Support Care Cancer (2016) 24:1649–1654
DOI 10.1007/s00520-015-2952-x

ORIGINAL ARTICLE

Pilot evaluation of scrambler therapy for pain induced by bone and visceral metastases and refractory to standard therapies

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Received: 25 May 2015 / Accepted: 14 September 2015 / Published online: 26 September 2015

Abstract
Purpose Scrambler therapy is a non-invasive neurocutaneous electrical pain intervention, effective for the treatment of neuropathic pain. Currently, few data about the efficacy of this treatment in cancer pain induced by skeletal and visceral metastases are available. The aim of this single-center case series is to evaluate the efficacy of scrambler therapy in reducing this kind of cancer pain after failure of standard treatments, including pharmacological therapies and radiation therapy.
Methods Twenty-five consecutive patients underwent scrambler therapy individually delivered by MC5-A Calmare for 10 daily sessions each of 30–40 min. Pain was measured by a numeric rating scale at baseline, as well as before and after each treatment session.
Results One hundred percent of patients reached a pain relief ≥50 %. Pain score was reduced from 8.4 at baseline to 2.9 after treatment, with a mean pain relief of 89 %. The sleeping hours improved from 4.4±1.2 to 7.5±1.1. The duration of pain control by scrambler therapy was 7.7±5.3 weeks. No adverse events were observed.
Conclusion Scrambler therapy does not present toxicity and allows opioids dosage reduction, and it is also a repeatable treatment. Present novel data support that scrambler therapy seems to be effective for the treatment of cancer pain. Further evaluation in randomized and controlled clinical trials should be performed to confirm our findings.

Keywords Scrambler therapy · Untreatable cancer pain · Metastatic bone and visceral pain · Electroanalgesia · Calmare®

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Introduction

The treatment of cancer pain is becoming an emerging debated issue due to the prolongation of survival of cancer patients which requires also the same evolution in quality of life. Among the factors that definitely influence the quality of life, cancer pain has the most negative impact. More than 80 % of cancer patients experience pain, and more than 50 % of patients with metastatic cancer complain of moderate to severe pain [1]. The availability of opioids with new dose formulations and types of administration has not been able to fully control cancer pain because of their side effects and time-limited effectiveness [2, 3]. Moreover, pain management is particularly challenging in patients with bone and visceral metastases, especially when they develop refractoriness to standard therapies [4].

Few novel non pharmacological strategies, as dorsal root ganglion pulsed radiofrequency or scrambler therapy, are investigated for the treatment of neuropathic refectory cancer pain [2, 4, 5]. Scrambler therapy consists in the use of an electrocutaneous nerve stimulation device that synthesizes 16 types of nerve action potentials causing "non-pain" information via cutaneous nerves transmission. It consists in positioning electrodes exactly on the proximal and the distant limits of the cutaneous region over the pain area and works converting "pain" information in non-pain information via electrical stimulation to the central nerve system. The intensity

of stimulation is set to the maximum value at which the patient does not feel discomfort [6]. The number and duration of sessions reported in the literature for neuropathic pain are respectively 10 sessions and 30–45 min for about ten consecutive days in a 2-week period.

Scrambler therapy has been mainly studied so far for the treatment of neuropathic pain, including postsurgical pain, postherpetic neuralgia, spinal cord stenosis, chemotherapy-induced peripheral neuropathy, and benign or chemotherapy-related neuropathic pain [6–11]. Initial data are available about the effects of scrambler therapy in the management of refractory cancer pain [1, 12].

Treatment of cancer pain refractory to standard treatments remains an unmet need in oncology, and therefore, we elected to investigate scrambler therapy in cancer patients who failed previous standard pain treatments with including medical therapy (opioids, neuroleptics, anti-inflammatories) and/or with locoregional treatments such as radiotherapy. Our population was affected by cancer pain related to the presence of bone/visceral metastases or primary tumor.

Methods

This is a retrospective case series. Twenty-five patients affected by cancer pain due to bone/visceral metastases or primary tumor and refractory to standard analgesic treatment were treated with scrambler therapy at Pain Unit and at the Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, Milan, Italy, between November 2013 and November 2014.

Patients were eligible as for these criteria: (i) least 18 years of age, (ii) presence of cancer pain with numeric rating scale (NRS) score ≥7, (iii) failure to respond/intolerance to standard treatment (opioids at maximum doses, anticonvulsants, antidepressants, anti-inflammatories, steroids, radiotherapy), (iv) written informed consent to scrambler therapy treatment, and (v) absence of any implantable medical device (pacemaker, defibrillator, metallic valves, spinal cord stimulators). Informed consent was obtained from all individual participants included in this retrospective study to collect their anonymous data. At baseline information about anamnesis, cancer history, pain onset, and location, previous and current pharmacological treatments both for pain and cancer, side effects related to pain management, and previous and current locaregional therapies (radiotherapy) were collected. Prescribed pain medication was not modified during the whole observational period.

Chronic cancer pain was assessed by NRS at baseline, before and after each treatment session. Pain relief was assessed also during the monthly follow-ups to evaluate the long term efficacy of scrambler therapy until death or lost to follow-up. Follow-up visits could be performed by a pain specialist, oncologist, and hematologist. At baseline and before each treatment session, patients were asked to report the number of sleeping hour. For patients lost to follow-up, the number of sleeping hours at night was collected.

Adverse events were collected during the whole observational period, if occurred. Informed consent was obtained from all individual participants included in this retrospective study to collect their anonymous data.

Scrambler therapy

The scrambler therapy was performed as follows: the impulses were transmitted by surface silver gel electrodes placed on the skin in the dermatome to the proximal and distant area of pain. On the first day of treatment, the primary pain area and its confines were identified by patient report. One electrode was placed distal and the opposing electrode proximal to painful area, along the lines of pain. Once the first pair of electrodes was placed, the scramble therapy was turned off, and the stimulation was increased up to the maximum tolerated intensity. If the patient did not report any pain relief, the stimulation was turned off and the electrodes were repositioned. Between 1 and 5 sets of electrodes could be used for each treatment. Once the first set of electrodes was properly positioned, additional electrode sets could be placed for a further coverage of painful area [5–13]. On the first day of treatment, the stimulation intensity was increased up to the maximum strength tolerated by the patient. On subsequently days, stimulation intensity was usually set at the highest tolerated level used in the previous session [13]. The frequency ranged from 43 to 52 Hz,, each session lasted 30–40 min, and a total of daily 10 sessions from Monday to Friday for 2 weeks were performed [5, 13].

Statistical analysis

Continuous data are summarized by mean±SD. Repeated one-way ANOVA for repeated measures was used to compare NRS scores over time. Post hoc comparisons were performed using Bonferroni corrections. All two-tailed p values <0.05 were considered statistical significant.

Non-parametric Wilcoxon signed rank test was used for testing differences between NRS pre- and post treatment at each session.

Statistical analysis was performed using IBM SPSS statistical software.

Results

Patients' characteristics and main results of scrambler therapy are reported in Table 1.

The average age was 62.0±12.5 (range 32–85) and 60 % of patients (15/25) were male. In 17 patients (68 %), chronic pain was related to bone metastases (82 % from solid tumors and 18 % from hematologic malignancies), and 8 cases (32 %)

Table 1 Patients' characteristics

ID	Age (years)	Tumor	Metastatic site	RT benefit
1	68	Lung cancer	Bone (thighbone)	No
2	32	Rectal cancer	Bone (thighbone)	Yes
3	39	Colon cancer	Bone (sacral vertebra)	No
4	67	Abdominal sarcoma	Bone (dorsal vertebra)	No
5	64	Colon cancer	Bone (left ribs)	No
6	69	Lung cancer	Bone (sacrum)	No
7	66	pancreatic cancer	Bone (sacrum) ND	
8	67	Urotelial Carcinoma	Bone (sacrum)	Yes
9	72	Urotelial Carcinoma	Bone (pelvis)	No
10	40	Non Hodgkin Linfoma	Bone (sacrum-iliac)	No
11	60	Mieloma	Bone (vetrebrae)	ND
12	76	Mieloma	Bone (thighbone)	No
13	57	Breast cancer	Bone (lombar vertebra, sacrum)yes	Yes
14	78	Prostatic cancer	Bone (thighbone, rib)	ND
15	50	Lung cancer	Bone (dorsal, lombar vertebra)	ND
16	63	Urotelial Carcinoma	Bone (sacrum, iliac wing)	No
17	59	Lung cancer	Bone (lombar vertebra)	No
18	66	Pancreatic cancer	Frenic involvement by liver metastasis	Yes
19	54	Pancreatic cancer	Tumor	No
20	55	Colon cancer	Frenic involvement by liver metastasis	ND
21	57	Lung cancer	Lung mass	No
22	57	Pancreatic cancer	Tumor	No
23	85	Colon cancer	Pelvis (psoas)	No
24	63	Pancreatic cancer	Tumor	ND
25	63	Head and Neck cancer	Parapharyngeal mass	No

RT radiotherapy, *Yes* pain reduction after RT, *No* absence of pain relief after RT, *ND* RT not done

suffered from pain due to primary tumor (37.5 %) or visceral metastases (62.5 %).

After 10 days of scrambler therapy, pain score significantly reduced from 8.4±1.4 to 2.9±1.5 (p=0.008), showing a constant and significant decrease during the whole treatment (ANOVA p=0.0001). Pain scale just after each daily treatment was always significantly lower than NRS just prior the session of scrambler therapy. (Fig. 1). Patients experienced a pain relief which lasted in the 24 h after daily treatment: NRS score prior each session showed a significantly decreased versus baseline condition.

The increase score of NRS at T6 corresponded to the restarting therapy after a weekend break of 2 days, but the pain intensity just prior to the session was still significantly lower than the score at baseline condition (p=0.00001).

Fifty percent of the population had a decrease in pain intensity of 3 points after 3 treatments.

At the end of scrambler therapy, the mean pain relief recorded was 89 %, and the mean improvement after each session was reported in Table 2. A reduction in pain from baseline ≥50 % obtained by the treatment lasted between 4 to 24 weeks (mean pain decrease duration was 7.7±5.3 weeks).

Seventeen patients did not complete all 10 days of scrambler therapy. Six patients spontaneously decided to discontinue the treatment because of no pain permanent condition, while the other eleven patients stopped because they underwent diagnostic investigations or chemotherapy. In Table 3, we reported individual NRS patients' scores over treatment days, percentage of pain relief, and reasons for loss to

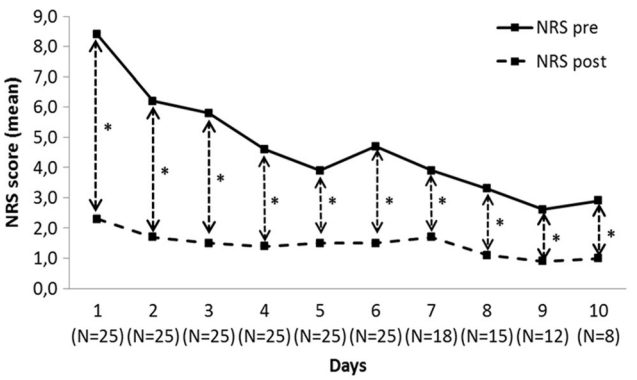

Fig. 1 NRS scores just prior and just after each daily treatment

Table 2 NRS pre, post treatment and percentage of improvement

Days	NRS pre	NRS post	Improvement %
1 (*N*=25)	8.4	2.3	73 %
2 (*N*=25)	6.2	1.7	73 %
3 (*N*=25)	5.8	1.5	72 %
4 (*N*=25)	4.6	1.4	73 %
5 (*N*=22)	3.9	1.5	65 %
6 (*N*=19)	4.7	1.5	72 %
7 (*N*=18)	3.9	1.7	58 %
8 (*N*=15)	3.3	1.1	73 %
9 (*N*=12)	2.6	0.9	67 %
10 (*N*=8)	2.9	1.0	65 %

follow-up. No adverse events related to scrambler therapy occurred during the observational period. At the end of the 10 days of treatment, sleeping hours increased from 4.4±1.2 to 7.5±1.1 (p=0.004), with a mean improvement of 70 %.

Reason for discontinuation of follow-up was related to patient's compliance (logistic issues to reach Hospital) in 6 cases and to the short life expectancy of 8 patients who gained pain control but died from cancer progression.

Two patients repeated the scrambler therapy after 12 and 24 weeks, respectively, obtaining clinical benefits.

Discussion

Chronic cancer pain refractory to opioid use is a major issue in the management of patients affected by metastatic solid tumors. Pain has a very negative impact on the quality of life of these patients also because the use of medical treatment often has important side effects without a satisfactory pain

Table 3 Table of individual NRS scores over treatment days

Patient ID	Treatment day										% Pain relief before last session
	1	2	3	4	5	6	7	8	9	10	
1	10	8	8	6	8	6	5	7	7	3	70 %
2	10	6	6	2	2	2	0	0	0	0	100 %
3	9	7	8	3	4	4	3	2	2	2	78 %
4	9	3	3	3	3	6	6[a]	6[a]	6[a]	6[a]	33 %
5	10	7	7	6	2	2[b]	2[b]	2[b]	2[b]	2[b]	80 %
6	8	7	7	3	3	3[b]	3[b]	3[b]	3[b]	3[b]	63 %
7	10	9	5	4	2	6	5	4	4[a]	4[a]	60 %
8	8	7	5	3	3	3	3	3	3[b]	3[b]	63 %
9	10	8	7	5	3	10	8	6	5	3	70 %
10	10	10	8	5	5	3	2	2	3	3[a]	70 %
11	7	6	6	4	4	4	3	3[a]	3[a]	3[a]	57 %
12	8	5	5	5	3	3[b]	3[b]	3[b]	3[b]	3[b]	63 %
13	9	8	7	6	4	3	3	3[a]	3[a]	3[a]	67 %
14	5	4	2	3	3	3[a]	3[a]	3[a]	3[a]	3[a]	40 %
15	7	5	4	2	1	1[b]	1[b]	1[b]	1[b]	1[b]	86 %
16	7	5	5	6	3	3[a]	3[a]	3[a]	3[a]	3[a]	57 %
17	9	6	5	5	6	4	3	3	3	3	67 %
18	8	4	9	8	6	6	6[a]	6[a]	6[a]	6[a]	25 %
19	8	6	6	7	5	7	5	3	2	2[a]	75 %
20	9	5	7	6	7	5	4	4	3	4	56 %
21	8	8	7	6	6	6	6	5	3	3	63 %
22	7	8	2	2	3	4	3	3	0	0[a]	100 %
23	8	8	6	6	5	4	5	5	2	5	38 %
24	6	0	0	0	0	0	0	0	0[b]	0[b]	100 %
25	9	6	9	7	6	6[b]	6[b]	6[b]	6[b]	6[b]	33 %
Average pain	8.4	6.2	5.8	4.5	3.9	4.2	3.6	3.4	3.0	3.0	64 %
(SD)	1.3	2.1	2.2	1.9	1.9	2.1	1.9	1.8	1.8	1.6	20 %

[a] Last value carried forward per patients lost to follow-up due to diagnostic investigation or chemotherapy

[b] Last value carried forward per patients who discontinued the treatment because of no pain permanent condition

relief. Scrambler therapy could be a therapeutic option for cancer pain management, but very few data are available about its efficacy in patients with pain induced by bone metastasis. In our experience, pain relief observed in our population is consistent with the results published in other cases report, uncontrolled studies [1, 7, 9, 10, 14], and in one randomized pilot trial [6].

In our series, we observed a pain reduction in all patients, with a mean NRS decreased from 8.4 before treatment to 2.9 at the end of 10 days of treatment, with a mean pain relief of 89 %.

A large fraction of our patient's population was affected by bone metastatic disease leading to chronic pain refractory also to radiotherapy. In this group of patients, scrambler therapy reached an early reduction of pain after just after the first session of treatment.

Adequate pain relief for cancer pain could often be obtained by a pharmacological approach according to the World Health Organization analgesic ladder [2]. The use of medical treatments could have important side effects without a satisfactory pain relief. During scrambler therapy, patients reported a decrease in the use of as-needed opioids,, with a consequent reduction of side effects, such as constipation, drowsiness, confusion, and nausea, that influence negatively the quality of life of these patients. Prescribed pain medication stayed stable during the whole observational period, but a reduction in the use of as-needed opioids obtained with scramble therapy represents an important benefit for cancer patients where the side effects of multiple concomitant medications often affect quality of life [15].

Seventy-six percent of patients included in this retrospective data collection were previous treated with radiotherapy, without a satisfactory pain relief. Radiotherapy for pain management could present frequent side effects, such as the initial exacerbation of pain during the treatment [16]. Moreover, radiotherapy often requires the interruption of chemotherapies in order to avoid additional toxicities. Conversely, the scrambler therapy can be performed safely during chemotherapy, without additional side effects.

Limitations of this data review include the retrospective design, the small simple size, and the relatively short period of follow-up, partially due to the short life expectancy of cancer patients, not allowing us to investigate the duration of pain relief in the mid and long term follow-up. As abovementioned, 8 patients died for cancer progression after short observational time, and 6 patients were lost to follow-up due to logistic issues (e.g., distance from the hospital) after reaching the pain control. In addition, there is not a control arm. However, the use of electrical stimulation did not allow a blinded study design including a control arm with placebo. In our case series, we investigated the use of scrambler therapy in patients affected by pain related to bone and visceral metastases, or primary tumor. Our data showed that the advantages of this technique are its safety, non-invasiveness, and the rapidity of response just after the first sessions.

Furthermore, scrambler therapy can be performed during anticancer treatment, such as chemotherapy, without interfering with the oncologic program, unlike of radiotherapy that often needs a treatment interruption in order to limit the potential side effects in case of radiosensitizer agents.

The scrambler sessions can be applied both as outpatient and inpatient setting, potentially reducing the lengthening of hospitalization due to cancer pain. It could be interesting to evaluate the effectiveness of scrambler therapy though the alteration of the mechanisms of enhanced pain sensitivity [17].

This is the first published consecutive single institution series of patients treated with scrambler therapy for cancer pain, selected on the basis of pain origin. Our findings suggest that scrambler therapy could represent a new opportunity for cancer patients with uncontrolled pain, resistant to standard treatments.

Future prospective, controlled trials are necessary to confirm the efficacy of this therapy for the management of cancer pain related to bone metastases from solid tumors.

Acknowledgments This data collection received no specific grant from any funding agency in the public, commercial or not-for-profit. Clinical investigators at Pain Unit and at the Niguarda Cancer Center are supported by Fondazione Oncologia Niguarda Ca' Granda Onlus and NOPAIN onlus.

Compliance with Ethical Standards

Ethical approval For this type of study, formal consent is not required.

Funding This data collection received no specific grant from any funding agency in the public, commercial or not-for-profit. Clinical investigators at Pain Unit and at the Niguarda Cancer Center are supported by Fondazione Oncologia Niguarda Ca' Granda Onlus and NOPAIN onlus.

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