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6 Programming

Various factors make ICS programming a very complex task: First, there are numerous possible combinations of parameters; Second, no sensory, motor, or other signs are generally produced during subthreshold stimulation; Third, for several conditions, clinical effects usually become noticeable several days beyond the time of stimulation parameter changes: benefit is delayed when the stimulator is switched “on” and plasticity-driven after-effects are prolonged when the stimulator is switched “off.” This is the reason why it is impractical and inefficient to assess the possible effects that may be produced by the stimulation of the cortex intraoperatively. Conversely, in other neuromodulation techniques, programming can be guided by the clinical effects that are produced as soon as the stimulator is switched “on,” like paresthesias in the painful limb after spinal cord stimulation or tremor arrest after thalamic or subthalamic nucleus stimulation (Arle and Shils 2011). Thus, it can take weeks to determine whether ICS is efficacious for the various conditions for which it is applied. Also in the case of pain, analgesia from intraoperative stimulation can sometimes be prolonged. A few rare cases of rapid clinical response (e.g. action tremor) are on record (Nguyen et al 1998).

Stimulation intensity appears to be the most difficult factor to determine. This parameter is all the more difficult to determine in that the only relevant value is the output current of the lead electrodes expressed in milliamperes (mA). According to our initial results, an intensity of about 2 mA was necessary and sufficient to effectively stimulate M1 and obtain a clinical effect. The first stimulators (Itrel 3, Synergy) did not directly indicate the values of the output current (I). Only the voltage (V) could be selected allowing deduction of the output current by calculating the impedance of the system (R) ($V=RI$). More recent stimulators (e.g. Prime Advanced, Restore) now directly indicate the output current. The output current values must be adjusted according to the distance between the electrode and the cortex. Higher intensity stimulation is obviously required in the presence of cerebral atrophy.

A trial period before permanent implantation may increase the risk of device infection at cortical level, so that, whenever possible, the whole ICS system is frequently implanted in a single session: this certainly applies to all conditions discussed in this volume, with the exception of pain, in which most authors test the results via temporary extensions. After implantation, the patient is kept in hospital for 1 week to ensure proper healing of the incision. During this time, several stimulation parameters are screened. At discharge, the stimulator can be switched “on.”

Chronic stimulation parameters (pulse width: 60-180 μ s; frequency: 20-60 Hz; voltage: 1-4 V) largely differ from those applied for intraoperative mapping. In particular, intensities used for bipolar chronic stimulation are far below motor

threshold, whereas intraoperative motor mapping obviously requires suprathreshold intensities. Some authors believe that the contact that is the intraoperative “best anode”(+) should be selected as the negative electrode (cathode) for chronic stimulation (see [chapter 5](#)): this suggestion is based on a very small sample of patients, and as of yet there has been no independent replication. Although the stimulation of the nervous tissue generally occurs in the vicinity of the cathode, this is not true in M1 ICS: due to the large size of the electrode and different orientations of the cortical nerve fibers (parallel and perpendicular to the laminae), various populations of axons can be activated under the cathode and anode making bipolar stimulation bifocal, i.e. with simultaneous activation. Bifocal also means that the neural activity evoked near the cathode may affect activity near the anode and viceversa via intracortical connections. In other words, despite the large center-to-center distance of the cathode and the anode (≥ 1 cm), some overlap of the corresponding stimulus-evoked fields is still present, which means that the electrical fields in the cortex below the cathode and the anode are different from real monopolar fields. Therefore, selecting more distant contacts for chronic stimulation does not increase the volume of cortical activation as previously suggested, but results in a more bifocal stimulation, activating more distinct neural pathways. Similarly, increasing stimulation intensity does not improve ICS efficacy that likely relates to fiber activation in superficial cortical layers, but recruits additional neural circuits that originate in deeper cortical layers.

Developments in stimulator and electrode designs have increased programming options. Instead of just 4 contacts and the ability to set a single contact configuration and electrical parameter configuration, new devices allow for a single program to contain multiple contact configurations with differing electrical parameters for each configuration.

While the program is running, each configuration is activated in a sequence specific to the manufacturer. These multiple configurations are extremely beneficial in allowing for the targeting of specific pain regions and even by adding multi-pulse patterns for a single region. Here we will focus on our experience with 23 patients with both pain and movement disorders using M1 ICS as treatment.

Programming of our pain patients includes a wide range of stimulation parameters with voltage varying from 2.2 volts up to 7.1V when using constant voltage devices and from 3 mA up to 17 mA when using constant current devices, pulse width varying from 120 μ s up to 330 μ s, and frequency varying from 50 Hz up to 130 Hz. This can be contrasted with other researcher groups who begin from 0.5V up to 10V, from 120 μ s up to 450 μ s and from 1Hz up to 130 Hz. All of our patients start with monopolar settings, but often bipolar settings are used with more anodal contacts. Most of the patients implanted with the newer constant current systems (Precisions Plus neural stimulator, Boston Scientific, Valencia, CA) have more than one program running. Prior to this all patients were implanted with the Medtronic quadripolar Resume lead and the Itrel II IPG (Medtronic, Minneapolis, MN). However, Itrel II and Synergy

(Medtronic) do not allow monopolar stimulation with the metal case of IPG as the distant indifferent electrode.

Initial patient programming typically begins within 24 hours of electrode implantation. Monopolar stimulation is used to evaluate all contacts using a stimulation rate of 210 μ s and a stimulation frequency of 130 Hz. The voltage is slowly raised to 4.0V or 8.0 mA (depending upon the device used) specifically looking for adverse motor movements and/or sensory changes. Additionally the patient state is evaluated with the primary concern being the possible generation of seizure activity during this evaluation (Henderson et al 2010). To date, we have had three seizures generated during the programming phase out of 23 patients, none of which occurred at the initial programming session. In the first patient, a focal motor seizure may have occurred 2 days after initial programming. This event was unwitnessed by medical personnel, yet the description fit well with the characteristics of this type of seizure. For this particular patient, a seizure was also generated during M1 mapping in the operating room. Since this time, all M1 ICS patients, where a seizure occurred during intraoperative mapping, are kept below 2.5 volts or 5 mA for the first two weeks post surgery. However, none of our patients were put on anti-epileptic medications, unlike other authors. The second programming seizure occurred at the 18 month follow-up in a post-stroke pain patient: a seizure was generated while raising the stimulator voltage from 4.0V up to 4.3V. Thereafter, voltage has been kept below 4.0V and no further seizure activity has been noted. The seizure lasted about 15 seconds. The patient was kept in the hospital overnight and no seizures have occurred since that time. In the third patient, a focal motor seizure, in the face region, was generated while increasing the amplitude of one of three configurations to 13 mA. This was at the 1 year follow-up. The seizure stopped within 3 seconds of reducing the stimulation. There was no electrographic recording during this particular event, yet the patient's description of a confused state after the event appeared to be more seizure-like than a pure motor event. The reason for the increase in this patient was due to a loss of benefit over time. Additionally this patient was programmed with three electrode combination and parameter sequences. Recently, we have had a patient develop what appeared to be a seizure disorder, with focal motor seizures and potentially more generalized events. However, despite multiple recording periods, no electrographic seizures have been recorded and this may turn out to be a unique development of pseudoseizures as the evaluation is ongoing.

In all cases of M1 ICS for pain, we have had to modify the programming settings. In some, the only modification was increasing the stimulation amplitude over time, while in other cases we have had to add multiple configurations. We initially choose new configurations based on the monopolar evaluation. Before adding multiple configurations, frequency and pulse width are adjusted for the single configuration. Pulse width is slowly increased looking for changes in effect. The most common change that we see is the recruitment of more "areas". Frequency changes tend to shift the location of the stimulation effect without causing an increased sensation over the

initial stimulated region. This is very helpful if we are close to the area of pain, but also close to a point where the stimulation is painful. When adding new configurations, the goal is to either bring in new regions or to modulate the pulse pattern at a single region. Modulation of a region is done by keeping the same electrode combinations, but modifying the electrical parameters. Presently, no device allows the setting of the time interval between each configuration, so they all run sequentially with a very short interval between each configuration. This is ineffectual outside of cases concerning pain, since most other indication effects grow over time, and the rapid flipping of parameters runs the real risk of overlooking useful combinations.

For initial programming of movement disorder patients each contact is tested in a fashion similar to the pain cases, yet the lead center contacts are activated initially with an amplitude at 3mA. This is chosen based on the OR mapping which makes sure that the electrode is centered over the hand and arm region. If the patient feels for whatever reason that they cannot tolerate these settings, then more lateral contacts are added while removing the contacts furthest from the new lateral contact. In our experience two contacts are able to be activated at the initial programming session.

It is here useful to mention the approaches taken by other authors. According to Pirotte for example (Pirotte et al 2009), MIICS induces pain relief within 10-15 minutes of the start of stimulation and lasting 15-120 minutes after the stimulation is switched off. Since in the first 3 days after implantation the pain often disappears or is strongly attenuated by general anesthesia, these authors usually wait for 3 days before starting the test run (i.e. patients are scheduled for surgery on Thursday, stay 24 hours in the intensive care unit and rest in their room during the weekend until Monday morning, when stimulation begins) or at least wait until the pain has returned to its disabling level. Some patients report that pain relief can remain stable for more than 24 hours, if the stimulation period is longer than 4 hours (so-called after-effect). Other patients describe that severe pain recurs when they switch the stimulation off for more than 2 days. The goal of the test period is to test all parameters during a short period of time, in order to decrease the risk of infection due to the presence of transcutaneous wires. Pain intensity is measured using a visual analog scale (VAS) by specially trained nurses or physicians; a pain diary has also to be completed by the patient. During the test, the bipolar combinations for which an analgesic effect has been observed must be re-tested many times in a single-blind (blinded patient) manner in order to exclude a placebo effect. This last step is crucial to consider the test as positive. Indeed, many combinations may appear as “good” only once, without being confirmed at further stimulations. Blinding is attained by covering and shielding the external stimulation device in the area of the lead combinations. Continuous stimulation is used during the test trial, but after IPG implantation, intermittent stimulation is programmed to avoid habituation, at least initially. In practice, a reproducible analgesic effect is often observed within the first 10 days of stimulation. In several cases, the coupling configuration is critical. Some patients mention a transient painful sensation (reported as a painful “click”) centered on the craniotomy when stimulation is switched on,

probably due to a direct stimulation of the dura. On occasion, stimulation may increase burning or tingling sensations.

A few caveats: 1) neurogenic pain can fluctuate significantly from one day to another; 2) patients tested in a hospital do not behave like at home. Furthermore, pain patients have large expectations that they strongly and very quickly jump to the conclusion that slight variations in pain levels can accurately predict successful outcomes.

Loss of effect after an initial excellent analgesia has been reported by many investigators. Switching from continuous to cyclical stimulation –or viceversa– may restore benefit in some cases within a few hours. Although pulse width and frequency may be increased as follow-up progresses, particularly in cases in which effects dwindle, the efficacy of stimulation changes very little with such incremental increases. On the other hand, some authors find that loss of efficacy may be due to keeping parameter settings constant, suggesting that perhaps longer-term plastic changes eventually catch up with ICS to limit its efficacy (see also Henderson et al 2004). Loss of effect can also be due to extensive fibrosis below and around the contacts: removal thereof may restore benefit (Canavero 2009).

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