Scrambler therapy efficacy and safety for neuropathic pain correlated with chemotherapy-induced peripheral neuropathy in adolescents: A preliminary study

Caterina Tomasello¹∗ | Rita Maria Pinto² | Chiara Mennini³ | Elena Conicella⁴ | Francesca Stoppa¹ | Umberto Raucci⁴∗

¹Anaesthesia and Intensive Care Department, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
²Haematology Oncology Department, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
³Scientific Direction, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy
⁴Pediatric Emergency Department, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy

Correspondence
Umberto Raucci, Emergency Department, Bambino Gesù Children’s Hospital, IRCCS, Sant’ Onofrio Square 4, Rome, 00165, Italy.
Email: umberto.raucci@opbg.net

∗Caterina Tomasello and Umberto Raucci contributed equally to the work.

Abstract

Purpose: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of chemotherapy, in need of effective treatment. Preliminary data support the efficacy of scrambler therapy (ST), a noninvasive cutaneous electrostimulation device, in adults with CIPN. We test the efficacy, safety, and durability of ST for neuropathic pain in adolescents with CIPN.

Patients and Methods: We studied nine pediatric patients with cancer and CIPN who received ST for pain control. Each patient received 45-min daily sessions for 10 consecutive days as a first step, but some of them required additional treatment.

Results: Pain significantly improved comparing Numeric Rate Scale after 10 days of ST (9.22 ± 0.83 vs. 2.33 ± 2.34; P < 0.001) and at the end of the optimized cycle (EOC) (9.22 ± 0.83 vs. 0.11 ± 0.33, P < 0.001). The improvement in quality of life was significantly reached on pain interference with general activity (8.67 ± 1.66 vs. 3.33 ± 2.12, P < 0.0001), mood (8.33 ± 3.32 vs. 2.78 ± 2.82, P < 0.0005), walking ability (10.00 vs. 7.56 ± 2.24 vs. 2.67 ± 1.41, P < 0.001), and relations with people (7.89 ± 2.03 vs. 2.11 ± 2.03, P < 0.0002; Lansky score 26.7 ± 13.2 vs. 10 days of ST 57.8 ± 13.9, P < 0.001; 26.7 ± 13.2 vs. EOC 71.1 ± 16.2, P < 0.001).

Conclusion: Based on these preliminary data, ST could be a good choice for adolescents with CIPN for whom pain control is difficult. ST caused total relief or dramatic reduction in CIPN pain and an improvement in quality of life, durable in follow-up. It caused no detected side effects, and can be retrained successfully. Further larger studies should be performed to confirm our promising preliminary data in pediatric patients with cancer.

KEYWORDS
adolescent, cancer, electrical pain stimulation, neuropathic pain, peripheral neuropathy, quality of life, scrambler therapy

1 INTRODUCTION

As advances in chemotherapy result in improved survival for many patients, a chief concern both during and after treatment is the presence of chemotherapy-related neurological side effects.¹² Chemotherapy-induced peripheral neuropathy (CIPN), sensory and motor nerve damage or dysfunction, can produce severe neuropathic pain (NP) occurring in a “stocking-glove” distribution and gait impairment that represent a common and serious clinical problem in many patients receiving cancer treatment.³ CIPN is often a cumulative dose-dependent side effect of several cytotoxic agents, resulting from the administration of platinum drugs, taxanes, vinca alkaloids, thalidomide, and new classes of antineoplastic agents such as epothilones, proteasome inhibitors, and immunotherapy.⁴–⁹ Moreover, confounding the understanding of the effects of these agents

Abbreviations: ALL, acute lymphoblastic leukemia; CIPN, chemotherapy-induced peripheral neuropathy; EOC, end of optimized cycle; NP, neuropathic pain; NRS, Numeric Rating Scale; QOL, quality of life; ST, scrambler therapy; TENS, transcutaneous electrical nerve stimulation
on the peripheral nervous system in children with cancer is the fact that many chemotherapy regimens used to treat childhood cancer include multiple agents that have potential for peripheral or central neurotoxicity.\textsuperscript{10} Severe CIPN has been reported in about 3\textendash{}7% of treated patients with single agents and up to 38% in those treated with multiple chemotherapeutic agents.\textsuperscript{11} In a meta-analysis, CIPN prevalence in adults was 68.1% when measured in the first month after chemotherapy, 60.0% at 3 months, and 30% at 6 months or more.\textsuperscript{7} Although NP is often discussed as a feature in adult cancer treatment, only recently has it become an area of active investigation in pediatric populations. The knowledge of global incidence of CIPN in pediatric cancer is lacking in literature. Nevertheless, a report on the incidence of neuropathic vincristine-related pain in children being treated for acute lymphoblastic leukemia (ALL) has revealed that 35% of patients experienced one episode of NP during treatment with 16% having at least one recurrence.\textsuperscript{12} Another study reported that the overall frequency of CIPN in pediatric oncology patients was 18.3%; tumor-specific CIPN rates were 18.9% for ALL, 9.4% for lymphoma, 17.9% for Wilms tumor, and 23.7% for brain tumor.\textsuperscript{13} Recently, it was reported that over 85% of a cohort of children with ALL, lymphoma, and solid tumors exposed to potentially neurotoxic agents had evidence of CIPN while on therapy; although some children demonstrated recovery from CIPN in the first 6 months after cessation of treatment, 40.3% had residual impairment based on pediatric modified total neuropathy score.\textsuperscript{10}

Despite the availability of various pharmacological and nonpharmacological treatments, the existing literature reveals the difficulty of controlling pain in patients with CIPN.\textsuperscript{8,9,14,15} No drugs capable of preventing the occurrence of CIPN or ameliorating its long-term course are available, and chemotherapy schedule modification is often required to limit its severity, which could potentially prevent patients from receiving the most effective treatment for cancer. Moreover, symptomatic therapy is often largely ineffective in reducing CIPN symptoms,\textsuperscript{16} and in the aftermath of treatment, it can have a profound effect on the quality of life (QOL) during survivorship.\textsuperscript{17} In recent years, scrambler therapy (ST), a novel electro-analgesia device, demonstrated encouraging and positive preliminary results in NP; in fact, various trials evaluated the possible role of ST in the treatment of multiple forms of NP in adults,\textsuperscript{18\textendash{}36} and some studies included exclusively patients with CIPN.\textsuperscript{20,28,31} A single pediatric experience described the efficacy of ST for acute pain treatment in a 12-year-old female.\textsuperscript{37} No data are present in literature with regard to the efficacy and applicability of ST on NP in CIPN pediatric population.

Our prospective preliminary study was performed to investigate the efficacy, applicability, and safety of ST on NP in adolescents with CIPN, with pain unresponsive to conventional drug treatment. Our specific primary objective was to estimate the efficacy of ST on pain control, evaluated with 11 points Numeric Rating Scale (NRS). Secondary specific objectives evaluated the following: the efficacy of ST on QOL, the weaning-off of combined drug, the safety of ST, the long-term effects, and the applicability of the device in pediatric patients, considering the need for continued communication between the enrolled patient and the physician.

### 2 METHODS

ST is a novel approach to pain control, approved as safe by the Federal Drug Administration, which attempts to relieve pain by providing "non-pain" information to the cutaneous nerves to block the effect of pain information. The device consists of a multiprocessor apparatus able to stimulate five artificial neurons by the application of surface electrodes on skin overlying the painful areas; it synthesizes 16 different types of nerve action potentials similar to endogenous ones, assembles them into sequences, and uses algorithms to determine a patient-specific cutaneous electrostimulation to reduce pain sequences.\textsuperscript{23} Electrodes similar to electrocardiogram gel pads were applied on the skin beyond the pain-affected area or on the most pain-free distal area. The opposing gel electrode was placed above the painful area, within the same dermatome. The current is regulated, and there are "shutoffs" automatically with power overloads.

### 3 PATIENTS

After obtaining approval from the local ethics committee and after receiving formal consent prior to ST from the child and parent, nine patients with cancer and chemotherapy-related NP, previously unresponsive to pharmacological treatment (from one to four drugs), were treated by a physician (CT or UR) with extensive expertise and experience in ST, according to a single protocol at the Bambino Gesù Children's Hospital. Patients were recruited from the Hematology and Oncology Department of the same hospital over a duration of 2 years. All enrolled children received instructions about the device and the complete procedure. Inclusion criteria included patients with age under 18 years, life expectancy greater than 3 months, presence of chemotherapy-related NP, NP not related to other nonchemotherapy factors, average daily pain score greater than 5 evaluated by NRS (0 is no pain and 10 is worst pain possible), absence of neurological cognitive impairment, and cooperating patients with the capability to indicate the grade, site, and variation of pain during ST. All patients completed chemotherapy before ST.

Patients were not eligible if they were enrolled in another pain protocol, had an adverse reaction to the use of electrodes in the past or skin conditions preventing the application of electrodes, had any form of implantable electrostimulator or other medical metal device such as pacemakers, defibrillator, vascular clips or stents, or cardiac valve, had a history of epilepsy or cerebral damage, and/or had an implanted drug delivery system.

Each patient received a 45-min daily session for up to 10 consecutive days as the first step, but given the minimal risk and cost involved in ST, we subsequently elected to treat patients who required additional treatment with flexible treatment schedules. Patients had the option to stop treatments for lack of significant benefit. Treatments were also stopped prior to 10 days if pain resolved. The intensity of the electric stimulus used to modulate and transmit synthetic nonpain information varied from patient to patient. Adaptation was achieved on the basis of the criterion of maximum intensity individually perceptible by the
Notes on biostatistics and interpretation of data

Statistics analysis

TABLE 1  Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Primary cancer</th>
<th>Disease status</th>
<th>Antineoplastic therapy</th>
<th>Pain site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>M</td>
<td>ALL</td>
<td>III CR</td>
<td>TACL</td>
<td>Lower limbs</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>F</td>
<td>ALL</td>
<td>III CR</td>
<td>Blinatumomab</td>
<td>Right leg—foot</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>M</td>
<td>ALL</td>
<td>II CR</td>
<td>CLOVE, VCR, DepoCyte</td>
<td>Lumbar spine, lower limbs</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>F</td>
<td>NB</td>
<td>I stage in CR</td>
<td>Topotecan</td>
<td>Left lower limb</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>F</td>
<td>HD</td>
<td>II stage in PR</td>
<td>Brentixumab, BEACOPP, fludarabine</td>
<td>Legs—feet</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>M</td>
<td>APL</td>
<td>III CR</td>
<td>Systemic cytarabine, DepoCyte</td>
<td>Lower limbs</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>M</td>
<td>ALL</td>
<td>II CR</td>
<td>TACL, CLOVE</td>
<td>Legs—feet</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>M</td>
<td>AML</td>
<td>I CR</td>
<td>DepoCyte, etoposide</td>
<td>Feet</td>
</tr>
<tr>
<td>9</td>
<td>13</td>
<td>F</td>
<td>ALL</td>
<td>IV CR</td>
<td>Blinatumomab, CLOVE, fludarabine</td>
<td>Lower limbs</td>
</tr>
</tbody>
</table>

M, male; F, female; ALL, acute lymphoid leukemia; NB, neuroblastoma; HD, Hodgkin disease; APL, acute promyelocytic leukemia; AML, acute myeloid leukemia; CR, complete remission; PR, partial response; Blinatumomab, Ab anti-CD 19; DepoCyte, liposomal cytarabine; BEACOPP, vincristine, etoposide, procarbazine; TACL, therapeutic advances in childhood leukemia, (vincristine + bortezomib); VCR, vincristine; CLOVE, clofarabine, etoposide.

We evaluated the degree of pain using the 0–10 NRS in various established situations to estimate the variation in QOL. We recorded the following for each patient during each daily session of ST treatment: (1) average pain in the previous 24 hr, (2) current pain, (3) pain during treatment, (4) pain after treatment, (5) pain interference with sleep, (6) pain interference with movement ability, and (7) pain interference in relations with other people. In addition to pain assessment, we used the Lansky performance status scale (score 10–100) to determine the global functional status of the studied patients, recording the value during each ST daily session and in the follow-up.

We also evaluated the reduction in the need for painkillers; the percentage decrease of the drugs was calculated compared to the dose at entry of ST (100 %), then reassessed at the end of the optimized cycle (EOC).

3.1 Notes on biostatistics and interpretation of data

ST standard cycle treatment lasts an average of 10 applications, which is modified to the following conditions: “Early termination”, it is expected to be terminated early when 24 hr after the last treatment the patient is free of pain; and “cycle extension”, a cycle extension beyond 10 treatments is expected (average duration) when (a) it is necessary to wean analgesic drugs during treatment with ST, as the patient is still suffering from pain, and (b) at the end of the standard cycle (10 applications), there is not complete relief from pain and in subsequent treatments, significant improvement continues to occur. The NRS data referring to the average cycle duration (10 treatments), and those relating to the EOC and to the patient’s needs are analyzed.

3.2 Statistical analysis

Descriptive summary statistics including means, standard deviations, and percentages formed the basis of analysis for the current study. The statistical significance was measured by a two-tailed paired t-test and repeated measures analysis of variance. A P-value of less than 0.05 was considered statistically significant.

4 RESULTS

A total of nine consecutive patients with CIPN were enrolled with an average age of 14 years and 2 months (range 12–17 years, five males and four females). Patients had a history of a variety of cancer types and were exposed to several cytotoxic agents (Table 1), with a strong relation between exposure to the inflicting chemotherapy agent and the onset of NP. In addition, NP could not be related to other nonchemotherapy factors contributing to NP.

All patients presented with chemotherapy-related NP involving the lower extremities (Table 1). Before starting the treatment with ST, our patients were treated with pharmacological therapy (from one to four drugs), without complete relief (Table 1). No patients received transcutaneous electrical nerve stimulation (TENS), invasive therapy, or other nonconventional therapy. All children were receiving a variety of analgesic drugs (opioids, gabapentin, amitriptyline, and duloxetine, variously combined) at study entry, which were tapered off during or after ST, if possible (Table 2).

Characteristics of the patients including age, gender, type of cancer, antineoplastic therapy, chemotherapy-related NP localization, utilized analgesic or anticonvulsant therapy with doses for each medication, and effects of ST are summarized in Tables 1 and 2.

In all the studied patients, the pain, scored using the 0–10 NRS scale, declined or disappeared. The number of consecutive sessions of ST necessary to obtain the best results varied between seven and 21 (Table 1). Particularly, pain was significantly improved, comparing NRS at the beginning of ST to that at day 10 of ST (9.22 ± 0.83 vs. 2.33 ± 2.34; P < 0.001) and at the EOC (9.22 ± 0.83 vs. 0.11 ± 0.33; P < 0.001) (Figure 1). Specifically, with ST tailored for each patient (Supplementary Figure S1), four patients completed ST within 10 days, four within 14 days, and one patient required 21 days.

The Lansky score significantly improved (from 10 up to 100) (baseline 26.7 ± 13.2 vs. 10 days of ST 57.8 ± 13.9, P < 0.001; baseline
**TABLE 2** Effects of scrambler therapy on Numeric Rate Scale, Lansky score, and pain medication use

<table>
<thead>
<tr>
<th>Pt</th>
<th>Pharmacologic treatment at the start of ST</th>
<th>Onset of NP with respect to exposure to chemotherapy</th>
<th>Start of ST with respect to onset of NP (days)</th>
<th>NRS at start of ST</th>
<th>NRS at the end of ST</th>
<th>Lansky score at start of ST</th>
<th>Lansky score at the end of ST</th>
<th>Duration of ST (days)</th>
<th>Pharmacologic treatment at the end of ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Opioids 0.03 mg/kg/hr Gabapentin 0.32 mg/kg/day Amitriptyline 0.43 mg/kg/day</td>
<td>18 days</td>
<td>38</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>80</td>
<td>21</td>
<td>Suspended</td>
</tr>
<tr>
<td>2</td>
<td>Opioids 0.02 mg/kg/hr Gabapentin 0.24 mg/kg/day Amitriptyline 0.40 mg/kg/day</td>
<td>During chemotherapy</td>
<td>58</td>
<td>20</td>
<td>0</td>
<td>70</td>
<td>8</td>
<td>Suspended</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Opioids 0.03 mg/kg/hr Gabapentin 0.20 mg/kg/day</td>
<td>5 days</td>
<td>26</td>
<td>9</td>
<td>0</td>
<td>40</td>
<td>80</td>
<td>13</td>
<td>Suspended</td>
</tr>
<tr>
<td>4</td>
<td>Opioids 0.02 mg/kg/hr Gabapentin 0.20 mg/kg/day</td>
<td>6 days</td>
<td>22</td>
<td>8</td>
<td>0</td>
<td>30</td>
<td>90</td>
<td>11</td>
<td>Reduced opioids by 66% Suspended gabapentin</td>
</tr>
<tr>
<td>5</td>
<td>Opioids 0.015 mg/kg/hr Gabapentin 0.25 mg/kg/day</td>
<td>During chemotherapy</td>
<td>38</td>
<td>9</td>
<td>0</td>
<td>30</td>
<td>60</td>
<td>7</td>
<td>Suspended</td>
</tr>
<tr>
<td>6</td>
<td>Opioids 0.04 mg/kg/hr Gabapentin 0.12 mg/kg/day</td>
<td>9 days</td>
<td>19</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>40</td>
<td>7</td>
<td>Suspended</td>
</tr>
<tr>
<td>7</td>
<td>Opioids 0.02 mg/kg/hr Gabapentin 0.21 mg/kg/day</td>
<td>During chemotherapy</td>
<td>24</td>
<td>10</td>
<td>0</td>
<td>50</td>
<td>90</td>
<td>13</td>
<td>Suspended</td>
</tr>
<tr>
<td>8</td>
<td>Opioids 0.04 mg/kg/hr Gabapentin 0.23 mg/kg/day Amitriptyline 0.4 mg/kg/day Duloxetine 1.25 mg/kg/day</td>
<td>During chemotherapy</td>
<td>22</td>
<td>9</td>
<td>0</td>
<td>20</td>
<td>60</td>
<td>14</td>
<td>Unvaried opioids Reduced gabapentin by 55% Suspended other drugs</td>
</tr>
<tr>
<td>9</td>
<td>Opioids 0.03 mg/kg/hr Gabapentin 0.17 mg/kg/day</td>
<td>34 days</td>
<td>44</td>
<td>8</td>
<td>0</td>
<td>30</td>
<td>70</td>
<td>8</td>
<td>Suspended</td>
</tr>
</tbody>
</table>

Patient no. 1 needed another ST cycle (5 day treatments) after 7 months from the first treatment cycle; the patient was still without pain after 1 year.

Pt, patient; ST, scrambler therapy; NP, neuropathic pain; NRS, Numeric Rate Scale; EOC, end of cycle that represents the end of all consecutive treatment with scrambler therapy.

26.7 ± 13.2 vs. EOC 71.1 ± 16.2, P < 0.001; after 10 days of ST 57.8 ± 13.9 vs. EOC 71.1 ± 16.2, P < 0.05 (Figure 2). In comparing the value at the beginning of ST (baseline) to that at the end of ST, significant improvement in QOL was reached considering pain interference with general activity, mood, walking ability, sleep, and relations with other people (Table 3).

During treatment with ST, medications including anticonvulsants were reduced gradually until complete withdrawal, if possible (Table 2). There was a significant reduction in drug consumption (opioids, anticonvulsants). The percentage reduction of painkillers was calculated compared to the dose at entry (100 %), then reassessed at the EOC. Opiates were totally eliminated in seven out of nine cases, greatly reduced in one, and unvaried in one. Anticonvulsants were eliminated in eight of nine cases, and reduced in one. Dosage variation was statistically significant (opioids P < 0.0001; anticonvulsants P < 0.0001) (Figure 3). In all treated patients, no side effects were noted.

The follow-up was evaluated for time intervals of 1, 2, 3, and 6 months or more after the EOC. Because of disease recurrence, follow-up was reduced to 1 month in two patients, at which time pain was absent in both. The remaining seven patients continued to report no pain throughout the follow-up period. Only one patient (no. 1, Tables 1 and 2) was in need of a quick recall of a cycle of five applications at 7 months after the first treatment cycle; after 1 year from the return cycle, the patient was still without pain.

5 | DISCUSSION

Our preliminary trial supports that ST therapy may be considered a promising effective and safe treatment for pediatric patients with chemotherapy-related NP, and also for long-term pain relief and for improvement in the interference of pain with normal life.
Chemotherapy forms the backbone of treatment for many types of pediatric cancers, but a main unfortunate and potentially dose-limiting side effect of treatment is neurotoxicity, including CIPN.6,11 CIPN is a disorder that is often challenging to treat and can be associated with a prolonged course of severe pain. Affected patients frequently complain of NP in their extremities and may have signs of paresthesia, hyperesthesia, impaired vibration and joint position sensation, ataxia, myalgia, and muscle weakness. Although symptoms of CIPN can improve with treatment completion, they may persist, and currently the treatment options for CIPN are quite limited in adults.14 These limitations of pharmacological efficacy brought on the need for investigation into alternative treatment options that are effective and well tolerated, without interfering with anticancer treatments. The number of patients affected is expected to increase with use of more aggressive treatments, and as patient survival with distant metastases improves.20 Nevertheless, despite the availability of various treatments, the existing literature reveals the difficulty of controlling pain in patients with CIPN. In fact, analgesics such as opioids and nonsteroidal anti-inflammatory agents are only moderately effective in treating symptoms of neuropathy.39 Multiple other agents have failed to show clear and long-lasting benefit for the treatment of CIPN, including antidepressants such as amitriptyline,40 nortriptyline,41 and duloxetine,42 and anti-epileptic agents such as gabapentin,43 lamotrigine,44 and pregabalin.45 Only a few agents have been tested in randomized controlled trials in adults with CIPN pain with mixed results, and aside from duloxetine, none of the pharmacologic methods demonstrated therapeutic benefit for patients with CIPN.3 Far fewer trials have been done in children with cancer. The use of these agents is often based on their efficacy in the treatment of non-CIPN NP, but this does not necessarily mean that they will be helpful for CIPN-related symptoms, especially in children.4,6 These limitations of pharmacological options brought on the need for research into alternative treatment options that are effective and well tolerated, without interfering with anticancer treatments. There are also nonpharmacologic approaches to treat CIPN, including noninvasive intervention (TENS, physical and occupational therapy), invasive interventions (sympathetic nerve blocks and sympathetic neurolysis, spinal cord and peripheral nerve stimulators, and intrathecal pump), and complementary and alternative medicine.14,15 Unfortunately, specific effective curative treatments are lacking in pediatrics. In fact, clinical trials for treatment of CIPN and related symptoms are rare in pediatrics and information is gained from the adult literature.6 Nevertheless, as seen in our patients, ST may be considered a therapeutic option in patients with NP, including those of pediatric age, similar to findings in adults.20,28,31 Previous adult studies of ST for CIPN treatment reported a reduction in pain score of 35%,28 53%,31 and 59%,20 considering 10 days of treatment.

### TABLE 3
Changes in quality of life considering the variation of pain interference with general activity, mood, walking ability, sleep, and relations with other people at the beginning of scrambler therapy (baseline) and at the end of scrambler therapy cycle

<table>
<thead>
<tr>
<th>Pain interference (0: none, 10: maximum) with:</th>
<th>Baseline</th>
<th>End of ST cycle</th>
<th>Difference</th>
<th>Paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>General activity</td>
<td>8.67 ± 1.66</td>
<td>3.33 ± 2.12</td>
<td>−5.34</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Mood</td>
<td>8.33 ± 3.32</td>
<td>2.78 ± 2.82</td>
<td>−5.55</td>
<td>P &lt; 0.0005</td>
</tr>
<tr>
<td>Walking ability</td>
<td>10.00</td>
<td>2.78 ± 1.22</td>
<td>−7.22</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td>Sleep</td>
<td>7.56 ± 2.24</td>
<td>2.67 ± 1.41</td>
<td>−4.89</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Relations with other people</td>
<td>7.89 ± 2.03</td>
<td>2.11 ± 2.03</td>
<td>−5.78</td>
<td>P &lt; 0.0002</td>
</tr>
</tbody>
</table>

ST, scrambler therapy.
We experienced that some patients required an extension of ST for a more effective improvement of pain and a tailored patient schedule program could be necessary. When considering the “traditional” 10 days of treatment, we achieved significant pain reduction, which was enhanced by prolonging the treatment.

Previous studies reported that the pain improvement was limited to 1–3 months of follow-up. However, we found a sustained effect of ST over time, as reported in another study, though the small sample size and the short follow-up in some patients because of patient death were limitations. According to preliminary experience, patients can be retreated successfully and maintained. Also in our series, a patient was successfully re-treated at 7 months from original treatment and was still pain-free after 1 year from the return cycle.

Another point to consider is that QOL is the primary goal for most patients immediately after diagnosis, and becomes more important later on. Due to the rising prevalence of cancer, more patients are living with the long-term side effects of cancer and its treatment, which can have a negative impact on patients’ QOL. The general opinion is that CIPN has a negative influence on QOL, mainly because it may result in serious limitations in daily functioning, with symptoms causing disruptions in physical functioning, daily activities, enjoyment, social relationships, and work. In addition, ST was numerically associated with an improvement in QOL, as measured by the betterments in general activity, mood, walking ability, sleep, and relations with other people in the current study (Table 3). Furthermore, we observed a significant increase in QOL as measured by the Lansky scale, which lasted over time. The primary purpose of the Lansky scale was to allow physicians to evaluate a patient’s ability to survive chemotherapy for cancer. Children, who might have more trouble expressing their experienced QOL, require a somewhat more observational scoring system such as the Lansky Scale, which was introduced in 1987. These positive results in the variation of the QOL are in agreement with the studies by Coyne et al. and Pachman et al. on CIPN in adult patients. However, of note, Smith et al. reported that there was no change in the formal QOL tool that they used.

An important observation, described in adults, was that the patients who were treated later in the study had better response to treatment, possibly due to the development of expertise of the treating providers, supporting that ST may be more effective when provided by an experienced treatment team; the variability between users can be considered a potential limitation of ST. We have tried to restrict this variability between users as ST was carried out by two doctors with expertise in ST treatment.

Analgesic drug consumption (opioids and anticonvulsants) in relation to ST showed a significant reduction. It is an advantage to treat patients free from anticonvulsant therapy because their mechanism of action is opposed to that of ST. In fact, an anticonvulsant drug may prevent the stimulus from progressing along the nerve fibers while ST needs that information to be received by such fibers. Anticonvulsants, especially in high dosage, may inhibit the effectiveness of ST due to their interference with the genesis of action potentials. In our patients, opioids and anticonvulsants were tapered off during ST and finally stopped, when possible. Limitations of this study include the small sample size, the relatively short period of follow-up in some patients due to primary oncologic condition, and the lack of randomization and control with the placebo arm. Also, the use of Lansky scale could be discussed. In fact, this measure is used widely in pediatric oncology but it is limited by looking solely at functioning. As it is the best known measure to pediatric oncologists, we have included it despite its limitations.

CONCLUSION

ST may be a good choice for patients with uncontrolled neuropathic cancer pain; and on the basis of preliminary data, it appears to have benefits in the treatment of adolescent patients with chemotherapy-related NP. Our small cohort of patients, previously unresponsive to drug therapy, seemed to respond to ST with relief or dramatic reduction in NP and improvement in the QOL. Although further studies are needed in a larger patient sample to validate our preliminary findings, the use of ST may be a therapeutic option to consider in the pediatric cancer population as the “first-line treatment” for CIPN given the efficacy, safety, and durability of its effects.

ACKNOWLEDGMENT

The authors would like to sincerely thank Maureen A. Mealy, Neurology Optica Clinical Research Director and Program Manager; Senior Research Nurse, Johns Hopkins Transverse Myelitis and Multiple Sclerosis Centers; and PhD student, Johns Hopkins University, for his precious collaboration in the English editing of this manuscript without profit.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

Umberto Raucci http://orcid.org/0000-0002-4881-2038
REFERENCES


**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

**How to cite this article:** Tomasello C, Pinto RM, Mennini C, Conicella E, Stoppa F, Raucci U. Scrambler therapy efficacy and safety for neuropathic pain correlated with chemotherapy-induced peripheral neuropathy in adolescents: a preliminary study. Pediatr Blood Cancer. 2018;e27064. [https://doi.org/10.1002/pbc.27064](https://doi.org/10.1002/pbc.27064)