Anesthesia Management for High-Intensity Focused Ultrasound (HIFU) Thalamotomy for Movement Disorders: A Case Series from the National University Hospital of the Philippines

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ABSTRACT

An increasing number of neurological conditions may be treated with high-intensity focused ultrasound (HIFU), among which is geared towards the control of tremors as seen in patients with Parkinson's Disease (PD), X-linked Dystonia Parkinsonism (XDP), and Essential Tremor (ET). HIFU thalamotomy is a noninvasive therapy for neurological conditions with debilitating tremors despite medication. To improve treatment accuracy and patient safety, neurosurgeons, neurologists, and anesthesiologists must work together perioperatively.

A total of 30 patients detailing their demographics, symptoms, and perioperative anesthetic management in a tertiary government hospital in Metro Manila was reviewed from October 2021 to March 2024. Most of the patients were diagnosed as PD tremor dominant, followed by XDP and ET. Majority of the cases were done under minimal sedation with local infiltration on the pin site while the rest were done under monitored anesthesia care combined with local anesthesia. Specific anesthetic agents were given to provide comfort and pain relief and reduce the risk of side effects.

During sonication, an essential element of the procedure, patients were closely monitored for the anticipated effects, such as paresthesia, headache, nausea, and vomiting, and were managed accordingly. Postoperatively, these patients were reported to have decreased tremors, stable vital signs, and adequate pain control. Collaboration among healthcare providers is one of the important elements for a successful outcome. This study highlights the importance of personalized anesthetic management in enhancing patient outcomes and the need for future studies about developing anesthesia protocols and strategies.

Keywords: HIFU thalamotomy case series, Parkinson's Disease, X-linked Dystonia Parkinsonism, essential tremor, anesthesia for HIFU thalamotomy

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INTRODUCTION

High-intensity focused ultrasound (HIFU) thalamotomy technology has gained interest due to its precision and noninvasiveness in targeting specific brain regions that are usually aimed in neurosurgical procedures. This treatment approach uses focused ultrasound waves from the magnetic resonance-guided high-intensity focused ultrasound (MRgFUS), resulting in heat ablation in the brain, especially the thalamus.[1,2] Recently, HIFU have been utilized to treat tremor disorder wherein medical management has already been exhausted.

Parkinson's Disease (PD) is a condition characterized by the loss of dopamine-producing cells in the substantia nigra resulting in symptoms such as tremors, stiffness, and

bradykinesia.[3] In treating unilateral tremor-dominant Parkinson's Disease (PD), MRgFUS thalamotomy shows similar effectiveness in controlling tremors comparable to radiofrequency ablation and deep brain stimulation (DBS). HIFU provides an option for targeting brain areas such as the ventral intermediate nucleus (Vim), subthalamic nuclei (STN), and internal globus pallidus (GPi) through cerebral ablation, thus reducing risks of bleeding and infection. Promising outcomes have been observed in alleviating motor symptoms of PD using MRI-guided HIFU subthalamotomy and pallidotomy. A study involving PD patients who underwent this treatment revealed that 62% had tremor control three months after treatment compared to 22% in the sham group. Moreover, a single open-label study investigated the use of MR-guided focused ultrasound subthalamotomy for PD, showed improvement in akinesia (36%), tremors (77%), and muscle stiffness (71%) six months after the treatment. In two open-label studies with PD patients who underwent MRI-guided pallidotomy, there was an improvement of up to 45% in motor function scores and a 52% decrease in dyskinesia six months post-operation. Nonetheless, additional study is needed as indicated by the authors.[4]

Additionally, X-linked Dystonia-Parkinsonism (XDP) also known as *Lubag* may be responsive to HIFU. It is an adult-onset, progressive neurodegenerative and debilitating condition that predominantly affects Filipino males whose maternal ancestry is from the Philippine island of Panay.[5] It mainly presents as torsion dystonia, later progressing to or replaced by parkinsonism.[6] It is most prevalent in Capiz (1 in 4,000 men) and has a global prevalence of 5.74 per 100,000 on Panay Island and 0.31 per 100,000 in the Philippines.[6] Among the 505 cases that have been studied in the island, a male-to-female ratio of 100:1 and an average onset at 39-40 years have been reported.[5,6] The two genes associated with this disease are DYT3 and TAF1.[5] Compared to other movement disorders, XDP has not received much treatment options. In a research study with three confirmed XDP patients, their average score on the XDP Movement Disorder Society of the Philippines (MDSP) Scale was 68.7 out of 200. Following HIFU therapy, their scores improved by 36.2% (18.7 vs. 15) at six months and 30.1% (68.7 vs. 45.5) at one year. However, the nonmotor subscale deteriorated by 350% after one year. While these results are promising, more research is needed to evaluate the safety and effectiveness of HIFU in treating XDP.[7]

Advancement in MRgFUS offers a solution in the management of Essential Tremor (ET), a common movement disorder among adult population, with an estimated prevalence of up to 9% in people older than 60 years.[8,9] This disease is characterized by a 4–12-Hz kinetic and postural tremor affecting the arms and less commonly the head, lower limbs, and voice with remarkable family history of a similar tremor, such manifestation often causes embarrassment and serious disability requiring treatment. As much as 50% of patients with ET develop intolerance despite compliance to recommended medications.[9] A study by Chang et al. showed that MRgFUS thalamotomy offers a sustained improvement in tremor score by 55% at six months, 53% after a year, and 56% at two years. This result highlight the effect in tremor suppression of ET patients over a two-year period without latent of delayed complications developed after the treatment.[10]

For the HIFU thalamotomy procedure to succeed, precise targeting and patient cooperation are needed.[11-13] As the patients remain immobile for several hours inside the MRI, it is important that they remain comfortable and awake throughout the procedure to assess the reduction of tremors and check the potential side effects brought about by the treatment. Therefore, the role of the anesthesiologist is vital to achieve ideal sedation levels, address pain, and alleviate nausea and vomiting, vertigo and anxiety.[14] It is important to consider certain factors to ensure patient immobility, comfort, and cooperation during the procedure.[13,14]

This report aims to describe our experience in perioperative anesthetic management, and the challenges and outcomes of patients undergoing HIFU for tremors. Detailed attention to the techniques, choices of drugs, and anesthetic considerations for each procedure phase will be discussed.

PRESENTATION OF CASES

We reviewed the records of patients who underwent HIFU in a single tertiary government hospital in Metro Manila from October 2021 to March 2024. The following data were extracted: demographics, co-morbidities, and disease presentation. Intraoperative data with emphasis on the anesthetic technique and the perioperative outcome were recorded.

A total of 30 patients were included in the study, with 73% having PD tremor dominant, followed by XDP (20%) and lastly ET (7%). The age of the patients ranged from 32 to 75 years, mean age of 56, with younger patients diagnosed with XDP as compared to those with PD. Majority of the patients were males (83%), mostly classified as ASA 2, with chronic medical issues such as hypertension (27%), diabetes mellitus and hypertension (20%), as illustrated in Table 1. Tremors, rigidity, and weakness were the most common symptoms encountered. All of the XDP patients had genetic testing and were confirmed to have mutation in the TAF1 gene.

Pre-procedural

In our institution, patients who are scheduled for HIFU are first assessed by a multidisciplinary team consisting of a neurosurgeon and a neurologist who specialize in movement disorders, as well as appropriate subspecialties for any patient comorbidities. Before the procedure, a head CT scan is performed to calculate the skull density ratio (SDR). An SDR value of 0.45 or higher is ideal for proceeding with the intervention. This assessment helps ensure that the structural integrity of the skull is sufficient for the planned intervention.

Table 1. Baseline Characteristics and Comorbidities of Patients with Movement Disorder

	(n = 30)
Movement Disorder, n (%)	
PD	22 (73)
XDP	6 (20)
ET	2 (7)
Gender, n (%)	
Male	25 (83)
Female	5 (17)
Age, mean SD, in years	56
ASA Classification, n (%)	
I	10 (33)
II	14 (47)
III	6 (20)
Co-morbidities, n (%)	
Hypertension	8 (27)
Diabetes Mellitus	2 (6)
Hypertension and Diabetes Mellitus	6 (20)
Dyslipidemia	3 (10)
Bronchial Asthma	4 (13)
Coronary Artery Disease	1 (3)
Osteoarthritis	1 (3)
Depression	1 (3)

SD= Standard Deviation

Table 2. Details of Anesthesia Procedure

	(n = 30)
Duration of procedure, in minutes, median, [interquartile range]	180 [180-210]
Anesthetic technique, n (%)	
MAC + local infiltration	6 (20)
Sedation + local infiltration	24 (80)
Challenges encountered, n (%)	
Headache (transient)	11 (37)
Nausea, dizziness (transient)	4 (13)
Paresthesia	1 (3)
Anxiety	1 (3)
Hypertension	1 (3)
Stereotactic Frame Related	1 (3)
Anti Tremor Medications, n (%)	30 (100)

Patients deemed suitable to undergo HIFU are then referred to a neuroanesthesiologist. During the pre-operative visit, review and examination of patient's medical history, laboratory test results, physical examination with special consideration on airway evaluation, specifically Mallampati scoring, mouth opening, thyromental distance, presence of oromandibular, pharyngeal and lingual dystonia, are conducted to determine the risk of aspiration and difficult airway. None of our patients displayed any signs of airway obstruction or stridor. Instructions regarding fasting guidelines are also provided. Detailed explanation of the stages of the procedure are discussed, as well as potential discomforts, including mild pain during head frame placement, extended periods in a supine position in the MRI suite, and the likelihood of headache, nausea, vomiting, and paresthesia during the sonication stage, as proper expectations are essential to the success of the procedure. These patients were constantly reassured that appropriate intervention will be given to treat these potential concerns.

All patients were maintained on anti-tremor medications prior to the procedure, which were withheld accordingly based on their pharmacokinetic half-lives, resulting to unopposed tremors for optimal treatment efficacy. Additionally, antihypertensive drugs that could impact tremors like propranolol were discontinued and replaced with alternative antihypertensives, if needed.

Peri-procedural

Table 2 provides a concise overview of the details of anesthetic procedure in this study. The treatment usually takes place within a single day and lasts approximately 180-210 minutes. On the day of the procedure, patients' heads were shaved prior to transport to the MRI treatment room. Upon arrival, non-invasive monitors, including NIBP, ECG, and pulse oximeter, were applied, and initial vital signs were recorded. Thirty minutes before the procedure, all patients were given prophylactic doses of intravenous pain medications, including paracetamol and ketorolac, as well as antiemetic medications such as ondansetron and dexamethasone. A stereotactic frame crown was then positioned on the skull while the patient was upright. A bolus of fentanyl 25-50 mcg IV was given, followed by local infiltration with bupivacaine isobaric 0.25% + lidocaine 1% + epinephrine 1:200,000 into the predetermined pin sites before finally applying and securing the pins. An elastic silicone membrane tailored to fit the patients' head diameter was affixed to seal the circulating degassed water interface between the transducer and the target to avoid unnecessary pressure on the skull. Subsequently, patients were then transferred to the MRI suite proper and positioned for the procedure. Oxygen support at 3 LPM via nasal cannula with a designated capnography and MRI-compatible monitors, were provided. At this stage, a planning MR scan was conducted to precisely determine the treatment target, wherein 20% of the patients tolerated the procedure with local anesthetic block on the pin sites and pre-operative pain medications while the majority (80%) of the patients required additional analgesia and sedation, necessitating dexmedetomidine infusion at a rate of 0.2-0.3 mcg/kg/hour to achieve comfort and tremor reduction. Throughout the treatment duration, patients were maintained on dexmedetomidine at a rate of 0.3-0.4 mcg/kg/hr, to ensure their participation during neurologic testing. The neuroanesthesiologist remained inside the MRI room to constantly monitor the patient's condition throughout the procedure. Potential events such as desaturation, vasovagal reaction, nausea and vomiting, headache, and anxiety were anticipated, and appropriate interventions were prepared. MRI-compatible monitors, an

anesthesia workstation, laryngoscope, and endotracheal tube were all on standby.

Challenges Encountered

Most common challenges often encountered during the procedure were as follows: transient headache (37%) with pain scale of 3-6/10 during the second stage of sonication when temperature was at 46–50˚C, described as pressing frontal pain, nausea, and dizziness (13%), and 3% having hypertension, anxiety, stereotactic frame-related discomfort, and paresthesia after the procedure. To manage pain, the following were conducted: for mild headache with 3-4/10 pain scale, administration of intravenous bolus of Fentanyl 25-50 mcg was done, while for moderate headache of 5-6/10, remifentanil infusion was given at concentration effect site of 0.5-1.0 ng/ml. Anxiety was addressed by constant words of re-assurance and motivation. As benzodiazipines were usually not administered to these patients for accurate neurologic examination, dexmedetomidine was titrated up and occasionally, the procedure was interrupted due to patient discomfort. For hypertension, nicardipine 200 mcg IV boluses or intravenous infusion was started at 0.5 mcg/kg/min, as needed for continuous control of blood pressure. For nausea, an additional dose of 4 mg IV ondansetron was given to the patient and betahistine 16 mg PO for persistent dizziness after the procedure.

Post-procedural

Upon completion, all patients underwent neurologic evaluation to assess the resolution of tremors. Most patients reported an immediate reduction in tremor severity, which were evaluated after 6 and 12 months upon follow-up with a neurologist specializing in movement disorders. Before being transferred back to their room, patients receive another dose of paracetamol, ketorolac, and ondansetron, with most of them having stable vital signs and adequate pain control.

DISCUSSION

PD, XDP, and ET are some of the neurological disorders that can compromise the quality of life of patients due to its incapacitating symptoms. Patients with PD manifests with motor parkinsonism, characterized by bradykinesia along with either resting tremor, rigidity, or both.[15] Conversely, ET patients usually have rest and movement-related hand tremor that may also affect the head, neck, and voice causing disability during voluntary acts like drinking, eating, and writing.[16] In contrast, XDP begins with focal dystonia, which generalizes and may occur with parkinsonism, resulting in substantial impairment.[5] These symptoms can significantly impair daily tasks, diminishing independence and general well-being.

HIFU has emerged as a promising non-invasive treatment for these movement disorders. It works by using ultrasound waves to focus on specific tissues in the thalamus, creating heat and thermal energy in that area.[17] The thermal energy causes coagulative necrosis, which disrupts abnormal neural circuits that generate tremors.[18,19] Heating results in target-specific tissue ablation that spares nearby tissue.[14] An important advantage of this procedure is that it allows for surgery-free ablation on the cranium thereby avoiding complications such as infection, bleeding, and reduces damage to nontargeted tissue.[14,20] This intervention enables treatment planning and ongoing real-time monitoring, facilitating the ability to adjust treatment parameters for the purpose of optimizing and tailoring treatment outcomes.[14]

Anesthetic Management

Anesthetic management for this procedure entails distinct challenges and target several factors in enhancing patient safety, comfort, and procedural efficacy. Majority of the cases are done under minimal sedation with local anesthesia, which caters to dual needs of ensuring success of the procedure while at the same time, guaranteeing a safe and comfortable patient experience.

Pre-operative Assessment

Anesthesiologist's role begins preoperatively with assessment of patient's medical history, co-existing medical disease, and medication regimen that can affect perioperative management. Factors such as neurologic conditions, cardiovascular status, and respiratory function must be considered carefully because they may impact the anesthetic management. Also, various criteria including the patient's contraindications for MRI, risk factors for bleeding or damage to surrounding tissue, and other conditions affecting the brain or cognition, are considered. Understanding these risks enables individualized anesthetic plan that are specific to each case.

Patient education is another important aspect of the preoperative visit. It is pertinent to explain that anesthetic options are available which include local anesthesia with or without sedation, highlighting the benefits, risks, and expected outcomes of each approach. Such open and clear communication helps in alleviating patient‘s apprehension, facilitate informed choices, and cultivate trust and confidence in the anesthesia team. Preoperative visit also provides an opportunity to address questions and concerns that the patient may have about the anesthesia or procedure.

Collaborative planning with other members of the healthcare team such as neurologist, neurosurgeon, radiologist, and nursing staff is essential during this time to ensure seamless perioperative care. This includes discussion of the timing of anesthesia induction, intraoperative monitoring, postoperative analgesia, and contingency plans for managing possible complications.

Anesthetic Considerations

Patient comfort and safety

Patients undergoing this procedure most often experience preoperative anxiety. However, caution in the administration

of benzodiazepines and other gamma-aminobutyric acid (GABA) agonists is employed to prevent interference in tremor assessment and cooperation. Benzodiazepines increase the duration of opening of GABA-A receptor resulting in tremor improvement.[21]

Discomfort commonly arises from the fixation of a silicone head frame, which is addressed by administration of a fentanyl IV bolus followed by a local injection of bupivacaine isobaric 0.25%, lidocaine 1%, and epinephrine 1:200,000 at the pin sites. Once positioned in the MRI tunnel, patients are required to remain still throughout the procedure while conscious and immobilized. An emergency stop button is provided with instruction that the procedure can be halted at any moment if significant discomfort or issues arise. Establishment of supportive environment through reassuring verbal communication plays a crucial role in alleviating tension among patients undergoing this treatment.[14] It is also vital that they are well informed about the various stages so that they are prepared and motivated to finish the procedure.

Sonication and its effect

Optimizing treatment results and patient safety requires knowledge of sonication and its effects. Sonication, the main component of this therapy, involves delivering focal ultrasound waves to the target brain tissues.[14] However, such effect necessitates careful management to ensure optimal outcomes.

To confirm the anatomical treatment target, the first stage entails the application of low-energy sonications, with temperature ranges between 41–46˚C, potentially causing discomfort to patients, which typically manifests as headache. In the second stage, energy is gradually increased to temporarily relieve tremors, as well as eliminate any adverse effects. At this point, temperature between 46 and 50˚C are maintained. After confirming absence of side effects and reduction of tremor, the process proceeds to third stage characterized as achieving permanent lesion, either by intensifying or extending the process to further increase the temperature to at least 57˚C, thereby causing protein denaturation. The size of tissue exposed to heat determines how big a resulting lesion will be caused by ultrasonic beams. Multiple sonications are conducted with the highest possible energy level to achieve a permanent effect. The sonication phase is considered complete when tremor control is achieved satisfactorily, while ensuring that temperatures do not exceed 60˚C.[14] As mentioned, patients may experience discomfort or pain at high energy levels, which are mitigated with pre-procedural pain medications such as paracetamol and ketorolac. They are also maintained on dexmedetomidine infusion, and at times, a bolus dose of fentanyl and additional infusion of remifentanil is given to address moderate pain. All these medications are adjusted necessarily to optimize patient comfort and safety. Furthermore, sonication may also trigger nausea and vomiting, further aggravating the risk for aspiration of this set of patients with a predilection to cervical dystonia. Our practice involves the administration of intravenous antiemetics, such as ondansetron and dexamethasone, 30 minutes before the procedure.

Patients are kept awake and responsive to facilitate real-time neurological monitoring to assess changes in tremor severity or other motor symptoms, providing immediate feedback for subsequent sonication.[10] The effects of this process require vigilant monitoring and appropriate interventions to optimize patient outcomes.

Anesthetic Agents

Anesthetic agent selection is essential for this procedure to avoid any drug interaction effects in the assessment of tremor and to address the pain and discomfort.

Local infiltration at the pin site

Infiltration of local anesthesia at the pin sites is done to block nociceptive signals, thereby minimizing discomfort associated with the placement of stereotactic frame crown. One of the primary advantages of infiltrating local anesthesia at pin sites is that it provides targeted pain relief without the need for systemic analgesics. This localized approach reduces the risk of systemic side effects related with opioid medications, such as respiratory depression and nausea.

Dexmedetomidine

Dexmedetomidine is a selective alpha-2 adrenergic agonist that acts by binding to presynaptic alpha-2 adrenergic receptors in the locus coeruleus and spinal cord.[22] Presynaptic activation of the α2 adrenoceptor prevents the release of norepinephrine, inhibiting the transmission of pain signals. Meanwhile, postsynaptic activation of α2 adrenoceptors in the central nervous system (CNS) reduces sympathetic activity, which can lower blood pressure and heart rate. Synergistically, these effects lead to analgesia, sedation, and anxiolysis.[23] This makes it suitable for this procedure to ensure comfort and cooperation without interference on the tremor assessment. Moreover, its minimal respiratory depression and stable hemodynamic effects contribute to the safety and stability of the patient during the procedure.

Recent studies have investigated the potential neuroprotective properties of dexmedetomidine beyond its primary anesthetic and sedative effects. The latest animal study revealed a correlation between this drug and the nigrostriatal circuit including its function on motor deficits, wherein dexmedetomidine alleviated motor impairments in a dose-dependent manner and protected dopaminergic neurons from degeneration in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD model. Its effects were observed in the nigrostriatal pathway, where it enhanced dopaminergic neuron activity and reduced the excitability of striatal neurons via dopamine D2 receptors. Additionally, dexmedetomidine prevented the increase in glutamatergic transmission from cholinergic interneurons (CINs), thereby improving motor function. It also lowered both the intrinsic

excitability and glutamatergic transmission of striatal D2 medium spiny neurons (D2-MSNs). Furthermore, D2 receptor antagonists inhibited dexmedetomidine's ability to restore motor function.[24] These findings suggest that dexmedetomidine, as a neuroprotective agent, supports the function of nigrostriatal neurons and improves motor deficits, offering a possible neural mechanism for the role of anesthetic drugs in PD progression. Since the effectivity of HIFU depends exclusively on patients' motor improvement, this study suggests that dexmedetomidine may diminish motor symptomatology ultimately leading to inaccuracy of this treatment modality.

Nevertheless, while these preclinical findings are promising, it is important to acknowledge the inherent limitations of translating results from animal models to human disease. Variability in neuroanatomy, disease progression, and pharmacokinetic responses between species may influence the applicability of these results to human patients. Further clinical studies are necessary to establish the efficacy, safety, and optimal dosing parameters of dexmedetomidine in the context of PD.

Remifentanil

Remifentanil is an ultra-short-acting phenylpiperidine opioid analgesic known for its high lipid solubility, resulting in a fast onset of action. It is immediately metabolized by non-specific blood and tissue esterases, allowing for rapid recovery.[25] This is advantageous for procedures requiring precise anesthesia and analgesia control. In our case, it was used as an adjunct to dexmedetomidine for patients experiencing moderate to severe pain. At TCI dose of remifentanil 0.5-1.0 ng/ml, patients experienced pain relief while side effects such as respiratory depression, truncal rigidity, bradycardia, hypotension, and nausea are prevented.

CONCLUSION

While HIFU for tremor management is still in its early phase, the current case series illustrate its efficacy in numerous patients. Collaborative efforts among healthcare teams are instrumental in the success of this intervention. Anesthetic management is paramount for ensuring patient comfort, safety, cooperation, and procedural efficacy. Dexmedetomidine and local anesthesia play pivotal roles in achieving sedation and alleviating discomfort without affecting GABA-related tremor assessment. Caution is needed when using benzodiazepines and other GABA agonists due to their potential impact on patient cooperation and tremor assessment. As a novel approach to management, further studies regarding its long term outcomes as a treatment option will be informative for this patient population.

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