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Review Article

Contributions of Implantable Power Generators to the Failures and Complications in Conventional Neuromodulation Therapy -

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ABSTRACT

Neuromodulation has become a standard of care in the management of movement disorders and chronic pain management while the list of indications has been growing recently. The conventional equipment has electrodes, connection wires and power generator, all implantable. Several studies and evidence based medicine support the treatment modality as a viable option although the device related complications demand rapid updates to reduce avoidable adverse events. Overall complication rates vary and range between 20 and 75%, most of them manageable conservatively. Implantable power generator appears to be a component that requires attention to reduce the events like infection and device related failure; mostly contributed by the related surgical procedure as well as the additional bulk of the battery. Almost all instances of pain following implantation were related to IPG pocket. Several reports have recently come up with the safety issues of the stimulation equipment and the recommendations propose actions to improve acceptability of the technique. As nanomaterials have improved the lead designs, a wireless access without an implantable power generator appears to be an attractive option to reduce the complications, while the acceptability can be improved for both cosmetic as well as cost reasons.

Keywords: Neuromodulation; Spinal cord stimulation; Implantable power generator; Wireless stimulation; Infection

INTRODUCTION

Chronic pain is one of the most common complaints accounting for frequent medical visits by general public and remains a prevalent health care concern [1,2].

Once the medical and surgical options run out, neuromodulation has been recommended as the treatment of choice. Spinal Cord and Peripheral Nerve Stimulations (SCS and PNS), along with their modifications, have been in use for four decades in the management of several refractory pain conditions like Failed Back Surgery Syndrome (FBSS), peripheral neuropathy, neuralgia, angina pectoris, peripheral vascular disease, Complex Regional Pain Syndrome (CRPS) and others [3-8]. SCS has been supported by Evidence Based Medicine (EBM) and proven to be cost effective compared to repeated surgeries or long term pain medication [4,9,10]. It is a time tested and widely accepted technology too in terms of safety and efficacy to be called as a standard of care for chronic pain [3,11,12]. Studies established its cost effectiveness in FBSS as well as complex regional pain syndromes [13,14]. Nevertheless, about 20% of patients do not proceed beyond the trial and only 50% of cases with successful trial go for long term therapy [8,13,15]. SCS/PNS failures could be attributed in some cases to the stimulation parameters, device malalignment, complications due to the implant dislocations/fractures and postural changes. The bulk of the implanted components, especially the IPG, could be contributing to these complications [3,16-18].

Apart from failures, SCS is associated with several complications related to the implanted components and failed stimulation. Surgically, it is a minimally invasive procedure with 30-40% overall complications like lead migration/fracture, Implantable Pulse Generator (IPG) site pain, infections, failed stimulation and rarely neurological injury. Some patients had allergic reactions to the implanted components [3,9,19-21].

Several modifications to the technology in recent years, periodic updates and peer reviewed recommendations facilitated reduction in complications and minimized the risks [9,22]. However, the complications related to the bulk of the implanted components still remain a big challenge and probably the unwanted parts need to be eliminated for better acceptance of this efficient therapeutic modality.

SCS rates of conversion from trial to permanent implantation

Due to various reasons including patient responses, implant performances, and adverse events, SCS trials do not proceed to become permanent implants. In select patient populations these rates

could be very appealing since they are between 65 and 80% for varied disease presentations [21]. But, from a census coming from nationwide application of SCS, the rates fall down to 41% [23].

These variable acceptance rates could be due to the differential efficacy of SCS: proven cost effective method for FBSS but not so established when it comes to neuropathic pain. They also might reflect the surgical technique employed by different pain management teams: the percutaneous method compared to open procedure, or the technology employed by physicians, since cylindrical electrodes are less invasive but the paddles are more stable in terms of reducing migration [24,25].

Shamji et al reviewed 11 studies on 542 patients and reported 9% IPG site pain and wound complications in 5%, but there were differences in percutaneous and surgical placement of implants. Wound complications occur more often with surgical placement of devices (5%) compared to percutaneous placement (2%), as expected, significant enough. Pain was also more with surgical procedure (12%) and less with percutaneous placements (7%). On the other hand, only percutaneous placement method had loss of therapeutic efficiency (4%; range of 0-14%) [26]. In the 542 patients followed in this work, there were 184 complications. Of these, 74 were related to the SCS device itself, 69 were related to the therapy, and 41 represented biological complications [26].

Complications of conventional neuromodulation equipment

Several adverse events follow implantation of the conventional devices that require three components to be surgically placed inside the patient body: the stimulation electrodes, the implantable power generator and the wires connecting these two along with the anchoring elements. Multiple incisions are required to place these parts to accomplish the therapeutic goals.

Pain related to implanted device components

Surgical incisions cause pain invariably, and the implantation of device components only makes it worse, especially at the IPG locations or the lead extension junctions due to the bulk of the material placed inside. In the PROCESS study 12% (5 of 42) patients had significant pain, probably attributed to the bulkier IPG, and one patient required surgical intervention [13]. It was 5% in the report by de Vos et al and 12% (86/707 patients) in the retrospective review by Mekhail et al with a range of 0-40% (and mean value of 5.8%) from a review of 20 studies by Turner et al [21,27,28]. Differences in the reports are possible since the location of IPG varies and thickness of

body fat at different places. Reports published so far have not verified this anatomical difference between buttock and anterior abdominal wall.

Surgical site inflammation and infection

Overall infection rates for SCS have been higher than other non-neuromodulation surgical procedures with a range between 2.5% and 14% compared to 2-5% of the latter; the risk factors like smoking, obesity, diabetes mellitus remaining constant variables [3,8,13,18,20,21,27]. The contributory role of these comorbidities probably remain the same for SCS too, although the significant relationship between infections following SCS implantation and these variables remains to be established firmly [21,29]. Most infections at surgical sites are superficial and probably do not reach the tissue planes of the implant [29] while deep fascia and/or muscle involvement compromises the device components [9].

Notably, the most common site of infection is the IPG implantation area. This is followed by lumbar incision site and electrodes, most often by *Staphylococcus aureus* [30]. Fortunately, epidural abscess is extremely rare along with infections along the nervous system like meningitis [29-32].

Wound infections (Superficial and Deep)

Surgery related infections make a major component of SCS complications and occur in 4-10% of cases, sometimes warranting implant removal. This rate is almost double the infections (2-5%) seen with other kinds of surgeries performed routinely in the US [21]. PROCESS study reported infections in 10% (4 out of 42) patients and 2 of them needed surgical intervention [13]. Kumar et al had to explant 10 implants due to infection among 14 cases of infection (3.4%) while 4 patients responded to antibiotic treatment [8]. Deep infections in the IPG pocket were recorded in 20 patients among 32 patients with surgical infections (4.5%) by Mekhail et al. Two patients had lead track infection and 10 had superficial infections at the site of lead introduction. Abscess formation was noticed in 18 patients with deep infections [21]. In a much larger review of 2972 implants, Cameron reported a 3.4% (100 cases) infection rate [3], similar to the observations by Engle et al [33]. Occipital nerve stimulations studies also had infection rate close to the SCS; 4% in report by Saper et al and 4.5% reported by Paemeleire et al [34,35]. Sacral nerve stimulators had wound issues in 7% and infection in 5% [36].

The most common site of infection in all these reports was the IPG pocket [18]. In the series reported by Follett et al. 54% of the infections were of IPG surgery site [31].

IPG and mechanical adversities on stimulation electrodes

Not only the infective complications, but the mechanical adverse events like lead displacements also had association with IPG.

Laboratory evidence showed that a correlation exists between the site of IPG and frequency of electrode migration/dislocations. Gluteal region had worse incidence of lead migrations compared to anterior abdominal wall possibly due to the anchoring pull happening during forward and lateral bending movements of the trunk. On the other hand, rotations twists of the trunks have increased electrode migrations when IPGs were placed in the anterior abdominal wall [37].

Altogether, the lead migration with buttock IPG was twice the number that happens with abdominal wall IPG placement, which apparently was recommended unless contraindicated [37,38].

IPG location has been noted as the notorious spot for infections in not only SCS patients, but in Deep Brain Stimulation (DBS) cases also. Thus, in neuromodulation practice, in general, IPG and the extension wires appear to contribute to sepsis more than anything else, and fortunately they can be explanted without disturbing the epidural components which are very uncommonly infected [20].

Battery failure

The current SCS technology still employs implantable components viz., electrodes, connection wires and power generator (battery). Issues with battery thus require surgical revisions while the bulk of the battery and the surgical wounds are prone for complications like hemorrhage and infection, apart from disconnections.

The IPG contains the battery and for depletions of energy, repeated surgical interventions are performed. Sometimes, depending upon the stimulation parameters or patient requirements, the battery expiration might come sooner than expected, the so called "battery failures" which occurred in 1.7% cases among 1900 patients [3]. This failure rate was 10.2% in the experience of Turner et al [27], while some of the reports did not mention these failures [8,13,21,28].

The power source depletion depends upon the anatomical location of the electrodes with respect to the spinal cord. The segment of spine as thoracic spine or cervical spine differ in the demands as well as the contacts functioning in order to deliver the required stimulation. This is now an important factor to consider since the technical advancements of the present day stimulation like high frequency, burst stimulation require a much higher amount of current compared to the conventional or low frequency stimulation. It would be impossible to deliver the stimulation without rechargeable batteries, which have lower life expectancy and limited clinical experience. Not only the limited life span, but higher awareness from the user end, makes the rechargeable batteries problematic with questionable cost-effectiveness [18,39,40]. Recharging the battery, on the other hand, is also uncomfortable to the patient because of the heat generated during the procedure.

As of now, repeated battery changes translates in to repeated surgical procedures and the complications that follow with surgery. However, there is no study so far has looked in to this common side effect of the present day IPG systems.

A report by Medtronic regarding the product report on 1983 SCS patients followed up for 7 years, had a total of 973 events. Among them, 30% (295) were product related and 70% (656) were non-product related; 96.3% of the former involved lead or extension wires while 90.2% of the latter had IPG related complications. The IPG related complications in nearly 600 of these cases included surgical site pain, infection, wound dehiscence and performance related failures [41,42].

SCS clinical work spanning over four decades still has to deal with equipment malfunction after all the research in to the biocompatible materials, refined anchoring systems, peer reviews, panel recommendations and training. Significant among the adverse events, IPG related complications appear to be completely avoidable considering the present day wireless technology. Table 1 shows the experiences from different centers [42-46].

DISCUSSION

Neuromodulation is a time tested efficient therapeutic modality in chronic pain management. Several studies established the role of SCS,

PNS and their variants as standard of care. However, the technology updates to improve the outcomes with reduced adverse events are yet to become accepted in routine practice. IPG related complications have been linked to failures of neuromodulation in several recent reviews and some rescue measures are in practice.

Infection control

It is not an easy endeavor to control infections that follow implantation of devices although superficial infections tend to respond very well to antibiotics tailored as per the bacterial growth. Occasionally, wound debridement provides additional control [8,31].

In their recent retrospective review of 2737 cases, Hoelzer et al reported a 2.45% infection rate with a slight reduction over the previously reported 3-6% incidence [30]. It also had conflicting findings like lack of association between infection and co-morbid factors like smoking and diabetes. The study did not report of the location of the infection site or control of infection with regard to explanation of the device. Follett et al. In their study, reported that 94% of their infected SCS patients (N = 114) required removal of the system, either complete or partial (Follett KA, Boortz-Marx RL, Drake JM et al. Prevention and management of intrathecal drug delivery and spinal cord stimulation system infections. *Anesthesiology* 2004; 100: 1582-1594). Deer et al had a 22.4% salvage in their cohort of 67 patients with infected SCS encouraging an aggressive non-surgical approach, especially in patients with superficial wound infections in the absence of systemic sepsis, a protocol recommended by others also [9,20,42,43].

IPG communication failures

Apart from being the source of wound complications from an additional surgical procedure, IPG can fail to communicate with the external telemetry devices leading to ineffective SCS. Unfortunately, IPG failures due to wrong implantations require repeated surgeries [9].

Apparently, hardware complications outnumber the reactive inflammation or infections and IPG contributed to these adverse events significantly. There is a learning curve in standardization of the technique and sometimes the novel techniques result in higher

rates of complications. Surgeons' experience plays a vital role in minimization of both device related and surgery related adverse events [9,42].

Wireless neuromodulation

One of the recent advancements in neuromodulation is wireless access to the built-in receiver in stimulation electrodes utilizing nanotechnology. This device involves minimally invasive percutaneous placement of stimulation electrodes only and does not require placement of battery or the connection cables inside the body. The power generator remains extracorporeal on a wearable antenna assembly. Several reports have been published in pilot studies in an attempt to establish its safety and efficacy. Further multicenter trials have been initiated and the results are encouraging [47-50].

The wireless technology is devoid of the IPG complications and is expected to mitigate the associated lead related adverse events like migration. In addition, the surgical exposure and operating time will be considerably low compared to the procedure utilizing the traditional equipment that requires implantation of the electrodes, their connection extensions and the IPG inside the body. Thus the wireless device will be offering not only cosmetically a better outcome, but also reduced hospital as well as overall health care expenses in the long run [50].

SUMMARY

SCS is a standard of care in pain management with cost effective outcome, but suffers from serious and avoidable complications of the present day technology that requires all the components to be implanted. Significant incidence of pain at the IPG site, followed by infection in some cases, have been constant adverse events in a successful SCS therapy, apart from communication failures and removal/reimplantation procedures to replace a nonfunctional or end of life battery. Wireless approach and nanotechnology available today bypass the implantation of IPG and its accessory connecting wires, thus reducing the affiliated complications. So far, in limited numbers, wireless power generators have shown encouraging results and have no IPG related complications since there was no need to implant the battery and its accessories. Further ongoing clinical trials and studies are expecting to provide the required support to this safer and cost effective treatment as an alternative to the present day SCS with unnecessary implantable components.

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Table 1: Complications due to implanted (IPG) components from the recent published literature.

Author and year	Number	Pain	wound compln	stimulation issues
Cameron 2004 ³	2972		3.4% (infection)	2.4% (+1.6% IPG failure)
Kumar et al 2008 ¹³	42	5 (12)	4 (10%)	5 (12%)
Turner et al 2010 ⁴⁶	28	7 (25%)	4 (14%)	4 (14%)
Van Buyten et al 2013 ⁴⁵	72	15 (20.8%)	5 (7%) infection	2 (2%)
		IPG pocket	5 (7%) hematoma	
Al-Kaisy et al 2014 ⁴⁴	83	7 (8.4%)	6 (7%)	2 (2.4%)
Deer et al 2014 ⁹		2.5% (IPG seroma)	10% (infection)	1.2% (IPG failure)
Shamji et al 2015 ²⁶	542	9% (IPG pain)	5%	
Hoelzer et al 2017 ³⁰	2737		67 (2.4%) infection	
Kleiber et al 2016 ⁴³	212	14 (6.4%)	9 (4.2%)	22 (10%)
		(Hematoma in 5 (2.6%))		

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