needed to study cost-effectiveness and clinical efficacy of EMS in comparison to pharmaceutical interventions, especially in consideration of missing relevant side effects. In addition, study

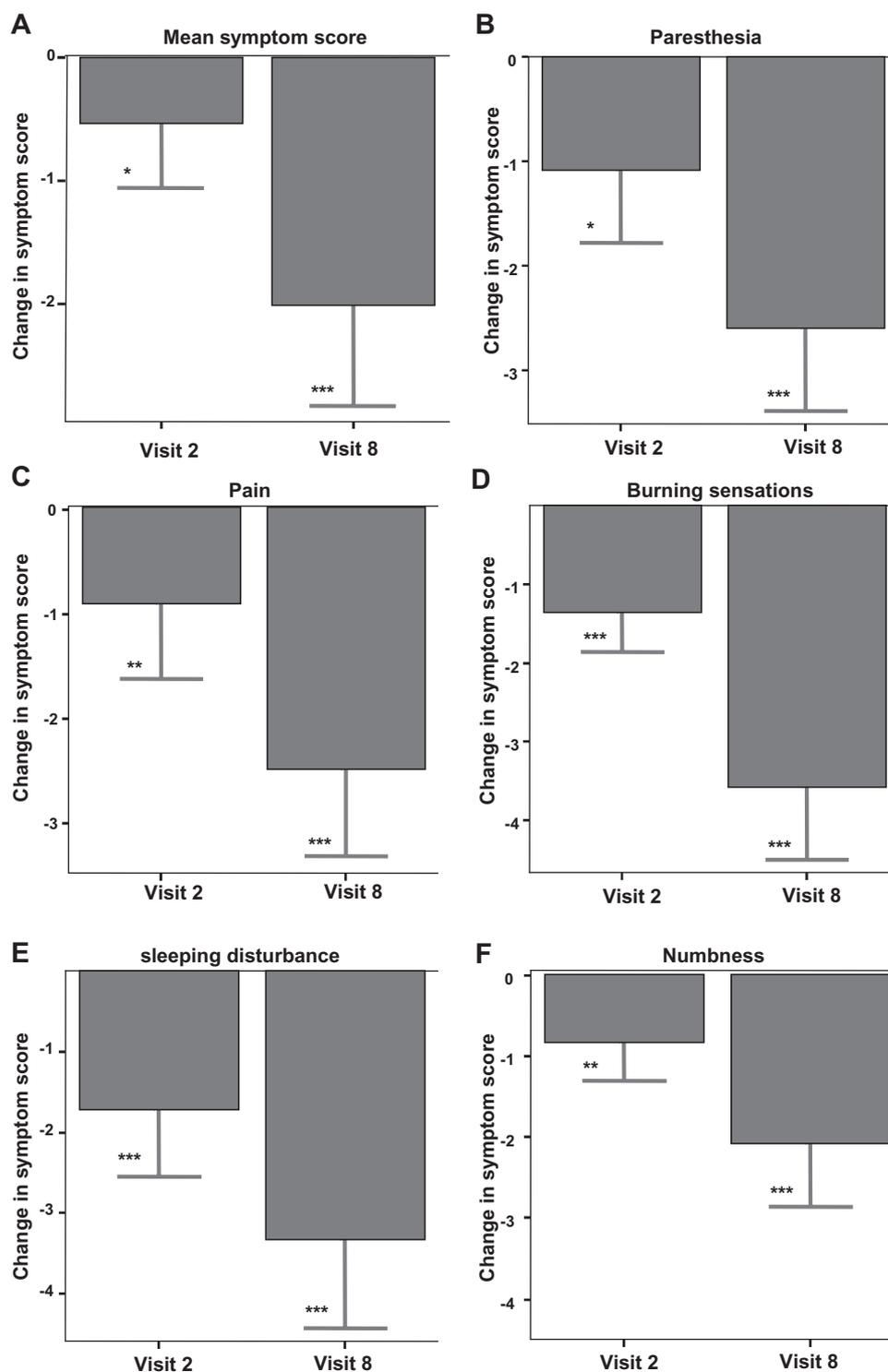


Figure 2 Treatment effects of external muscle stimulation (EMS) on symptoms of diabetic neuropathy were analyzed in participants in the upper tertile of the respective scores to study patients that are significantly affected by the specific symptom. (A) Mean symptom score, (B) paresthesia, (C) pain, (D) burning sensation, (E) sleeping disturbances, and (F) even numbness were significantly improved on visit 2 and visit 8. Treatment effects were strongest for the reduction of burning sensations and sleeping disturbances (D, E). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs the respective symptom score at baseline. Data are given as the mean change in symptom score \pm SD.

Table 3 Symptom scores at baseline and on the eighth visit for all patients followed up (N = 81) and patients in the upper tertile of the respective baseline symptom score

| | All Patients Followed Up (N = 81) | | Patients in the Upper Tertile of Symptom Scores | | |
|-----------------------|-----------------------------------|-------------|---|-------------|------|
| | Baseline | 8th visit | Baseline | 8th visit | (N) |
| Mean | 5.1 ± 2.1 | 3.8 ± 2.1** | 7.6 ± 1.1 | 5.6 ± 2.0** | (26) |
| Paresthesia | 5.2 ± 2.4 | 3.8 ± 2.4** | 7.5 ± 1.5 | 4.9 ± 2.2** | (30) |
| Pain | 5.1 ± 3.0 | 3.7 ± 2.7** | 8.3 ± 1.0 | 5.7 ± 2.4** | (31) |
| Burning sensation | 5.2 ± 3.1 | 3.7 ± 2.4** | 8.5 ± 1.2 | 4.9 ± 2.5** | (29) |
| Sleeping disturbances | 4.8 ± 2.8 | 3.4 ± 2.5** | 7.9 ± 1.4 | 4.6 ± 2.8** | (30) |
| Numbness | 5.4 ± 3.1 | 4.6 ± 2.8* | 8.6 ± 1.1 | 6.5 ± 2.4** | (33) |

* $P < 0.01$; ** $P < 0.001$ as given by paired *t*-test.

(N) is the number of patients in the upper tertile of the respective baseline symptom score that were followed up to visit 8. Data are given as mean ± standard deviation.

protocols will have to include measures of depression as additional endpoint which is known to have important associations with symptomatic neuropathy and treatment effects [8].

In the lack of a control group, numbers needed to treat can be estimated utilizing placebo data from previously published studies on tricyclic antidepressants and traditional anticonvulsants in which a moderate relief of pain by 30% was considered as the cut-off for treatment response [5]. In these published studies [9–12], 4 out of 81 patients on placebo treatment experienced a moderate $\geq 30\%$ symptom relief compared with 38 out of the 81 patients treated with EMS in this study. This would correspond to a number needed to treat of 2.4 in our study and argue for EMS being a very effective treatment option. However, these considerations remain speculative and treatment effects need to be clarified in future placebo-controlled trials. A specific placebo device that causes superficial skin stimulation without influences on muscle and nerves was not available for this study and will have to be constructed for this purpose.

In conclusion, EMS was shown to be of some benefit in ~40–70% of the type 2 diabetes patients treated depending on the definition of treatment response (i.e., $\geq 30\%$ reduction in mean symptom score or self-reported), is free of significant side effects, and led to an accentuated improvement in burning sensations and sleeping disorders. Forty-one percent of patients currently or previously treated with pain medication had an improvement of mean symptoms by $\geq 30\%$. This data have to be judged in view of the results obtained in clinical trials of pharmaceutical interventions that resulted in numbers needed to treat of ~2–4 and led to significant side effects [13–16]. This study was performed in an uncontrolled design. Future controlled trials including pharmaceutical interventions will be needed to clearly define the clinical and economic efficacy of this treatment option.

Acknowledgments

Parts of this study were supported by the Lautenschläger Diabetes Foundation (PMH, PPN) and the Juvenile Diabetes Research Foundation (AB, PPN). gbo Medizintechnik AG supplied the treatment devices for EMS and consumables.

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