Validation and Perspectives of Neuromodulation in Japan

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Abstract

Neuromodulation in functional neurosurgery is closely related to the development and availability of devices such as implantable electric stimulators and pumps. All such devices used in Japan are developed and made in foreign countries, and no made-in-Japan device exists. Introduction and approval by the government took many years for most devices, during which time many patients had to continue to live in our medically conservative country. The history of neuromodulation is summarized in Japan and the problems surrounding neuromodulation pointed out. Everyone has to aware of such circumstances and make every effort to improve the internationally unusual situation of neuromodulation in Japan. Otherwise, Japan will become a medically isolated country in the near future.

Key words: neuromodulation, deep brain stimulation, implantable pump, device-lag

Introduction

Neuromodulation encompasses various definitions in both its entity and activity. Neuromodulation includes treatments that involve the stimulation of various nervous tissues in the central nervous system, peripheral nervous system, or autonomic nervous system, that lead to “modulation” of activity. By definition, neuromodulation is a therapeutic modification of activity through stimulation or medication, both of which are introduced by implanted devices. Implanted devices are usually neural stimulators and drug delivery devices such as pumps. This is a very important field of functional neurosurgery for management of not only intractable pain and movement disorders but also various types of neurological dysfunctions.

Since the 1990s, we have been involved extensively in introducing neuromodulation devices to Japan, including not only in clinical practice but in clinical trials, government approval process, and negotiations with industries. Based on this experience, we would like to review the history of neuromodulation in Japan, clarify the problems now faced, and propose possible solutions.

Implantable Electrical Stimulation Devices for Pain

Tsubokawa48,52) and Tanikawa46) were the first neurosurgeons to perform deep brain stimulation (DBS) and spinal cord stimulation (SCS) in Japan. From the late 1970s to the early 1990s, the only available implantable devices for DBS and SCS were based on the X-trel system (Medtronic, Inc., Minneapolis, Minnesota, USA) that used electro-magnetic conduction to deliver electrical energy from a coil antenna placed over the body surface. In the early 1990s, a completely implantable pulse generator called Itrel-3 (Medtronic, Inc.) became available, and a clinical trial was conducted for both intracranial stimulation and SCS. Itrel-3 was approved for pain management in 1994 in Japan, although the US Food and Drug Administration (FDA) does not approve DBS for pain even today because not enough objective data has been obtained. Motor cortex stimulation (MCS) for intractable pain was introduced in early 1990s. The plate type quadripolar electrode for SCS is used for MCS,22,49–51) but this type of electrode is approved only for SCS. Therefore, even today, the use of plate type electrode in MCS is off-label use in
its strict sense, at least in Japan.

**Vagal Nerve Stimulation (VNS) for Intractable Epilepsy**

Vagal nerve stimulation for intractable epilepsy in humans was first reported in 1990. Multi-center clinical trial of VNS for intractable epilepsy started in 1992 and VNS was implanted 1993 for the first time in Japan. The detailed data obtained in the 30-case study with favorable results was submitted to the Ministry of Health and Welfare (MHW; the forerunner of Ministry of Health, Labour and Welfare [MHLW]) in 1998 for VNS to be approved in Japan. VNS had already received approval in Europe in 1994 and the USA in 1997 for general practice for intractable epilepsy. However, because of unknown reasons, we had to wait for 7 years until the final decision of the MHW. By that time, the device used for the clinical trial in Japan had been replaced by a new model in USA, and the submission using the old model was no longer valid, so the submission had to be withdrawn in 2005. The MHLW finally approved VNS for intractable epilepsy in 2010. It took 18 years for VNS to be approved in Japan.

**Electrical Stimulation Device for Movement Disorders**

Itrel-2 or Soletra (Medtronic, Inc.) became available in 2000 in Japan, and was approved without clinical trial. I started DBS for movement disorders in 1998 when we had to use only the X-trel system. DBS with Soletra was approved only for “tremor” of Parkinson disease (PD), essential tremor, and other origins. Subthalamic nucleus (STN) stimulation became recognized as effective treatment for other symptoms of PD than tremor, and a dramatic surge of interest in STN DBS occurred in the early 2000s. Most PD patients now undergo STN DBS not only for tremor but also for wearing-off, freezing gait, and dyskinesia, but even today DBS is approved officially only for tremor. I started globus pallidum interna DBS for generalized dystonia in 2000, and its efficacy in generalized dystonia is well established today. However, this is also an off-label use of DBS in Japan.

**Implantable Pumps for Chronic Intrathecal Infusion**

In 1990, I approached a Japan pharmaceutical company, Nihon Ciba-Geigy K.K. (Tokyo), asking about the possibility of introduction of intrathecal baclofen treatment (ITB) for spasticity. Although Penn and Kroin had reported usefulness, safety, and effectiveness of ITB in severe spasticity patients, the company answered that they had no intention at all to start ITB in Japan because ITB is too risky and not cost effective in Japan. I personally imported baclofen solution for intrathecal use from Switzerland and started bolus intrathecal injections through lumbar puncture. Until the end of the 1990s in Japan, there was no possibility of introducing ITB using a chronic implantable drug pump that had been approved and widely used in the US since 1992 and European countries since 1994. Because Daiichi Pharmaceutical Company (the forerunner of Daiichi Sankyo Co., Ltd., Tokyo) had been manufacturing a generic form of oral baclofen (Gabalon) in Japan, I asked this company to start clinical trials of ITB. The trial started in 2002 and ITB was officially approved in 2006. This clinical trial was unique and the first in Japan because of the combination of trials of both drug and device at the same time.

About 500 baclofen pumps have been implanted so far in Japan, whereas more than 50,000 pumps are used worldwide. Such implantable pumps for chronic intrathecal administration have been more widely used in pain management using morphine, local anesthetics, and other medications. More than 110,000 patients have undergone pump implantation worldwide, in contrast to none in Japan. Even today, we cannot use implantable pumps for pain management.

**Phrenic Nerve Pacing**

Electrical stimulation of the phrenic nerve started in 1960s in the USA for patients with central hypoventilation syndrome. It is an established treatment, and many patients have received implantation of phrenic pacers with long-term ventilation. Even small children with central hypoventilation syndrome have benefited from this treatment. The cause of hypoventilation includes high cervical spinal cord injury, brainstem hemorrhage, tumors in the craniovertebral junction, sleep apnea syndrome, atlanto-axial dislocation, and so on. In Japan, this treatment is not approved at all, although a few patients underwent implantation of the pacing device imported personally by some neurosurgeons. The device system is not affordable for most patients, and I reported off-label use of spinal cord stimulator for phrenic ventilation. This is a compromised technique, but function is quite satisfactory, and some patients have been using this pacing method for nearly 10 years. At this moment in Japan, there is no possibility at all for the pacing system to be officially approved. This is mainly because...
Table 1 Neuromodulation devices and indications not approved or recognized in Japan

<table>
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<td>DBS for addiction</td>
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<td>DBS for anorexia</td>
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<td>Phrenic nerve pacing</td>
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<td>Diaphragm pacing</td>
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<td>pain</td>
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<td>14, 21, 36</td>
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A: approved; abili®: stimulator developed by IntraPace®, Inc., Mountain View, California, USA; Bion®: microstimulator developed by Boston Scientific Neuromodulation Corp., Valencia, California, USA; CardioFit®: stimulation system developed by BioControl Medical, Yehud, Israel; CVRx’s RheosTM: hypertension therapy device developed by CVRx Inc., Minneapolis, Minnesota, USA; DBS: deep brain stimulation; Neuropace™: investigational device for epilepsy developed by NeuroPace, Inc., Mountain View, California, USA; OCD: obsessive-compulsive disorder; R: in research; SANTE®: US clinical trial called SANTE® (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy); SCS: spinal cord stimulation.

the number of hypoventilation patients is too small to set up an official clinical trial that usually requires an enormous budget.

Other Devices

Many neuromodulation devices and indications have not been approved or recognized in Japan. Table 1 lists such types of devices and procedures. Some are widely accepted for general practice, while others are still in the investigational stage. Most new devices become approved in Europe first, and then in the US by the FDA.

Problems in Japan

Most neuromodulation devices used in Japan became available many years after introduction and approval in foreign countries. Compared even with South Korea and China, Japan is far behind in introducing such devices that are indispensable for neuromodulation. Such a situation is called “device-lag.” The government has already noticed this problem and is trying to introduce improvements, but the pace of change is still slow. There are several reasons for such delay. Even if a device is widely used outside Japan, and its efficacy is already proven, the government requires clinical trial in the Japanese population in most cases. Such clinical trials are very expensive and might not be cost-effective from the view of device companies, and they hesitate. Most medical practitioners are too busy for daily clinical practice to set up or engage in clinical trials. Because medicine in Japan is generally all covered by social insurance, hospital administrators are not well accustomed to the procedures of clinical trials. Nowadays, most academic hospitals have administrative divisions for clinical trials, but medical practitioners are not well aware of the necessary procedures for clinical trials.

Although Japan has extremely high technology expertise, very few companies manufacture implantable medical devices. This is partly due to the Japanese culture to try to avoid risks associated with such devices, but also due to very strict regulation by the government. One of the problems is that the pharmaceutical affairs law that controls medication, devices, and medical equipment regulates medical devices. There are no specific laws only for medical devices. I heard from many physicians saying, “If Japanese companies such as Sony Corporation (Tokyo) or Panasonic Corporation (Kadoma, Osaka) make implantable devices, they can make much superior specification to the existing devices.”
may be true, but they do not discuss or consider seriously why this is impossible in Japan. Such conversation always finishes as small and non-productive talk. The Science Council of Japan pointed out in 2008 the lack of research and development facilities and work force in Japan for the introduction of innovative medical devices. They wished to promote such scientific activities as a direction of medical industry in Japan. However, little seems to have happened since then.

Because neuromodulation is closely related with companies, medical practitioners specialized in this field tend to be biased both consciously and unconsciously. Device companies promote their devices by supporting meetings, training courses, or seemingly attractive pamphlets. We cannot deny that many physicians may be influenced by such commercialism. Companies may try to deny conventional pure-surgical techniques without adequate academic validation. They may use attractive “catch-phrases” like “DBS for PD, the sooner the better” without sufficient scientific validation. They may pressure the government for their product to be approved earlier with inadequate clinical data.\(^1\)\(^1\) We medical personnel have to be aware of such kinds of risks and careful to be independent from industries and not to be biased. However, it is also true that such attitudes may evoke conflicts with industries. We have to consider companies as a good partner and keep a “beautiful” distance from them.

With the introduction of neuromodulation techniques for psychiatric disorders,\(^3\)\(^4\)\(^5\) neuro-ethics is becoming a very important field of neuroscience. There are some specialists of neuro-ethics in Japan, but they seem too ideological and not based in the clinical forefront medical practitioners are facing every day. Even today, all neuromodulation treatment for psychiatric disorders is in the investigational stage, but the efficacy for intractable depression and obsessive-compulsive disorders is promising. By setting up well-designed protocols, starting studies on neuromodulation for psychiatric disorders in Japan should be regarded feasible and warranted.

Although there are more than 7000 neurosurgeons in Japan, they say they are too busy to specialize in one particular field of neurosurgery. Most neurosurgeons in Japan have to deal with all fields of neurosurgical conditions such as acute stroke, traumatic brain injury, and brain tumor. They also have to manage hypertension, headache, dementia, and even prevention of ischemic stroke. Becoming sub-specialized is often difficult even in academic hospitals. Such circumstances present one of obstacles for functional neurosurgery or neuromodulation to develop. If we look at Western countries, there are few functional neurosurgeons who are specialized in both epilepsy surgery and movement disorder surgery, whereas in Japan, one functional neurosurgeon has to cover pain, movement disorders, epilepsy, spasticity, and even transcranial magnetic stimulation. Scattered and shallow sub-specialization is a serious problem in neurosurgery in Japan.

**Future Perspectives**

To improve the circumstances surrounding neuromodulation in Japan, all medical personnel must first be aware of the above-mentioned problems. Then we need serious discussion on what to do or not to do. We also have to consider if neuromodulation is truly better than any other conventional approaches. Without such serious efforts, Japan will be medically isolated from the rest of the world in the near future. Everyone must have a sense of crisis and urgency, and move forward.

**References**


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