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Treatment of Cancer Pain with Noninvasive Brain Stimulation

To the Editor:

Although therapeutics for the treatment of pain have developed considerably in the last few years, they still may fail to alleviate pain in cancer patients or become associated with significant undesirable side effects. Pain because of pancreatic cancer may be an example of such an instance. Patients with locally advanced or advanced pancreatic cancer often require increasing doses of opioid pain medications to control their pain. Although effective in pain control, opioids are often associated with adverse side effects: constipation, nausea, confusion, and drowsiness. Other treatment options—such as radiation or celiac plexus block—may not provide sustained pain relief.[1–4]

Recent advances in the techniques of noninvasive brain stimulation may offer alternative therapeutic options for pain control. We recently reported that transcranial direct current stimulation (tDCS), based on the application to the scalp of a weak direct current that flows between two relatively large electrodes—an anode and a cathode[5]—is a an effective method of reducing pain in patients with spinal cord injury and fibromyalgia.[6,7] The present case provides proof-of-principle evidence that tDCS can exert clinically meaningful analgesic effects in patients with pain because of pancreatic cancer.

Case

A 65-year-old woman was diagnosed with pancreatic cancer after one year of pain of increasing intensity in the upper abdominal area. The diagnosis of pancreatic cancer was made with a computed tomography scan of the abdomen, showing an image suggestive of a necrotic mass in the tail of the pancreas. A subsequent biopsy confirmed adenocarcinoma of the pancreas. Surgical treatment was not considered because of the local invasion and the presence of metastatic lesions. The patient began chemotherapy with gemcitabine, which resulted in a partial alleviation of her pain. However, after six months, her pain returned and codeine and paracetamol (acetaminophen) were initiated. At the time of the study, she was taking 180 mg of codeine per day (four times a day) and up to 2 g of paracetamol. With this treatment regimen, she had pain levels that varied, on average, from 1 to 6 on a scale from 0 to 10. She reported that her pain was especially severe when the effects of codeine were wearing off (two to four hours after the previous dose) (Fig. 1 shows her daily variation of pain). In addition, she reported severe constipation with this dosage of codeine.

After giving written informed consent, the patient participated in a research protocol investigating the effects of noninvasive brain stimulation in patients with chronic pain. The protocol was approved by the local research ethics committee. She was blinded to the treatment condition, and received sham and active tDCS in a randomized order. We measured pain, cognitive effects, and side effects using the following instruments: numeric scales for pain, mood, and anxiety; Mini-Mental State Examination (MMSE); Stroop test; Forward and Backward Digit Span; and a questionnaire for adverse effects. During the day of stimulation, medication was withheld to evaluate her response without the effects of analgesics. We also asked her immediately after each tDCS session to guess which type of stimulation she received. She responded that she believed she received active stimulation in both situations (could not differentiate). Importantly, the rater was also blinded to the treatment received by the patient.

Direct current was transferred by using a saline-soaked pair of surface sponge electrodes and delivered by a custom-developed, battery-driven, constant current stimulator with a maximum output of 10 mA and electrode size of

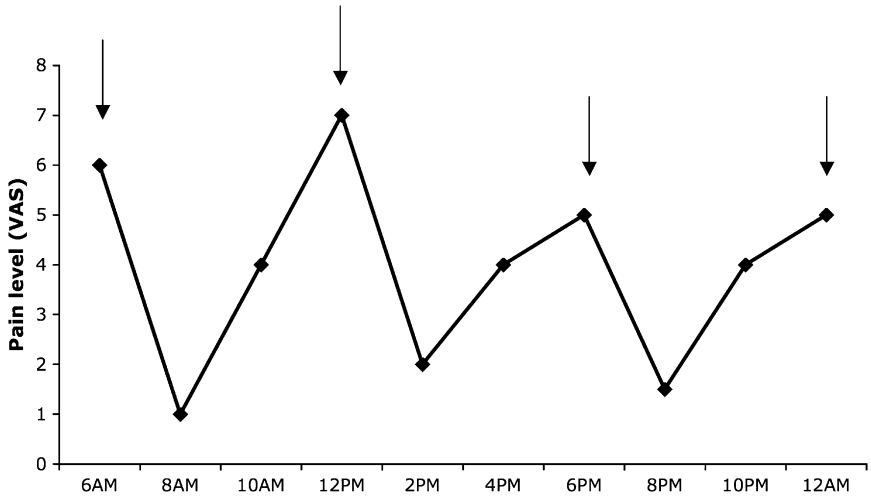

Fig. 1. Daily mean variation of pain levels as indexed by visual analog scale. Arrows indicate the time of medications intake (6 AM, 12 PM, 6 PM, and 12 AM). The patient was taking 45 mg of codeine and 500 mg of paracetamol.

35 cm^2. The anode electrode was placed over C3 (using EEG 10/20 system—corresponding to the primary motor cortex)[6] and the cathode electrode was placed over the contralateral supraorbital area.

During sham stimulation, the patient had no change in pain levels and pain worsened two hours after the tDCS (increase of two points). However, after active stimulation, she reported that she was pain free (her pain decreased from four to zero) and the benefit lasted for several hours. The effect was particularly remarkable as she reported that she usually could not tolerate skipping one dose of her medication for more than four hours (Fig. 2).

There were no adverse effects. After sham stimulation, her MMSE did not change, digit span forward did not change, digit span backward increased one sequence (two to three), and Stroop colors performance execution time decreased from 25.63 to 22.89 seconds. After active stimulation, MMSE, digit span forward and backward did not change, and Stroop colors execution time also decreased from 23.06 to 20.56 seconds. There were no changes in mood and anxiety after either sham or active stimulation.

Comment

This case report shows that active, but not sham, tDCS can acutely alleviate pain because of advanced pancreatic cancer. In addition, we also showed that, in this patient, this treatment was not associated with adverse events, cognitive changes, or mood changes. We previously showed that another technique of

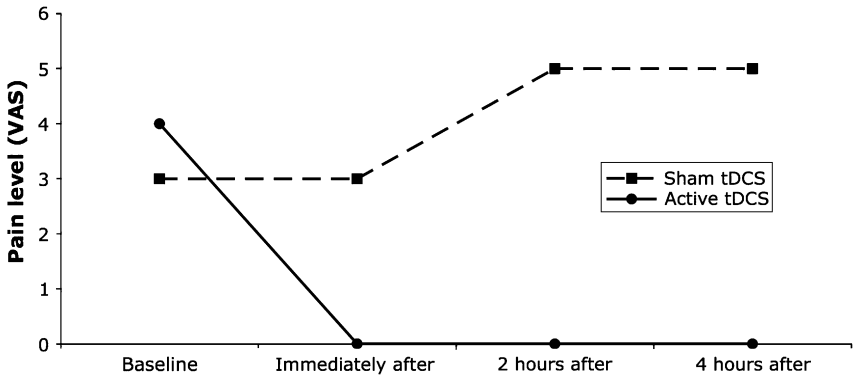

Fig. 2. Pain levels during treatment with sham and active tDCS. During treatment with tDCS, medications were withheld.

noninvasive brain stimulation (repetitive transcranial magnetic stimulation) can also significantly suppress chronic visceral pain in patients with chronic pancreatitis.[8]

Prior work done in patients with chronic pancreatic inflammation suggests that sustained chronic visceral pain from pancreatic disease affects: 1) the interaction and modification of various somatic sensory modalities between the ascending pathways;[9,10] 2) the activation of spinal gating mechanisms through the dorsal column neural synapses;[11] and 3) reorganization in the cortical representation of visceral sensation, including a suppression of local GABAergic and a potentiation of glutamatergic activity. In fact, chronic pancreatitis patients report a decrease in pain when given ketamine, a noncompetitive antagonist of glutamatergic N-methyl-D-aspartate (NMDA) receptors.[12] NMDA receptors enhance brain excitability, can control synapse maturation, and modulate other receptors, such as the gamma-aminobutyric acid type A (GABA-A) receptors.[13]

The rationale of using the primary motor cortex as the target comes from studies using epidural motor cortex stimulation,[14,15] suggesting the potential therapeutic utility of motor cortex stimulation. Upregulation of motor cortex excitability might modulate pain perception through indirect effects via neural networks on pain-modulating areas, such as thalamic nuclei, as suggested by neuroimaging.[14]

Several limitations should be discussed. First, this is a report of one case only. However, we believe this is important to report to encourage future research in this area. Second, we did not measure the long-term effects of this therapy. Therefore, it is unclear whether the effects would be long-lasting if several sessions of tDCS are applied; this should be further explored. We previously showed that five consecutive sessions of tDCS in chronic pain because of spinal cord injury results in pain alleviation that lasts five days[6]; however, mechanisms of pain in pancreatic cancer are certainly different.

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Palliative Medicine and Intensive Care Medicine—Two Sides of the Same Coin?

To the Editor:

Intensive care medicine and palliative medicine both deal with the limits of life-sustaining care. Decision making in matters of life and death is one of the greatest challenges for physicians, because it may be an area of conflict with regard to aspects of patient autonomy, medical prognosis, and the ethics of medical care.

Superficially, palliative medicine and intensive care medicine seem to be at the opposite ends of care; one is known as "talking medicine" and the other as "apparatus medicine." In palliative medicine, symptom control and alleviation of suffering are the focus of care to achieve or maintain the best possible quality of life in patients with incurable, advanced, and life-limiting diseases. Even though appropriate symptom control may result in prolongation of life, this is not a major goal of treatment and, therefore, can be seen as one of the essential differences between palliative and intensive care medicine. Palliative medicine regards dying as a natural process and neither seeks to prolong life nor to hasten death. However, palliative medicine cares for a much larger target group than the dying; a great number of palliative patients benefit from palliative care measures for a period of months or even years.

In intensive care medicine, the main focus of care lies on prolongation of life and restoration of health, whenever possible; symptom control and alleviation of suffering are also essential aspects of intensive care unit treatment.[1]

It is not unusual that decisions in intensive care medicine must be made in an instant, particularly when dealing with an emergency