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Randomized Trial

The Efficacy of Scrambler Therapy for the Management of Head, Neck and Thoracic Cancer Pain: A Randomized Controlled Trial

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Background: Pain is still a common feature in all types of cancers including head and neck and thoracic cancer. Neuromodulatory techniques have gained popularity over opioids in recent times because of the risks associated with chronic opioid therapy. There are no clinical trials evaluating the efficacy of scrambler therapy (ST) for the management of pain due to head and neck and thoracic cancer.

Objective: This trial was undertaken to evaluate the efficacy of scrambler therapy (ST) for pain relief and to assess the possible effect of ST on the dosage of opioids in patients suffering from cancer pain.

Study design: A randomized control trial (RCT) was performed.

Setting: The trial was conducted at the Pain and Palliative Care Unit of the Dr. B.R. Ambedkar Institute Rotary Cancer Hospital of All India Institute of Medical Sciences, New Delhi, India.

Method: Forty patients were included in each of the 2 arms, control and Intervention. In both arms, patients were given pain management drugs. In the intervention group, patients additionally received 10 consecutive sessions of ST with one follow-up after 7 days. A numeric rating scale (NRS-11) was used to measure pain. Drug dosage was also recorded.

Results: Overall, pain decreased in both arms. However, pain decreased more in the intervention arm as compared to the control arm. The total change in the mean score of the NRS-11 from baseline to follow-up was 3.1 and 6.19 in the control and ST arms, respectively. Differences between pain scores in both arms became significant from day 3 onwards. Mean morphine dose was significantly lower in the intervention arm from day 7 onwards.

Limitations: The study followed the patients until one week after the last treatment session and encouraged patients to return for treatment if their pain returned to previous levels within 10 days. Moreover, patients in the control arm received the standard of care in the form of pharmacological treatment but did not receive either transcutaneous electrical nerve stimulation (TENS) or a sham (placebo) procedure.

Conclusions: The trial showed that ST is an effective treatment for the management of pain due to head and neck and thoracic cancer. On the basis of this study, the use of ST for the management of refractory cancer pain in head and neck and thoracic cancer is recommended.

Key words: Calmare Therapy, cancer pain, noninvasive pain treatment, numerical rating scale, opioids, RCT, scrambler therapy, TENS

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Pain continues to be a common issue for all type of cancers. In head and neck and thoracic cancer, too, hard-to-control pain is a frequent problem. Head and neck cancer (HNC) is a heterogeneous group of malignant tumors that develop from the nasal cavity, oral cavity, oropharynx, hypopharynx, and larynx, and pain is a frequent problem. Treatment for HNC is primarily localized, involving surgical resection, radiotherapy, and/or chemotherapy. HNC patients may face disease-related and treatment-related complications, which makes the pain mechanism complex (1). A significant effort is still to be made to achieve ideal pain control and better daily functioning in patients suffering with HNC (1).

Patients suffering from thoracic cancer, too, have specific pain management needs. Two common cancers of thoracic origin are lung cancer and breast cancer. Multiple studies show that, in lung cancer patients, holistic pain and symptom management leads to longer survival, higher satisfaction among patients and caregivers, and even decreased health care costs (2). Breast cancer is another common cancer of thoracic origin (3). Unfortunately, pain management often remains insufficient or ineffective in breast cancer patients (4). Moreover, for many breast cancer patients, pain and symptoms do not end with effective treatment of the disease (5).

In these cancers, pain is often managed with opioids. Many cancer patients and cancer survivors require chronic opioid therapy that lasts for more than 3 months (6). Opioids provide a favorable risk-benefit ratio and are very effective (7). Even though serious adverse events involving the use of opioids can occur, these medications are still largely prescribed in the majority of patients for relief from cancer pain (8). However, it is quite challenging to find a proper balance between suitable opioids while minimizing the risks associated with chronic opioid therapy (6,9).

Therefore, the importance of nonpharmacological modalities of treatment will increase with time as more of these modalities become available and are proven effective (6). In this context, transcutaneous electrical nerve stimulation (TENS) and scrambler therapy (ST) are neuromodulatory techniques that are more frequently used (10,11). ST is a relatively new method that was introduced in the early 2000s. It has been used for the management of pain, including cancer pain. Pain relief associated with ST has been found significant and long-lasting among various groups of patients (6). Therefore, it could be a good choice for patients for whom pharmacological pain management has brought insufficient relief.

ST uses a device that produces 16 different electrical current signals. These signals simulate normal nerve action potential (12). Correct positioning of the electrodes around the area of pain will normally lead to immediate pain relief (12,13). ST replaces the pain signals with nonpain signals before they reach the central nervous system. The device produces sensations that appear to be self-generated and replace pain sensation with nonpain (14). Each ST session takes about 30 to 45 minutes. Most patients experience pain relief from the first sitting itself, and pain relief continues thereafter. Pain relief is expected to persist for weeks to months after treatment (15).

A recent review of the literature has shown that ST is very effective for the management of chronic pain, including cancer pain (15). There is even evidence that ST reduces drug intake. In a multicenter retrospective analysis of the efficacy of ST for the management of chronic pain, ST resulted in significant reduction of pain medication (16). A randomized control trial (RCT) on the effectiveness of ST for chronic neuropathic pain also showed that ST led to significant reductions in pain medication dose (12).

A few studies point towards the potential efficacy of ST for the management of pain in patients suffering from HNC and thoracic cancer. A case study showed the positive effect of ST in a patient suffering from breast cancer-related lymphedema. The pain was reduced without an increase in lymphedema (17). Similarly, when Smith et al (18) administered ST to 3 patients suffering from chronic postmastectomy pain, they observed a 75% reduction in pain that lasted several months. There was also a prospective study of 219 patients, including 17 breast cancer patients and 12 lung cancer patients. The results showed a statistically significant reduction in pain from the beginning of treatment through 2 weeks of treatment and 2 weeks of follow-up ($P < .0001$) (19). In a single-arm trial on the efficacy of ST for pain induced by bone and visceral metastases it was found that in all patients, including 5 patients suffering from lung cancer, one breast cancer, and one HNC, pain was reduced by at least 50% and 89% on average. Pain relief lasted 7.7 ± 5.3 weeks after treatment (20).

While these available studies do show the potential effectiveness of ST for the management of cancer pain, the evidence, including that for HNC and thoracic cancer, has some important shortcomings. Only some prospective studies, case studies, and just one pilot RCT have been conducted on patients suffering from

cancer-related pain. The latter trial included a relatively small number of cancer patients suffering from chemotherapy-induced peripheral neuropathy (CIPN). According to this study, only a few patients reported enough pain relief, and, overall, ST was not found to be very effective for the management of pain (21). This finding markedly contrasts with that of other studies that overwhelmingly showed a beneficial effect of ST (15). For example, among nonpharmacological interventions, ST appears to be most promising with significant decreases in levels of CIPN (22). The treatment given for pain relief using the scrambler device seems to decrease pain among CIPN patients (23). Further evidence is required to evaluate the efficacy of ST, particularly for the management of cancer pain.

Considering the persistent need for this kind of evidence in the form of RCTs, we decided to conduct such a trial based on the available pilot studies and single-arm trials showing the promising effects of ST on cancer patients in general and HNC and thoracic cancer patients in particular. The clinical trial that is described here aims to assess the efficacy of ST for the management of pain caused by HNC and thoracic cancer. The primary objective of this trial was the evaluation of efficacy of ST for pain relief. The secondary objective of this trial was to assess the possible effect of ST on the intake of morphine and tramadol.

Methods

This was an open-label parallel design RCT. Permuted block randomization was used for equal allocation of patients between both arms. The study was conducted in the Palliative Care Unit of Dr. B.R.A. IRCH, All India Institute of Medical Sciences, New Delhi (India). It was approved by the ethical committee (Institutional Review Board) of the institute. The study was registered in the clinical trial registry India (CTRI). The CTRI acknowledgement number is Ref/2015/08/009516. The sample size for this study was calculated using a superiority margin of 4 units with an observed difference of 5.06 and a standard deviation (SD) of 1.5. With 90% power, 5% significance level, and 10% dropout, the minimum sample size had to be 76, i.e., 38 patients in each arm. A total of 80 patients were included in the study with 40 each in the intervention and control arms. The diagrammatic flow chart for the randomization is shown in Fig. 1. Patients were

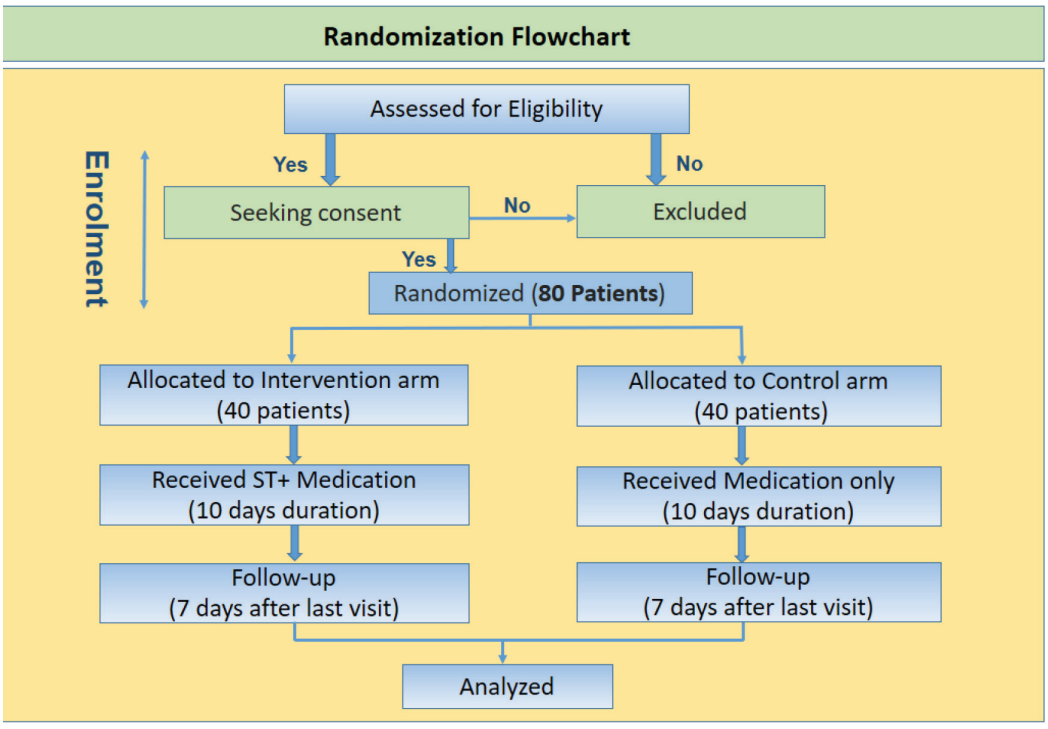

Fig. 1. *Randomization flow chart.*

randomized into the arms using a computer-generated random sequence. Accordingly, 80 cards were printed designating patients to either the control arm or the intervention arm. These cards were inserted into envelopes by the statistician (Vishwajeet Singh), which were closed, sealed, and handed over in the computer-generated random order to the investigator who provided ST (Komal Kashyap). Patients undergoing treatment at the Palliative Care Unit who met the inclusion criteria were presented with the possibility to participate in the trial by the treating physicians. Patients who met the inclusion criteria and expressed interest in participating were referred to one of the investigators who explained the study's purpose and procedures in detail. Patients were enrolled in the study after providing written consent to participate in the study and being determined eligible according to the inclusion and exclusion criteria as given below in Table 1.

In both arms, patients were given pain management drugs in the Palliative Care Unit of Dr. B.R.A. IRCH AIIMS, as per standard protocol based on the World Health Organization (WHO) analgesic ladder. The outcome measure physical pain was assessed with the Numeric Rating Scale (NRS-11), a numeric scale on which patients indicate pain intensity by mentioning a number ranging from 0 to 10 with 0 meaning "no pain" and 10 meaning "worst possible pain" (24). In both arms, pain was assessed 5 days a week (Monday to Friday) for 2 weeks and again at follow-up 7 days later. Pain medication was adjusted if required. For patients in the intervention arm, pain was assessed each day prior to ST therapy.

In the intervention group, in addition to the standard treatment, patients received ST for 40 minutes on each of these days. The site of maximum pain was determined with the dermatome. Subsequently, electrical stimulus was applied and the intensity was increased gradually. The intensity of the electrodes was set to the maximum value at which the patient did not feel discomfort. The placement of electrodes was individualized according to site of pain and dermatome involved.

For both arms, in addition to the NRS-11 score, the prescribed dose of oral opioids was recorded every day of therapy as well. For each patient, the total dose (mg) per day was calculated for morphine and tramadol. The doses of morphine and tramadol were compared between the 2 arms. Since there are no clear generally accepted guidelines for equivalent dose calculation between tramadol and morphine, both were compared separately. After each ST session and the follow-up session, patients were questioned regarding possible side effects.

The statistical analysis was performed as per the standards of analyzing RCTs. All categorical variables were described by absolute/relative frequency distribution with percentage, and quantitative variables were described by mean (standard deviation)/median (quartile range). To find the association between qualitative independent variables, the chi-square test/Fisher exact test was used. To find out the difference of quantitative variables between the arms, the t test/Wilcoxon test was used. P values less than .05 were considered statistically significant. STATA/SE Version 14.2 (StataCorp LP, College Station, TX) was used for the statistical analysis.

Results

A total of 80 patients were randomized into the 2 arms with 40 patients in each arm. One patient was lost to follow-up in the intervention arm after the ninth day of therapy. The patient stated that he had complete relief of pain and found further treatment redundant. No clinically relevant baseline differences were observed between the patients in both arms. Details of patients' demographic and clinical characteristics are given in Tables 2 and Table 3, respectively.

The mean (± SD) NRS-11 pain scores at the beginning of the first session were 6.57 (± 0.75) in the control arm and 6.65 (± 0.83) in the ST arm. This difference was

Table 1. *Inclusion and exclusion criteria*

Inclusion Criteria	Exclusion Criteria
Diagnosed with head and neck or thoracic (breast, lung) cancer Experiencing persistent pain of oncological origin, with an average NRS-11 more than 4. 18-70 years of age Able to complete the questionnaire by themselves or with assistance Life expectancy more than 3 months	History of an allergic reaction or previous intolerance to TENS Use of an investigational agent e.g., (neurolytic block, TENS, or enrolled in other study) for pain control concurrently or less than 30 days Pacemaker user Unwilling or unable to follow protocol requirements Pregnant women and nursing women Significant psychiatric illness that may affect ability to participate in a research study (e.g., mania, psychosis, schizophrenia)

Abbreviations: NRS-11, Numeric Rating Scale; TENS, transcutaneous electrical nerve stimulation

Table 2. *Demographic characteristics*.

Variables	Control (n = 40)	Intervention (n = 40)	Total (n = 80)	*P*
Age				
Mean (SD)	47.4 (11.22)	52 (9.98)	49.7 (10.80)	.06
Median (quartile-range)	50 (36-55.5)	50 (46.5-60)	50 (40-59)	
Gender				
Men (n (%))	26 (65.00)	27 (67.50)	53 (66.25)	.81
Women (n (%))	14 (35.00)	13 (32.50)	27 (33.75)	
BMI (kg/m^2)				
Mean (SD)	22.80 (3.98)	24.93 (5.37)	23.87(4.81)	.05
Median (quartile-range)	22.77 (20.33-25.23)	24.16 (21.48-27.44)	23.48 (20.79-26.47)	

Abbreviations: BMI, body mass index; SD, standard deviation

Table 3. *Clinical and cancer-related details*.

Variables	Control (n = 40)	Intervention (n = 40)	Total (n = 80)	*P*
Cancer Type				
Head and neck	23 (57.50)	22 (55.00)	45 (56.25)	.82
Thoracic	17 (42.50)	18 (45.00)	35 (43.75)	
cT Stage				
T1	0	0	0	.53
T2	8 (20.00)	6 (15.00)	14(17.50)	
T3	19 (47.50)	24 (60.00)	43 (53.75)	
T4	13(32.50)	10 (25.00)	23 (28.75)	
cN Stage				
N0	16 (40.00)	17 (42.50)	33 (41.25)	.20
N1	13 (32.50)	16 (40.00)	29 (36.25)	
N2	11 (27.50)	5 (12.50)	16 (20.00)	
N3	0 (0.00)	2 (05.00)	2 (2.50)	
cM Status				
M0	32 (80.00)	33 (82.50)	65 (81.25)	.77
M1	8 (20.00)	7 (17.50)	15 (18.75)	
Family history of CA				
No	39 (97.50)	35 (87.50)	74 (92.50)	.20
Yes	1 (02.50)	5 (12.50)	6 (7.50)	
Recurrence				
No	38 (95.00)	36 (90.00)	74 (92.50)	.67
Yes	2 (05.00)	4 (10.00)	6 (7.50)	
Type of pain				
Neuropathic	5 (12.50)	12 (30.00)	17 (21.25)	.06
Mixed	35 (87.50)	27 (67.50)	62 (77.50)	
Nociceptive	0 (0.00)	1 (02.50)	1 (1.25)	
Surgery				
No	23 (57.5)	20 (50.00)	43 (53.75)	.28
Completed	17(42.50)	20 (50.00)	37 (46.25)	
Chemotherapy				
No	15 (37.50)	16 (40.00)	31 (38.75)	.75
Ongoing	6 (15.00)	8 (20.00)	14 (17.50)	
Completed	19 (47.50)	16 (40.00)	35 (43.75)	
Radio therapy				
No	18 (45.00)	18 (45.00)	36 (45.00)	.71
Ongoing	1 (02.50)	3 (07.50)	4 (5.00)	
Completed	21 (52.50)	19 (47.50)	40 (50.00)	

Abbreviations: CA, cancer; cT, clinical tumor; cN, clinical nodes; cM, clinical metastases

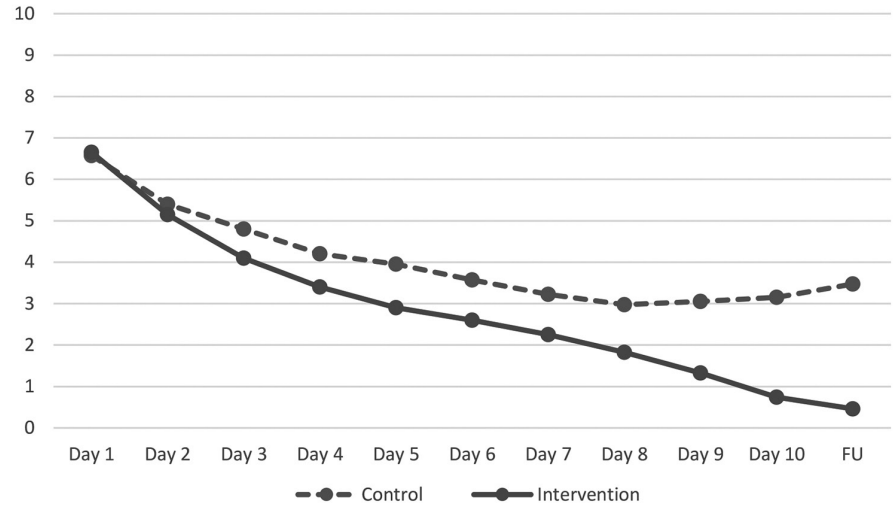

Fig. 2. *Mean pain scores in control and intervention arm*

Table 4. *Pain score (NRS-11) – details.*

NRS-11	Control	Intervention	*P*
Day 1 Mean (SD) Median (quartile-range)	6.57 (.75) 6 (6-7)	6.65 (.83) 7 (6-7)	.67
Day 2 Mean (SD) Median (quartile-range)	5.40 (1.01) 5 (5-6)	5.15 (1.25) 5 (4.5-6)	.33
Day 3 Mean (SD) Median (quartile-range)	4.80 (1.04) 5 (4-5)	4.1 (1.39) 4 (3-5)	.01
Day 4 Mean (SD) Median (quartile-range)	4.20 (1.043) 4 (3.5-5)	3.40 (1.41) 3.5 (2.5-4)	.01
Day 5 Mean (SD) Median (quartile-range)	3.95 (0.87) 4 (3-5)	2.90 (1.39) 3 (2-4)	< .001
Day 6 Mean (SD) Median (quartile-range)	3.57(0.96) 3(3-4)	2.60 (1.30) 3 (2-3)	< .001
Day 7 Mean (SD) Median (quartile-range)	3.22(0.97) 3 (3-4)	2.25 (1.33) 2 (1-3)	< .001
Day 8 Mean (SD) Median (quartile-range)	2.97 (1.07) 3 (2-3)	1.82 (1.24) 2 (1-2.5)	< .001
Day 9 Mean (SD) Median (quartile-range)	3.05 (1.15) 3(2-4)	1.32 (1.07) 1 (0-2)	< .001
Day 10 Mean (SD) Median (quartile-range)	3.15 (1.00) 3 (3-3.5)	0.74 (0.75) 1 (0-1)	< .001
Follow-up Mean (SD) Median (quartile-range)	3.47 (1.12) 3 (3-4)	0.46 (0.55) 0 (0-1)	< .001

not statistically significant ($P = .67$). Figure 2 shows the evolution of pain scores in both the arms. Overall, pain decreased in both arms. However, from the second day of treatment onwards, there was a difference in mean pain scores with patients in the control arm experiencing slightly more pain than patients in the intervention arm. The difference in mean pain increased throughout the treatment and follow-up period. From the eighth day of treatment onwards, mean pain in the control arm ceased to decrease and slightly increased. This evolution further magnified the difference in mean pain score.

The differences in mean pain scores between both arms were compared using the 2-sample t test or Wilcoxon rank sum test depending upon the distribution of the data. On the first and second day, the differences in NRS-11 scores were not statistically significant. However, from the third day onwards, the pain scores became significantly lower in the ST arm as compared to the control arm. On the tenth day, the mean NRS-11 score was 3.15 (± 1.00) in the control arm, and 0.74 (± 0.75) in the ST arm ($P < .001$). The total change in mean NRS-11 score was 3.42 in the control arm and 5.91 in the ST arm. A significant difference was maintained at the time of follow-up measurement. The mean NRS-11 pain score on

each day and the comparison between both arms are shown in Table 4.

A chi-square test showed that there was no significant association between the numbers of patients receiving tramadol or morphine in both arms. Initially, 56 patients (Control = 29, Intervention = 27) received morphine and 24 patients (Control = 11, Intervention = 13) received tramadol (P = .63). At baseline, the average daily dose of morphine was 66.25 mg (± 58.76). In the control arm, it was 65.86 mg (± 52.07) and in the intervention arm it was 66.67 mg (± 66.21) (P = .97). For tramadol, the average daily dose was 239.58 mg (± 113.23). The t tests showed no significant differences in dose of tramadol between both arms at any day in the trial (Table 5). Figure 3 shows that the mean dose of tramadol stayed nearly flat in both arms throughout the trial and that the differences in mean dose between both arms were limited. However, in the intervention arm, a reduction in the dose of morphine was observed from day 5 onwards, as can be seen in Table 6 and Figure 4. The difference in the prescribed dose of morphine in both arms became significant from day 7 onwards (Table 6). At day 7, the dose of morphine was reduced to 48.27 (± 29.63) from 66.67 (± 66.21) in the intervention arm, whereas it increased to 73.10 (± 54.06) from 65.86 (± 52.07) in the control arm. In the intervention arm, one of the patients who had been on morphine since the beginning of the trial went without morphine from day 5 onwards. The detailed distributions of doses of tramadol and morphine have been presented in the tables below (Table 5 and 6). Assessment of side effects revealed no adverse effects of ST in any of the enrolled patients.

Table 5. *Distribution of dose of tramadol between arms.*

Tramadol	Control	Intervention	P
Day 1			
n (%)	11 (45.83)	13 (54.17)	
Mean (SD)	245.45 (112.20)	234.61 (114.35)	.98
Median (quartile-range)	200 (150-400)	200 (150-300)	
Day 2			
n (%)	11 (45.83)	13 (54.17)	
Mean (SD)	245.45 (117.16)	215.38 (106.81)	.68
Median (quartile-range)	200 (150-400)	200 (150-300)	
Day 3			
n (%)	11 (45.83)	13 (54.17)	
Mean (SD)	245.45 (117.16)	215.38 (106.81)	.68
Median (quartile-range)	200 (150-400)	200 (150-300)	
Day 4			
n (%)	11 (47.83)	12 (52.17)	
Mean (SD)	245.45 (117.16)	225 (105.52)	.90
Median (quartile-range)	200 (150-400)	200 (150-300)	
Day 5			
n (%)	11 (47.83)	12 (52.17)	
Mean (SD)	245.45 (117.16)	212.5 (113.07)	.55
Median (quartile-range)	200 (150-400)	175 (150-300)	
Day 6			
n (%)	11 (50.00)	11 (50.00)	
Mean (SD)	245.45 (117.16)	200 (109.45)	.33
Median (quartile-range)	200 (150-400)	150 (100-300)	
Day 7			
n (%)	11 (50.00)	11 (50.00)	
Mean (SD)	245.45 (117.16)	200 (109.54)	.33
Median (quartile-range)	200 (150-400)	150 (100-300)	
Day 8			
n (%)	11 (50.00)	11 (50.00)	
Mean (SD)	245.45 (117.16)	200 (109.54)	.33
Median (quartile-range)	200 (250)	150 (200)	
Day 9			
n (%)	11 (50.00)	11 (50.00)	
Mean (SD)	259.09 (122.10)	200 (109.54)	.21
Median (quartile-range)	200 (150-400)	150 (100-300)	
Day 10			
n (%)	11 (52.38)	10 (47.62)	
Mean (SD)	250 (114.02)	190 (122.02)	.15
Median (quartile-range)	200 (150-400)	125 (100-300)	
Follow-up			
n (%)	11 (57.89)	8 (42.11)	
Mean (SD)	250 (114.02)	218.75 (119.34)	.42
Median (quartile-range)	200 (150-400)	225 (100-300)	

Discussion

This trial indicates that ST may be an effective treatment for many cases in which the mainstay drugs, opioids, are ineffective. ST even seems to offer substantial pain relief without the dreaded adverse effects of opioids. As in previous studies (10,20,25,26), no adverse effects were observed in patients who had received ST. At the same time, case studies and small single-arm trials have shown that ST reduces cancer pain (10,18,27-29).

Yet, the available evidence on the efficacy of ST for the management of cancer pain is contradicted by the trial that was conducted by Smith et al (21), who compared differences in pain experience between a group of cancer patients receiving ST and a group of patients receiving a sham procedure. Interestingly, the

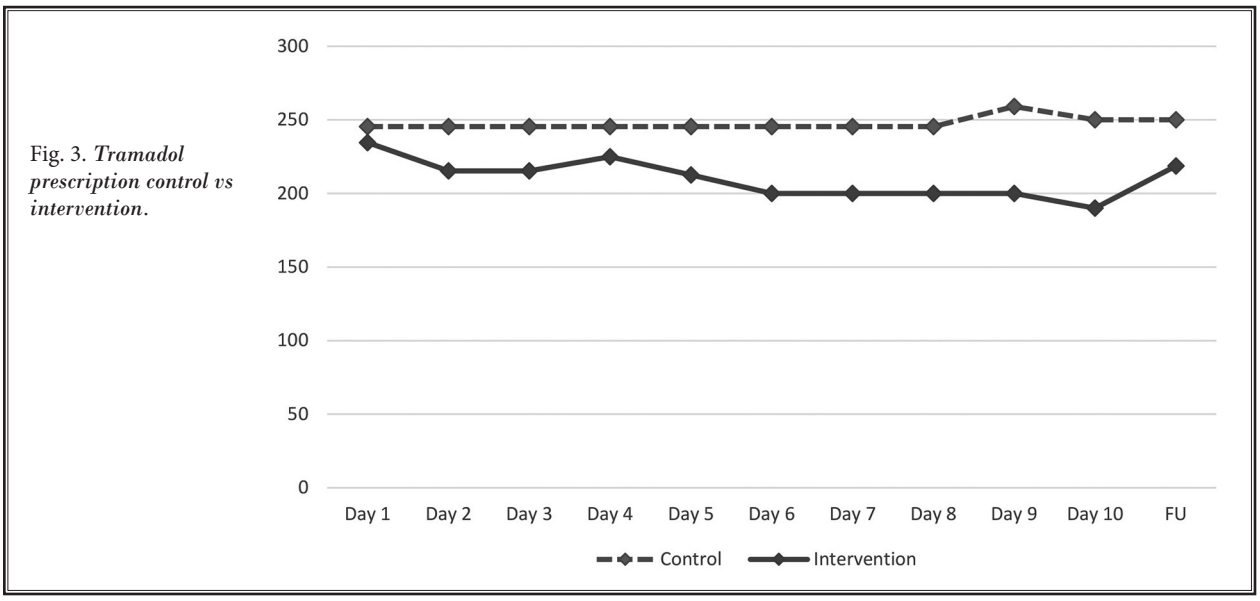

Fig. 3. *Tramadol prescription control vs intervention.*

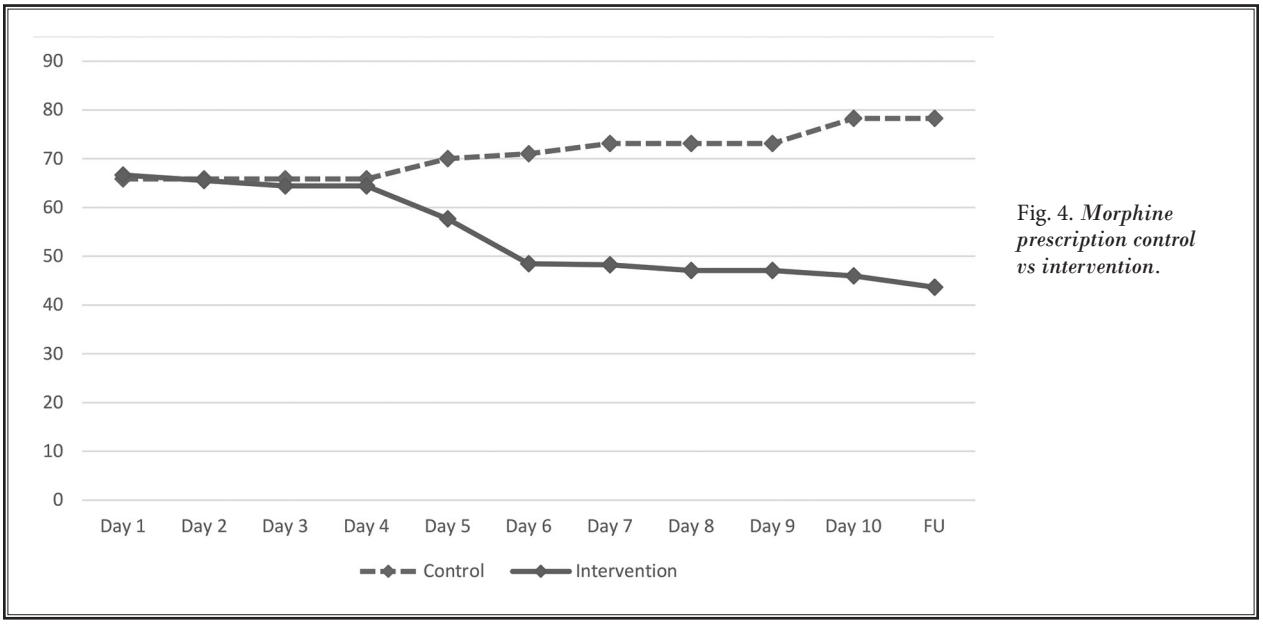

Fig. 4. *Morphine prescription control vs intervention.*

investigators did not observe statistically significant differences in pain experience between the groups. Their observation sharply contrasts with the findings of the current trial, which showed significant differences in pain between the intervention arm and the control arm from the third day of therapy onwards. Smith et al offer various explanations as to why there was no significant association. The most obvious explanation is the fact that their research design included a sham procedure, which the trial described in this study did not include. However, as Smith et al concede, there may have been significant issues with the sham design which may have impacted the results. Smith et al argue that the lack of a significant difference between arms might actually have been due to the way in which they designed the sham procedure, which might have provided effective treatment even though the electrodes had been placed incorrectly. Moreover, as indicated

above, there is another important difference between the current trial and that of Smith et al. The current trial included a substantially larger group of study subjects, 80, whereas Smith et al included 35 patients. It is possible that the absence of significant effect in the trial of Smith et al was due to the very small sample size. Even though the larger sample of the current study may provide a more reliable answer regarding the efficacy of ST in cancer pain, in the future, robustly designed larger randomized controlled trials should be conducted in order to add further evidence and reduce the possibility of confounding factors. A last difference between the current trial and that of Smith et al is that Smith et al studied one particular kind of pain: chemotherapy-induced peripheral neuropathy, while the current study focused on various kinds of pain caused by 2 types of cancer: HNC and thoracic cancer. This type of cancer pain requires different placement of the ST channels and, therefore, the results of the 2 trials are not exactly comparable. Thus, the current trial provides a valuable piece of evidence pointing towards the effectiveness of ST for the treatment of refractory cancer pain.

The current trial indicates that ST has a positive effect on physical pain reduction and drug intake, without any side effects. This is a significant finding considering the adverse effects that pain medications and particularly opioids can have. The main side effects of opioids include sedation, dizziness, constipation, physical dependence, tolerance, nausea, constipation, pruritus, respiratory depression, and opioid-induced hyperalgesia (8). Nevertheless, opioids continue to be widely prescribed in the majority of patients despite so many side effects, including sometimes death (8).

There has been evidence that ST reduces drug intake in non-cancer pain. The case described by Congedi et al (30) of a child with acute mixed pain refractory to pharmacological treatment showed progressive drug reduction after pain reduction and drugs were prescribed when needed. In the study by Ghatak et al (31) on the effectiveness of ST in 8 patients suffering from lower back pain, all patients except one found the studied system of therapy much more acceptable than pills, needles, or even long supervised exercise sessions. ST resulted in significant reduction of pain medication in a multicenter retrospective analysis by Compagnone et al (16). They found that 55 out of 77 patients went without opioids by the end of the therapy sessions. Stronger evidence for the drug-reducing effect of ST can be found in the RCT by Marineo et al (12). They showed that ST led to significant reductions in pain medication dose. The results of the trial that have been described in this article add to this

Table 6. *Distribution of dose of morphine between arms.*

Morphine	Control	Intervention	*P*
Day 1			
n (%)	29 (51.79)	27 (48.21)	
Mean (SD)	65.86 (52.07)	66.67 (66.21)	.97
Median (quartile-range)	30 (30-80)	60 (30-90)	
Day 2			
n (%)	29 (51.79)	27 (48.21)	
Mean (SD)	65.86 (52.07)	65.56 (66.06)	.97
Median (quartile-range)	30 (30-80)	60 (30-60)	
Day 3			
n (%)	29 (51.79)	27 (48.21)	
Mean (SD)	65.86 (52.07)	64.44 (66.41)	.82
Median (quartile-range)	30 (30-80)	30 (30-60)	
Day 4			
n (%)	29 (51.79)	27 (48.21)	
Mean (SD)	65.86 (52.07)	64.44 (66.41)	.82
Median (quartile-range)	30 (30-80)	30 (30-60)	
Day 5			
n (%)	29 (52.73)	26 (47.27)	
Mean (SD)	70 (52.03)	57.69 (39.73)	.37
Median (quartile-range)	60 (30-80)	30 (30-60)	
Day 6			
n (%)	29 (52.73)	26 (47.27)	
Mean (SD)	71.03 (51.50)	48.46 (29.49)	.06
Median (quartile-range)	60 (30-80)	30 (30-60)	
Day 7			
n (%)	29 (52.73)	26 (47.27)	
Mean (SD)	73.10 (54.06)	48.27 (29.63)	.04
Median (quartile-range)	60 (30-90)	30 (30-60)	
Day 8			
n (%)	29 (52.73)	26 (47.27)	
Mean (SD)	73.14 (54.67)	47.11 (29.74)	.02
Median (quartile-range)	60 (30-90)	30 (30-60)	
Day 9			
n (%)	29 (52.73)	26 (47.27)	
Mean (SD)	73.14 (54.67)	47.11 (29.74)	.02
Median (quartile-range)	60 (60)	30 (30-60)	
Day 10			
n (%)	29 (52.73)	26(47.27)	
Mean (SD)	78.27(59.10)	45.96(28.57)	.01
Median (quartile-range)	60(30-90)	30(30-60)	
Follow-up			
n (%)	29 (52.73)	26 (47.27)	
Mean (SD)	78.27 (59.10)	43.65 (24.48)	.01
Median (quartile-range)	60 (60)	30 (30-60)	

evidence by providing evidence from a larger sample of patients. Moreover, the fact that, in this trial, ST was administered along with pain medication indicates that the therapy can be even more effective if it is combined with medication for treatment of cancer pain. On the other hand, it is important to note that the difference in tramadol between both arms was not significant at any time during the trial. This is most likely because in the hospital were the trial was conducted, following WHO guidelines, morphine and tramadol are prescribed differently. Morphine is a strong opioid whereas tramadol is a weak opioid (32). As a consequence, when pain becomes less, physicians at the hospital where the trial was conducted reduce morphine first before reducing tramadol. Therefore, it is within the line of expectation that tramadol would be reduced less significantly than morphine.

This study compared the standard of care (medication therapy) with the standard of care plus ST. The fact that the control intervention did not include either a placebo (sham procedure) or TENS might be seen as a limitation. However, given the paucity of data on the efficacy of ST for the management of cancer pain, establishing ST's efficacy over mere standard of care is relevant and important, particularly for HNC and thoracic cancer pain where no prior trial data exist. Moreover, as the study by Smith et al has shown, sham-procedures for ST that will not influence findings are hard to design. A first possibility for a sham procedure is to only put electrodes and provide no stimulation to patients. However, since patients would feel no stimulation, they would be able to figure out that they had been assigned to the sham-procedure group. A second possibility it to place the electrodes incorrectly as done by Smith et al. However, as Smith et al argued, this might still lead to some improvement in pain. A third possibility is to give stimulation outside the therapeutic threshold, but this procedure, too, might provide some pain relief as the researcher would need to come close enough to the therapeutic threshold lest the patient become aware that he or she had been assigned to the sham-procedure group.

Besides the absence of a sham procedure, this study was not blinded. However, due to our research design, the risk of bias due to lack of blinding was very limited. The primary outcomes of our study were reduction in NRS-11 score and minimization of drug intake. The NRS-11 score was recorded based on feedback from the patient. The physical therapist who registered pain scores administered the assessments in the same standard way to each patient. Drugs were prescribed by physicians who were aware of whether or not the patients were receiving ST, but who were not directly involved in the study.

Also, with only one follow-up one week after the 10 therapy sessions, the current study could not establish the long-term effectiveness of ST for the treatment of pain caused by HNC and thoracic cancer. However, at follow-up, all patients were informed that they could contact the investigators if the pain became worse within 10 days after follow-up. In that case, further ST treatment would be provided to patients in the intervention arm free of cost. None of the patients contacted the investigators with pain complaints. This is indicative of the potential long-term effectiveness of ST.

Conclusion

This is the first RCT conducted on HNC and thoracic cancer patients treated with ST for pain management, while only limited prior literature on the effectiveness of ST for the management of cancer pain is available. The current study is the first of its kind to investigate this relatively new approach for the management of cancer pain for HNC and thoracic cancer patients. Using a robust research design, this RCT on the effectiveness of ST included a sufficiently large number of patients. The trial showed that ST is an effective treatment modality for the management of pain due to HNC and thoracic cancer. It reduced pain effectively and decreased the use of opioids. On the basis of this study, use of ST for the management of refractory cancer pain in HNC and thoracic cancer is recommended.

Author Contributions

Komal Kashyap designed the study protocol along with Sushma Bhatnagar, administered ST to the research subjects, registered the data, and contributed to data analysis. Komal Kashyap wrote the first draft of the manuscript, incorporated changes, and approved the final version. Vishwajeet Singh contributed to the draft of the research protocol, analyzed the data, provided feedback on drafts of the manuscript, and approved the final version of the manuscript. Seema Mishra provided feedback throughout the research process and approved the final version of the manuscript. Sada Nand Dwivedi oversaw data analysis, provided feedback on drafts of the manuscript, and approved the final version of the manuscript. Sushma Bhatnagar designed the study protocol and provided revision for intellectual content throughout the research process. She provided

feedback on drafts of the manuscript and approved the final version.Disclosure/Conflict of Interest

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The authors declare that they have no conflicts of interest.

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References

1. Cho SF, Rau KM, Shao YY, et al. Patients with head and neck cancer may need more intensive pain management to maintain daily functioning: A multicenter study. *Support Care Cancer* 2019; 27:1663-1672.
2. Ferrell B, Sun V, Hurria A, et al. Interdisciplinary palliative care for patients with lung cancer. *J Pain Symptom Manage* 2015; 50:758-767.
3. Hebert JR, Ghumare SS, Gupta PC. Stage at diagnosis and relative differences in breast and prostate cancer incidence in India: Comparison with the United States. *Asian Pac J Cancer Prev* 2006; 7:547-555.
4. Brawley OW, Smith DE, Kirch RA. Taking action to ease suffering: Advancing cancer pain control as a health care priority. *CA Cancer J Clin* 2009; 59:285-289.
5. Tasmuth T, von Smitten K, Hietanen P, et al. Pain and other symptoms after different treatment modalities of breast cancer. *Ann Oncol* 1995; 6:453-459.
6. Chwistek M. Recent advances in understanding and managing cancer pain. *F1000Res* 2017; 6:945.
7. Christo PJ, Mazloomdoost D. Cancer pain and analgesia. *Ann N Y Acad Sci* 2008; 1138:278-298.
8. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician* 2008; 11:S105-S120.
9. Smith TJ, Saiki CB. Cancer pain management. *Mayo Clin Proc* 2015; 90:1428-1439.
10. Coyne PJ, Wan W, Dodson P, et al. A trial of scrambler therapy in the treatment of cancer pain syndromes and chronic chemotherapy-induced peripheral neuropathy. *J Pain Palliat Care Pharmacother* 2013; 27:359-364.
11. Cruccu G, Aziz TZ, Garcia-Larrea L, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007; 14:952-970.
12. Marineo G, Iorno V, Gandini C, et al. Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: Results of a pilot, randomized, controlled trial. *J Pain Symptom Manage* 2012; 43:87-95.
13. Smith TJ, Coyne PJ, Parker GL, et al. Pilot trial of a patient-specific cutaneous electrostimulation device (MC5-A Calmare(R)) for chemotherapy-induced peripheral neuropathy. *J Pain Symptom Manage* 2010; 40:883-891.
14. Marineo G. Inside the scrambler therapy, a noninvasive treatment of chronic neuropathic and cancer pain: From the gate control theory to the active principle of information. *Integr Cancer Ther* 2019; 18:1534735419845143.
15. Majithia N, Smith TJ, Coyne PJ, et al. Scrambler therapy for the management of chronic pain. *Support Care Cancer* 2016; 24:2807-2814.
16. Compagnone C, Tagliaferri F. Chronic pain treatment and scrambler therapy: A multicenter retrospective analysis. *Acta Biomed* 2015; 86:149-156.
17. Lee JS. Efficacy of scrambler therapy on breast cancer-related lymphedema. *J Phys Ther Sci* 2018; 30:1370-1371.
18. Smith T, Cheville AL, Loprinzi CL, et al. Scrambler therapy for the treatment of chronic post-mastectomy pain (cPMP). *Cureus* 2017; 9:e1378.
19. Ricci M, Fabbri L, Pirotti S, et al. Scrambler therapy: What's new after 15 years? The results from 219 patients treated for chronic pain. *Medicine (Baltimore)* 2019; 98:e13895.
20. Notaro P, Dell'Agnola CA, Dell'Agnola AJ, et al. Pilot evaluation of scrambler therapy for pain induced by bone and visceral metastases and refractory to standard therapies. *Support Care Cancer* 2016; 24:1649-1654.
21. Smith TJ, Razzak AR, Blackford AL, et al. A Pilot randomized sham-controlled trial of MC5-A scrambler therapy in the treatment of chronic chemotherapy-induced peripheral neuropathy (CIPN). *J Palliat Care* 2019; 825859719827589.
22. Al-Atiyyat N, Obaid A. Management of peripheral neuropathy induced by chemotherapy in adults with cancer: A review. *Int J Palliat Nurs* 2017; 23:13-17.
23. Cathcart-Rake EJ, Hilliker DR, Loprinzi CL. Chemotherapy-induced neuropathy: Central resolution of a peripherally perceived problem? *Cancer* 2017; 123:1898-1900.
24. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. *J Pain Symptom Manage* 2011; 41:1073-1093.
25. Ricci M, Pirotti S, Scarpi E, et al. Managing chronic pain: Results from an open-label study using MC5-A Calmare(R) device. *Support Care Cancer* 2012; 20:405-412.
26. Lee SC, Park KS, Moon JY, et al. An exploratory study on the effectiveness of "Calmare therapy" in patients with cancer-related neuropathic pain: A pilot study. *Eur J Oncol Nurs* 2016; 21:1-7.
27. Pachman DR, Weisbrod BL, Seisler DK, et al. Pilot evaluation of scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. *Support Care Cancer* 2015; 23:943-951.
28. Kashyap K, Joshi S, Vig S, et al. Impact of scrambler therapy on pain management and quality of life in cancer patients: A study of twenty cases. *Indian J Palliat Care* 2017; 23:18-23.
29. Tomasello C, Pinto RM, Mennini C, et al. Scrambler therapy efficacy and safety for neuropathic pain correlated with chemotherapy-induced

peripheral neuropathy in adolescents: A preliminary study. *Pediatr Blood Cancer* 2018; 65:e27064.

30. Congedi S, Spadini S, Di Pede C, et al. Use of scrambler therapy in acute paediatric pain: A case report and review of the literature. *Case Rep Pediatr* 2016; 2016:2628919.
31. Ghatak RK, Nandi SN, Bhakta A, et al. Prospective study of application of biological communication (cybernatics) in management of chronic low back pain – a preliminary report. *Nepal Med Coll J* 2011; 13:257-260.
32. World Health Organization staff, World Health Organization. *Cancer Pain Relief: With a guide to opioid availability*. Geneva, World Health Organization, 1996.