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An Exploratory Study on the Effectiveness of "Scrambler Therapy" in Patients with Cancer Pain: a pilot study

Abstract

Introduction

Scrambler therapy is a novel approach for pain control that uses EKG-like pads, which are applied above and below the site of pain. It is a method to control pain that attempts to relieve pain by providing "non-pain" information via cutaneous nerves to block the effect of pain information. So it is necessary to evaluate effects of scrambler therapy to widen clinical range of management. We performed an exploratory study on the effectiveness of "scrambler therapy" in patients with various cancer pain syndromes.

Material and method

Eleven cancer patients diagnosed with cancer-related metastatic bone pain (n = 5), chemotherapy-induced peripheral neuropathy (n = 4), postherpetic neuralgia (n = 1) and postradiotherapy pain (n = 1) were analyzed in the study. Scrambler therapy was applied for 40 minutes (one treatment per day) during the ten consecutive days to these patients. The primary endpoint was an 11-point numerical rating scale (NRS) pain score during the therapy and at one month after the procedure. The secondary endpoint was Likert scale, satisfaction scale, change of opioid consumption dose and brief pain inventory (BPI).

Result

NRS are significantly decreased in the patients with cancer pain syndromes during the scrambler therapy (p-value=0.009) and pain relief was sustained at least two weeks after the 10th treatment. Even though regular opioid dose was not changed remarkably, the consumption of rescue opioid was reduced

significantly (p-value = 0.01) than initial consumption dose of rescue opioid. All components of BPI except normal work (p-value = 0.066) are improved than before treatment.

Conclusion

Scrambler therapy was helpful to relieve cancer-related pain. We assessed NRS, Likert scales, satisfaction scales, BPI and checked dose of opioid consumption. Consequently breakthrough pain was relieved than background pain more. Breakthrough pain relief made quality of life improve in cancer pain syndromes. It was revealed through BPI which several components associated with quality of life were improved. However, the mechanism of pain scrambler therapy was unknown yet. Further evaluations about scrambler therapy will be needed to explain exact mechanism. Also, a small number of patients and no control group were limitations of this study.

Key words: Cancer pain, Numeric rating scale, Noninvasive approach, Scrambler therapy

Introduction

Cancer is a rising global health burden. It is estimated that in 2030, cancer deaths will be tallied at over 13million according to World Health Organization (WHO) (1). So the quality of life of cancer patients has been urgent and the interests in this problem is rising. Especially cancer pain was closely related to the problem of quality of cancer patients (2). However, successful management of cancer pain especially in patients who had advanced bony metastasis very difficult. According to Yakovlev et al (3), up to 15 % of nearly 7 million patients exhibiting pain reported unsuccessful pain relief even with conventional pain management. It is challenging for the clinicians to control cancer pain with available analgesic drugs. Because pharmacologic treatment of cancer pain was not enough satisfied, as well as was accompanied with complications. In Table 1, some examples of cancer pain syndrome and medications are introduced.

To reduce these complications, an evolving hypothesis for pain relief suggests direct nerve stimulation (4). This direct nerve stimulation technique such as scrambler therapy may be one of the complementary measures to relieve refractory pain. Scrambler therapy using electro-analgesic device (MC-5A® Calmare, Competitive Technologies Inc. USA) (Fig. 1) is noninvasive approach for pain control and ECG like pads are applied above and below the site of painful area (Fig. 2). The scrambler device consists of multiprocessor apparatus that are able to simulate 5 artificial neurons by the application of surface electrodes around the surface of painful areas. The device is able to synthesize 16 different types of nerve action potentials similar to the endogenous kinds and string them into sequences. The goal of pain scrambler therapy is to provide "non-pain" information to the cutaneous nerves to block the effect of pain information.

The scrambler therapy has efficacy about pain control in several preliminary studies (5, 6). In the first published trial (5), 11 terminal cancer patients (3 pancreas cancer, 4 colon cancer and 4 gastric cancer)

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suffering from drug resistant visceral pain were studied during their first ten treatment sessions. Pain was markedly reduced after the treatment. In the second published study (6), 52 patients with chronic neuropathic pain were randomized to receive treatment with the pain scrambler device or treatment with medication. The visual analogue scale (VAS) was decreased by 5.8 points out of 10 in the pain scrambler group. On the other hand, only by 0.7 points out of 10 in medication only group. Also no complications were observed in the pain scrambler patients' group. (7)

Herein, we first tried to determine whether pain scrambler therapy could decrease cancer pain in the 11-point numeric rating scale (NRS). Secondary, we tried to investigate brief pain inventory (BPI), 7-point Likert scale, 5-point satisfaction scales and change of opioid consumption.

Method

Study design

The single-arm open-labeled study, approved by our Institutional Review Board was focused on cancer related pain in patients who received only conservative therapy for more than 6month.

Patients

Fifteen cancer patients who had different kinds of cancer such as breast cancer, prostate cancer, multiple myeloma and stomach cancer were enrolled for this study. All patients were eligible if they had metastatic bone pain, chemotherapy-induced peripheral neuropathy, postmastectomy pain and postradiation pain as diagnosed by their oncologist. Each patient must meet all of the following inclusion criteria.. Cancer pain syndrome (mentioned above), the patients who had received, but not currently receiving for at least 4 weeks, neurotoxic chemotherapy, the patients who have pain or symptoms of more than ≥ 1 month's duration attributed to chemotherapy-induced or cancer-related peripheral neuropathy, the pain which must have been stable for at least 2 weeks, an average daily pain rating of score ≥ 4 out of 10, using NRS score: 0 is no pain and 10 is worst pain possible. Patients who are ≥ 18 years of age, patient's life expectancy ≥ 3 months and ECOG Performance Status 0, 1, or 2.

Patients meeting any of the following exclusion criteria were not to be enrolled: still receiving neurotoxic or potentially neurotoxic chemotherapy, or receipt of such therapy within 4 weeks. Any of the following condition: pregnant women, nursing women, women of childbearing potential or their sexual partners who were unwilling to employ adequate contraception and use of an investigational agent for pain control concurrently or ≤ 30 days. History of an allergic reaction or previous intolerance to transcutaneous electronic nerve stimulation is not included. Patients with implantable drug delivery systems or heart stents or metal implants such as pacemakers, automatic defibrillators, aneurysm clips,

vena cava clips and skull plates. Patients had a history of myocardial infarction or ischemic heart disease within the past six months. Additionally patients with history of epilepsy, brain damage, symptomatic brain metastases. The patients who had prior celiac plexus neurolysis, or other neurolytic pain control treatment within 4 weeks. Skin conditions such as open sores that would prevent proper application of the electrodes. Other medical or other condition(s) that in the opinion of the investigators might compromise the objectives of the study.

Treatment

Scrambler therapy was applied for 40 minutes (one treatment per day) for ten consecutive days in these patients. The initial consultation to discern the most effective pattern for electrode placement will take up to 40 min. Treatments were performed on consecutive days. Up to two days may be skipped to allow for weekend days, if needed. The stimulus was increased to the maximum intensity individually bearable by the patient that did not cause any discomfort. And this manipulation was carried out by only one pain specialist to reduce bias.

Efficacy assessment and follow up (Fig. 3).

Totally fifteen patients were recruited for this study. Four patients could not finish scrambler therapy as scheduled. The primary endpoint was an 11-point NRS score during the therapy and at one month after the procedure. Before the initiation of treatment, NRS was checked for the baseline score. The first follow up was after 1 week from the baseline. When 10th scrambler treatment was finished, NRS was checked again. The last follow up is 4 weeks from the baseline, or 2 weeks after treatment was finished. NRS, brief pain inventory (BPI) and Opioid consumption were checked at each point. All opioid doses are converted by a daily morphine oral dose equivalents (8) and we compared baseline opioid consumption dose with it at final follow up.

Statistics

When the normality assumption was not met, the Wilcoxon signed rank test was used to assess the statistical significance of differences between baseline NRS and final follow up NRS. Change of opioid consumption was applied with the same analysis between two time points. There was p-value < 0.05 and confidence level of 95%. Data were analyzed with the IBM SPSS (for windows, version 19) software.

Result

Patients' characteristics

  A total of 11 patients who visited at our integrated care center prior to treatment and finished scrambler therapy as scheduled from September in 2012 to April in 2013 were analyzed. The types of pain were devided into 4 categories of cancer-related metastatic bone pain (n = 5), chemotherapy-induced peripheral neuropathy (n = 4), postmastectomy pain (n = 1) and postradiotherapy pain (n = 1).

  All patients were over 50 year old and did not get any other pain management except pharmacological therapy. Pharmacological therapy was accorded to the most up-to-date WHO cancer patient guideline, included amitriptyline, gabapentin, tramadol, and opioid. Two patients who had bone metastatic pain presented numbness because there was metastasis in the cervical vertebra and invasion of spinal nerve root as well. Demography of sexual distribution is shown in the following Table 2.

  Response of scrambler therapy

  Figure 4 shows the trends of all patients' pain score. The pain score of 10 patients out of total 11 patients (90.9%) showed pain reduction after 5 sessions of scrambler therapy. On the contrary, 2 patients' pain scores were not decreased even after finishing all sessions of treatments. After 4 weeks from baseline, or at final follow up, NRS scores of all patients were decreased significantly compared with NRS scores at baseline in Table 3 (p-value =0.009). All secondary endpoints also showed significant improvement. The consumption of regular opioids did not change remarkably. But the consumption of rescue opioid dose was reduced significantly than before treatment in Table 3 (p-value = 0.01). Five-point satisfaction scales were generally high scored. Four patients are 5 point and other 7 patients are 4 point. Zero point means very unsatisfied and 5 point means very satisfied with treatment. So it means that almost all patients who participated in this study satisfied with scrambler therapy. Likert scales were checked twice after 2 weeks from baseline and after 4 weeks from baseline respectively to evaluate immediate pain relief. Figure 5 shows there is no significant difference of pain relief between 2 time points (p-value = 0.406). Pain relief

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immediately after treatment was not significantly better than at final follow up. We saw across the board improvements in all the components of BPI except normal work (p-value = 0.066) and they were sustained at least 2 weeks (Table 3). Pain history within 24 hours was checked using BPI questions 3, 4, 5, and 6. Mean NRS score of current pain, pain at worst, pain at least and average pain score within 24 hours are decreasing subsequently from baseline to final follow up (Figure 6).

Discussion

In this study, we assessed BPI to measure both the intensity of pain and interference of pain in the patient's life. Because each component of the measurement process (i.e., choice of an instrument to measure pain, timing and frequency of measurement, measurement of symptoms accompanying pain or its treatment, and measurement of functional status) is important in developing an accurate and comprehensive assessment of cancer pain (9). This study was focused on subjects as only cancer pain patients and BPI was added to assess cancer pain history.

Control group were not recruited well because their general condition was poor and could not be followed up regularly. It was also difficult to interview with BPI in detail for them. Patients were reluctant to attend this study as control group.

The period to apply the scrambler therapy was planned for 2 weeks in this study. Definite period of treatment was not determined yet. The previous studies recommended 2 weeks (10-12) and it seemed to be reasonable considering patient's convenience. However, Monika Haack et al (13) reported that ulnar nerve stimulation for 2 weeks activated pain inhibitory circuit and it takes 4.8 ± 1.1 days in healthy controls. J. Martelluci et al (14) insisted 51months on average to modulate sciatic nerve in the nerve stimulatory treatment of chronic pelvic pain. So the treatment period of 2 weeks could be needed more for chronic cancer pain patients. The period of scrambler therapy is considered to be applied differently, depending on the pathologic conditions of each patient.

The mechanism of scrambler therapy has not been clearly revealed, similar to other electrical stimulation therapies such as TENS or spinal cord stimulation (SCS). According to Jensen MP et al (15), direct patient-specific nerve stimulation was raising the gate threshold for pain at the spinal cord and reducing "wind up" (central sensitization of the spinal cord and brain that amplifies the abnormal

feelings). This made impulses from the damaged nerve calm down and reduced psychological maladaptation to pain. Scrambler therapy provides "no-pain" information to the periphery sensory nerve receptors through attached electrode patches and this is conveyed to the central nervous system and remembered by the system to relieve patients' pain (7). This electrical stimulus is conducted through C-fiber and Aδ fiber, which usually convey pain, but it is not a method of simply stimulating the peripheral pain nerves that cause pain. Marineo et al (5) explained that it is also different from dulling the senses of the patient, so that he or she can still feel normal stimulation on the treated area after scrambler therapy. It is called as modulation of peripheral and central nervous system. In the previous study, the reason why tactile allodynia of PHN patients' or neuropathic pain of cancer pain was disappeared was suggested that scrambler therapy may be associated with modulation mechanism of peripheral and central nervous systems (6, 11, 12).

After the scrambler therapy is completed, two patients did not improve pain score. They are metastatic bone pain patients. The error of performance by pain specialist can be the first reason. Metastatic bone pain did not follow as dermatome. And metastatic cancer patients usually complaint their pain pattern with diffuse and ambiguous. Improper position of electrodes did not role as artificial sensory neurons and degrade an accuracy of sensory modulation process. The second reason was patient's nerve injury. Two patients had metastasis in the cervical vertebra and invasion of spinal nerve root. Since the device triggers A-delta fibers and C fibers, thus directly pain ways, if information is degraded or doesn't flow correctly, the effect was decreased. Perception anomalies can reduce or even prevent synthetic information of "non-pain" to flow.

Metastatic bone pain combined neuropathic as well as nociceptive factors. it does not exist as a single entity, but instead may be considered as a combination of background pain and breakthrough pain (16). Both pain mechanism were not proved clearly yet (17). This complicated cancer pain pathophysiology

indicates the need for the use of non-opioid analgesics or other intervention technique in combination with opioids (18, 19). In this study, regular opioid consumption for background pain control did not change remarkably. But dose and frequencies of rescue opioid reduced significantly compared before treatment for all patients (Table 3). It means that "no-pain" information modulation using scrambler therapy helps breakthrough pain rather than background pain. Breakthrough pain has been defined in recent guidelines as "transitory exacerbations of pain that occur on a background of stable pain otherwise adequately controlled by around-the-clock opioid therapy (20)." And uncontrolled breakthrough pain was reported that it could make worse individual quality of life, for example, functional impairment, depression and relationship failure (21, 22). Pain scrambler therapy reduced the frequency of breakthrough pain and made patient's life quality much better. It was revealed through improvement of BPI in all aspects which were related quality of life except normal work.

However, there are some limitations in this study. First, sample selection and lack of blinding might have produced a bias in favor of the scrambler therapy. All patients who participated in experiments are referred to control pain from oncological medical part when oncologists failed cancer pain management with medication. As mentioned by previous studies (10), some of changes could be due to placebo, regression to the mean over time, and recovery. And one pain specialist who applied electrodes to patients was not blinded. So it is difficult to argue the effect of scrambler therapy without control group. Second, the number of patients who take part in this study was limited. Because the patients had not enough much life span and their general condition was poor. Four patients lost follow-up during the period of this study. Two patients died and other 2 patients failed to visit hospital everyday for 2 weeks because of their general condition. Third, the patients group was not homogenous so the effects could be different. For example, one patient with spine metastatic cancer pain had chemotherapy with docetaxel previously. So it is not clear whether bone metastatic cancer pain or not.

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Conclusion

Even though there were no control groups and limited patients, the magnitude of the pain relief effect was significant compared with the initiation of the scrambler therapy. This study was explored various pain relief effects using NRS, 7-pointed Likert scale and 5-pointed satisfaction scales. As result, breakthrough pain was more effectively relieved than background pain after scrambler therapy. However, it is necessary to apply selectively the scrambler device for cancer pain patients who had no nerve injury and perception anomaly. The mechanism that the pain scrambler creates synthetic action potential similar to endogenous nerve stimulation and relieves pain has not been proven yet. Further evaluation will be needed to explain the mechanism.

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Table 1. Cancer pain syndromes.

Syndrome	Prevalence	Therapies proven to give relief	Unrelieved
Chemotherapy-induced peripheral neuropathy(24)	25-35%	Nothing proven	No specific data but substantial
Postmastectomy pain	20%(25),47%(26), 13%(27)	Gabapentin, opiates	No specific data but substantial
Postherpetic neuropathy(28)	Not reported	Gabapentin, opiates, dorsal root ganglion block	No specific data but substantial
Postthoracotomy neuropathy (29)	24-60%	Paravertebral nerve block, intercostal block, opiates	No specific data but substantial
Postradiation pain (30)	Depends on site and dose	Gabapentin, opiates	No specific data but substantial
Metastatic bone pain	Not reported	Not reported	No specific data but substantial

Table 12. Patient's demography.

Patient group	Post RT pain (n = 1)	Bone metastasis pain (n = 5)	CINP (n = 4)	Postherpetic pain (n = 1)
Gender				
Male	0	3	2	0
Female	1	2	2	1
Location	Trunk	Extremity, trunk	Extremity	Trunk
Type of symptoms	Pain	Pain and numbness	Pain	Pain
Type of cancer	Breast cancer	Multiple myeloma, Prostate cancer, Gastric cancer	Multiple myeloma, Prostate cancer	Gastric cancer

RT = Radiotherapy; CINP = Chemotherapy induced neuropathic pain; PT =Pharmacologic therapy.

Table 3. Comparison of NRS, Consumption of rescue opioid dose and BPI at baseline and after 4weeks from baseline.

	Baseline	After 4weeks from baseline	Z statistic	P value
NRS	7 (6,8)	3 (3,6)	-2.608	0.009
Consumption of rescue opioid	10 (10,15)	5 (0,10)	-2.585	0.01
BPI				
General activity	9 (8,10)	10 (8,10)	-2.527	0.012
Mood	10 (7,10)	10 (8,10)	-2.823	0.005
Walking ability	10 (8,10)	8 (6,10)	-2.539	0.011
Normal work	10 (9,10)	7 (4,8)	-1.841	0.066
Relationship	5 (3,8)	6 (5,8)	-2.375	0.018
Sleep	9 (5,10)	5 (4,10)	-2.814	0.005
Enjoyment of life	5 (2,6)	8 (5,10)	-2.415	0.016

Data are presented as median (25percentile, 75 percentile).
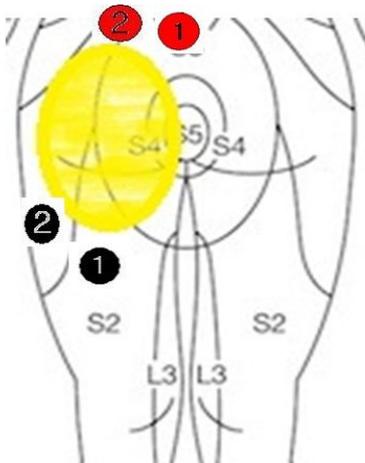
Figure 1. Scrambler device (11).

Figure 2. Electrodes are applied around the painful skin area during the scrambler therapy.

Yellow circle = Painful skin area; Black and red circle = electrodes; L3, S2, 3, 4, 5 = Dermatome.

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│   Participants recruitment   │
│         (n = 15)             │
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               │
               ▼
┌─────────────────────────────┐
│    Eligibility assessment    │
│         (n = 15)             │
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┌─────────────────────────────┐
│     Scrambler therapy        │
│  5 times / week for 2 weeks  │                ┌─────────────────────┐
│         (n = 15)             │                │   Lost to follow up  │
└─────────────────────────────┘                │       (n = 4)        │
               │────────────────────────────── └─────────────────────┘
               ▼
┌─────────────────────────────┐
│    Follow-up evaluation      │
│  Baseline and at week 1, 2, 4. │
│         (n = 11)             │
└─────────────────────────────┘
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               ▼
┌─────────────────────────────┐
│     Statistical analysis     │
│         (n = 11)             │
└─────────────────────────────┘
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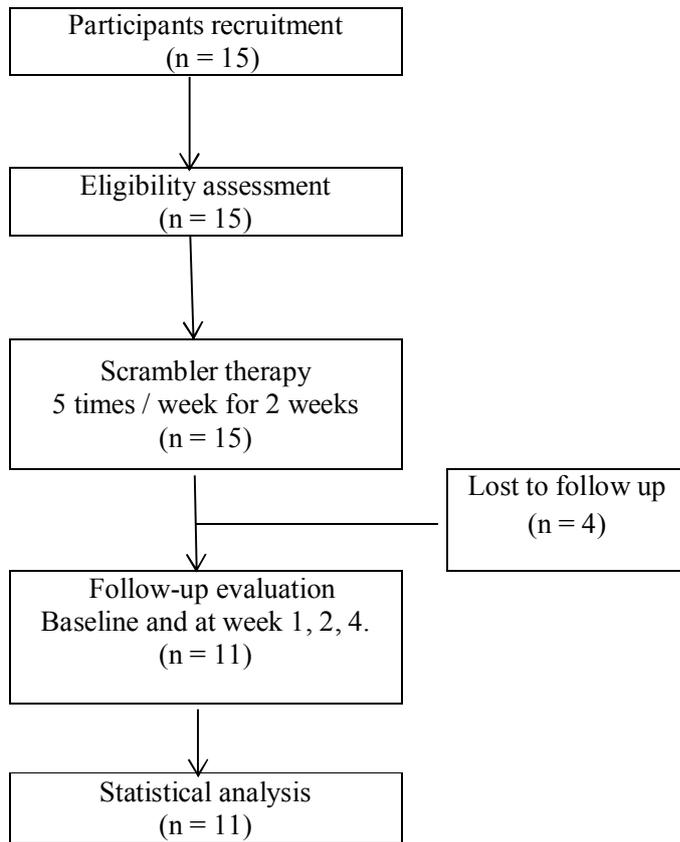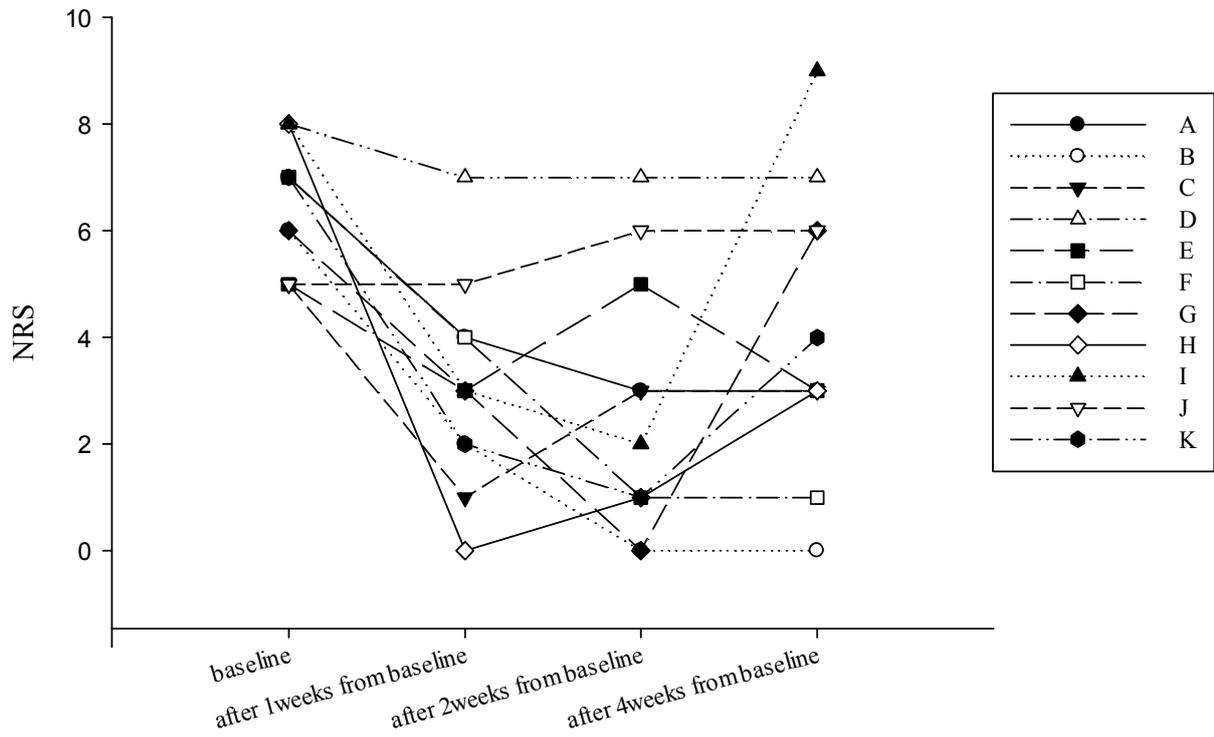
Figure 3. Follow-up flow chart.

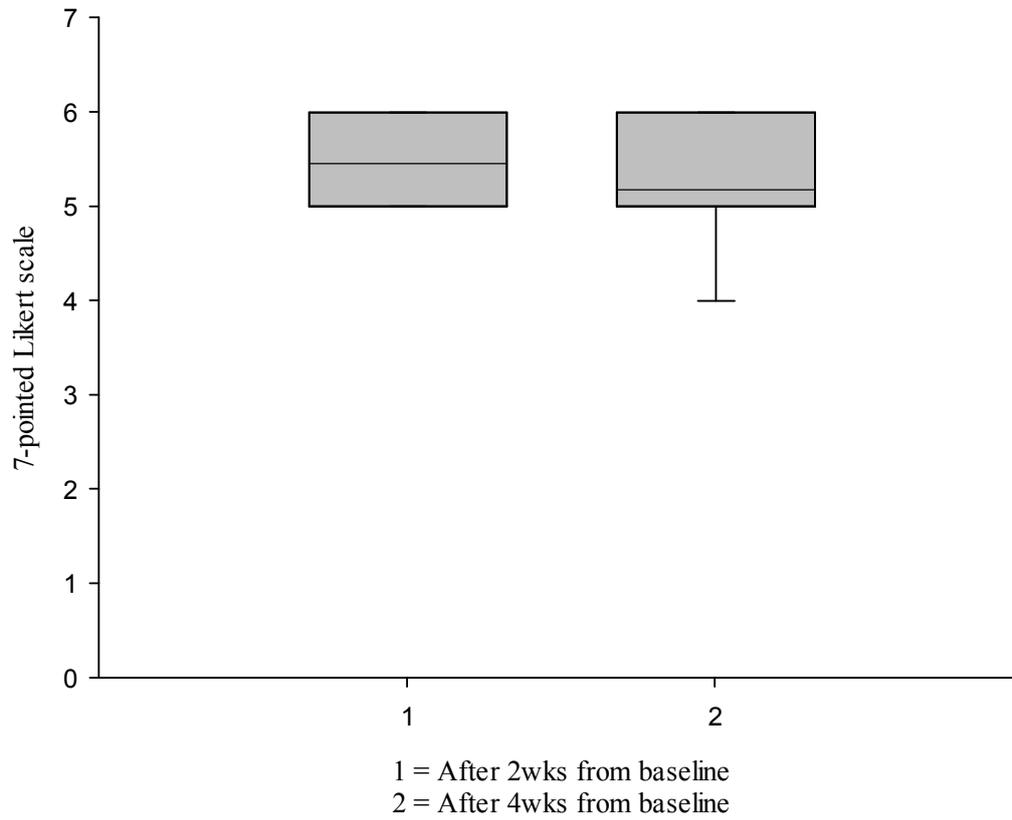Figure 4. Numeric rating scale (NRS) score of all patients during the scrambler therapy.

Figure 5. Comparison of Likert scales after 2weeks from baseline and after 4weeks from baseline; Extremely painful = 0; Completely pain relief = 7.
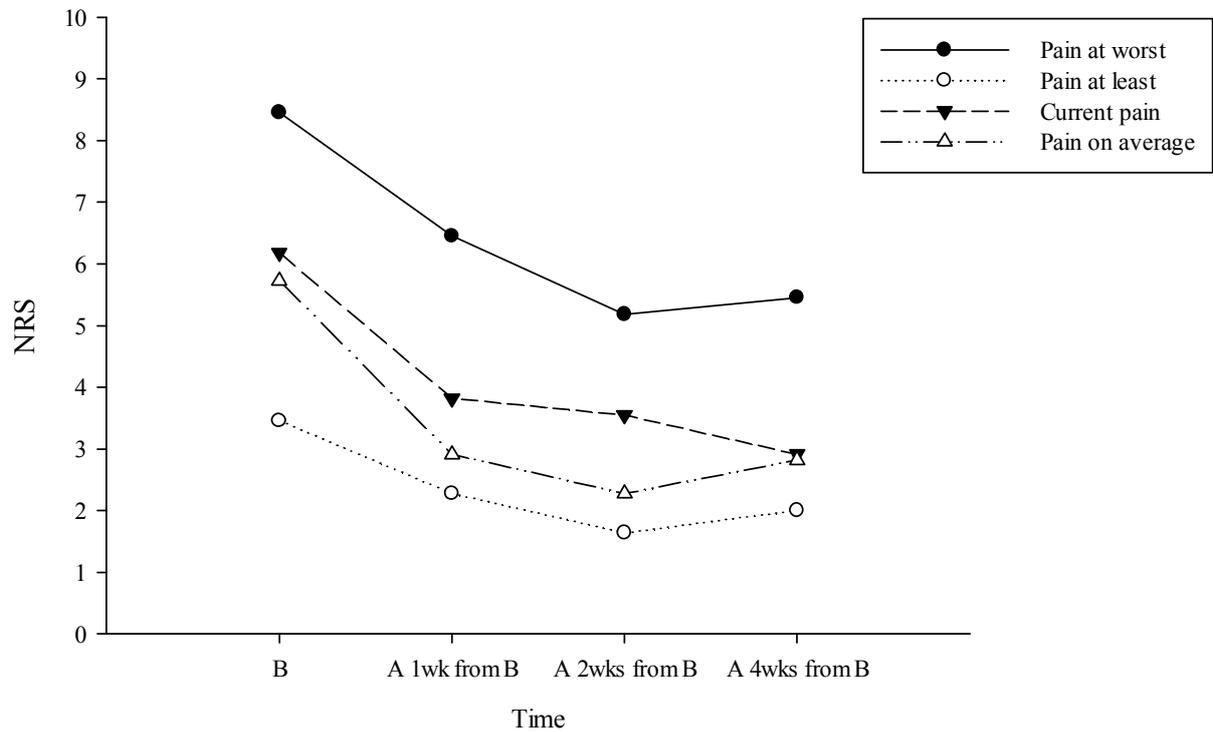
Figure 6. BPI questions 3, 4, 5, and 6; summary from baseline to subsequent week (average of all patients). Baseline and from 1week to 4weeks after scrambler therapy; A = After, B = Baseline.