Case Report

Successful Spinal Cord Stimulator Trial and Permanent Implant in Patient with Diabetic Peripheral Neuropathy on Chronic Dual Antiplatelet Therapy

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The safety of neuraxial anesthetic techniques in the setting of oral and parenteral anticoagulation is an area of growing interest and clinical inquiry as the multitude of anticoagulant medications rapidly increases. Additionally, the indications for spinal cord stimulation therapy are evolving as both technique and technology in the field continue to advance. The estimated incidence of spinal hematoma following epidural injection has been estimated to be 1 in 150,000 – 200,000. However, there is very little data on the risk of indwelling spinal cord simulation leads and chronic use of anticoagulant medications. We would like to report a recent case for consideration in which a spinal cord stimulator trial was successful and led to permanent spinal cord stimulator implantation in a patient with diabetic peripheral neuropathy taking life-long aspirin and clopidogrel therapy secondary to extensive coronary and carotid atherosclerosis. The report serves as a novel case to encourage exploration into the topic of anticoagulation therapy with indwelling spinal cord stimulator leads. The case brings up a number of critical questions that cannot clearly be answered with the current literature and some interesting topics for discussion including the need for acute systemic anticoagulation in the future for vascular interventions and risk stratification for those patients selected for spinal cord stimulation.

Key words: spinal cord stimulation, dual antiplatelet therapy, diabetic neuropathy, chronic pain syndrome, epidural hematoma, anticoagulation

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The safety of neuraxial anesthetic techniques in the setting of oral and parenteral anticoagulation is an area of growing interest as the multitude of anticoagulant medications increases. Additionally, the indications for spinal cord stimulation (SCS) therapy are evolving as both technique and technology in the field continue to advance. However, there is very little published data on the risk of indwelling SCS leads and chronic use of anticoagulant medications.

After a patient on daily chronic dual antiplatelet therapy with clopidogrel and aspirin presented to our clinic with a chronic pain syndrome that was amenable to SCS therapy, we performed an extensive literature search on the topic. We specifically wanted to address the risks associated with SCS therapy with concomitant clopidogrel and aspirin administration and the future prognosis of this patient, including the possible need for therapeutic heparin administration for vascular or cardiopulmonary bypass surgery. We reviewed the ASRA Practice Advisory on "Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy" (8) to draw correlates between epidural techniques for acute pain management and the risks of SCS therapy. The ASRA literature also provided perspective on the potential risks of therapeutic heparin administration for cardiopulminary bipass (CPB) and vascular surgery for patients with indwelling epidural SCS leads.

Estimates place the risk of epidural hematoma associated with epidural anesthetics at one in 150,000 (1). It appears that the most important risk factors associated with spinal hematoma and epidural/spinal anesthesia are the presence of an anticoagulant drug or clotting disorder at the time of initiation of epidural/

spinal anesthesia or at the time of epidural removal, bloody or difficult attempts, advanced patient age, and anatomic spinal abnormalities. It is not clear whether the experience of the interventionist was a factor in the development of spinal hematoma (2).

After we had completed the trial and permanent implantation of the patient, *Regional Anesthesia and Pain Medicine* published 3 case reports describing the development of epidural hematomas associated with patients on aspirin at the time of percutaneous spinal cord stimulator trial lead removal (3,4). None of the reported patients were on dual antiplatelet therapy at the time of the stimulator trials. Benzon and Huntoon (5) provided an opinion that new guidelines should be developed based on the experiences of the reporting authors and the patient outcomes.

The research we performed prior to the new case reports did not provide many clear answers to our clinical question. Spincemaille et al (6) reported on all adverse events associated with 60 patients with peripheral vascular disease and related pain treated with SCS therapy during a period of 2 years. There were no epidural hematomas reported, and although it was not explicitly described, the risk profiles of the patient population suggest that some form of chronic anticoagulation or antiplatelet therapy would have been warranted for a subset of the population (6). In a literature review study by Cameron (7) designed to determine the safety and efficacy of SCS including a total of 3,679 patients, there were 8 documented cases of epidural hematoma; however, there was no indication of when they occurred and whether the patients were on antiplatelet or anticoagulation therapy. The focus on the risk of epidural hematoma is supported by the neurologic outcomes of patients with spinal hematoma following neuraxial blockade. Only 38% of those who developed spinal hematoma following spinal or epidural blockade had partial or good neurologic recovery (2). Additionally, the probability of partial or good neurologic recovery is clearly dependent on the time to surgical intervention. If signs of spinal hematoma are missed or diagnosis is delayed for more than 8 hours, the chances of a poor neurologic outcome are greatly increased (2). However, the above trials did not specifically address the risks associated with dual antiplatelet therapy with aspirin and clopidogrel and indwelling epidural catheters.fAspirin and clopidogrel act independently to inhibit platelet function. Aspirin acts through acetylation of platelet cyclooxygenase, preventing the formation of thromboxane A2. Clopidogrel is a theinopyridine compound that prevents platelet aggregation through the noncompetitive inhibition of P2y12 receptors, which are normally activated by ADP, and it prevents the activation of GPIIb/IIIa receptors on the surface of platelets. The platelet inhibition by both drugs is irreversible and formation or transfusion of new platelets is the only way to allow complete return of normal platelet function. There is level 1C evidence recommending holding clopidogrel 5 – 7 days prior to the time neuraxial anesthetic intervention based on pharmacology, surgical review, and labeling precautions (8). The recommendations combined with case reports of the development of spinal hematoma following neuraxial instrumentation with concurrent therapy with oral anticoagulants guide the current practice to hold clopidogrel prior to neuraxial anesthetic techniques (9). Although neither aspirin nor clopidogrel has been associated with a well-established risk for spinal hematoma when restarted after instrumentation, there is insignificant literature to facilitate an evidence-based clinical practice for indwelling epidural catheters or leads. Therefore we used clinical judgment, case report data, and considerations for future patient needs to evaluate the risk versus benefit of SCS therapy in our patient with diabetic peripheral neuropathy taking both aspirin and clopidogrel indefinitely.

Case Presentation:

Institutional Review Board (IRB) approval was not needed for the purposes of this case report at our institution. The patient to be described consented for the use of his case in our report. The patient, a 49-year-old male, presented to our clinic with a chief complaint of bilateral lower extremity pain. He described the pain as progressive in nature, present for the last 10 years, and unbearable in the last 6 months. He ranked his pain on a 0 – 10 verbal numeric rating scale (NRS) as 10/10 at its worst, 6/10 at its best, and at the time of examination he rated his pain as an 8/10. He described the pain as constant but varying in intensity. Quality of the pain was described as burning and stabbing, and the pain became exacerbated by walking long distances (> 10 yards). It was located in both lower extremities in a stocking distribution and was worst distally. His previous pain management consisted of hydrocodone-acetaminophen, oxycodone-acetaminophen, gabapentin, and duloxetine without satisfactory results. He had been on some form of opioid therapy for at least 5 years. His current pain and anticoagulant medications were pregabalin 150mg PO BID, amitriptyline 25mg PO

QHS PRN, hydrocodone-acetaminophen 7.5-325mg po BID, aspirin 325mg PO QD, and clopidogrel 75mg PO QD. His past medical history included carotid stenosis, coronary artery disease, hypertension, hyperlipidemia, type 2 diabetes mellitus, proliferative diabetic retinopathy, diabetic peripheral neuropathy supported by electrodiagnostic testing, obesity, and stroke without residual neurologic compromise. The patient's past medical history of recurrent and diffuse coronary artery disease requiring multiple stents in addition to his carotid atherosclerosis prompted his primary cardiologist to maintain the patient on life-long dual antiplatelet therapy using clopidogrel and aspirin. His past surgical history consisted of coronary artery stent placement (total of 8 stents, with 3 drug-eluting stents placed 10 months prior to presentation to our clinic) and carotid endarterectomy. He reported a social history significant for a 17 pack-year history of smoking, but denied alcohol or illicit drug use. He denied tobacco use for the last 14 years.

His laboratory values were all normal including a creatinine of 0.8, AST 18, ALT 17, alkaline phosphatase 70, platelet count: 232, INR: 1.04.

Our assessment was the patient was suffering from a chronic pain syndrome due to diabetic peripheral neuropathy that had been refractory to all other reasonable therapeutic options and should be considered for SCS therapy. Targets for the therapy were the lower extremities distal to the knees where the patient described most of his pain. Goals for the therapy included decreased pain score by 50% on the NRS and significant improvement (> 50%) of ambulation without having to stop secondary to pain. Since his last coronary stents (DES) were placed less than 12 months ago, we waited until a full year had passed before considering holding his dual antiplatelet therapy for the surgery. After discussion with his primary cardiologist about the risks of taking him off clopidogrel, it was decided that he would restart dual antiplatelet therapy following completion of his trial but that it would be acceptable to hold the medication for 7 days prior to bringing him to the operating room.

After the above literature review was conducted (with the exception of the most recent case reports in the journal of Regional Anesthesia and Pain Medicine) and perioperative risks specific to this patient were assessed related to SCS, the patient decided to proceed with the SCS trial. The patient continued his 325mg daily dose of aspirin throughout the trial and permanent implantation secondary to his significant cardiovascular risks. The patient did not take his clopidogrel for 7 days prior to the trial. The patient was brought to the operating suite and one 16 electrode Boston Scientific spinal cord stimulator lead was placed in the epidural space at the T12-L1 interspace after atraumatic epidural needle placement with a 14 gauge introducer needle. The lead was advanced to the final position at the level of the T8 vertebral body in a midline location. Sensory testing was performed and adequate paresthesia coverage of the patient's pain in the bilateral lower extremities below the knees was obtained. He was scheduled for follow-up in one week for evaluation. He was instructed to hold his clopidogrel until that time. When he returned, he reported dramatically improved pain in his lower extremities. He described the pain as 3/10 bilaterally and he was able to ambulate for a half mile, which he had not been able to do prior to spinal cord stimulator placement without having to stop secondary to pain. He was able to completely eliminate opioid utilization for his usual pain during the trial period. He desired to proceed for permanent implant. The trial lead was removed and he resumed clopidogrel the following day.

He was scheduled for permanent implant 2 months later and began his dual antiplatelet therapy in the interim. He held the clopidogrel again for 7 days prior to his permanent implant placement. Two 16 electrode Boston Scientific Infinion leads were placed on each side of midline with the top contact at T8 in the epidural space after 2 separate atraumatic epidural needle placements. He was instructed to hold his clopidogrel until all surgical site drainage had completely stopped which was another 7 days. He was educated on the symptoms and signs of epidural hematoma development and we told him to present to the closest emergency room immediately should any of the symptoms develop at any time during his sustained SCS therapy. The information gathered to support the clinical decisions outlined above are discussed below.

Discussion

The topic of neuraxial anesthetic techniques in the setting of anticoagulation and/or antiplatelet therapy is obviously one of great interest in acute as well as chronic pain management. With the myriad of therapeutic options, it is difficult to find literature that supports each clinical situation. In addition, with the devastating consequences of complications, it's challenging to design studies to answer the questions raised by our case. We found that there was limited data to guide our decision, but ultimately we found the clinical risk

vs. benefit profile to be acceptable based on our patient and the existing literature. As this case report serves to support interest in this topic, we hope it will inspire future research to develop practice guidelines.

Our review of current literature at the time of the trial and implant was able to guide the perioperative management as it relates to the implantation of the spinal cord stimulator. Adapting the recommendations from the ASRA practice guidelines for holding dual antiplatelet therapy for neuraxial anesthetic techniques to our case, we held the patient's clopidogrel for 7 days prior to instrumentation as well as maintained his aspirin therapy throughout the perioperative period (2). We discussed at length the proposed benefits as well as possible risks of the procedure and therapy with the patient's vascular and cardiac specialists.

The topic of risk associated with an indwelling epidural catheter or lead was a more complex one to research. Although expert opinion suggests that indwelling epidural catheters are contraindicated in the setting of theinopyridine therapy, the ASRA Practice Advisory does not address this topic in its publication. This may be due to the fact that the duration of acute pain management with indwelling epidural catheters is typically short-term (within one week of insertion). This reasonably allows the perioperative team the option to hold dual antiplatelet therapy until catheter removal in order to mitigate risk. However, with permanent SCS therapy, however, this would present an unacceptable vascular risk in patients such as the one described in the above case.

It appears that the most important risk factors associated with spinal hematoma and epidural/spinal anesthesia are the presence of an anticoagulant drug or clotting disorder at the time of initiation of epidural/spinal anesthesia or at the time of epidural removal, bloody or difficult attempts, advanced patient age, and anatomic spinal abnormalities (2). It may be reasonable to abort a case if difficult or traumatic lead insertion occurs during either the trial or permanent implant procedure. It also suggests that if acute therapeutic anticoagulation is required, the catheter or lead should not be removed, as removal poses a great risk for the development of spinal hematoma if a patient is therapeutically anticoagulated with heparin, especially in the setting of uninterrupted clopidogrel therapy (2). This is evidenced by a series reported by Vandermeulen et al (2) in which 15 of 32 patients who developed a spinal hematoma in the setting of an indwelling epidural catheter did so immediately following catheter removal. In addition, 9 of these 15 patients were therapeutically anticoagulated with heparin.

Considering our patient's history, it is possible that he may require vascular surgery or cardiac surgery requiring cardio-pulmonary bypass. Although the perioperative risk of spinal hematoma with indwelling SCS is dependent on the blood loss of the procedure, presence of preoperative coagulopathy, time required on cardio-pulmonary bypass, and perioperative heparin therapy, there is data on the subject that helped guide our clinical decision. Epidural anesthesia has been studied in the setting of vascular surgery. Following guidelines suggesting epidural placement > one hour prior to administration of intravascular unfractionated heparin, a large published series found that "intraoperative systemic heparinization does not seem to represent a significant risk" for the development of spinal hematoma (10). Additionally, continued postoperative heparinization in these patients is commonly performed provided guidelines for catheter manipulation and removal are followed (8). The authors of such studies do caution practitioners to be vigilant and cognizant of the potential increased risk for spinal hematoma. Moreover, there are large case series in both pediatric and adult populations addressing heparin administration to facilitate initiation and maintenance of cardio-pulmonary bypass to patients with indwelling epidural catheters. In studies on pediatric patients, a total of 250 cardiopulmonary bypass cases where epidural placement was done following induction and one hour prior to heparin administration, no spinal hematomas were reported (11,12). In adult patients, no spinal hematomas were reported by a prospective case series conducted by Sanchez and Nygard (13) with epidural placement the night before surgery in 558 patients undergoing coronary bypass surgery.

Ultimately, the greatest fear related to this case is the devastating consequences of a spinal hematoma causing spinal cord ischemia and neurologic injury. Although risk mitigation and evaluation is important, it is equally important to have a plan of action in the event of these complication. The case reports presented by Giberson et al (4) and Buvanendran and

Young (3) were certainly concerning since those patients were only on aspirin and not dual antiplatelet therapy. In light of the recent case reports, we may have reconsidered our plan for the trial and implant. However, our patient was fully informed of the risk and adamant that he had little quality of life in his current situation. The new guidelines under development for

SCS and anticoagulants must also take into account other patient co-morbidities that would also pose a great risk with cessation of all antiplatelet medications. We decided to continue aspirin during the trial and implant of our patient after considering his severe coronary disease and history of carotid stenosis. It would be unfortunate to permanently exclude the growing population of patients who have other diseases requiring some form of anticoagulation and chronic pain amenable to stimulation from benefitting from the therapy.

It may be surmised that with proper education, a patient with a SCS may be able to detect the early signs of epidural hematoma and present for evaluation early enough to prevent the sequelae of spinal cord hematoma and neurologic injury. We considered the health care resources immediately available to our patient as well as his capacity to understand the signs, symptoms, and urgency for evaluation related to the development of a spinal hematoma. We informed our patient, that in the event of progressive sensory or motor blockade he should present to the nearest emergency department for evaluation.

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