

# ANESTHESIOLOGY™ 2014

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Session: L039  
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## **Wake Up Your Surgery Is Not Over** Prabhakar Devavaram, M.B., B.S. Boston Children's Hospital, Boston, MA

**Disclosures:** This presenter has no financial relationships with commercial interests

### **Stem Case and Key Questions Content**

You have started your new pediatric anesthesia attending position in a tertiary pediatric hospital. You are scheduled to anesthetize a 13 year old female with idiopathic scoliosis for posterior spinal fusion (PSF) from thoracic level 2 to lumbar level 4. She weighs 50 kg, and is ASA 2 category due to asthma; which is well controlled. The lab studies were normal including a hematocrit of 32 %. Patient has donated 2 units of blood in the last month for the surgery. You plan an intravenous (IV) induction, neuromuscular blockade (NMB), endotracheal intubation, arterial line (A-line), large bore peripheral IV catheters, and care of the patient in the prone position. For the maintenance of anesthesia you plan to use inhaled general anesthetics and a continuous infusion of an opioid for pain control. Sufentanil infusion was selected based on its context sensitive half time.

- 1) What is context sensitive half time (CSHT)?
- 2) How does it help in choosing the opioid for this case?

Next morning you discuss your plan with the surgeon (Dr. S). Dr. S mentions that in his practice in an allied center, the anesthesia team provides intrathecal (IT) morphine before the surgery, and he has found that the pain control is superb. He has also noticed less blood loss and wonders if we could do that. He also mentions that neuromonitoring during the case includes somatosensory evoked potential (SSEP) and motor evoked potential (MEP). In discussion, Dr S reports that prior to the use of MEP monitoring, he would regularly perform a wake up test after instrumentation. But, he would like to keep this as a back plan up since there have been times when the neuromonitoring had been inaccurate or there had been uncertainty if the cord was at risk.

- 3) Potential complications of intrathecal opioid use?
- 4) Role of intrathecal opioid in spinal procedures?
- 5) Does intrathecal opioid use affect neuromonitoring?
- 6) What is a wake up test?

You explain to the patient the plan for intrathecal morphine administration, general anesthesia and other aspects of the procedure, which includes blood transfusion and possible ICU care. You also discuss the possibility of wake up test and practice the test with her. The parent asks

- 7) Is there a risk of awareness with a wake up test?

In the OR, after positioning and ASA monitoring, you perform the spinal and give her 5mcg/kg of

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preservative free morphine. Then you anesthetize her with propofol, NMB and sufentanil 25 mcg. You proceed to intubate and start working on the A-line. The neuro-monitoring technician comes to you and requests you use total intravenous anesthesia with propofol for this patient so that she can get good signals.

- 8) What are the different modes of intra-operative neuromonitoring (IOM)?
- 9) How anesthesia and physiological factors affect the monitoring?

You explain that your plan is to use a nitrous /narcotic based anesthesia. You plan to use isoflurane at 0.4 % max for the duration of the case and if she doesn't get good signals you are willing to change your plan.

The case progress on to the operative stage and the neuro-monitoring team seem happy with the signals they are receiving. The next hour is uneventful but for a 10% increase in the mean arterial pressure (MAP). Dr. S is now performing osteotomies at multiple levels of the thoracic vertebra and wants to use hemostatic agents.

- 10) What are the different hemostatic agents and their mechanism of action?

Dr. S leans over the drape and requests that the MAP is kept in the low 60s. To decrease the MAP temporarily, you increase the inspired isoflurane concentration. The neuro-monitoring team reports that the signals are not good now, so the isoflurane is reduced to 0.4%.

- 11) What are the different drugs one can use for controlled hypotension?

During the course of the case the blood loss is estimated to be 1200mls and over the last hour the urine output decreases to 0.5ml/kg. You take an arterial blood gas (ABG) to look at the pH, hematocrit and electrolytes.

- 12) What are your transfusion triggers?

You transfuse the patient with two units of autologous blood and cell saver blood. The wake-up test was not necessary since the signals were good and you plan on extubation. Earlier we discussed the context sensitive half time of intravenous opioids.

- 13) Do similar concepts exist for recovery from inhaled anesthesia?

The next day you go to the ward to check on Ms.B. Her parents tell you that she had been pain free but itching the whole night.

- 14) Etiology of Itching? Role of neuraxial opioids.

- 15) How would you treat this patient? What are the pain management options?

## Model Discussion Content

The discussion is intended to derive general principles for management of patients undergoing spinal surgery. The first discussion is of CSHT. Recovery from anesthesia is determined by the rate of decrease of drug from its effect compartment after the drug administration is terminated. Although terminal half-life of a drug has been used to measure of duration of drug effect, the rate at which the actual drug effect declines depends on both elimination and redistribution from

the central compartment. For example studies investigating the pharmacokinetic and pharmacodynamic relationship of the phenylpiperidine derivatives suggest that terminal half-life of the drug is of limited value because it does not help to predict to what extent the concentration decline of the drug may be prolonged after repetitive doses or continuous infusion. Hughes et al attempted to simulate the decline of central compartment drug concentration following variable length opioid infusion. CSHT is defined as the time required for plasma drug concentration to decline by 50%, starting from the plasma concentration found at the end of the infusion. (2)

Beyond a 2-hour infusion period, CSHT of fentanyl increased six fold compared to alfentanil, propofol and sufentanil. While CSHT is not half-life, it has practical significance as a time to recovery index during opioid infusions. (1,2).

For most anesthetic drugs CSHTs are markedly different from their elimination half-life during variable infusion duration. CSHT is independent of duration for certain anesthetics (Remifentanyl 2.5 min), (Propofol 12min at 1 hour and 38 min at 8 hours) or prolonged (fentanyl 1 hour at 24minutes and 8 hours at 280 minutes). Sufentanil has a CSHT of 35minutes at 300 minutes infusion duration and 60 minutes at 600 minutes. The choice of sufentanil infusion will maintain analgesia while allowing predictable emergence for the wake up test. (3)

Regarding the role of intrathecal opioids in spinal surgery, intrathecal opioids provide excellent analgesia but come with the risk of delayed respiratory depression. Overall use of intrathecal morphine is felt to be safe practice; analgesia without significant patient controlled analgesia (PCA) use and a trend towards decreased intra-operative blood loss. In addition to the respiratory depression, adverse effects of neuraxial opioids include pruritus, nausea and vomiting. The incidence of these complications can be as high as 30-60%. The management of side effects is not always successful and may also interfere with analgesia (for example; naloxone infusion for pruritus. Goodarzi et al have demonstrated no effect on the latency and amplitude of SSEPs after IT morphine (4). Studies on the effect of IT morphine on MEP are lacking at this point.

Epidural catheters placed in the epidural space before closure can also be used in post op pain management. These include single and dual catheter (Lumbar and Thoracic site) and use of opioid or combination of opioid and local anesthetic. Most of the studies are limited and one should be aware of risks such as infection, local anesthetic toxicity due to higher dosing, cost increase as well as side effects such as delayed respiratory depression (4).

Spine surgery is associated with a small incidence of neurological impairment. Combined surveys of Scoliosis Research Society (SRS) and European Society for Deformities of the spine suggest an incidence of 0.72% in 1975. This has been reduced to 0.3% and all were partial cord lesions. Children with curves greater than 100 degrees, congenital scoliosis, kyphosis and post radiation deformities appear to be at greatest risk of complication. SRS has issued a position statement concluding that neurophysiologic monitoring can assist in early detection of

complications and possibly prevent post-operative morbidity. (5)

There are four main methods of intra-operative monitoring of spinal cord function during spinal surgery. These include; the ankle clonus, Stagnara wake-up test, SSEP and MEP. The ankle clonus test is done during emergence. If the spinal cord is injured the cord undergoes a period of spinal shock and there is loss of reflex activity. This test is rarely done in clinical practice.

For the wake up test, the plane of anesthesia is lightened after instrumentation of the spinal cord and prior to closure of the incision. As the patient becomes more conscious she is instructed to first perform an action involving muscle groups above the level of any potential cord damage. When a positive response is obtained the patient is asked to move her legs and integrity of spinal cord is tested. The wake-up test is easy to administer, reliable, has no extra cost and requires no equipment. The major limitation is the test does not provide information about sensory tract. Risks include falling off the operating table, extubation in the prone position, and other problems related to change in patient position such as pressure point issues, Arterial line dislodgement or misplaced bite block. Its also conceivable that a wake up test could be normal after the last corrective maneuver has been applied but before the onset of resultant neurological deficit.

There is also potential for awareness and recall during the wake-up test. McCann et al evaluated bispectral index (BIS) and postoperative recall during intra-operative wake-up test during scoliosis surgery. In their study they demonstrated significant increase in BIS numbers during wake-up test, with a small incidence of explicit recall; which was independent of anesthetic technique. (6,7)

Evoked potentials (EP) are electrophysiological responses in the nervous system to sensory and motor stimulation. IOM of EP assesses the functional integrity of neural pathways in anesthetized patients (while undergoing procedures that place the nervous system in jeopardy). The dorsomedial sensory tract carries discriminatory touch, proprioception and vibratory senses. Fibers are projected to the contralateral primary somatosensory cortex. The lateral and anterior corticospinal tracts control voluntary movement. Most motor fibers (85%) cross the midline to descend in the contralateral spinal cord as the lateral corticospinal tract; the remainder (15%) as the anterior spinal tract in the ipsilateral spinal cord. SSEPs are elicited by electrically stimulating a mixed peripheral nerve (Usually posterior tibial, peroneal or sural) and recording the response at sites cephalad to the level at which surgery is performed. The EP waveform consists of a series of peaks and valleys presented as a graph of voltage over time and are described in terms of amplitude, latency and morphology.

Latency is the time from a stimulus to the peak of response and amplitude is peak-to-peak voltage difference. SSEP waveform activity can be recorded at the popliteal fossa after posterior tibial nerve stimulation and at Erb' s point after median nerve stimulation. Spinal potentials recorded over the cervical and lumbar spinous processes confirm the delivery of the stimulus to

the central neural axis. Cortical SSEPs are recorded on the scalp overlying the contralateral primary sensory cortex. The sub cortical SSEP recorded over the second cervical vertebra can be useful intra-operatively since it is not very susceptible to anesthetic effects. The midlatency cortical SSEP is moderately sensitive to anesthetic depression, but clinically useful recordings can be recorded with modification in anesthetic technique. Latency changes of 7-10% and amplitude decrease of 45-50% may occur without postoperative neurologic changes. Most would consider amplitude decrease of 50%, and latency increases of 10% to be significant changes reflecting loss of integrity of neural pathways; (provided these changes are not caused by anesthetics or temperature). (8)

As a result of reports of postoperative paralysis despite normal intraoperative SSEPs, monitoring of the motor tracts of the spinal cord is used as a more sensitive indicator of risk to spinal cord. The area of spinal cord most vulnerable to ischemic injury is the motor pathway supplied by a single anterior spinal artery. This is fed by segmental contribution by radicular arteries at different vertebral levels. The largest radicular artery is the artery of Adamkiewicz, which arises between T8-L4.

MEP monitoring is divided according to; site of stimulation (motor cortex, spinal cord), method of stimulation (electrical, magnetic) and site of recording (spinal cord, peripheral mixed nerve, muscle). Stimulation cranial to the site of surgery is transmitted to the motor tract in the spinal cord, then to the peripheral nerves and muscle caudal to the site of surgery. The use of NMB is not contraindicated, but if NMB blockade is too deep, responses are unobtainable. Epilepsy and proconvulsant medications are relative contraindication because of the concern of brain injury from prolonged seizure activity due to electrical current required for stimulation. One problem with MEP monitoring is deciding when and how much change in the signal is significant and indicative of spinal cord ischemia. While some centers use the same criteria used in SSEP, other centers require a greater degree of change, such as 75% decrease in amplitude. Compound muscle action potential (CMAPs) is generated by the summation of potentials from depolarization of multiple muscle fibers.

#### Effect of anesthetics on SSEP and MEP

Inhaled anesthesia causes dose dependent decrease in both SSEP and MEP. At equipotent concentration, the MEP is affected to a greater degree than SSEPs. Overall, the volatile anesthetics (dose dependent) decrease the amplitude and increase the latency of SSEPs. The latter cortical waveform is most sensitive to volatile anesthesia with marked attenuation at 0.5% minimum alveolar concentration (MAC). Volatile anesthetics cause significant dose dependent depression of myogenic amplitudes at clinically relevant doses. Increasing numbers of patients lose recordable MEP, even with multipulse stimuli, as concentration of inhaled anesthetic exceeds 0.5 MAC.

Nitrous oxide (60-70%) generally diminishes cortical SSEP amplitude by about 50% while leaving cortical latency and subcortical waves unaffected. It potentiates the depressant effect of volatile anesthetics and most intravenous anesthetics. Nitrous oxide depresses MEPs as well.

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Most anesthesiologists tend to avoid nitrous oxide due to its effects on neuromonitoring. IV anesthetics generally affect SSEPs less than inhaled agents. Propofol has been associated with higher cortical SSEP amplitudes despite anesthetic concentrations equivalent to nitrous oxide or sevoflurane. Despite the depressive effect on the motor system, the rapid metabolism and titratability of propofol has made it a popular drug during EP monitoring. Propofol depresses the amplitude of myogenic MEP. When serum propofol levels are maintained with an infusion of 20-25 mcg/kg/min and supplemented by opioid and nitrous oxide, CMAP responses were noted in 100% of patients. Even with propofol infusion at 100mcg/kg/min acceptable signals are recorded with multipulse stimulation.

Benzodiazepines have only mild to moderate depressant effect on SSEP amplitude. MEP amplitude is unaffected by midazolam and is similar to etomidate. Fentanyl, Sufentanil and Remifentanil minimally depress SSEP and MEP.

The cerebral effects of alpha 2-adrenoceptor agonist appear to act at the Locus coeruleus, rather than causing general inhibition of synaptic pathways. Clonidine and dexmedetomidine have minimal effect on SSEP. There are no published data of Clonidine on MEP. Dexmedetomidine has a dose related depression of MEP and the ability to interpret these results may depend on the anesthetic depth. Depth of anesthesia monitoring is recommended. Side effects include hypotension, which may be a concern since the drug effect could be prolonged in longer duration of infusion.

After anesthesia induction baseline SSEP/MEPs are recorded and compared to subsequent event-related changes. (5,6,8,9)

Recently there has been renewed interest in ketamine as an adjunct to general anesthesia. Benefits in spinal surgery may include enhanced cortical SSEP, minimal effects on subcortical SSEP and minimal effect on MEP amplitude, apart from its pain control properties in the intra and postoperative period. The use of sub-anesthetic dose would provide pain relief, anesthetic depth and avoid postoperative delirium.

The key is to provide a stable concentration of the hypnotic component of anesthesia. There is probably no difference between inhaled anesthesia (<1MAC) and propofol (<6mg/kg/hr). Short acting medications provide greater flexibility should the monitoring signals deteriorate. Monitoring the anesthetic depth with processed EEG is useful to have but addition of ketamine may confound the EEG monitoring (by increasing it). (5)

Physiological factors affect SSEP signals, such as in hypothermia (increased latency), hyperthermia (decreased amplitude), hypotension (decreased amplitude), hypoxia (decreased amplitude), hypocarbia (increased latency) and anemia (increased latency).

The blood sparing techniques used in spinal surgery include methods aimed at decreased bleeding (manipulating the coagulation cascade and controlled hypotension) and methods

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aimed at decreasing homologous transfusion (acute hemodilution, planned autologous transfusion and cell saver systems).

The use of synthetic antifibrinolytic agents to decrease perioperative blood loss after scoliosis surgery has produced mixed results. Epsilon-Aminocaproic Acid (EACA) and Tranexamic acid (TA) are analogues of lysine, which inhibit fibrinolysis by preventing conversion of plasminogen to plasmin. They have been shown to decrease intraoperative blood loss and transfusion requirements. Both drugs are cleared renally; thrombosis of the kidneys and ureters may occur if urologic bleeding is present.

To be most effective, an effective plasma concentration of the antifibrinolytics should be established before skin incision.  $\epsilon$ -Aminocaproic acid decreases the EBL by 25% during the perioperative period. In contrast, an initial dose of tranexamic acid (10 mg/kg) followed by an infusion of 1 mg/kg/hr failed to significantly decrease blood loss. High-dose tranexamic acid (100 mg/kg loading dose, followed by an infusion of 10 mg/kg/hr) did decrease blood loss by 40% but did not affect transfusion requirements. Post hoc analysis in patients with secondary (neuromuscular) scoliosis showed significant reduction in blood loss and transfusion requirements. The correct dose of tranexamic acid remains elusive, but it may be one half of the high dose reported previously. (5)

Desamino-8-D-arginine vasopressin (DDAVP) is a synthetic analogue of vasopressin. It has significantly less pressor activity than vasopressin. DDAVP promotes hemostasis by the release of both Factor 8 and Von willebrand factor from endothelial storages. The evidence for the efficacy of DDAVP in orthopedic procedures in patients with normal coagulation system is lacking.

Controlled hypotension has been used to minimize blood loss during scoliosis surgery since it was first described more than 30 years ago. Ganglion-blocking agents have been superseded by  $\beta$ -blockers, direct arterial vasodilators, calcium channel blockers, and  $\alpha$ 2-agonists. It remains uncertain whether reduced blood loss results from lowered blood pressure or lower cardiac output. A target mean arterial pressure (MAP) of 50 to 65 mm Hg has been recommended.

Although this appears to be safe, concerns that the margin of safety for cerebral and spinal cord ischemia is reduced by controlled hypotension. Especially when there is the potential for periods of hypovolemic hypotension, in the setting of drug-induced (controlled) hypotension. Because of these concerns and the concomitant use of hemodilution, less extreme degrees of hypotension are usually employed. (5)

There are different agents used in controlled hypotension and we will review the commonly used agents.

Sodium nitroprusside (SNP) is one of the agents used for control of intraoperative blood pressure. It's a direct acting non-selective vasodilator and its mechanism of action is by release

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of nitric oxide. Adverse effects includes rebound hypertension, increased intracranial pressure, ablation of hypoxic pulmonary vasoconstriction (HPV), platelet dysfunction and cyanide toxicity. The adrenoceptor antagonists have been used as primary agents for controlled hypotension. Although different agents have been used labetalol and esmolol are the commonly used adrenoceptor agonists. Labetolol is a competitive antagonist at alpha 1, beta 1 and beta 2 receptors. It has no effect on intracranial pressure and does not inhibit HPV. Esmolol is a short acting selective beta 1 adrenoceptor antagonist. It has a rapid onset of action (3 minutes) and plasma elimination half-life of 9 minutes. The rapid metabolism is due to hydrolysis by erythrocyte esterases and elimination unaffected by renal or hepatic dysfunction.

In modern practice, moderate hypotension with good control of the heart rate can often be achieved without the use of specific vasoactive drugs by using a remifentanyl infusion titrated to the desired blood pressure. Although not considered a hypotensive agent, intrathecal morphine decreases blood loss and may facilitate blood pressure control. Dexmedetomidine may be used as part of a technique for controlling blood pressure. (5,11).

We will next discuss blood transfusion. Blood product transfusion is common in spinal surgery. The minimum acceptable hematocrit varies, but most healthy children tolerate hematocrit in the 20-25 % range. At the start of the case maximum allowable blood loss is calculated. Clinically important prolongation of prothrombin time and partial thromboplastin time greater than 1.5 times normal is significant. This usually occurs when blood loss exceeds 1.5 times blood volume and replacement has been with packed red blood cells and crystalloids or colloids. In these circumstances fresh frozen plasma administration is indicated. Clinical bleeding related to platelets does not occur when the count remains above 50,000/mm<sup>3</sup>.(12)

A more sophisticated approach to the washout of inhalational anesthetics is to use the CSHT, which is a measure of the time to decrease the anesthetic partial pressure by 50%. Context sensitive decrement times for inhaled anesthetics has been described. It aids in understanding the differences in recovery from different inhaled anesthetics. The tutorial by Eger and Shafer (13) will be discussed.

Postoperative pain management after spinal surgery is usually with patient controlled analgesia (PCA), which should include a basal infusion as well. In our patient basal infusion is not required because IT morphine would be expected to provide baseline analgesia for 24 hours. Over time the PCA is converted to an oral form of analgesia, which should include long acting opioids, and short acting opioids for breakthrough pain. The common medications for PCA are morphine, hydromorphone and fentanyl. Oral medications include oxycodone, morphine and hydromorphone. Specifically long acting medication should be prescribed for 3-5 days only. Methadone has a role in acute pain management since its mechanism of action includes NMDA antagonism as well as being a mu receptor agonist. Other favorable features of methadone are its long half-life and minimal expense.

The incidence of pruritus after opioid use has been reported to be about 1% after systemic

administration and varies between 30% and 90% after neuraxial use. Unmediated C-fibers, which originate in the skin, transmit itch impulses to the ipsilateral dorsal horn of the spinal cord, where they synapse with itch-specific second order neurons. These secondary neurons immediately cross over to the opposite anterolateral spinothalamic tract and travel to the thalamus, where they synapse with third order neurons. The third order neurons travel to the somatosensory cortex of the post-central gyrus.

The central mechanisms of intrathecal and epidural opioids may be related to the cephalic spread of the drug in the cerebrospinal fluid and its action on the medullary dorsal horn and trigeminal nucleus in the medulla. Opioid receptors are present in the trigeminal nucleus and this would explain the location of opioid induced pruritus, which is usually in the facial areas innervated by the trigeminal nerve. Kjellberg et al performed a meta-analysis on the pharmacological control of opioid-induced pruritus and concluded that prophylactic naloxone, naltrexone, nalbuphine or droperidol were effective, though the minimal effective doses remain unknown. They also reported that there is a lack of valid data on the efficacy of interventions for established pruritus. (14)

## References

1. Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology* 1991;74:53-63.
2. Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992;76:334-41.
3. Cote and Lerman's. *A Practice of Anesthesia for Infants and Children* W.B. Saunders, 2013. 5th edition. Page 79
4. Tobias JD. A review of intrathecal and epidural analgesia after spinal surgery in children. *Anesth Analg* 2004;98:956-65
5. Cote and Lerman's. *A Practice of Anesthesia for Infants and Children* W.B. Saunders, 2013 5th edition. Orthopedic and spinal surgery. Pages 627-52
6. Raw DA, Beattie JK, Hunter 1M. Anaesthesia for spinal surgery in adults. *Br J Anaesth* 2003;91:886-904.
7. McCann ME, Brustowicz RM, Bacsik J et al. The bispectral index and explicit recall during the intraoperative wake-up test for scoliosis surgery. *Anesth Analg* 2002;94:1474-8.
8. Banoub M, Tetzlaff JE, Schubert A. Pharmacologic and physiologic influences affecting sensory evoked potentials: implications for perioperative monitoring. *Anesthesiology* 2003;99:716-37.
9. Lotto ML, Banoub M, Schubert A. Effects of anesthetic agents and physiologic changes on intraoperative motor evoked potentials. *J Neurosurg Anesthesiol* 2004; 16:32-42.
10. Tobias JD. Strategies for minimizing blood loss in orthopedic surgery. *Semin Hematol* 2004;41:145-56.
11. Tobias JD. Controlled hypotension in children: a critical review of available agents. *Paediatr Drugs* 2002;4:439-53.
12. Cote CJ. *A Practice of Anesthesia for Infants and Children* W.B. Saunders, 2013. 5th edition: Strategies for blood product management and reducing transfusion 198-220.
13. Eger E, Shafer SL. Tutorial: Context-Sensitive Decrement Times for Inhaled Anesthetics. *Anesth Analg* 2005;101:688-96.

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14. Waxler B, Dadabhoy Z, Stojiljkovic L et al: Primer of postoperative pruritus for anesthesiologists. *Anesthesiology* 2005; 103: 168-78.