

ORIGINAL ARTICLE

Matrix stimulation in cancer pain: Methodology, safety and effectiveness

M. Mücke^{1,2,3,*}, M. Tils^{2,*}, R. Conrad⁴, D. Kravchenko², H. Cuhls², L. Radbruch^{2,5}, M. Marinova⁶, V. Peuckmann-Post⁷, R. Rolke⁷

1 Department of General Practice and Family Medicine, University Hospital Bonn, Germany

2 Department of Palliative Medicine, University Hospital Bonn, Germany

3 Center for Rare Diseases Bonn (ZSEB), University Hospital Bonn, Germany

4 Department of Psychosomatic Medicine and Psychotherapy, University Hospital Bonn, Germany

5 Centre for Palliative Care, Malteser Hospital Bonn/Rhein-Sieg, Germany

6 Department of Radiology, Medical School & Hospital, University Hospital Bonn, Germany

7 Department of Palliative Medicine, Medical Faculty RWTH Aachen University, Germany

Correspondence

Martin Mücke

E-mail: martin.muecke@ukbonn.de

*These authors contributed equally to the work.

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Abstract

Background: This feasibility study addresses the applicability of matrix electrodes for the reduction of ongoing pain in cancer patients via low-frequency electrical stimulation (LFS).

Methods: Low-frequency matrix stimulation (4 Hz) was applied to the skin within the 'Head's zones' referring to the tumour localization of cancer pain patients. Pain at baseline was compared to a 3-day treatment interval consisting of 5 min of matrix stimulation in the morning and evening followed by a 3-day follow-up period without therapy. Main outcome parameters included numeric rating scale values (rating scale 0–100), painDETECT, HADS, and German pain questionnaire, as well as the opioid intake, calculated as the oral morphine equivalent (OME).

Results: Twenty patients with cancer pain (aged 64.4 ± 10.3 ; 9 women) were examined. In the majority of patients, the pain was classified as nociceptive. The mean pain reduction achieved by matrix therapy was 30%, under stable daily controlled-release opioid doses between 177 and 184 mg/day (OME). Seventeen patients (85%) were responders, defined by a pain reduction of at least 30%, while four responders experienced a pain reduction of over 50%. The only side effect was short-term erythema.

Conclusion: Findings are consistent with the concept of synaptic long-term depression in cancer pain induced after conditioning LFS. Despite the short, but well-tolerated, treatment duration of 2×5 min/day, effects persisted throughout the 3-day follow-up.

Significance: Cutaneous neuromodulation using LFS via a matrix electrode has been shown to be a safe intervention for effectively reducing cancer pain in palliative care patients.

1. Introduction

The World Health Organization (WHO) estimates that the annual global cancer incidence will rise from 14 million in 2012 to approximately 21.6 million by

the year 2030, emphasizing the importance of adequate pain relief. Cancer pain is a symptom with various causes and diverse manifestations, which tremendously impacts the quality of life. It can be

classified by aetiology into tumour caused, therapy caused, tumour related and tumour unrelated (van den Berg, 2008; Cuhls et al., 2013). Sixty percent of the pain cases are primarily caused by the tumour and can be triggered by infiltrative and lytic growth, nerve compression or blood vessel compression with thrombus formation or inflow congestion (Larbig et al., 2002; van den Berg, 2008; 2012). Fifteen to twenty percent of the cases exhibit therapy caused pain (Portenoy and Hagen, 1990; Zeppetella et al., 2000). This can be the result of chemotherapy, radiation therapy, or the surgery itself. Ten percent suffer from tumour related pain, for example, from pressure ulcers or secondary myofascial pain due to assuming a relief posture for too long (Svendsen et al., 2005). To improve the quality of life of these patients, it is necessary to provide sufficient pain management, which can be divided into tumour specific and symptomatic therapies (Nauck and Eulitz, 2007).

The tumour specific therapies aim to shrink or eliminate the tumour by utilizing radiotherapy, chemotherapy, surgery, radioisotope therapy or hormone therapy (Nauck and Eulitz, 2007). The symptomatic treatment consists of the WHO established pain ladder whose efficacy has been validated in multiple clinical studies (Zech et al., 1995). Unfortunately, the use of the recommended medication is often associated with side effects (Cherny et al., 2001; O'Mahony et al., 2001). It would thus be beneficial to develop a pain management therapy with as few side effects as possible. Many studies have already looked into alternative methods for treatment (Bao et al., 2014). TENS (transcutaneous electrical nerve stimulation) is an alternative non-invasive therapy for applying electrical currents to the skin and deeper tissues. This technique is suited to induce both large and small nerve fibre activation that may lead to secondary changes of spinal synaptic activity depending on the frequency and amplitude of that peripheral input (Mücke et al., 2014).

Using this type of large and small fibre input, TENS acts via peripheral and central mechanisms that involve neuroplasticity of spinal as well as brain projection neurons (Hurlow et al., 2012; Johnson et al., 2015). A novel approach to treat cancer pain, with fewer side effects than traditional medical treatment, was developed in the form of low-frequency electrostimulation (LFS) using a matrix electrode. In contrast to flat gel electrodes that are frequently used for TENS, a matrix electrode consists of a variable number of small pin-like grouped contacts acting as a cathode referenced against a thicker surrounding contact area that is used as an anode. In a previous study, we were

able to show that a 4 Hz electrical nerve stimulation using a matrix electrode led to high current densities predominantly across superficial layers of the skins that reduced deep pain sensitivity in healthy human subjects most likely via central synaptic modulation of peripheral sensory input (Mücke et al., 2014). This finding is consistent with the concept of a centrally mediated heterosynaptic long-term depression (LTD) of the human nociceptive system (Sandkühler et al., 1997; Sandkühler and Gruber-Schoffnegger, 2012). It was a striking finding that this type of stimulation did not only affect the treated skin area (homotopic effect), but also deeper tissues (heterotopic effect) that are also involved in cancer pain. Based on these results, we have now translated this concept to a feasibility study in cancer patients using a wearable (soft tissue) matrix electrode to assess (1) short- and long-term effects towards a pain reduction within minutes to days, (2) the proportion of responders and (3) the amount of basal and rescue opioid medication under this type of low-frequency electrical matrix stimulation.

2. Materials and methods

The trial was a prospective, single-centred and open feasibility study in patients with cancer pain. The study design and protocol were reviewed and approved by the local ethics committee, registered in the German Clinical Trials Register No. DRKS00009614 (Deutsches Register klinischer Studien, DRKS) and performed in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice. Written informed consent was obtained from each patient.

2.1 Study population

Between 2014 and 2015, a total of 20 patients with cancer pain (11 male, nine female; aged 64.4 ± 10.3 years) were evaluated for this study. The patients were recruited from the Centre of Integrated Oncology (CIO), the palliative ward of the University of Bonn, and from the Malteser Hospital Bonn.

2.2 Inclusion and exclusion criteria

Inclusion criteria were as follows: patients with cancer pain with a minimum age of 18 years, and written consent obtained after a detailed explanation of the investigation. Exclusion criteria comprised contraindications to the use of electrical stimulation, such as the presence of cardiac pacemakers or other implanted electronic devices, severe cardiac

arrhythmia, osteosynthesis, neurological diseases, peripheral vascular diseases, pregnancy, women currently breastfeeding, haemophilia, and skin or soft tissue disease. Previous experience with electrical stimulation methods was also an exclusion criterion to avoid an expectation bias.

2.3. Materials used

2.3.1 Tissue based matrix array electrode

The matrix electrode array is a three-dimensional multi-electrode array integrated in a wearable tissue. By coating it with so-called ball grids (ball grid array), point-wise contact with the skin is ensured. The matrix array was used as the cathode and consisted of a contact surface with eight rows and 16 columns, which form an $8 \times 16 = 128$ skin contact pin matrix. The pin-type electrodes were made of dry, electrically conducting and silver-coated threads/strings (Elitex[®]) applied to an electrically non-conductive textile. Four stripes of anodes are characterized by a combined skin contact area of $4 \times 11.0 \text{ cm} \times 0.5 \text{ cm} = 22 \text{ cm}^2$. Altogether 128 matrix pins – soldered with a spacing of 2.5 mm – with a size of about 1 mm^2 each, represent a combined cathode stimulation area of about 1.3 cm^2 . This design reflects a size-ratio anode/cathode of about 17. The stimulation mode was predominantly superficial because the highest density of the electric current is within the upmost layer of the skin called cutis.

2.3.2 Stimulator

A constant flow stimulator was used for the monophasic cutaneous neuromodulation (model DS7A; Digitimer Ltd., Hertfordshire, UK). To perform frequency-specific stimulation, a trigger unit (model 182A, function generator; WAVETEK, San Diego (CA), USA) was connected to the DS7A.

2.4 Stimulation paradigms

Based on results of our previous study (Mücke et al., 2014) on the effectiveness of different stimulation frequencies, we used 4 Hz low-frequency matrix stimulation over 5 min with a pulse length of 200 μs as the conditioning stimulus (=1200 stimuli in total). Stimulation intensity was incrementally adjusted to the first painful sticking or pricking sensation felt under the matrix electrode. This type of percept was usually reached using current intensities between 1 and 3 mA.

The stimulation area varied for each individual patient according to tumour location (Fig. 1) with the most painful spot being chosen for treatment, if multiple pain areas were present. Stimulation was applied locally to the skin surface with magnitude of amperage being set before each treatment. The NRS was used to evaluate the pain perception before and after stimulation. The current cancer pain therapy using basal opioids, non-opioid analgesics, and co-analgesics was continued consistently over the course of the study. Patients were always allowed to ask for as much rescue opioid on-demand medication as needed. The patients' actual maintenance pain medication as well as the on-demand rescue medication quantity was later extracted from the patient files. Basal controlled-release and on-demand fast-release rescue opioid doses were converted into an oral morphine equivalent (OME; mg/day) that was one of the outcome parameters.

2.5 Study design

The examination period of this feasibility study lasted 1 week. Tumour type, tumour propagation, and staging including ECOG (Eastern Cooperative Oncology Group, an index assessing mobility), were used for the evaluation of eligibility for the study and were extracted from the patients' files. The patients were asked to rate their ongoing cancer pain intensity using a numerical rating scale (NRS) with numbers between 0 and 100 (with zero being no pain; 100 being the strongest pain imaginable) three times a day over the course of seven days. Matrix stimulation was applied to the patients for 5 min in the mornings (8–10 am) and afternoons (3–5 pm) on days one, two, and three. Baseline pain levels were assessed at study entrance (day 0; under maintenance of pain relief medication). Pain intensity during the 3 days after matrix therapy (follow-up: days four, five and six) was used as a measure for the control condition.

The patients were additionally asked to fill in three questionnaires: painDETECT, Deutscher Schmerzfragebogen (German pain questionnaire; GPQ), as well as the Hospital Anxiety and Depression Scale (HADS). The painDETECT questionnaire has been developed as a screening tool to identify neuropathic pain components. Its validity and reliability have been confirmed in several studies (Alkan et al., 2013; Matsubayashi et al., 2013). The following cut-offs have been suggested for screening purposes: score ≤ 12 (neuropathic component unlikely) and ≥ 19 (neuropathic component likely; Mathieson and

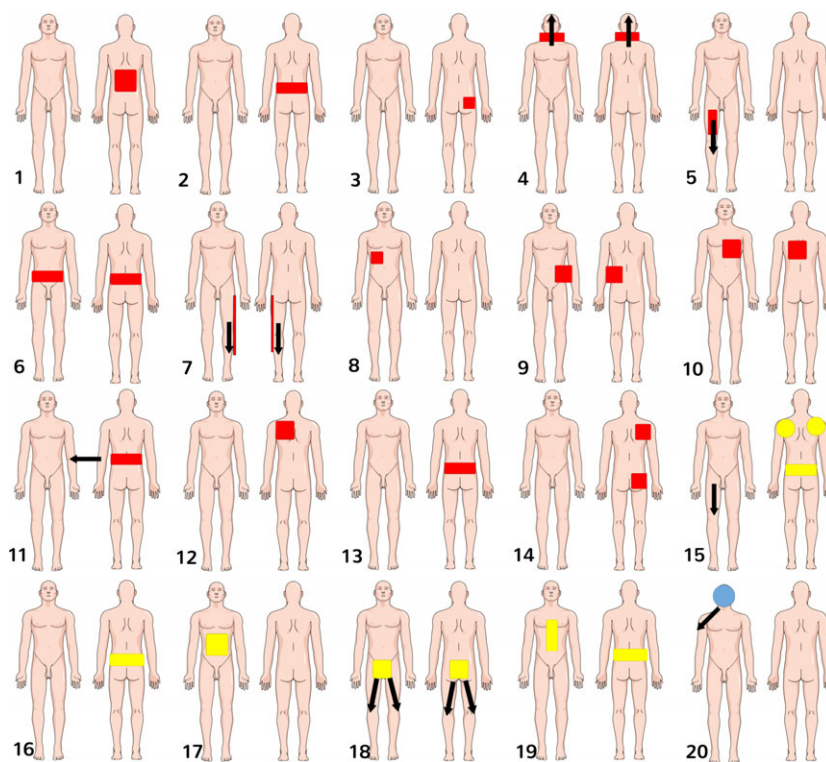


Figure 1 Pain localisation. Pain drawings from 20 cancer patients. Arrows indicate pain radiation. Red areas show painful regions of cancer patients classified as being 'nociceptive' according to the painDETECT questionnaire. Yellow areas represent the painful spots of unclear pain patients, while blue areas correspond to the one patient with 'neuropathic' pain.

Lin, 2013). The GPQ, has been developed by the German Chapter of the International Association for the Study of Pain. It comprises demographic data, phenotypic characteristics, affective and sensory qualities of pain, pain-relieving and -intensifying factors, previous treatment, pain-related disability, a depression scale, comorbidities, social factors and health-related Quality of Life (Nagel et al., 2002). The HADS consists of 14 questions, of which seven relate to anxiety and seven to depression that are presented in a thematically alternating way (Herrmann-Lingen et al., 2011).

Any adverse reactions to the stimulation, such as erythema, swelling, pain, bruising at the site of matrix stimulation, discomfort, palpitation, and dizziness, were recorded in a free text in the case report form (CRF). Furthermore, patients' satisfaction (not at all, moderate, good, very good) after stimulation was recorded in the CRF.

2.6 Data evaluation and statistics

The statistical analysis was calculated using Statistica 7.1 (StatSoft Inc., USA). The three daily NRS

values (0–100 rating scale; "0" = no pain to "100" = most intense pain imaginable) were used to evaluate the long-term effects. The daily mean value was calculated for day 0 (baseline), days 1–3 (therapy), and days 4–6 (follow-up). Patients were divided into responder and non-responder groups based on the pain reduction (displayed in percent) during the course of the study. The short-term effect was calculated by looking at the percentage differences between NRS values just before and immediately after matrix stimulation (days 1–3 only). The usage and amount of maintenance and on-demand opioid drugs was also compared. Questionnaires were evaluated using a standardized evaluation sheet.

Based on patients' pain drawings (Margolis et al., 1986) and calculation of body surface (Du Bois and Du Bois, 1989) on the basis of height and weight, we calculated the size of the pain area (Table 1). In the next step, we calculated the ratio between matrix stimulation area and pain area in percent. Furthermore, we analysed the association between this ratio and the change in pain intensity by Pearson correlation.

Table 1 Pain and stimulation characteristics.

Patient	Type of tumour	Body surface (m ²) ^a	Size of pain area (m ²) ^b	Primary/ Referred Pain	Ratio size of stimulation area/pain area (%)
1	Endometrial stromal sarcoma	1.94	0.05	Primary	41.38
2	Prostate cancer	2.29	0.13	Primary	17.53
3	Colorectal cancer	1.96	0.15	Referred	15.36
4	Pancreatic cancer	1.64	0.06	Primary	36.71
5	Lung cancer	1.46	0.06	Referred	34.37
6	Lung cancer	1.83	0.04	Referred	54.84
7	Oropharyngeal cancer	1.69	0.19	Primary	11.88
8	Prostate cancer	1.78	0.10	Referred	22.55
9	Pancreatic cancer	2.07	0.12	Primary	19.39
10	Giant-cell tumour (left thigh)	1.69	0.09	Primary	23.75
11	Lung cancer	2.1	0.08	Primary	28.67
12	Gastric cancer	1.96	0.07	Referred	30.72
13	Lung cancer	1.89	0.14	Primary	15.93
14	Pancreatic cancer	1.56	0.09	Primary	25.73
15	Urothelial cancer	2.10	0.06	Primary	38.23
16	Oropharyngeal cancer	2.08	0.23	Primary	9.65
17	Lung cancer	1.46	0.04	Referred	54.99
18	Prostate cancer	2.20	0.12	Referred	18.25
19	Gastric cancer	1.53	0.09	Referred	26.24
20	Multiple myeloma	1.87	0.10	Referred	21.47

^aBody surface calculated by $0.007184 \times W0.425 \times H0.725$ (Du Bois and Du Bois, 1989).

^bSize of pain area based on patients' pain drawings (Margolis et al., 1986).

3. Results

Patients suffered from different tumours: six (30%) from GIT tumours, five (25%) from urinary tract tumours, and four (20%) from lung cancer. The remaining patients (25%) had cancer of the oropharynx, larynx, diffuse large B-cell lymphoma, multiple myeloma, a giant-cell tumour of bone and squamous-cell carcinoma of the skin (Table 2).

The location for stimulation was determined separately for each individual (Fig. 1): the back was chosen for 11 (55%) patients, the shoulders and sides for three (15%) patients, the legs for two (10%) patients, and the abdomen for one (5%) subject. The electrical current was newly determined before each stimulation session with the average being 1.44 ± 0.48 mA for responders and 1.63 ± 1.4 mA for non-responders.

3.1 Pain reduction – short-term effects

The NRS values were measured before and shortly after stimulation in the mornings and evenings (Fig. 2). Stimulation in the morning on day 1 led to a 25.7% decrease in the average NRS value from 49.5 to 36.8. In the evenings this decrease was 24.8%, down 10 points from 40.3 to 30.3 (NRS 0–100).

On day 2 the average morning NRS value was 43.4 before therapy and 35.3 after, a decrease of 18.7%. In the evenings, it decreased from 30.5 to 24.3, down 20.3%.

On day 3 the average morning NRS value decreased by 23.1% (from 36.8 to 28.3) and the evening value decreased by 12.5% (down from 30.0 to 26.3).

3.2 Pain reduction – long-term effects within days

Patients continued to rate their perceived pain intensity three times per day even during the follow-up phase (control condition). The average NRS value before therapy (baseline) was 53.8. Mean pain intensity on day 1 of the therapy was 41.4 corresponding to a pain reduction of 23%; on day 2 the average pain intensity was 38.0, and on day three 35.5, a decline of 34% compared to the baseline condition (day 0). Pain reduction from baseline to the therapy phase (average from days 1–3) was 30% (Fig. 3).

The average NRS scores increased only slightly during the control phase without matrix stimulation (follow-up phase) on day 4 (NRS 41.3), day 5 (NRS 38.0), and day 6 (NRS 36.8). This corresponds to an overall reduction of 31.6% from day 0 to day 6

Table 2 Clinical characteristics.

Age (years)	Gender	Cancer type	ECOG	Current pain level (NRS 0–10)	Worst pain last month (NRS 0–10)	Average pain last month (NRS 0–10)	painDETECT based pain classification	Opioids	Metamizole	NSAIDs	AD	AC
50	f	Gastrointestinal	4	5	10	9	Nociceptive	•	•	•	•	•
51	m	Gastrointestinal	2	3	8	5.5	Nociceptive	•	•	•	•	•
65	f	Gastrointestinal	1	1	10	5	Nociceptive	•	•	•	•	•
68	f	Gastrointestinal	3	8	10	10	Unclear	•	•	•	•	•
68	f	Gastrointestinal	3	6.5	9	6	Nociceptive	•	•	•	•	•
69	m	Gastrointestinal	2	4	10	3	Nociceptive	•	•	•	•	•
50	f	Genitourinary	2	5	10	6	Unclear	•	•	•	•	•
54	m	Genitourinary	3	6	9	5	Unclear	•	•	•	•	•
57	m	Genitourinary	2	4	7	5	Nociceptive	•	•	•	•	•
65	m	Genitourinary	3	1	6	4	Unclear	•	•	•	•	•
72	m	Genitourinary	3	4	10	6.5	Nociceptive	•	•	•	•	•
54	f	Lung	2	7	10	4	Nociceptive	•	•	•	•	•
56	m	Lung	2	6	10	6	Nociceptive	•	•	•	•	•
69	f	Lung	2	7	10	6	Nociceptive	•	•	•	•	•
54	m	Lung & larynx	0	0	10	4	Nociceptive	•	•	•	•	•
71	f	Pharynx	2	1.5	8	4	Nociceptive	•	•	•	•	•
78	f	Bones	2	8	10	7.5	Nociceptive	•	•	•	•	•
80	m	Hematopoietic system	2	8.5	10	5.5	Nociceptive	•	•	•	•	•
76	m	Hematopoietic system	1	6	10	6	Unclear	•	•	•	•	•
81	m	Skin	2	3	10	5	Neuropathic	•	•	•	•	•
64.4 (mean)	55% m 45% f	Mean ± SD	2.2 ± 0.9	4.7 ± 2.5	9.4 ± 1.2	5.7 ± 1.7		100%	90%	40%	45%	20%

f, female, m, male; •, regular intake of medication (NSAIDs = non-steroidal anti-inflammatory drugs); AD, antidepressants; AC, anticonvuls. Clinical features of cancer pain patients (n = 20; age range 50–81 years).

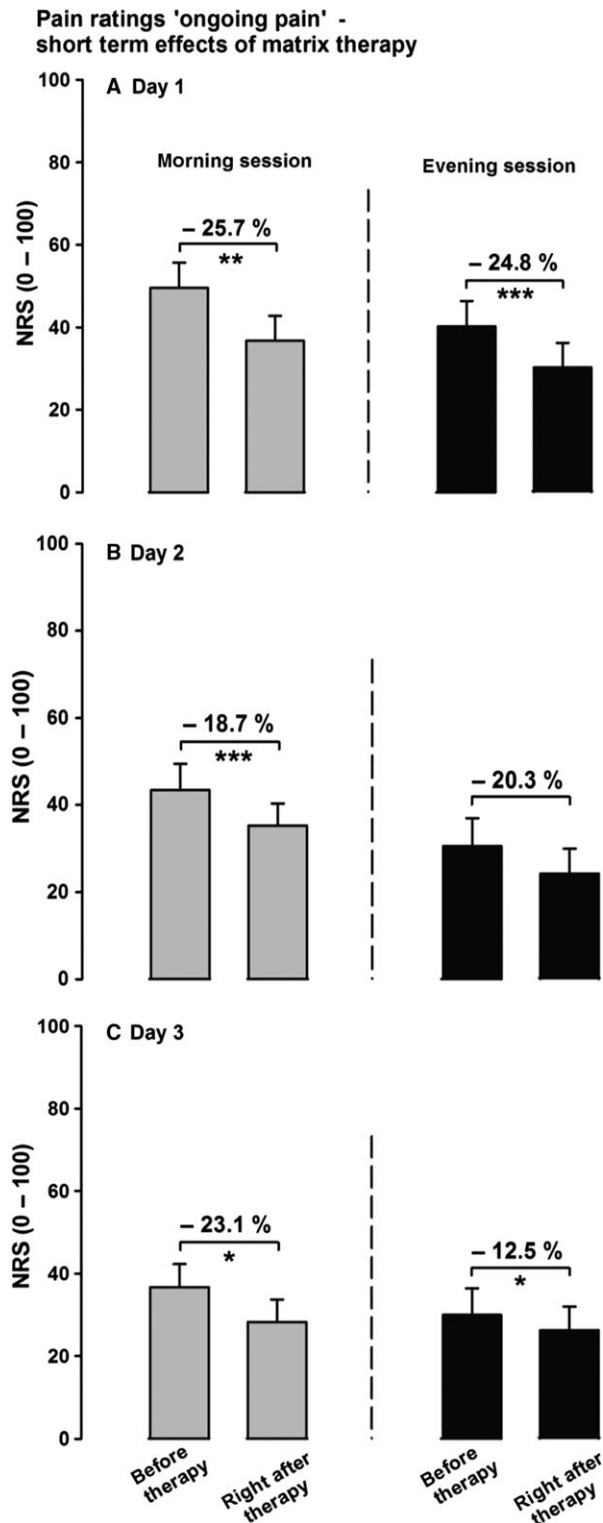


Figure 2 Ongoing cancer pain ratings: short-term effects of matrix therapy. (A) Day 1; (B) Day 2, (C) Day 3. The bars represent the mean \pm SEM pain ratings (NRS 0–100) just before and immediately after matrix stimulation for the morning and evening sessions. Stars denote the level of significance with * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$.

(Fig. 3) – even after discontinuation of the matrix therapy during days 4 to 6.

Mean pain reduction for primary pain caused by the tumour ($n = 11$) was 30.8% (day 1–3) and 28.3% (day 4–7). Average pain reduction for referred pain ($n = 9$) was 36.1% (day 1–3) and 34.2% (day 4–7).

3.3 Responders to matrix therapy

Patients were divided into responder and non-responder groups. A responder was defined as a patient experiencing a pain reduction of at least 30%. A non-responder was defined as a patient who experienced a pain reduction of $<30\%$. The amount of pain reduction (%) was calculated as a function of the average from day 0 in relation to the averages of the other days. From the 20 patients who underwent treatment, 65% (13 patients) reported a pain decrease under matrix therapy $>30\%$ compared to the baseline condition. Four patients (20%) reported a pain decrease of over 50%. Two of the 17 responders showed a pain decrease of 81% (Fig. 4).

3.4 Influence of the matrix electrode on the NRS values

Significant ANOVA-main effects were found when comparing the NRS values of all the different study phases (Table 3). Significant effects were seen comparing baseline values to the therapy as well as to the follow-up phase (ANOVA; each $p < 0.001$). The

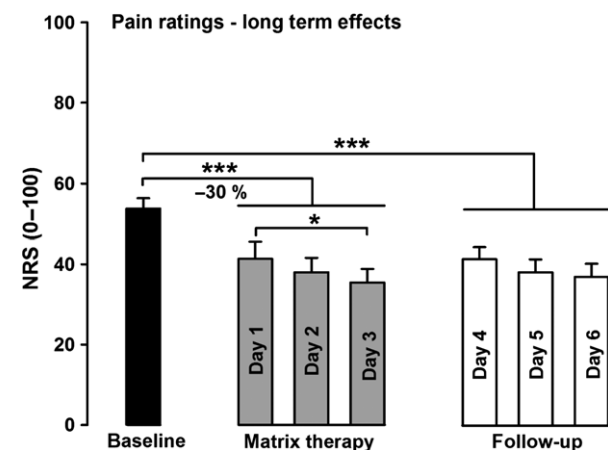


Figure 3 Ongoing cancer pain ratings: long-term effects of matrix therapy. Baseline = day 0; matrix therapy = days 1–3, follow-up control phase = days 4–6. Under matrix stimulation the ongoing cancer pain intensity was reduced by 30%. This effect was still present during the follow-up phase without any matrix therapy. Stars denote the level of significance with * $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$.

therapy phase and follow-up phase did not significantly differ from each other.

The different day times (morning, noon, evening) did not show significant differences. However, evening values showed significantly smaller initial values when compared to morning values (Fig. 2).

3.5 Consumption of basal and rescue opioid medication under matrix therapy

No significant ANOVA-main effects were seen (Table 3) when comparing basal opioid doses or on-demand rescue opioids during the study (baseline vs. therapy: $p = \text{n.s.}$; baseline vs. follow-up: $p = \text{n.s.}$; therapy vs. follow-up: $p = \text{n.s.}$). The amount of daily-consumed basal slow-release opioids was relatively stable for all patients over the course of seven days (Fig. 5). The average amount of fast acting on-demand rescue opioids consumed on day 0 (baseline) was 73.9 ± 144.1 mg/day. During the 3 days of matrix therapy this value slightly increased to a mean value of 83.0 ± 170.8 mg/day. During the follow-up phase, mean rescue opioid intake decreased to 43.2 ± 81.9 mg/day. However, this decrease failed to be statistically significant.

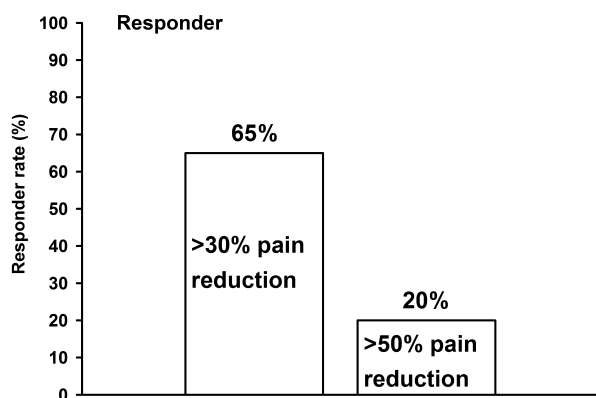


Figure 4 Responder versus non-responder. About two-thirds of this patient population reported a pain decrease >30% (responder). Twenty percent showed a more than 50% decrease in ongoing cancer pain.

3.6 painDETECT questionnaire to screen for a nociceptive vs. neuropathic pain component

painDETECT global sum scores were indicating nociceptive pain in 14 patients (70%), unclear pain stratification in five patients (25%), and neuropathic pain in one patient (5%).

The responder criterion was not associated with the painDETECT global sum score in this small and unevenly distributed group of subjects; responder classification according to the painDETECT global score: 11 nociceptive, 1 neuropathic and 1 undetermined (Table 4).

The current average pain intensity among the responders was 4.3 ± 2.6 of 10, with a maximum value of 9.3 ± 1.0 , and average pain intensity in the prior 4 weeks of 5.3 ± 1.5 . Similar values were seen in the non-responder group with a current pain intensity of 5.4 ± 2.4 , a maximum value of 9.4 ± 1.5 , and average pain intensity in the prior 4 weeks of 6.1 ± 2.0 . Radiating pain was reported by 61.5% of the responders and 42.9% of the non-responders ($p = \text{n.s.}$). Pain dynamics were also perceived to be different between the two groups. “Persistent pain with slight fluctuations” was reported by 38.5% in the responder group while only 14.3% shared this experience among the non-responder group ($p = \text{n.s.}$). “Persistent pain with pain attacks” was reported by 46.1% of the responders compared to 57.1% of the non-responders ($p = \text{n.s.}$). Values for “pain attacks with intermittent pain free intervals” and “pain attacks with intermittent painful intervals” were rare, each with 7.7% for the responders and 14.3% for the non-responders ($p = \text{n.s.}$).

3.7 Anxiety, depression and chronification of the pain syndrome

Based on the HADS questionnaire our patients showed relevant amounts of anxiety (global sum score 8.7 ± 5.9) and depression (global sum score

Table 3 ANOVA: Pain reduction and opioid consumption under matrix therapy.

Parameter	Pain reduction		Basal opioid medication (OME)		Rescue opioid medication (OME)	
	F-value	p-value	F-value	p-value	F-value	p-value
(1) Baseline vs. matrix therapy	8.43	<0.001	2.11	n.s.	0.56	n.s.
(2) Baseline vs. follow-up	12.5	<0.001	2.44	n.s.	1.78	n.s.
(3) Matrix therapy vs. follow-up	0.01	n.s.	2.31	n.s.	1.62	n.s.

OME, oral morphine equivalent; n.s., not significant.

Three different repeated measurement ANOVAs (main effects: F- and p-values).

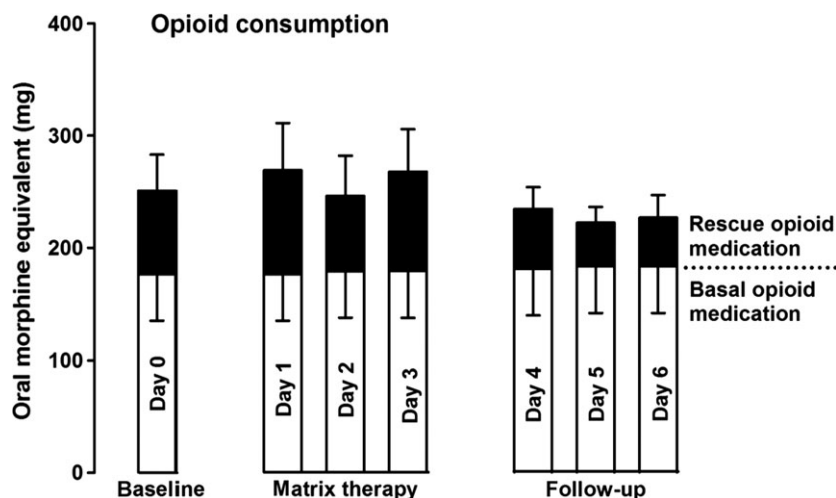


Figure 5 Opioid consumption. Open bars represent the daily basal controlled-release opioid dose (calculated as OME = oral morphine equivalents in mg/day). Filled parts of those bars correspond to the daily dose of fast-acting rescue opioids (OME). All dose differences (basal and rescue opioids) between study days were stable (n.s.; ANOVA, post hoc tests).

10.8 ± 5.5) on group level. All cancer pain syndromes had a high grade of chronification (von Korff-Index 3.8 ± 0.6; depicted from German pain questionnaire; GPQ). There was also a relevant psychological stress level (7.6 ± 4.6 GPQ) and a clearly reduced overall well-being (15.8 ± 8.8 GPQ). All of these parameters did not differ significantly between responders and non-responders (Table 4).

3.8 Clinical characteristics of pain in relation to matrix stimulation

The size of matrix stimulation area was 0.02 m² (see Table 1, Fig. 6). Average pain size was 0.1 m² (SD 0.05 m²; range 0.04–0.23 m²). Ratio of stimulation area to pain size in percent was on average 27.38% (SD 12.83%, range 9.65–54.98%). Eleven patients were stimulated at the main pain area, which was caused by the primary tumour. In nine patients (45%), the predominant pain area was defined by referred pain and stimulation took place at this site.

3.9 Adverse events and patients' satisfaction with intervention

After matrix stimulation, all patients showed a slight erythema that completely disappeared after 15–30 min. There were no burns, no allergic reactions, swelling, pain, bruise at the place of matrix stimulation, or discomfort, palpitation and dizziness reported (Table 5).

4. Discussion

In our feasibility study, we assessed the effects of low-frequency (4 Hz) monophasic cutaneous neuromodulation using a matrix electrode towards a reduction in ongoing pain intensity in advanced stage cancer patients. A previous study has already shown a reduction in evoked pain intensity after matrix stimulation in healthy subjects (Mücke et al., 2014). In this study, we demonstrated short-term effects that led to a pain intensity reduction of more than 20% on average right after a 5-min matrix stimulation procedure. The amount of immediate pain reduction was greater on treatment day 1 compared to days 2 and 3. However, the mean ongoing cancer pain intensity was also progressively reduced by about 30% comparing the baseline day and the treatment period of days 1–3. During each of these three treatment days matrix effects were more prominent in the morning than in the evening sessions, while opioid consumption was stable. Matrix therapy was effective for primary as well as for referred pain. This finding points to overall short-term and long-term effects of matrix therapy within minutes to days. This effect decreased with the reduction in ongoing pain intensity, indicating a possible ceiling effect, when ongoing cancer pain intensity reached mean values of about 30 (NRS 0–100; Fig. 2). It has to be noted that our group of cancer patients showed a currently moderate mean ongoing cancer pain intensity of 53.8 (baseline NRS 0–100) under a stable medical treatment according to the

Table 4 painDETECT and other questionnaires comparing responders and non-responders.

painDETECT items	Responder	Non-responder	p-value
NRS 0–10: current pain	4.3 ± 2.6	5.4 ± 2.4	n.s.
NRS 0–10: worst pain in the last 4 weeks	9.3 ± 1.0	9.4 ± 1.5	n.s.
NRS 0–10: average pain in the last 4 weeks	5.4 ± 1.5	6.1 ± 2.0	n.s.
Global painDETECT sum score	9.3 ± 7.1	9.3 ± 6.3	n.s.
<i>Clinical relevant findings (Score > 3)</i>			
Burning	23.1%	28.6%	n.s.
Prickling	7.7%	0%	n.s.
Allodynia	15.4%	0%	n.s.
Attacks	46.1%	28.6%	n.s.
Thermal	7.7%	14.3%	n.s.
Numbness	15.3%	14.3%	n.s.
Pressure	23.1%	14.3%	n.s.
<i>Descriptor specification > as individual mean</i>			
Burning	38.5%	57.1%	n.s.
Prickling	23.1%	28.6%	n.s.
Allodynia	53.8%	42.9%	n.s.
Attacks	46.1%	57.1%	n.s.
Thermal	15.4%	14.3%	n.s.
Numbness	30.8%	14.3%	n.s.
Pressure	38.5%	57.1%	n.s.
Radiating pain	61.5%	42.9%	n.s.
<i>Pain progression pattern</i>			
Persistent pain with slight fluctuations	38.5%	14.3%	n.s.
Persistent pain with pain attacks	46.1%	57.1%	n.s.
Pain attacks with intermittent pain free intervals	7.7%	14.3%	n.s.
Pain attacks with intermittent painful intervals	7.7%	14.3%	n.s.
<i>Other questionnaires</i>			
<i>Hospital anxiety and depression scale (HADS)</i>			
HADS (anxiety global sum score)	9.4	7.4	n.s.
HADS (depression global sum score)	11.2	10.0	n.s.
<i>German pain questionnaire GPQ</i>			
Cancer pain severity (v. Korff chronification score)	3.6	4.0	n.s.
Psychological stress level	8.0	6.7	n.s.
General well-being	16.2	15.1	n.s.

painDETECT items of cancer patients ($n = 20$) presented for responders (pain reduction >30%; $n = 13$), and non-responders ($n = 7$); painDETECT does not allow for response prediction upon its items.

HADS global sum scores (0–7: non-demonstrative; 8–10: suspicious; >10: demonstrative); GPQ psychological stress level (range 0: 'no stress' to 21: 'severely stressed'); General well-being (range 35: 'best possible' to 0: 'worst possible').

p-values are derived from unpaired *t*-tests.

WHO ladder. Matrix stimulation added another 30% pain reduction to this clinical situation. The technical approach of this study is different to large-surface gel electrodes that are used for TENS, where in contrast

to the matrix array electrode a flat and more profuse skin contact exists. This flat type of skin contact results in a more profuse tissue stimulation with lower currents per skin tissue volume. Since nociceptive free nerve endings are found in the superficial layers of the skin (Randić et al., 1993), they can be more effectively stimulated by a matrix electrode. In extension to TENS gel electrodes, the wearable soft tissue matrix electrode design allows for the stimulation of larger skin areas. In our study, stimulation with the matrix electrode covered between 10 and 55% of the primary pain area (Table 1) and were placed over the referring 'Head zones'. It is important to note that stimulated skin areas – whether they primarily overlay the cancer or not – are used to transport low-frequency electrical stimulation to their referring spinal cord dorsal horn neurons. In a chronic pain situation, these stimulated skin regions may correspond to higher number of enlarged receptive fields of these spinal wide-dynamic-range neurons (WDR-neurons; Mücke et al., 2014). These WDR-neurons represent the first relay station of the central pain projection pathway to the brain (Apkarian et al., 2005). Animal experiments in rodents have shown that excitability of these neurons may be a key element of spinal nociceptive learning mechanisms (Coghill et al., 1993). It is likely that in patients with permanent cancer pain, these neurons are sensitised due to the increased ongoing peripheral afferent input originating from nerve fibre activation in deeper (visceral) tissues surrounding the tumour. Part of this central sensitization may be neuronal learning mechanisms such as synaptic long-term potentiation (LTP) of the nociceptive system that can also be induced in healthy human subjects using high frequency electrical stimulations. Interestingly, this evoked-type of LTP in a human surrogate model can be reversed by applying low-frequency stimulation (LFS) that may induce another neurobiological learning mechanism leading to a decreased processing of afferent input, namely synaptic long-term depression (LTD) of such WDR-neurons (Klein et al., 2006). Both LTP and LTD reflect long-lasting changes of synaptic strength and have been intensively assessed to understand memory processing on a macro- and micro-level (Artola and Singer, 1993; Bliss and Collingridge, 1993). In this study, we applied LFS using a matrix electrode with high intradermal current densities to activate as many small calibre nerve fibre endings as possible and to use this afferent input to the above mentioned spinal projection neurons to reduce their excitability, hence aiming to reduce ongoing cancer pain intensity. This

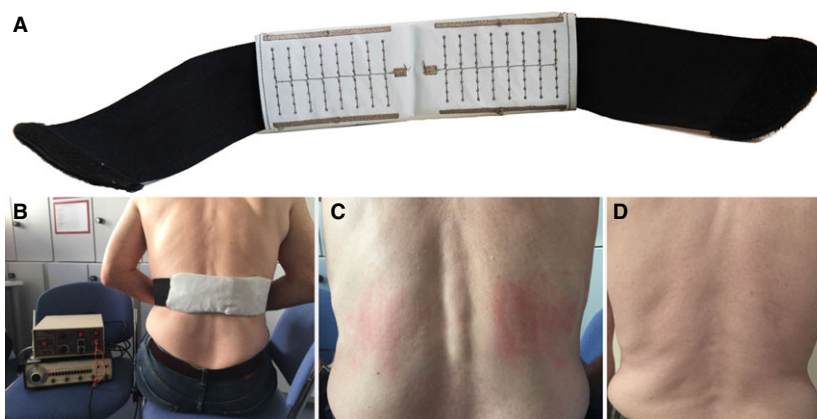


Figure 6 Erythema. (A) Matrix array electrode; Documentation of typical erythema after matrix stimulation. (B) Stimulation, (C) Immediately after stimulation, (D) 15 min after stimulation.

Table 5 Side effects of Matrix stimulation.

Patient	Erythema	Burn	Allergy	Pruritus	Discomfort	Nausea	Dizziness
1	•	—	—	—	—	—	—
2	•	—	—	—	—	—	—
3	•	—	—	—	—	—	—
4	•	—	—	—	—	—	—
5	•	—	—	—	—	—	—
6	•	—	—	—	—	—	—
7	•	—	—	—	—	—	—
8	•	—	—	—	—	—	—
9	•	—	—	—	—	—	—
10	•	—	—	—	—	—	—
11	•	—	—	—	—	—	—
12	•	—	—	—	—	—	—
13	•	—	—	—	—	—	—
14	•	—	—	—	—	—	—
15	•	—	—	—	—	—	—
16	•	—	—	—	—	—	—
17	•	—	—	—	—	—	—
18	•	—	—	—	—	—	—
19	•	—	—	—	—	—	—
20	•	—	—	—	—	—	—
	100%	0%	0%	0%	0%	0%	0%

approach is based on the concept that somatic afferent input from stimulated nociceptive nerve fibres of the skin converges to such WDR-neurons that receive afferent input from visceral nociceptors in the vicinity of the cancer (Jänig, 2014; Luz et al., 2015). These skin areas are called ‘Head’s zones’ and represent the referred pain areas for a pain that originally stems from another visceral region or organ (Henke and Beissner, 2011). A well-known example is a myocardial infarction. In the case of a heart muscle ischaemia, the brain receives nociceptive input from the spinal cord dorsal horn lamina I projection

neurons that refer their afferent input to the left arm, even though that input stems from the heart. This type of referred pain can only be explained via involvement of central nociceptive processing. Our finding of a clearly reduced ongoing cancer pain intensity points to the involvement and a possible sensitization of such central projection neurons that is at least partially reversed by LFS applied to the upper layers of the skin containing small calibre nociceptive nerve fibre endings also projecting to these neurons. The matrix technique makes use of such peripheral nociceptors to transmit LFS to those

possibly sensitized dorsal horn neurons to achieve a normalized state of activity, hence resulting in a reduction in the cancer pain while the visceral input stemming from the tumour area is still present. However, we cannot entirely exclude other possible peripheral effects of this type of electrical stimulation therapy. Others have described that direct electrical current treatment has modified, for example, mitochondrial function in a human lung cancer cell line under in vitro conditions. Effect intensity was time and dose-dependent with prominent functional cell decrease after 18 h (Holandino et al., 2016). We argue against such peripheral effects in our model, because pain reduction was immediately present after a 5 min-stimulation procedure. Moreover, electrical currents were distributed under each pin with high intensity only in superficial skin layers (Mücke et al., 2014). Another study revealed increased cell death rates in human leukaemic cells after anodal stimulation (Veiga et al., 2005). In contrast to that finding in non-solid tumour cell lines, we have demonstrated that electrical field properties after cathodal stimulation are consistent with the concept of a preferential current distribution of upmost skin layers containing small nerve fibres for impulse generation to a secondary reduction in spinal projection neuron excitability. Moreover, cancer cell apoptosis cannot be reached within minutes when using electrical currents between 1 and 3 mA (200 μ s) as in our model. Accordingly, the fast pain decrease right after the stimulation procedure (Fig. 2) seems to rather reflect a change in nociceptive system function than cancer morphology.

The effectiveness of TENS seems to depend on different measures such as adequate dosing (frequency, amplitude and impulse duration), medication usage, outcomes measured and the clinical population to be studied (Sluka et al., 2013). Based on animal experiments in rodents, the effectiveness of low-frequency TENS is at least in part mediated through the activation of spinal cord opioid receptors that can be blocked by naloxone (Sluka et al., 1999). This finding is consistent with the matrix stimulation approach. However, interactions with patients' cancer pain opioid medication are possible, because low-frequency TENS or matrix stimulation may activate spinal μ -receptors mediated by endogenous opioids. Intensive stimulation may have the risk for the development of opioid tolerance, resulting in an increased need for opioid medication. In accordance, it has to be noted that in this study, our patients showed a slightly higher consumption of on-demand (rescue) opioids during the

treatment phase compared to baseline and follow-up. However, this slight increase failed to be significant.

4.1 Adverse effects

Matrix stimulation was safe in this sample of patients with advanced cancer. There were no side effects, except for a slight erythema due to hyperaemia (Fig. 6; Table 3). Particularly burns or allergic reactions were not observed. Patients' self-report indicated no symptoms like discomfort, palpitation, dizziness or other. All patients were satisfied with the intervention.

In this study, the stimulated areas had intact skin. As no patient had cancer-related ulcerations, we cannot conclude on the effectiveness and safety of matrix stimulation in ulcerated cancer areas.

Our previous study in healthy subjects confirmed the 4 Hz stimulation frequency as being particularly effective for achieving a LTD like reduction in evoked pain intensity (Mücke et al., 2014). Hence, the abovementioned concept could elucidate, why TENS and matrix therapy may differ. A Cochrane review included three high quality studies on the effect of TENS on cancer pain (Hurlow et al., 2012). Two studies failed to demonstrate that TENS was superior to placebo. One feasibility study showed that TENS might improve cancer bone pain on movement. However, this valuable study was designed as a feasibility study and not designed to test for the effectiveness of TENS (Bennett et al., 2010). Moreover, a higher frequency of 80 Hz was used during the 60 min TENS procedure. Other studies have shown that stimulation using such high frequencies can induce long-term potentiation of the nociceptive system, that is, increase in nociceptive activity including a possible central sensitization of spinal nociceptive projection neurons. In this study, we used LFS with the intention to induce LTD of the nociceptive system.

The study investigated cancer patients with different pain etiologies. According to the painDETECT global sum score most of the patients (70%) were classified to have pain with a mainly nociceptive origin. Only one patient (5%) was classified as being 'neuropathic', while 25% of patients remained with an unclear pain classification. Average pain intensity during the last 4 weeks was 5.7 (NRS 0–10) with a maximum score of 9.4. In advanced-stage cancer about 80% of patients suffer from moderate to severe pain (Bruera and Kim, 2003; Paice and Ferrell, 2011) characterized in about 70%

of the cases to be of nociceptive origin (Caraceni and Portenoy, 1999). Therefore, pain characteristics of our patient group can be seen as typical for a sample of advanced stage cancer patients underlining external validity of our findings. This finding is supported by relatively high ECOG scores of 2 or 3 in most cases (Table 2).

Overall 65% of patients were responders as defined by an overall pain reduction of more than 30%. However, neither NRS pain scores, HADS scores nor other painDETECT subitems, global sum scores, gender or age were able to predict the matrix therapy response. This finding indicates that most likely the amount of central sensitization of central nociceptive neurons in relation to the amount/intensity of the conditioning visceral input from the cancer is the most important predictor of the central synaptic strength to be reduced. To our knowledge, there is no clinical predictor for this type of neuroplasticity identified today.

Another study question was whether the intake of both basal and rescue opioids was stable or reduced under matrix therapy. First, it has to be noted that the daily basal opioid dose was very high and ranged between 177 and 184 mg/day (OME). This finding indicates that our patient group was severely affected by the cancer pain. Mean baseline ongoing cancer pain intensity under this opioid treatment was 53.8 (NRS 0–100), reflecting a still burdening pain syndrome. It is an important finding that the basal opioid consumption was very stable during the study week. Moreover, the amount of fast-acting rescue opioids did only show slight changes that failed to become statistically significant (Fig. 5). This finding is important as the mean change in ongoing cancer pain intensity during the matrix treatment phase cannot be explained by an increase in the daily opioid doses. Interestingly, during the follow-up (3-day wash-out) phase without any matrix therapy, the daily amount of rescue opioids was slightly reduced but the difference did not reach statistical significance. This result is consistent with the concept of matrix therapy effects that last for days rather than minutes or hours. Further randomized controlled trials will be important to assess the duration of such effects.

4.2 Limitations

Due to the small number of subjects ($n = 20$), the study can only be rated as a proof of concept. However, recruitment of cancer pain patients is difficult since patients suffer from a variety of symptoms. In the long

run, randomized controlled trials using matrix stimulations with sham frequencies have to confirm the effectiveness of matrix therapy in cancer patients. Nevertheless, this feasibility trial strikingly showed a statistically significant pain reduction of 30% during treatment days. Another limitation of this study, is the fact that we used a Digitimer device which did not allow us to compare our monophasic stimulation paradigm with a biphasic approach. Biphasic matrix stimulation could possibly be more effective in activating small calibre epidermal nerve fibres which transmit LFS to the nociceptive projection neurons in the spinal cord, thus inducing long-term depression and hence reducing pain transmission.

4.3 Risk of bias

There was no random sequence generation or allocation concealment as patients were selected consecutively from the inpatient groups of the two above mentioned recruiting centres in Bonn. In this feasibility study, there was no patient or observer blinding as the low-frequency matrix stimulation was always applied followed by a 3-day washout period (follow-up) without any matrix application.

5. Conclusions

Our findings indicate that 4 Hz low-frequency stimulation using a matrix electrode may be a promising approach as a complementary therapy to cancer pain relief. The high acceptance rate and the absence of major side effects underline the practicability of this easily applicable approach. The significant overall pain reduction of 30% during the treatment days associated with a statistical trend towards a reduced consumption of fast acting on-demand opioids demonstrates the potential of this innovative technology, which takes advantage of the LTD mechanism. Our previous and current study results are consistent with the concept of matrix therapy inducing a centrally mediated heterosynaptic LTD for reducing deep pain sensitivity in cancer pain.

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Author contributions

Conceived and designed the experiments: MM RR. Performed the experiments: MM, MT. Analyzed the data: MM

MT HC LR RC VPP DK RR. Contributed reagents/materials/analysis tools: MM MT RR. Contributed to the writing of the manuscript: MM MT DK RC RR.

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