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ORIGINAL ARTICLE

Managing chronic pain: results from an open-label study using MC5-A Calmare® device

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Abstract
Background Despite state-of-the-art therapeutic strategies for pain, some types of chronic pain remain difficult to treat. We evaluated the effectiveness of an innovative neuromodulative approach to the treatment of chronic pain using electrical stimulus integrated with pharmacological support.
Methods The MC5-A Calmare© is a new device for patient-specific cutaneous electrostimulation which, by "scrambling" pain information with "no pain" information, aims to reduce the perception of pain intensity. We prospectively treated 73 patients with cancer- (40) and non-cancer-related (33) pain whose pain management was unsatisfactory. The primary objective of the study was to assess efficacy and tolerability of the device. Pain intensity was assessed daily with a Numerical Rating Scale (NRS) for the duration of treatment (2 weeks) and then on a weekly basis for the 2 weeks of follow-up.
Results Mean pain value at T0 (pre-treatment value) was 6.2 [±2.5 SD (standard deviation)], 1.6 (±2.0) ($p<0.0001$) at T2 (after the 10th day of treatment), and 2.9 (±2.6) ($p<0.0001$) at T4 (after the second week of follow-up, i.e., 1 month after the beginning of treatment). Response after the second week of treatment showed a clear reduction in pain for both cancer (mean absolute delta of the reduction in NRS value=4.0) and non-cancer (mean delta=5.2) patients. The pain score had decreased by 74% at T2. On the basis of pre-established response criteria, there were 78% of responders at T2 and 81% at T4. No side effects were reported.
Conclusions Our preliminary results suggest that cutaneous electrostimulation with the MC5-A Calmare© can be hypothesized as part of a multimodality approach to the treatment of chronic pain. Further studies on larger numbers of patients are needed to assess its efficacy, to quantify the effects of inter-operator variability, and to compare results obtained from the active device versus those from a sham machine.

Keywords Pain · Pain management · Electrocutaneous stimulation · Scrambler therapy

Introduction

Chronic pain affects numerous aspects of quality of life, and people with long-lasting pain experience a multitude of negative physical, psychological, social, and spiritual feelings [1]. A European telephone survey (EFIC) showed that chronic moderate to severe pain occurred in 19% of the adults contacted, seriously affecting daily activities and social and working life. The majority had not received specialist pain treatment, and 40% felt that their pain had been poorly managed [2]. As far as cancer pain is concerned, a recent survey (EPIC) highlighted that 56% of the 5,084 adult patients contacted reported suffering moderate to severe pain on a monthly basis or more often; only 41% of the population selected for a more extensive survey were receiving strong opioids at the time [3].

While a correct use of the World Health Organization (WHO) analgesic ladder results in successful pain manage-

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ment in 90% of patients, some studies have also reported inadequate pain control in 40–70% of patients, resulting in the emergence of a new type of pain epidemiology, i.e., "failed pain control", caused by a series of obstacles preventing adequate cancer pain management [4, 5]. A number of features causing failed pain control have been identified: barriers to appropriate management (institutional, professional, and patient/family-related), individual genetic diversity, and physiopathological features of pain (neuropathic pain, breakthrough and/or incident pain, cancer-induced bone pain) [6, 7].

Similarly, in non cancer-derived pain, maximum-dose pharmacological therapy may not be successful in providing an acceptable level of pain control, and side effects may discourage physicians from increasing doses to obtain effective therapeutic results [8]. New strategies are therefore needed to improve current approaches to the treatment of chronic cancer and non-cancer pain.

A number of new proposals to reduce chronic pain include the use of electrical nerve stimulation, e.g., neuromodulation with electrical stimulus (spinal cord stimulation and subcutaneous peripheral nerve stimulation) and transcutaneous electrical nerve stimulation (TENS) [9]. These methods coadjuvate pharmacological treatments of chronic pain and aim to inhibit pain impulse transmission through an electric stimulus.

Various hypotheses have been put forward to explain the mechanisms of action for the clinical benefit obtained from electrical nerve stimulation, e.g., supraspinal processes, modulation of descending inhibitor pathways, peripheral release of calcitonin, increase in gate control for pain threshold, reduction in windup phenomenon, and reduction in impulses from damaged nerves [8, 10, 11].

Although nerve stimulation techniques have been shown to be useful in a number of case series or small randomized studies [8, 12, 13], conclusive results have yet to be obtained due to the paucity of placebo-controlled trials conducted [14–17]. MC5-A Calmare®, a novel device for neuromodulation using electrocutaneous nerve stimulation, was recently commercialized. Preliminary studies on the device have highlighted a certain degree of efficacy in providing relief from refractory chronic pain [18, 19].

The objective of our study was to assess efficacy and tolerability of MC5-A Calmare® in patients with difficult cancer-related and non-cancer-related pain.

Patients and methods

The device

Calmare® MC5-A Model (Competitive Technologies, Fairfield, CT, USA) consists of a multiprocessor (ST5) with five channels or sets of electrodes capable of stimulating "artificial neurons", which enables up to five pain areas in the same individual to be treated simultaneously. It produces sequences of 16 exogenous nerve action potentials that stimulate endogenous nerves. The connected electrodes transmit the artificial stimulation to the patients' nociceptors, modulating the pain response [10, 18].

From a practical point of view, the painful region is identified and assigned as closely as possible to dermatomes using a standard map. Electrodes are applied beyond the pain-affected area and the opposite electrodes are placed above the painful area, if possible, within the same dermatome. Each ST5 channel has two electrodes with special connectors. Before positioning the electrodes, the patient is asked to exert gentle pressure on the skin with his/her fingers to find the confines of the area of pain to be treated. If this is not possible, the operator himself must attempt to identify the zone involved. If the area chosen is the right one, the patient will immediately be aware of a sharp reduction in pain without any discomfort from the stimulation. According to the manufacturer, the only immediate sign indicating the correct use of the device is the disappearance of pain in the targeted areas [18, 20], with a sensation of pressure rather than pain. The electrical stimulation used in MC5-A Calmare® therapy is low and its safety has been approved by the FDA. The current is regulated and there are automatic shutoffs in the event of power overloads. At the highest setting ("70" on the dial from "10" to "70"), the amperage is 3.50–5.50 mA, with a voltage range of 6.5–12.5 V. The maximum current density is 0.0002009 W/cm^2. The average charge for "charge per phase" is 38.8 μC, which is similar to that of conventional TENS devices. The phase duration is 6.8–10.9 ms and the pulse rate is 43–52 Hz [10].

The use of the ST5 is contraindicated in patients with pacemakers, automatic defibrillators, aneurysm clips, vena cava clips, skull plates, and undiagnosed pain. Electrodes should not be placed on the carotid sinus region of the body or on the head, and the cost–benefit ratio should be accurately evaluated in pregnant women and individuals with epilepsy.

Patients

Inclusion criteria were as follows: individuals >18 years of age, capable of understanding the Italian language, and with normal cognitive function. Patients were asked to report their degree of chronic pain, whether cancer-related or not, using the Numeric Rating Scale (NRS) [21, 22] and were eligible if they had an NRS ≥5 despite the best pain therapy in place, or if they judged the outcome of pain therapy as "unsatisfactory". Patients who did not obtain a satisfactory result could, after consulting us, increase the number of

Table 1 Patient characteristics

Variable	Cancer-derived pain, *n* (%)	Non-cancer-derived pain, *n* (%)	Total, *n* (%)
Patients	41 (56)	32 (44)	73
Age, years: median value (range)	65 (28–79)	67 (28–87)	66 (28–87)
Gender			
Male	26 (63)	12 (38)	38 (52)
Female	15 (37)	20 (62)	35 (48)
Performance status (ECOG)			
0	10 (24)	10 (32)	20 (28)
1	18 (44)	18 (56)	36 (49)
2	10 (24)	2 (6)	12 (16)
3	3 (8)	1 (3)	4 (6)
4	0	1 (3)	1 (1)
Concomitant diseases/comorbidities			
Hypertension	13 (32)	12 (38)	25 (34)
Diabetes	12 (29)	1 (3)	13 (18)
Ischemic cardiopathy	0	6 (19)	6 (8)
Renal insufficiency	2 (5)	0	2 (3)
Anemia	0	1 (3)	1 (1)
None of the above	15 (37)	17 (53)	32 (44)

administrations as needed up to a maximum of four per day; more than four excluded them from the study. Patients with serious psychiatric disorders or those who had received or were going to receive chemotherapy, hormone therapy, or radiotherapy during the study period and which, in the opinion of the investigator, could influence the level of pain were excluded from the study.

Coinciding with the first day of treatment (T0), patients were examined, interviewed, and asked to complete a specially designed questionnaire into which an Italian version of the Brief Pain Inventory was incorporated [23]. The following topics were investigated: personal and clinical characteristics of patient and illness, painful area to be treated, and pain characteristics (history, cause, type, pathophysiology, time presentation, intensity, therapies, and satisfaction with therapies). An "ad hoc" informed consent was signed by all patients. Patients were recommended not to modify their current drug pain treatment for the duration of the neuromodulation in order to highlight the real pain relief provided by the ST5.

Treatment schedule and results evaluation

Ten sessions of electrocutaneous stimulation therapy (from Monday to Friday for two consecutive weeks), each lasting 30 min, were planned. Pain intensity was assessed before and after each treatment. Comparison with pre-treatment intensity (T0) was made at T1 (after the first week), T2 (after the 10th day of treatment), and after each of the two additional weeks of follow-up (T3 and T4). At the end of the study period, patients were asked to complete a questionnaire on their satisfaction with the treatment.

Three levels of response were identified. Special attention was paid to the T0/T2 comparison (pre-therapy and end of cycle values, respectively) and T0/T4 comparison (pre-therapy and end of follow-up values, respectively). As reported by Serlin and co-workers [24], mild pain was given a 1–4 rating, moderate pain a 5–6 rating, and severe pain a 7–10 rating.

Table 2 Characteristics of patients with cancer pain

Variable	*n*	%
Primary site of tumor		
Colorectum	9	22
Lung	8	20
Pancreas	7	17
Male urogenital tract	4	10
Head and neck	4	10
Breast	3	7
Female urogenital tract	3	7
Others	3	7
Metastatic sites:		
Viscera	22	54
Lung	14	34
Liver	11	27
Others	13	32
Bone	12	29
Locally advanced disease	7	17
Central nervous system	4	10

Table 3 Pain characteristics

Variable	Cancer-derived pain, *n* (%)	Non-cancer-derived pain, *n* (%)	Total, *n* (%)
Cause of pain			
From cancer	39 (96)	0	39 (54)
From antitumor therapy	1 (2)	0	1 (1)
Neither of the above	1 (2)	32 (100)	33 (45)
Physiopathology of the main components of pain			
Nociceptive	23 (56)	13 (41)	36 (49)
Somatic	15 (37)	13 (41)	28 (38)
Deep	15 (37)	12 (38)	27 (37)
Superficial	0	1 (3)	1 (1)
Visceral	8 (20)	0	8 (11)
Neuropathic	14 (34)	19 (59)	33 (45)
Peripheral	13 (32)	19 (59)	32 (44)
Central	1 (2)	0	1 (1)
Mixed characteristics	4 (10)	0	4 (6)
Pain duration			
<7 days	0	1 (3)	1 (1)
From 7 days to 1 month	0	0	0 (0)
From 1 to 3 months	10 (24)	3 (9)	13 (18)
>3 months	31 (76)	28 (88)	59 (81)
Periodicity in days/months/years			
Always present	19 (46)	27 (84)	46 (63)
With periods of remission	22 (54)	5 (16)	27 (37)
Pain characteristics			
Continuous	4 (10)	7 (22)	11 (15)
Continuous + intense episodes	31 (76)	24 (75)	55 (75)
Only intense episodes	6 (14)	1 (3)	7 (10)
Intense episodes (alone or associated with continuous pain)			
Spontaneous	22 (54)	17 (53)	39 (53)
Incidental	14 (34)	7 (22)	21 (29)
Data missing	1	1	2
Sensitivity evaluation			
Hyperalgesia	16 (39)	7 (22)	23 (31)
Paresthesia	12 (29)	12 (37)	24 (33)
Hyperesthesia	13 (32)	3 (9)	16 (22)
Allodynia	9 (22)	6 (19)	15 (20)
Tactile hypoesthesia	8 (19)	3 (9)	11 (15)
Thermal hypoesthesia	5 (12)	3 (9)	8 (11)
Hypoalgesia	4 (10)	2 (6)	6 (8)
Anesthesia	2 (5)	0	2 (3)
Dysesthesia	1 (2)	2 (6)	3 (4)
Analgesia	1 (2)	0	1 (1)
None of the above	7 (17)	12 (37)	19 (26)

Statistical analysis

The work was based on a consecutive case series of selected patients who fully satisfied inclusion criteria. All patients underwent treatment according to the standard protocol. As this was a prospective, exploratory non-controlled study, each patient was his/her own control and T2 and T4 pain intensity values were compared with single baseline (T0) values. The definition of responders, partial responders, and non-responders was based on the variation in scores at different follow-up times with respect to baseline, according to the aforementioned criteria. Follow-

ing the calculation of the study dimension based on the level of accuracy of the estimate equal to 10%, with alpha= 5% and two-tailed tests, a recruitment of 62 patients was planned.

Mean values and relative standard deviations were calculated for continuous variables; plots of mean values and 95% confidence intervals (95% CI) for each T point were presented. The normality of distributions was assessed by Shapiro–Wilk test and, as all distributions were normal, the statistical significance of NRS pain intensity was measured using the paired *t* test. A repeated measures analysis of variance (ANOVA) was used to determine whether there were significant differences in the way mean NRS scores changed over time. Statistical analyses were carried out using SAS statistical software (release 9.1; SAS Institute, Cary, NC, USA) and *p* values of <0.05 were considered to be statistically significant.

Results

A total of 82 patients were recruited for the study from July 2008 to March 2010. Nine of these could not be evaluated following treatment interruption and hospital admission due to rapid health deterioration. The characteristics of the 73 evaluable patients are reported in Table 1. Median age was 66 years (range 28–87), 38 patients (52%) were male and 35 (48%) female; 41 were cancer patients and 32 non-cancer patients. Of those in the cancer group, 39 had cancer-derived pain, one had anticancer therapy-related pain (evaluated as cancer pain), and one had pain of different origin; this last was evaluated as non-cancer pain. Cancer patients were more often male while non-cancer patients were mainly female. Performance status was slightly better in the non-cancer group. The most frequently involved primary tumors were those of the colorectum (22%), lung (20%), and pancreas (17%) (Table 2).

Pain characteristics are reported in Table 3. Pain had been present for more than 3 months in 81% of patients and in a continuous manner with intense episodes in 75% of subjects. Upon entry to the study, it was confirmed that patients were undergoing chronic pain treatment according to WHO guidelines: 50 patients were taking strong opioids, 13 weak opioids, 21 NSAIDs, 22 glyocorticoids, and 37 antidepressants and anticonvulsants (data not shown). Cancer patients had a prevalence of nociceptive pain (56%) whereas neuropathic pain (59%) was more frequent in non-cancer patients. In the latter group, pain was long lasting (88%>3 months) and without periods of remission (84%), while pain experienced by cancer patients was of a slightly shorter duration (76%>3 months) and more often had periods of remission (54%). We did not find any relevant differences between the two categories of patients in terms of pain and sensitivity characteristics.

Mean baseline NRS values preceding treatment were 6.2 [±2.5 SD (standard deviation)] for the entire group, 5.4 (±2.5) for patients with cancer pain, and 7.0 (±2.3) for patients with non-cancer pain (Fig. 1). All values had decreased significantly by the end of the second week of treatment (T2) to 1.6 (±2.0) ($p<0.0001$), 1.4 (±1.8) ($p<0.0001$), and 1.8 (±2.2) ($p<0.0001$), respectively, and were still significantly reduced at the end of the second week of follow-up (T4): 2.9 (±2.6) ($p<0.0001$), 2.6 (±2.5) ($p<0.0001$), and 3.4 (±2.7) ($p<0.0001$), respectively. Mean values decreased constantly (at each T point) during treatment (ANOVA for repeated measurements—p <0.0001 for all three groups).

In particular, we focused on patients with the most clinically significant pain, i.e., the subgroup with severe pain. In individuals with a baseline pain intensity ≥7, a

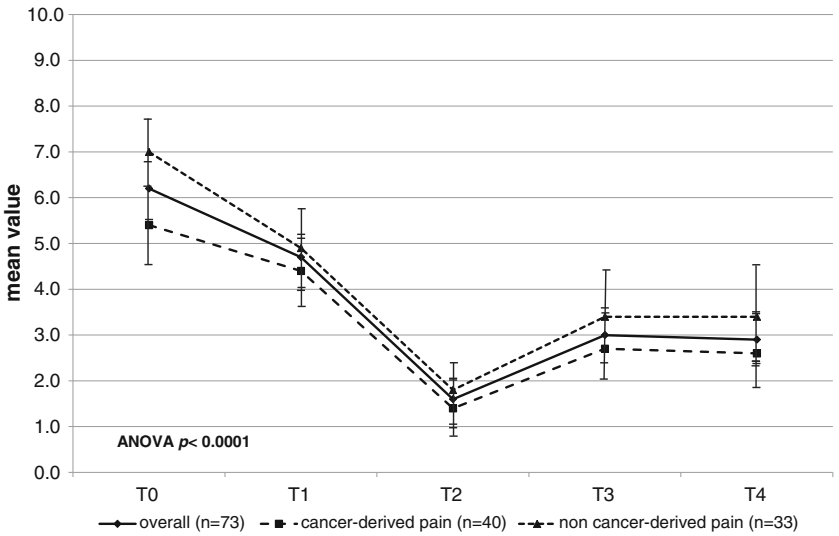

Fig. 1 Average pain intensity at follow-up. *T0* pretreatment, *T2* after 2 weeks' treatment, *T4* after a further 2 weeks of follow-up

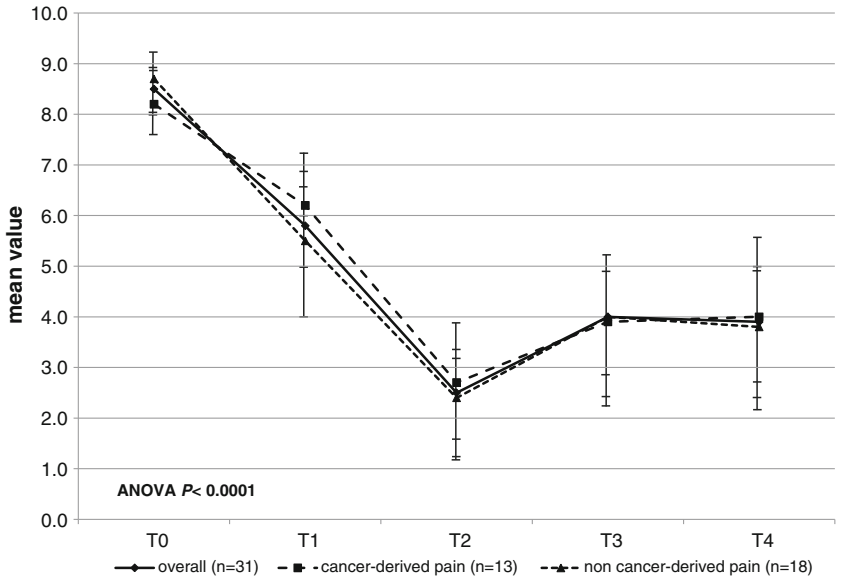

Fig. 2 Average pain intensity at follow-up (patients with pain ≥7 at baseline). *T0* pretreatment, *T2* after 2 weeks' treatment, *T4* after a further 2 weeks of follow-up

decrease from 8.5 (±1.1) to 2.5 (±2.3) was observed (T2) for the entire subgroup (31 patients) ($p<0.001$); specifically, from 8.2 (±1.1) to 2.7 (±2.3) at T2 ($p<0.0001$) and 4.0 (±3.2) at T4 ($p<0.0001$) for patients suffering from cancer pain, and from 8.7 (±1.1) to 2.4 (±2.3) at T2 ($p<0.0001$) and 3.8 (±2.9) at T4 ($p<0.0001$) for patients with non-cancer pain (Fig. 2).

At T2, there were 57 responders overall, i.e., 78% of the studied population, of whom 49 (67%) were complete responders, eight (11%) partial responders, and 16 (22%) non-responders. In the group of patients suffering from cancer-related pain, 71% responded (64% complete, 7% partial response) and 29% did not, while the group with non-cancer-derived pain was composed of 85% of responders (70% complete response, 15% partial response) and 15% of non-responders.

At T4, 81% of the overall population had obtained a response (73% complete, 8% partial) and 19% had not; the subgroup with cancer pain comprised 78% of responders (76% complete, 2% partial) and 22% of non-responders, while that of non-cancer-related pain was composed of 82% of responders (67% complete, 15% partial) and 18% of non-responders. Differences in response were not statistically significant in terms of pain pathophysiology (nociceptive/neuropathic), pain duration (1–3 months or >3 months), and pain characteristics (continuous pain/continuous plus breakthrough pain/episodic pain alone) (data not shown).

Patients' opinions on the therapy are reported in Table 4. Eighty-eight percent said that pain did not increase during treatment and 97% confirmed that they would be willing to repeat the procedure. Patients partially or totally satisfied with their pain treatment passed from 68% at T0 to 89% at T2 and to 82% at T4 (data not shown). Compliance was good. Careful monitoring during the 2 weeks of treatment and the subsequent 2 weeks of follow-up did not reveal any side effects from the use of the device (data not shown).

Discussion

Chronic pain is undoubtedly an epidemiologically and qualitatively relevant health problem. Although traditional pain therapies are described as capable of controlling most types of pain, some patients continue to suffer from "difficult" pain [25, 26], highlighting the need for a multimodality approach to this problem. Neuromodulation with electrical stimulus would seem to contribute to improving pain treatment results.

Preliminary studies have highlighted a certain degree of efficacy of the MC5-A Calmare®, a new instrument for electrocutaneous nerve stimulation, in relieving chronic

Table 4 Patients' opinions of Scrambler therapy

	Response	
	No *n* (%)	Yes *n* (%)
Questions regarding Scrambler therapy		
Was the method used painful?	73 (100)	0
Did the method used cause any discomfort?	71 (97)	2 (3)
Was pain relief too slow?	46 (63)	27 (37)
Did pain stay the same or increase?	64 (88)	9 (12)
Did you feel particular sensations?	70 (96)	3 (4)
Was pain relief insufficient?	48 (66)	25 (34)
Would you repeat this treatment?	2 (3)	71 (97)

pain [10, 18, 19]. The first study was conducted on a small series of 11 patients with pancreatic cancer; all were considered responders on the basis of the author's response criteria (reduction in pain intensity and gradual increase in duration of analgesia and pain threshold), and nine were able to suspend pharmacological treatment as a result [18]. A second study was carried out on 226 patients suffering from severe non-cancer, drug-resistant, neuropathic pain and reported 80% of responders (pain relief >50%), 10% of partial responders (pain relief from 25% to 49%), and 10% of non-responders (patients with pain relief <24% or VAS >3) [19].

Recently, Smith and co-workers [10] reported data on the effectiveness of ST5 in 16 patients with chemotherapy-induced peripheral neuropathy (CIPN). The primary objective of the study was to determine whether MC5-A Calmare® reduced CIPN in cancer patients by 20%. This end point was met in 15 of the 16 evaluable patients (94%), and the pain score fell by 59% (from 5.81 to 2.38 at the end of 10 days). No toxicity was registered. Overall, four of the 16 patients reported a complete disappearance of pain and the majority experienced a 64% reduction in pain. Some patients also had a complete or partial return of normal sensation and relief from numbness. Conversely, Smith observed no effect on other pain scales, no differences in morphine oral equivalent dose pre-/post-Calmare therapy, and no changes in quality of life or symptoms other than those related to pain. The effect over time was maximum on day 10 (at the end of the treatment period) and gradually decreased as time passed (pain scores were evaluated on days 14, 30, and 60). Overall, a moderate benefit in terms of long-lasting pain relief was observed, although a number of patients needed to repeat the treatment. The authors concluded that the device appears to be effective in reducing pain in refractory CIPN patients, without side effects.

Our study, whose preliminary data were presented at the 2010 ASCO Annual Meeting in Chicago [27], focused on both cancer and non-cancer pain, and was designed and carried out as a prospective analysis. Response after the second week of treatment showed a clear reduction in pain for both cancer (mean absolute delta of the reduction in NRS value=4.0) and non-cancer (mean delta=5.2) patients. The results, although clinically evident and statistically significant in both subpopulations of patients, were more impressive in the non-cancer pain group. This may be due to the fact that the mean pain value of cancer patients at T0 was lower than that of non-cancer subjects, implying that the cancer patients had already received effective pharmacological treatment. Results were maintained at T2, with a slight increase in pain at T3 which remained stable at T4. Furthermore, none of the patients reported side effects and the majority were willing to repeat the treatment.

One strength of our work lies in the fact that the MC5-A Calmare® device was utilized by a dedicated pool of operators well versed in standard reproducible techniques for electrode application. However, no studies seem to have been carried out to assess variability with regard to the positioning of electrodes and the strength of impulse administered.

Our study also has a number of weaknesses: single-site-based, unblinded evaluation, and short follow-up. Although the risk of a placebo effect obviously existed, such effects reported in the literature are much lower (9% efficacy in placebo arm) than the reduction in pain observed by us [12]. Pain reduction at T0 was around 74% and at T2 was similar to that reported in previous studies carried out on the device [10, 18, 19] and on other instruments using direct nerve stimulation [11–13].

In conclusion, these preliminary results will hopefully encourage others to test MC5-A Calmare® in larger populations. Further research could shed light on possible factors associated with resistance to treatment (20% of patients) and/or with the loss of efficacy shown by some responsive patients over time. The potential recovery of the original benefit in the latter subgroup could also be investigated. It would be interesting to compare results obtained from an active device with those from a sham one in an attempt to identify the possible placebo effect produced by the machine and by the intensive professional caregiver approach used.

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Conflict of interest There are no conflicts of interest to declare.

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