PROPOFOL AND KETAMINE FOR TARGETED MUSCLE REINNERVATION AFTER LIMB AMPUTATION: A CASE REPORT

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propofol, ketamine, TIVA, targeted muscle reinnervation, phantom limb pain.

Abstract

Surgical procedures that require neuromuscular monitoring present unique challenges to the anesthesia provider. Specific patient characteristics such as phantom limb pain or chronic opioid use can further complicate perioperative management. The following case presentation illustrates the anesthetic management of a patient exhibiting these complications who presented for surgery with a prior transhumeral amputation. Nerve reassignment was planned with the eventual goal of a thought-controlled prosthesis. Anesthesia was maintained by the combination of propofol and ketamine along with adjuncts such as hydromorphone, midazolam and glycopyrrolate. These drugs and similar anesthetic combinations cause minimal changes to neurophysiologic monitoring while decreasing various types of neuropathic pain and provide an effective alternative for treating patients with chronic pain.

Introduction

Targeted muscle reinnervation (TMR) is a ground-breaking procedure that gives upper extremity amputees the ability to control prosthetic limbs via reassigned nerves. Approximately 50 such procedures have been performed worldwide, and the following case is the second to have been implemented at a large, metropolitan research hospital. Instead of relying on residual muscle strength alone, TMR allows for movement stimulated by electromyogram (EMG) nerve signals.1 Prostheses are then controlled by simply thinking about desired actions- a process closely resembling life prior to amputation.1 Choice of intra-operative anesthetic plays a considerable role both during and after the procedure. Total intravenous anesthesia (TIVA) shows tremendous ability to reach surgical and patient specific goals in regard to effective neuromonitoring and pain control.

Case Summary

A 49-year-old, 63 kg man presented for TMR after a motor vehicle accident that resulted in a transhumeral amputation. The following nerve transfers were planned: median to clavicular head of pectoralis major, ulnar to sternal head of pectoralis major, and radial to coracobrachialis. Past surgical history included a posterior cervical spine fusion of C5-C6, as well as a rod placement in the right lower extremity. The patient suffered permanent contracture of the lower extremities as well as left upper extremity phantom limb pain. Each of the following medications were prescribed 3 times per day: methadone 20 mg, carisoprodol 350 mg, baclofen 20 mg, gabapentin 600 mg, and nortriptyline 50 mg. Every 4 hours, 10 mg of oxycodone was prescribed as needed and was taken at regular intervals daily. The preoperative chemistries, hematological values and coagulation profile were all within normal limits. Vital signs were as follows: blood pressure 119/60 mm Hg, normal sinus rate at 100 beats/min, respiratory rate of 16 breaths/min, saturation of peripheral oxygen ($Sp0_2$) 100% (room air), pain score 7/10 (chronic, sharp). In the preoperative holding area, 2 mg midazolam were administered via an existing 20 gauge intravenous (IV) catheter.

Upon entering the operating room, standard monitors were placed, and 100% oxygen (O_2) at 12 L/min was simultaneously delivered to the patient by face mask. After an initial set of vital signs was obtained, IV anesthetic induction was initiated with lidocaine 100 mg, propofol 120 mg, and ketamine 100 mg. Due to the patient's prior cervical spine injury, neck flexion and extension were avoided during supraglottic insertion of a size 5 laryngeal mask airway (LMA). An end tidal carbon dioxide measurement of 36 mm Hg was present upon the third breath, and air movement was auscultated bilaterally and equally. The O_2 flow rate was decreased to 3 L/min, and the LMA was secured prior to 90 degree rotation of the operative table. The airway was reassessed. An 18 gauge peripheral IV was aseptically placed in the right antecubital fossa.

General anesthesia was maintained with a mixture of propofol 50 ml (10 mg/ml) and ketamine 0.5 ml (100 mg/ml). The infusion was initiated at a rate of 80 mcg/kg/min and titrated to 110 mcg/kg/min based upon response to surgical stimulus. A concurrent one-time dose of glycopyrrolate 0.2 mg was also administered. Intermittent doses of hydromorphone were given according to sympathetic response, for a total of 6 mg throughout the case. Spontaneous respirations resumed and were maintained between 8 and 15 breaths/min. The systolic blood pressure ranged from 100 to 125 mm Hg, and the heart rate was between 95 and 105 beats/min. For the duration of the case, $Sp0_2$ remained 100% with an intraoperative fraction of inspired O_2 of 0.5. The patient did not receive neuromuscular blockers at any point. Ondansetron 4 mg was also given. Neuromonitoring was conducted via EMG, motor evoked potentials (MEPs), and somatosensory evoked potentials (SSEPs) by a technician.

Upon emergence, the patient was transported to the postanesthesia care unit with O_2 delivery by simple face mask at 6 L/min. The patient denied pain, nausea, or recall of the procedure. There were no untoward events. The patient recovered in the hospital

for a single day, was discharged home, and had tentative plans to be fit for prosthesis in 6 months.

Discussion

The anesthetic combination of propofol and ketamine was chosen for its beneficial impact on pain management and based on the need for neuromonitoring. Procedures that require neurophysiologic monitoring of motor activity by way of MEPs and EMGs dictate that neuromuscular blocking agents be used judiciously. Train-of-four twitch height should be maintained around 30% or, clinically, 1 to 2 twitches.[2] In contrast, SSEP monitoring involves purely sensory-evoked information, and in such cases, skeletal muscle contraction and neuromuscular blocking agents do not need to be tightly regulated.[2] Since motor function was of concern, neuromuscular blocking agents were not used during this case. For further discussion, most anesthetic agents, not just those acting at the neuromuscular junction, can either suppress or enhance both the amplitude and latency of waveforms being recorded.[3]

Halogenated volatile anesthetics produce a dose-dependent decrease in amplitude and increase in latency of MEP signals.[3] Wang et al. reiterate this concept and describe that at levels greater than 0.5 minimum alveolar concentration (MAC), inhalational anesthetics produce great variability in neurophysiologic readings.[3] While use of propofol can also induce a dose-dependent effect similar to volatile anesthetics, the impact is much less severe, and the agent provides stable neuromonitoring conditions. Additionally, the use of ketamine in conjunction with propofol has been shown to enhance signal waveforms.[3] It is important to recognize that no matter the technique chosen, low MAC inhalational agent, TIVA, or a combination of both, abrupt changes in the concentration of these agents can challenge the validity of results and cause misinterpretation of the information provided.[3] Changes to the anesthetic technique should be avoided if possible, and when initiated, the changes should be communicated

with the surgical team and the neuromonitoring technician.

Phantom limb pain is particularly hard to control and not well understood. It is believed that *N*-methyl-D-aspartate (NMDA) receptors play a critical role in this pain pathway.[4] Since this is the same receptor antagonized by ketamine, its use with various types of neuropathic pain has been investigated. Alviar et al. studied various pharmacologic interventions for this pain pathway and found dichotomous results in regard to ketamine's benefits. While the agent did provide a significant amount of analgesia, the less desirable effects produced by dissociation of the thalamocortical and limbic systems led to increased secretions, hallucinations, loss of consciousness and sedation.[4] With similar findings, Sigtermans et al. evaluated the use of ketamine in decreasing symptoms of patients suffering from continuing pain, hyperalgesia, and allodynia. In the randomized, double-blind, placebo-controlled study, 60 patients received either an infusion of low-dose ketamine or normal saline over 5 days and were followed for 12 weeks.[5] According to the study findings, the low-dose ketamine infusion resulted in clinically significant reductions in pain for 11 weeks as compared to the placebo, but it also caused psychomimetic side effects, headache, and nausea.[5] For all of these reasons, in this case, prior to ketamine administration, midazolam was given as a premedication to offset potential emergence delirium, and glycopyrrolate was given in conjunction to decrease muscarinic side effects. The patient did not report any phantom pain immediately postoperatively, nor did he have hallucinations.

Patients suffering from chronic pain undeniably present a challenge with respect to controlling perioperative discomfort. Suboptimal relief is often encountered, especially with high doses of opioid taken on a long-term basis. Loftus et al. suggest that perhaps the best way to treat an opioid-dependent patient is by tapping into opioid-independent pathways.[6] In a randomized, double-blind, placebo-controlled study, the researchers evaluated

patients with chronic pain undergoing major spine surgery, all of whom had been taking opioids for a minimum of 6 weeks. Results indicated that patients in the treatment group, receiving ketamine, required decreased doses of opioid intraoperatively, immediately postoperatively, and at 6 weeks post-procedure (24% $P = 0.006$, 37% $P = 0.029$, and 71% $P = 0.041$ less opioid, respectively).[6] Of note, reductions in analgesic requirements did not coincide with any increases in undesirable side effects. Loftus et al. conclude that ketamine's beneficial role in treatment of chronic pain is not limited to antagonism of NMDA receptors but incorporates other factors such as modulation of neurotransmitters associated with depression and reduction of opioid mu, kappa and delta receptor sensitization.

Conclusion

Use of propofol and ketamine for TMR was effective in meeting the surgical and anesthetic goals of this case. Neuromonitoring was not compromised; the patient was adequately anesthetized, and the need for chronic pain control was addressed. Use of propofol and ketamine in combination with adjunct medications such as midazolam, glycopyrrolate, and hydromorphone proves to be a suitable anesthetic plan for this and similar situations.

The number of patients presenting for care following amputation will continue to grow. This anesthetic technique may be utilized for warriors returning home, those involved in traumatic injury, or anyone following the loss of a limb. Amputees present following a variety of injuries, and many of them occur while serving in the United States military. The *New York Times* recently explained that the utility of TMR for American service members is becoming increasingly apparent. More than 1570 soldiers lost limbs while serving in either Iraq or Afghanistan.[7] These individuals will experience many inconveniences, including phantom limb pain and a reduction in overall independence that muscle reinnervation may improve. The Marine Corps member featured in the article underwent TMR and is now practicing

daily activities with his new mechanical arm, as well as surfing, swimming and kayaking.[7] It is important that anesthesia providers recognize the beneficial impact that these procedures can have on an individual's quality of life and be able to provide effective anesthetic management for such cases.

Summary of Key Points

Procedures requiring neuromuscular monitoring present unique challenges to the anesthetist. Further complications arise when patients suffer from neuropathic or chronic pain. When choosing an anesthetic plan to meet these goals, the following key points may be considered.

- Propofol can cause dose-dependent decreases in amplitude and increases in latency; however, the effects are much less pronounced than with the use of volatile anesthetic agents. The use of propofol allows for fairly stable neuromonitoring conditions.
- In contrast to many other anesthetic agents, ketamine enhances neuromonitoring waveforms.
- Ketamine antagonizes NMDA receptors, which are believed to play a role in neuropathic and phantom limb pain.
- Ketamine is an antagonist at various opioid receptors, making it an effective alternative in the treatment of chronic pain patients.
- Regardless of the anesthetic technique employed, the provider should not abruptly change the anesthetic when neuromonitoring is being utilized. Effective and ongoing communication between the anesthesia provider, surgeon, and neuromonitoring technician is crucial.

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References

1 Kuiken TA, Li G, Lock BA, et al. Targeted muscle reinnervation for real-time myoelectric control of multifunction artificial arms. *JAMA*. 2009;301(6):619-628. doi: 10.1001/jama.2009.116.

2 Seubert CN, Mahla ME. Neurologic monitoring. In: Miller R, ed. *Miller's Anesthesia*. 7th ed. Philadelphia, PA: Churchill Livingstone; 2010:1477-1541.

3 Wang AC, Than KD, Etame AB, La Marca F, Park P. Impact of anesthesia on transcranial electric motor evoked potential monitoring during spine surgery: a review of the literature. *Neurorsurg Focus*. 2009;27(4):1-4. PMID:19795956.

4 Alviar MJ, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. 2011. *The Cochrane Library*. http://onlinelibrary.wiley.com./doi/10.1002/146551858.CD006380.pub2/full. Accessed January 28, 2012.

5 Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. *Pain*. 2009;145(3):304-311. PMID:19604642.

6 Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology*. 2010;113(3):639-646. PMID: 20693876.

7 Dao J. Learning to accept, and master, a $10,000 mechanical arm. *The New York Times*. November 27, 2012:A1.