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Transcranial direct current stimulation as a tool for postoperative pain management : a review of the current clinical evidence

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Abstract : Adequate control of acute postoperative pain remains a challenge, and many patients still experience moderate to severe pain. Surgery is also a major cause of chronic pain, which cannot reliably be prevented with available interventions. Current analgesic regimens are also associated with severe side-effects. Consequently, we are in need of new techniques to better manage pain in the perioperative period. Transcranial direct current stimulation (tDCS) – a non-invasive neuromodulation technique – affects pain perception in human volunteers. Its ease of use, relatively low cost and absence of serious side effects make it an ideal candidate for clinical practice and a recent review concluded that it reduces pain intensity and improves quality of life of chronic pain patients. This article aims to review the clinical evidence for its use as a tool for postoperative pain management. In summary, seven randomized controlled trials have included over 310 patients and report encouraging results, most notably a considerable reduction in postoperative opioid use. More studies are needed to better establish the place of tDCS in this setting and to determine the optimal stimulation protocols.

Keywords : Postoperative pain ; transcranial direct current stimulation ; analgesia

Introduction

Despite currently used analgesic techniques, adequate control of acute postoperative pain remains a challenge, and many patients still experience moderate to severe pain after their surgery (1). Unrelieved pain is associated with increased morbidity, functional and quality-of-life impairment, delayed recovery, higher health care costs, and prolonged opioid use (2). Moreover, current postoperative analgesic regimens are associated with severe side effects, including long-term opioid use, misuse, and addiction (3). Recent studies have also raised security concerns with other analgesic drugs, e.g. an increased risk of respiratory depression when gabapentin (4) or pregabalin (5) are combined with opioids.

Surgery is also a frequent cause of persistent pain (6, 7). Chronic postsurgical pain (CPSP) is defined as pain that develops after a surgical procedure and persists at least three months, when all other causes of pain (e.g. infection, recurring malignancy, …), as well as pain from a pre-existing pain problem have been excluded (8). CPSP affects up to 50% of patients after common surgical procedures, worsening quality of life and increasing health care use (9). Chronic pain is hard to treat, but the programmed nature of the surgical trauma could offer a window of opportunity for primary preventive measures (10). Unfortunately, a recent review of the available perioperative interventions for CPSP prevention concluded that, currently, none reliably prevent its development (11).

The non-invasive application of electrical currents to the brain and the spinal cord has been used in research and clinical practice since the beginning of the 20th century (12). Among the various forms of non-invasive brain stimulation techniques, tDCS has several characteristics, which make it an ideal candidate for clinical use : low risk, non-invasive and painless, lack of serious side effects, ease of administration and relatively low cost (13). Because participants only feel a light tingling sensation during the first minutes of stimulation, regardless of stimulation duration, adequate patient blinding can be obtained in clinical trials by delivering a very short

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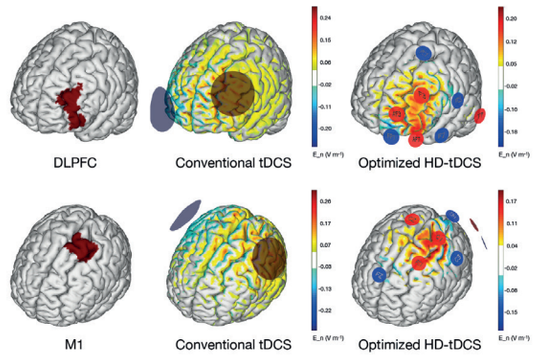

Fig. 1 — *Left:* anatomical location of areas commonly targeted with tDCS for pain control: dorsolateral prefrontal cortex (DLPFC) and primary motor cortex (M1) ; *middle:* widespread electrical field generated by a traditional tDCS montage, using two sponge electrodes ; *right:* more focalized electrical field generated by an optimized HD-tDCS montage, using 8 electrodes (adapted with permission from (58)).

stimulation mimicking the initial experienced scalp sensations at the beginning of real stimulation (13).

During tDCS, a weak direct electrical current is delivered through two or more electrodes placed on the subject's scalp. The resulting physiological effects depend on several parameters (13). First, the targeted brain structures (Figure 1, left) are of importance. For pain relief, these are most commonly the primary motor cortex (M1) (14) or the dorsolateral prefrontal cortex (DLPFC) (15). Second, the type and configuration of electrodes have an influence. Originally, two large sponge electrodes were used, resulting in a rather widespread electric field (Figure 1, middle). More recently, the use of several smaller electrodes, referred to as high-definition tDCS (HD-tDCS) with at least one 'active' electrode surrounded by four or more 'return' electrodes, has demonstrated improved focus of the stimulation (Figure 1, right) (13,16). Third, the polarity of the active electrode located over the target makes a difference. It is commonly reported that the anodal electrode over the target region increases its excitability, while the cathodal electrode decreases it (17). Fourth, the current dose is thought to determine the effectiveness of the neuromodulation. It is determined by the intensity and duration of the stimulation, commonly set to 1 or 2 mA and 20 minutes, respectively (13).

Several studies have demonstrated that tDCS alters pain perception in humans. A recent meta-analysis concluded that anodal tDCS of M1 but not of the primary somatosensory cortex (S1) increases sensory detection and pain thresholds in healthy volunteers and decreases pain levels in chronic pain patients (18). In a study on healthy men, Flood *et al.* (19) showed that one 10-minute session of anodal HD-tDCS over M1 significantly increases pain pressure thresholds as well as the magnitude of conditioned pain modulation (CPM). Earlier, Borckardt *et al.* (20) demonstrated that a single session of anodal HD-tDCS over M1 significantly reduces the slope of temporal summation of thermal pain in healthy volunteers. Anodal tDCS over M1 also reduces the intensity and extent of mechanical secondary hyperalgesia induced by capsaicin-heat application, possibly through the activation of descending pain modulation pathways (21). Moreover, a recent Cochrane review concluded that there is evidence – albeit of low-quality – that tDCS of M1 or DLPFC reduces pain intensity and improves quality of life in chronic pain patients (22).

In the present article, we aim to review the current clinical evidence for the use of tDCS in the management of acute postoperative pain.

Methods

We performed a PubMed search (up to December 2018) with the following terms : 'post-operative pain' OR 'postsurgical pain' AND 'trans-cranial direct current stimulation' OR 'tDCS', focusing on adult randomized, controlled trials. We excluded studies not available in English or French language. All titles and abstracts were examined to exclude irrelevant studies.

We extracted data about participants (number of patients, gender), intervention (tDCS montage, number, timing, and duration of sessions, current intensity, polarity, electrodes' size, current density), control condition (sham stimulation), adverse events, and outcomes (opioid use, pain scores).

Results

Our literature search retrieved seven randomized controlled trials investigating the use of tDCS as a postoperative pain management tool. We present the characteristics of each study in Tables 1 to 3 and summarize their findings in the text below.

In 2013, Dubois *et al.* randomized 59 patients scheduled for lumbar spine surgery to receive a single session of anodal, cathodal or sham tDCS over the left DLPFC (23). Anesthesia and postoperative analgesia were standardized. Patients underwent stimulation in the recovery room. Outcomes – morphine consumption and pain levels over the two first postoperative days – were similar in both groups. No serious adverse events were noted. About half of the patients described some

mild itching under the electrodes and one patient in the cathodal group experienced a visual flash at the start of the stimulation.

Borckardt *et al.* randomly assigned 40 patients scheduled for unilateral total knee arthroplasty (TKA) to receive four 20-minute sessions of real (n = 20) or sham tDCS (n = 20) (24). The anode was positioned over M1 – contralateral to the operated knee – and the cathode over the right DLPFC. Patients received two sessions on the day of surgery and two sessions on the first post-operative day. Patients who had received real tDCS consumed significantly less opioids up to 48 hours after surgery, without reporting higher pain. Adverse events were not reported.

In a follow-up study, Borckardt *et al.* enrolled 61 patients undergoing TKA and randomly assigned them to one of four groups : (A) anode : M1, cathode : right DLPFC ; (B) anode : left DLPFC, cathode : primary somatosensory cortex ; (C) anode : left temporal-occipital junction, cathode : medial anterior pre-motor area (active-control condition) ; (D) sham tDCS, with electrode placement similar to group A or B (randomly selected) (25). The timing of the sessions was the same as in their previous study. Anodal stimulation over the DLPFC decreased opioid consumption as compared to anodal stimulation over M1 and to sham. Surprisingly, anodal tDCS over M1 increased opioid consumption. Pain scores were similar in all groups and no serious adverse events were reported.

Glazer *et al.* included lumbar spine surgery patients in a randomized, double-blind, sham-controlled clinical trial (26). Twenty-seven patients received four 20-minute sessions of either active or sham tDCS, with the anode positioned over M1 and the cathode over the right DLPFC. Patients received two sessions on the day of surgery and two sessions on the first post-operative day. Average hydromorphone consumption was significantly reduced in the real tDCS group as compared to the sham group (12.6 ± 9.9 mg and 16.5 ± 12.7 mg, respectively). Pain intensity levels were similar in both groups. The authors reported no serious adverse events.

In 2017, Khedr *et al.* published the results of a randomized, sham-controlled trial where 50 patients undergoing unilateral TKA randomly received one daily session during four postoperative days of either real or sham tDCS (27). The anode was placed over M1, while the cathode was positioned on the contralateral arm. Opioid consumption was significantly reduced in the tDCS group as compared to the sham group. Secondary outcome measures (Leeds Assessment of Neuropathic Symptoms and Signs questionnaire and pain scores) were similar. Adverse events were not reported.

Ribeiro *et al.* conducted a double blinded, sham-controlled, randomized trial, where patients scheduled for hallux valgus surgery were assigned to receive two preoperative 20-minute sessions of either anodal or sham tDCS over M1 (28). The first session was planned the night before surgery, and the second in the morning before the procedure. Patients in the real tDCS group reported significantly lower pain scores and needed less opioids than patients assigned to the sham group. Adverse events were not reported.

In 2018, Jiang *et al.* reported the findings of a single-blind, randomized, sham-controlled trial including 32 patients having underwent lumbar spine surgery (29). On postoperative day one, half of the patients received one 20-minutes session of anodal tDCS over M1, while the other half received sham tDCS. Patients in the real tDCS group saw their pain intensity significantly decreased immediately after the intervention, while no effect was seen in the sham group. Interestingly, changes in pain intensity were correlated with changes in alpha and beta bands of the spectral power of the EEG in frontal regions. Some patients complained about mild discomfort during the first minutes of stimulation, which did not require its interruption.

Discussion

In summary, seven randomized clinical trials (310 patients) have investigated the effect of tDCS on postoperative opioid consumption and pain scores, with encouraging results. Most studies found a significant opioid-sparing effect (between 23 and 76%), but little difference in perceived pain intensity (24-28). In one trial, two preoperative tDCS sessions reduced pain intensity and opioid consumption during the first 48 hours after hallux valgus surgery (28). Furthermore, tDCS appears safe, as no study reported any serious adverse events.

What are the optimal tDCS parameters?

Nearly all studies (6 out of 7) have positioned the anode over M1 and all but one (25) reported positive results (24,26-29). Position of the return electrode was more variable : contralateral arm (27), supraorbital (28, 29) or DLPFC region (24-26). Two trials targeted the DLPFC : one negative (anodal and cathodal) (23) and one positive (anodal) (28).

All studies, except one (29), used large conventional sponge electrodes (23-28). These montages are expected to induce broad current flows extending beyond the targeted area (30). HD-tDCS has been developed to increase the stimulation focus of superficial cortical regions such as M1 (20) or DLPFC (26), however it has not been tested yet in the field of postoperative pain management.

Multiple sessions seem necessary to observe long lasting after-effects. Indeed, a single tDCS session did not seem to reduce pain and morphine consumption after surgery (23). Similarly, all positive studies applied a current intensity of 2 mA, in contrast to 1 mA for the aforementioned negative trial (23). The timing of sessions could also be important. While the vast majority of trials only applied tDCS postoperatively (23-27, 29), the only study which found a significant decrease in pain intensity used two preoperative sessions (28). The only common setting in all trials was the duration of the stimulation sessions, namely 20 minutes (23-29).

In conclusion, as there is great heterogeneity in the targeted brain regions, dose, and timing of sessions, it is difficult to reach a definitive recommendation on the best stimulation protocol. Tentatively, we would propose a protocol with multiple 20-minute anodal tDCS sessions at 2 mA, starting preoperatively, targeting either M1 or the DLPFC.

After which types of surgery could tDCS be effective?

The available studies have included patients undergoing various orthopedic procedures : knee arthroplasty, lumbar spine and hallux valgus surgery. Consequently, the effects of tDCS in different surgical models – e.g. abdominal surgery – remain to be investigated. Encouragingly, tDCS has been shown to relieve pain in patients with chronic abdominal pain (31) and repeated sessions of transcranial magnetic stimulation – another non-invasive brain modulation technique – was suggested to reduce pain and opioid consumption after gastric bypass surgery (32).

Could the effects of tDCS be enhanced – or reduced – by other analgesic techniques?

Current recommendations for the management of postoperative pain advocate the use of multimodal regimens, including both pharmacological and non-pharmacological modalities (33). The majority of trials investigating a multimodal approach combining tDCS with systemic or locoregional analgesic techniques found that it could contribute to achieve two of the goals of multimodal analgesia, namely reduce opioid consumption and improve pain scores (24, 25, 27, 28). An additional goal of multimodal analgesia is the reduction of opioid-related adverse events, but none of the studies included this in their outcomes. Therefore, we suggest that future trials not only assess opioid consumption, but also opioid-related adverse effects.

On the other hand, the combination of two interventions can also result in antagonism. Studies on healthy volunteers have demonstrated that high doses of dextromethorphan – an NMDA antagonist – suppressed the excitability enhancement usually observed after anodal tDCS of M1 and assessed by motor evoked potentials (34). Aside from the stimulation parameters discussed above, the absence of effect observed in the study conducted by Dubois *et al.* (23) could also result from the fact that all patients received two potent NMDA-blockers, ketamine and magnesium sulfate, potentially blocking the effects of the stimulation. Further studies are needed to clarify the impact of certain components of multimodal analgesia regimen on the efficacy of tDCS. Moreover, it is critical that future studies report on the specific anesthesia and analgesia techniques received by the patients. Two of the reviewed studies, for instance, only indicated that patients underwent general anesthesia, without additional information (26, 29).

Besides pharmacological interventions, tDCS could conceivably also be combined with other non-invasive neuromodulation techniques, such as transcutaneous spinal direct current stimulation (tsDCS) or peripheral transcutaneous electrical nerve stimulation (TENS).

Similar to tDCS – but at the level of the spinal cord – tsDCS delivers direct currents through the skin (35). In healthy volunteers, there is evidence that anodal tsDCS could alter the spinal transmission and/or processing of nociceptive inputs. Modulation of nociceptive laser-evoked brain potentials (36), increased pain tolerance (36), reduction of mechanical pain sensitivity (37) and reduction of temporal pain summation (38) have been reported. However, anodal or cathodal tsDCS does not appear to significantly affect hyperalgesia induced by high-frequency electrical stimulation (39). Very recently, Lenoir *et al.* (40) showed a selective and segmental effect of tsDCS on nociceptive processing. Specifically, they found that low thoracic (but not cervical) tsDCS selectively altered nociceptive responses originating from the feet, suggesting

Table 1

Demographic and clinical characteristics of patients in the selected studies

Reference	Study design	Blinding	Surgery type	Number of patients	Anesthesia	Postoperative analgesia
Dubois *et al.* (2013)	RCT	Double blind	Lumbar spine surgery	63	GA (propofol, sufentanil, sevoflurane, ketamine, MgSO4)	Paracetamol Morphine PCA
Borckardt *et al.* (2013)	RCT	Single blind	TKA	40	GA (propofol, fentanyl, sevoflurane) + femoral catheter + sciatic nerve bloc	Femoral catheter Hydromorphone PCA
Glaser *et al.* (2016)	RCT	Double blind	Lumbar spine surgery	27	GA (not detailed)	Hydromorphone PCA
Khedr *et al.* (2017)	RCT	Double blind	TKA	50	Spinal anesthesia (bupivacaine, fentanyl)	Ketorolac Paracetamol Nalbuphine
Borckardt *et al.* (2017)	RCT	Double blind	TKA	58	GA (propofol, fentanyl, sevoflurane) + femoral catheter + sciatic nerve bloc	Femoral catheter Hydromorphone PCA
Ribeiro *et al.* (2017)	RCT	Double blind	Hallux valgus surgery	40	Spinal anesthesia (bupivacaine, morphine) + sedation (propofol, fentanyl, midazolam)	Paracetamol Tramadol Morphine
Jiang *et al.* (2018)	RCT	Single blind	Lumbar spine surgery	32	GA (not detailed)	Dezocine

GA: general anesthesia; MgSO4: magnesium sulfate; PCA: patient-controlled analgesia; RCT: randomized controlled trial; TKA: total knee arthroplasty.

Table 2

Details of tDCS interventions in the selected studies

Reference	Number (duration) and timing of sessions	Type of electrode	Intensity	Anode		Cathode	Control group
Dubois *et al.* (2013)	1 session (20 min Recovery room	Sponge 35 cm²	1 mA	A	Left DLPFC (F3)	Right ear	Sham tDCS
				C	Right ear	left DLPFC (F3)	
Borckardt *et al.* (2013)	4 sessions (20 min) D0 (+30 min, + 4h) D1 (morning, + 4h)	Sponge 16 cm²	2 mA	M1 knee area (C1–C2)		Right DLPFC (F4)	Sham tDCS
Glaser *et al.* (2016)	4 sessions (20 min) D0 (+30 min, + 4h) D1 (morning, + 4h)	Not detailed	2 mA	Superior motor cortex (Cz)		Right DLPFC (F4)	Sham tDCS
Khedr *et al.* (2017)	4 sessions (20 min) D1–D4	Sponge 24 cm²	2 mA	M1 knee area (C1–C2)		Contro-lateral arm	Sham tDCS
Borckardt *et al.* (2017)	4 sessions (20 min) D0 (+30 min, + 4h) D1 (morning, + 4h)	Sponge 16 cm²	2 mA	A	left DLPFC (F3)	S1 knee area (CPz)	Sham tDCS, electrodes similar to group A or B (randomly selected)
				B	M1 knee area (C1–C2)	right DLPFC (F4)	
				C	left temporo-occipital junction (P3)	medial anterior premotor (FCz)	
Ribeiro *et al.* (2017)	2 sessions (20 min) D–1 (4–8 PM) D0 (8–10 AM)	Sponge 35 cm²	2 mA	Left M1		Right supra-orbital region (FP2)	Sham tDCS
Jiang *et al.* (2018)	1 session (20 min) D1 in the morning	"Dry electrode", anode : 2,5 cm²; cathode : 12,5 cm²	2 mA	Left M1 (C3)		Right supra-orbital region (FP2)	Sham tDCS

D–1: day before surgery; D0: day of surgery; D1–4: postoperative day one to four; mA: milliamperes; DLPFC: dorsolateral prefrontal cortex; M1: primary motor cortex; tDCS: transcranial direct current stimulation; F3–4, C1–3, Cz, CPz, FCz, FP2: standardized scalp positions in the international 10–20 EEG system.

that tsDCS could act by modulating the synaptic transmission and/or local processing of nociceptive input at spinal segmental level. As tDCS and tsDCS modulate nociceptive processing at different levels, their combined application could produce additive or synergistic effects. A recent pilot trial confirmed the feasibility and safety of this approach in chronic pain (41). Nine patients suffering from chronic headache received one daily application for five consecutive days (20 minutes of tDCS followed by 20 minutes of tsDCS), without serious side effects (41).

Table 3

Outcomes and results of the selected studies

Reference	Primary outcome	Results	Secondary outcomes	Results
Dubois *et al.* (2013)	Opioid consumption D1–D2	No statistically significant difference between the groups.	VAS at rest D1–D2 VAS at movement D1–D2 Depression 48h.	No statistically significant difference between the groups.
Borckardt *et al.* (2013)	Not defined, probably cumulative opioid consumption over 48h	Decreased opioid consumption (46%) in the real tDCS group.	VAS and mood, before and after each tDCS session.	No difference in VAS or mood.
Glaser *et al.* (2016)	Cumulative opioid consumption	Decreased opioid use (23%) in the tDCS group.	BPI least pain BPI worst pain BPI pain on average.	No difference in BPI scores.
Khedr *et al.* (2017)	Opioid consumption D1–D4	Decreased opioid use (59 *vs.* 33% decrease between D1 and D4) in the tDCS group.	VAS D1–D4 LANSS D1–D4.	Decreased LANSS score in tDCS group. No difference in VAS between the groups.
Borckardt *et al.* (2017)	Not defined, probably cumulative opioid consumption over 72h.	Decreased opioid consumption in group A (DLPFC) but increased opioid consumption in group B (M1).	VAS and mood, before and after each tDCS session.	No difference in VAS or mood.
Ribeiro *et al.* (2017)	VAS 48h at rest and during walking.	Reduced VAS 48h in the tDCS group (3.1 vs. 5.5).	Opioid consumption Score variation during CPM-task BPCP score BDNF (blood and spinal).	Decreased analgesic use (73%) in the tDCS group. Improvement in CPM efficiency in the tDCS group. No difference in BDNF.
Jiang *et al.* (2018)	NRS immediately after tDCS.	Reduced NRS in the tDCS group.	Resting EEG in prefrontal cortex	Change in spectral power (alpha 2 and beta 1 band) in Fp1, correlated with the decrease in NRS.

BDNF: brain-derived neutrophic factor; BPCP score: Brazilian Profile of Chronic Pain score; BPI: Brief Pain Inventory; CPM: conditioned pain modulation; D1–4: postoperative day one to four; DLPFC: dorsolateral prefrontal cortex; LANNS: Leeds Assessment Neuropathic Symptoms and Signs questionnaire; M1: primary motor cortex; NRS: numerical rating scale; tDCS: transcranial direct current stimulation; VAS: visual analog scale; Fp1: standardized scalp position in the international 10–20 EEG system.

TENS is a peripheral neuromodulation technique which is currently recommended for postoperative pain management (33, 42). Several clinical studies have demonstrated the superiority of combining TENS and tDCS over either technique applied alone for managing chronic neuropathic (43) and low back pain (44, 45) patients. To our knowledge, no studies have tested any of these combinations in a postoperative setting.

Could subgroups of patients benefit more from tDCS?

Patients have been included in the clinical trials based only on the type of surgery they were about to undergo, without taking account of their individual risk for intense acute post-surgical pain and CPSP (46). Preoperatively, the balance between inhibitory and facilitating mechanisms of pain modulation could be assessed by measuring the magnitude of conditioned pain modulation (CPM) and temporal summation of pain (TSP) protocols (47). Based on individual pain modulation profiles, patients would be expected to express a higher (or lower) clinical pain phenotype and be more (or less) at risk of developing a chronic pain condition (48). This concept has been validated in the perioperative setting. Patients with enhanced TSP report higher acute pain scores after thoracic surgery (49) and are more prone to develop persistent pain after knee (50,51) and hip (52) arthroplasty. On the other hand, patients with inefficient CPM are more at risk for CPSP after knee arthroplasty (51), thoracotomy (53) and abdominal surgery (33). As tDCS can significantly reduce TSP (20) and strengthen CPM (19), it is possible that the preoperative pain modulating profile of each patient could predict the analgesic effects of the technique. Interestingly, it has been shown that low back pain patients with diffuse reduced pressure pain thresholds, which could be interpreted as a sign of altered pain processing, responded better to combined tDCS and peripheral electrical stimulation than patients with high pain pressure thresholds (44).

Another group deserving special attention is those patients receiving chronic opioid therapy before their surgery. They are often less easy to manage in the postoperative period : they report higher pain scores, need more analgesics and resolve their pain more slowly than opioid-naïve patients (54). These poor outcomes could be a

result of opioid-induced hyperalgesia, whose existence has been demonstrated preoperatively in opioid-treated patients (55). Recently, Braulio *et al.* have shown that tDCS over M1 reduces the magnitude of remifentanil-induced hyperalgesia in healthy volunteers (56). Consequently, one could hypothesize that perioperative tDCS sessions could be particularly useful in the management of pain of opioid-dependent patients.

Could tDCS prevent CPSP development?

The strongest predictor for the development of CPSP is the intensity and duration of acute postoperative pain. Better pain management – e.g. through the use of promising techniques like tDCS in a multimodal analgesia approach – could potentially reduce its incidence (11, 57). Moreover, as mentioned in the previous section, tDCS affects pain-modulation mechanisms that could in turn influence the likelihood of CPSP occurrence (19, 20, 51). As no clinical study has followed patients up for more than a couple of days, we currently have no data to support or disprove an effect of perioperative tDCS sessions on CPSP development.

Conclusion

In summary, the available evidence suggests that tDCS considerably reduces opioid use after various surgical procedures, whereas its effects on pain perception are less clear. More studies are needed to better establish the place of tDCS in this setting and to determine the optimal stimulation protocols.

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