Lauren E. Berninger, DO and Thomas J. Smith*, MD

Scrambler therapy for incident pain in bone metastases

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Abstract: Incident pain, described as pain induced by bone metastasis and produced by movement, can be devastating. The high doses of opioids needed to control such pain may sedate the patient and cause additional complications. Treatment of incident pain with pharmaceuticals has rarely been studied; only eight patients have been reported in the literature who did not receive additional opioids. We present the case of a 69 year old man with shoulder destruction due to bone metastases who was able to use his arm for normal activities without pain after three sessions of scrambler therapy, a non-invasive form of electrical neuromodulation that requires further study.

Keywords: incident pain; neuromodulation; pain from bone metastases; scrambler therapy.

Pain induced by bone metastasis is frequently encountered but difficult to treat [1]. Specifically, “incident pain,” one type of breakthrough pain defined as pain produced by movement, has proven remarkably challenging to control [2]. The etiology of incident pain can include pathologic fractures and bone damage due to metastatic disease [2]. While opioids have proven partially effective in the treatment of incident bone pain [2, 3], higher doses – even to the point of sedation – are often required [4, 5]. Thus, the search for interventions to treat incident pain is essential.

Scrambler therapy, a noninvasive procedure most frequently used in the setting of neuropathic pain [6, 7],

is one possible intervention that may be beneficial for patients with incident pain. Scrambler therapy employs electrocutaneous nerve stimulation that incorporates a variety of nerve action potentials responsible for nonpain information [8]. Use of the device involves electrode placement surrounding the “proximal and distal limits of the cutaneous region over the pain region” to trigger the central nervous system to transform “pain information into nonpain information” [9]. In this case report, we present a patient with a history of metastatic non small cell lung cancer experiencing incident bone pain who received successful scrambler therapy treatment and for whom conventional medical management was unsuccessful.

Case description

A 69 year old man with a history of advanced non small cell lung cancer with hepatic and bony metastasis was referred to a palliative medicine clinic in October 2020 for management of intractable right shoulder pain. Pain, along with allodynia, was elicited by any movement and severely limited functional use of the patient’s dominant right arm. Computed tomography (CT) imaging of the right shoulder revealed a destructive lytic mass in the right scapula with an associated surrounding soft tissue mass and multiple small lucent lesions in the right humeral head (Figure 1A). Ineffective therapy before our intervention included radiation 5 months prior and cryoablation to the right scapular mass 1 month prior. His pharmacologic regimen included extended release oxycodone 40 mg by mouth every 12 hours, oxycodone immediate release 40 mg by mouth every 4 hours, liquid gabapentin 750 mg by mouth every 8 hours, and acetaminophen 1,000 mg by mouth every 6 hours. This regimen remained unchanged over the course of his treatment with scrambler therapy.

The MC-5A scrambler therapy device (GEOMC, Inc.) was used to provide treatment to this patient. Electrodes pairs were placed (Figure 1B) in an “X” pattern across the areas of most pain, 2 cm distal from the pain, across the affected dermatomes (Figure 1B and C). The patient was asked to rate his pain on a scale of 0–10 using a numeric

***Corresponding author: Thomas J. Smith, MD,** Professor of Oncology, Harry J. Duffey Family Professor of Palliative Medicine, Johns Hopkins Medical Institutions, Sidney Kimmel Comprehensive Cancer Center, 600 N. Wolfe Street, Blalock 369, Baltimore, MD 21287-0005, USA.

E-mail: tsmit136@jhmi.edu. <https://orcid.org/0000-0003-3040-6434>

Lauren E. Berninger, DO, Johns Hopkins Medical Institutions, Baltimore, MD, USA. <https://orcid.org/0000-0003-3897-441X>

Figure 1: (A) Computed tomography of this 69 year old man's right shoulder revealed a destructive lytic mass in the scapula with an associated surrounding soft tissue mass and multiple small lucent lesions in the right humeral head. (B) Lead placement on patient's right shoulder. (C) Lead placement shown on dermatomes.

rating scale pre- and posttreatment. Each session included 30 minutes of stimulation after electrode placement.

The device consists of a multiprocessor apparatus able to simulate five artificial neurons by applying surface electrodes on the skin overlying the painful areas. The electrical stimulation used in MC-5A scrambler therapy is low, and the FDA has approved it as safe [8]. The current is regulated and there are “shutoffs” automatically if the power overloads. At the highest setting of 70 (range, 10–70), the amperage (A) is 3.50–5.50 mA, with a voltage range of 6.5–12.5 V; maximum current density is only 0.0002009 W/cm². The scrambler synthesizes 16 different types of nerve action potentials similar to endogenous kinds and strings them into 256 constantly varying sequences, very different from the typical square waveform used in transcutaneous electrical nerve stimulation (TENS). The average charge per phase is 38.8 μ C, similar to conventional TENS devices approved by the FDA and in routine practice. The phase duration is 6.8–10.9 ms, and the pulse rate is 43–52 Hz, less than most standard TENS devices, which operate a square wave with the possibility of using frequencies greater than 52 Hz. Patients can receive to 10 treatments, but therapy is stopped if the pain remains at 0 for 24 hours posttreatment.

After one session of scrambler therapy, the patient reported improvement in his right shoulder pain from a 4 (pretreatment) to a 0 (posttreatment) that lasted approximately 7 hours. Following the third day of scrambler therapy, his right shoulder pain remained at 0 and he was again able to use his right arm to eat. The patient underwent six sessions of scrambler therapy over the course of 10 days (October 20, 21, 23, 26, 27, and 29, 2020). His pre- and posttreatment pain on sessions 4–6 remained at 0, and he remained pain free for weeks until his death (Figure 2).

Figure 2: Pain scores pre- and posttreatment by day of treatment.

Discussion

Incident pain is a serious challenge faced by oncology professionals and patients alike. There are eight patients reported in the literature who benefited from drug treatment that did not involve additional opioids [5, 10]. Several literature searches were conducted on PubMed by the senior author (T.J.S.) beginning in 2012 and most recently in September 2020, using the terms “incident pain,” “movement pain,” “bone pain,” and “incident pain,” “with treatment,” and “without treatment.” The references of the Mercadante et al. [5] and Caraceni et al. [10] studies were also reviewed. Gabapentin demonstrated effectiveness as an adjunctive medication in a small study ($n=6$) of patients with incident bone pain, lasting up to 3 months [10]. Burst ketamine, an N-methyl-D-aspartate (NMDA) antagonist, was successful in conjunction with opioid switching in two patients who were sedated on high dose opiate therapy [5].

The scientific basis for scrambler therapy relief of metastatic bone pain is inferential, as there have been no preclinical studies reporting the mechanism. Bone metastases cause pain by several neuropathic and inflammatory mechanisms, including growing into local nerves, expanding tissue with pressure, and releasing inflammatory mediators, as reported by Falk and Dickenson [11]. One hallmark of incident pain (and was observed in this patient) is allodynia and hyperalgesia [3]. Experimental animal models of bone metastases show the development of mechanical allodynia along with a reduction in the pain threshold [12], as observed in this case. To date, there have been no mechanistic studies in either animals or humans showing how scrambler therapy relieves pain. In the single randomized study to date that measured allodynia, relief of allodynia was often experienced within minutes (as in this case) and reduced to near zero at 1 month, persisting for 3 months [13]. In our own experience, relief of allodynia happens in minutes in cases like postherpetic neuralgia and is highly predictive of long lasting pain relief [14]. Starkweather et al. [15] observed statistically significant down regulation of serum neuroinflammatory peptides like nerve growth factor, and this may be involved in long term relief.

Many therapies considered effective in the management of bone pain, when critically examined, have little or no effect. The most extensive review of bisphosphonates or denosumab concluded that these agents have only weak evidence for pain treatment and work almost exclusively by preventing new skeletal related events [16]. Moreover, they would not fix the problem of motion/incident pain. Similarly, a Cochrane review [17] and an update [18] found

little proof that nonsteroidal antiinflammatory agents were effective for cancer pain treatment. Even corticosteroids, long thought effective in cancer pain, reduced pain levels by only 0.84 on a 0–10 scale and the evidence for that was weak [19]. In comparison, radiation therapy can control bone pain in 70–80% of patients [20].

Novel therapies that decrease reliance on pharmacologic interventions are necessary not only to improve pain, but also to limit the adverse effects of escalating doses of opiate and other pain medications. Nontoxic and noninvasive scrambler therapy warrants further study in the treatment of incident pain. A study of scrambler therapy in 25 patients with bone and visceral metastasis showed that 100% of patients quickly achieved at least a 50% reduction of pain that lasted a mean of 7.7 months [9]. Notably, scrambler therapy was effective even in patients whose pain had been resistant to radiation [9].

The main limitations of scrambler therapy include time, lack of provider awareness of the intervention, cost, a limited number of machines, and the dearth of providers trained to use the device. Because our case report is limited to one patient’s subjective experience, additional research is needed to further study the effects of scrambler therapy on incident pain.

Conclusions

This patient with a history of advanced non small cell lung cancer with hepatic and bony metastasis experienced immediate and prolonged relief from scrambler therapy. The device is easy to use and typically well tolerated by patients, in our clinical experience. As more patients receive scrambler therapy, we remain hopeful that its use will become increasingly mainstream in complex cancer pain treatment, including for patients experiencing incident bone pain.

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Author contributions: Dr. Smith provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Dr. Berninger drafted the article and Dr. Smith revised the article critically for important intellectual content; Dr. Smith gave final approval of the version of the article to be published; and both authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests: None reported.

Informed consent: The patient signed consent for use of his story and photographs while in the Post Anesthesia Care Unit, in the presence of Dr. Smith following a cancer biopsy looking for genetic targets for treatment on Phase I trials. Dr. Smith brought both pages back to his office but misplaced the second (signed) page. The patient died in hospice about 6 weeks later and therefore we are unable to obtain an additional informed consent form.

Ethical approval: Case reports of three or fewer patients do not require Johns Hopkins Institutional Review Board approval.

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