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Front Cover:

Seth Quiambao, RN, BSN, a graduate student enrolled in the University of Southern California (USC) Program of Nurse Anesthesia meets his ‘patient’, CRNA David Godden, MS (an alumnus of the USC program), in preparation to conduct a preoperative anesthesia assessment. Mr. Quiambao also has a case report published in this issue of the ISJNA.

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Or, use this direct link: http://www.aana.com/studentjournal
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Risk of Rhabdomyolysis in the Morbidly Obese

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Keywords: anesthesia, rhabdomyolysis, obesity, post-operative risk

Morbid obesity is a risk factor for the development of postoperative rhabdomyolysis (RML). Rhabdomyolysis is associated with multiple causes and differential diagnoses.\(^1\) This case report describes the events of a morbidly obese, 52 year-old female patient following a right knee arthroscopy, whom on postoperative day one presented with generalized myalgia, elevated creatine kinase (CK) levels, and a decrease in renal function. Prior to surgery, the patient presented with multiple risk factors for developing RML, including a BMI greater than 50 kg/m\(^2\), hypertension, and type II diabetes. During the perioperative period, this patient encountered multiple triggers that can contribute to RML.

**Case Report**

A 52-year-old female patient presented for a right knee arthroscopy. The patient weighed 145.5 kg and was 165 cm tall, with a BMI of 53.4 kg/m\(^2\). The patient’s pertinent medical history included: hypertension, exercise induced asthma, obstructive sleep apnea, type II diabetes, occasional heartburn, depression, anxiety, and gout. Past surgical history included tonsillectomy, bilateral myringotomy with tubes and caesarean section with no anesthesia complications. The patient denied having any drug allergies and her current medication regimen included: metformin, sitagliptin phosphate, lisinopril, paroxetine hydrochloride and allopurinol. The last dose of these medications was the day before surgery. The patient reported using biphasic positive airway pressure (Bipap) at night for the treatment of obstructive sleep apnea. Preoperative lab values showed decreased renal reserve with a glomerular filtration rate (GFR) of 50 mL/min/1.73m\(^2\), blood urea nitrogen (BUN) 27 mg/dL, and creatinine of 1.2 mg/dL. All other lab values were within normal limits.

Anesthesia was induced with intravenous (IV) propofol 300 mg and lidocaine 100 mg. After mask ventilation was confirmed, succinylcholine 120 mg IV was administered. Following induction of anesthesia and muscle relaxation, tracheal intubation was performed without difficulty. The patient was then placed with her upper extremities neutral and abducted less than 90 degrees. Her left lower extremity was placed in low lithotomy position and all pressure points were padded. The surgeon placed the patient’s right hip in the neutral position and her right knee in passive flexion. A right thigh tourniquet was inflated to 300 mm Hg. The surgical procedure proceeded without complications. During the operation, fentanyl 250 mcg IV was administered along with ketorolac 30 mg IV. The total procedure time was forty minutes and the total amount of time the tourniquet was inflated was twenty-eight minutes. Following the procedure, the patient met extubation criteria, was extubated, and then taken to the post anesthesia care unit (PACU). The patient received a total of 1400 mL of 0.9% normal saline throughout the perioperative period.
the perioperative period. The patient voided after surgery but the amount was not documented. After meeting discharge requirements in the PACU, the patient was discharged home.

On postoperative day one, the patient presented to the emergency department. Following an uneventful night, she developed generalized myalgia that significantly increased throughout the day. Prescribed postoperative pain medications failed to relieve the pain. An emergency room clinician documented the following data: vital signs within normal limits, no changes on electrocardiogram, and an unremarkable physical assessment. Laboratory values showed an elevated CK level of 607 IU/L, an elevated myoglobin level of 341.4 mcg/L, acute renal insufficiency with a decreased GFR of 30 mL/min/1.73m², BUN 53 mg/dL, and creatinine 1.9 mg/dL. Her troponin I level was within normal limits at a level of 0.014 ng/mL. In the emergency department, the patient was given one liter of 0.9% normal saline, ketorolac 30 mg, and hydromorphone 1 mg. After these interventions, the patient stated her pain was almost completely relieved. The patient was encouraged to increase her fluid intake and was discharged home without further complications.

Discussion

RML is the result of striated muscle breakdown. Fluid pulled into the damaged muscle area causes swelling and systemic hypovolemia. Damage to the myocyte causes an efflux of potassium, lactic acid, myoglobin, and CK. Increased amounts of lactic acid and other organic acids may result in metabolic acidosis. Myoglobin in the presence of oliguria and aciduria is nephrotoxic creating a high risk of renal failure. Elevated CK levels are relatively benign but serve as a marker for myocyte membrane permeability. The patient’s postoperative lab values showed an increase in BUN, an increase in creatinine, and acute renal insufficiency. These lab values along with elevated levels of CK and myoglobin suggest acute postoperative rhabdomyolysis as a possible cause of renal insufficiency. An arterial blood gas was not obtained. However, it would have been useful to rule out metabolic acidosis that could have developed in conjunction with RML, acute renal insufficiency, and/or a history of metformin administration. For example, metabolic acidosis from the patient’s metformin use may have further reduced kidney function as acidic urine in the presence of myoglobin can be nephrotoxic.

Risk factors and triggers for RML can vary widely because many conditions can cause skeletal muscle injury and ischemia. Risk factors specific to muscle ischemia include excessive weight, diabetes, vascular disease, hypertension and long operative times. Other triggers and risk factors of RML include the use of succinylcholine, surgical trauma, improper positioning, tourniquet use, excessive alcohol consumption, use of hydromethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, and malignant hyperthermia. While the patient was carefully positioned and the surgical time was relatively brief, this patient did present with several risk factors and triggers for RML, including morbid obesity, hypertension, diabetes, the use of succinylcholine and the use of a thigh tourniquet. Though the patient takes allopurinol, which is associated with
myalgias, this risk factor may have been offset by the medications effect in reducing uric acid production.²

Elevations in serum creatinine and creatine phosphokinase (CPK) levels unexplained by other reasons and complaints of buttocks, hip, or shoulder pain in the postoperative period should raise the suspicion of rhabdomyolysis.⁵ Local symptoms of RML include: muscle pain, swelling, weakness, bruising and tenderness.², ⁴ Systemic symptoms of RML include: fever, malaise, nausea, emesis, confusion, agitation, delirium, anuria, and tea-colored urine.² The patient presented to the emergency room with generalized myalgia and postoperative lab values showing an increase in creatinine and CK. After ruling out heart and brain ischemia, the diagnosis of RML can be confirmed by CK levels five times above the normal value. ¹, ², ⁴ The patient in this case study did not present with CK levels five times the normal value. Therefore, the patient did not meet diagnostic criteria for RML, but would be considered to have a less severe condition sometimes referred to as hyperCKemia.³

Multiple techniques can be used to prevent RML in the morbidly obese surgical patient. Prevention methods include: padding pressure points, use of pneumatic beds, combining two surgical tables, limiting surgical time, changing the patient’s position intraoperatively, aggressive fluid replacement in the perioperative period, early ambulation, discontinuing HMG-CoA reductase inhibitors, close postoperative monitoring, and avoidance of nephrotoxins.¹, ², ⁴ The meticulous padding and positioning of the patient in this case study would be expected to have decreased her risk for RML. The patient in this case may have benefited from increased fluid administration to better compensate for her fluid deficits. Measuring urine volume output in the PACU, and testing for myoglobinuria in the emergency department may have also helped guide fluid management. The use of ketorolac in the operating room and again in the emergency room could be questioned in this case study due to the impaired renal function of the patient and the risks of renal failure associated with ketorolac.

Once the diagnosis of RML is confirmed prompt treatment is necessary to prevent further complications. Treatment measures focus on preserving renal function in order to prevent acute renal failure.² Early, aggressive fluid administration is the primary treatment to prevent hypovolemia and to flush the kidneys of nephrotoxic debris.² Fluid replacement should produce and maintain a urine output of >1.5mL/kg/hr until myoglobinuria is cleared.² The patient in this case may have benefited from encouraged fluid intake upon discharge from PACU. Serial urine myoglobin levels and CK levels could have been drawn on postoperative day two to ensure the levels were decreasing. Normal urine output volumes, free of myoglobin, suggest adequate hydration.²

Morbidly obese patients present a unique risk of acute postoperative RML. It is important to be aware of patients’ individual risks as well as the triggers they encounter perioperatively in order to prevent RML in the postoperative phase. There is a serious risk of renal failure associated with RML and it is therefore important to recognize, diagnose and treat acute postoperative RML promptly.
References


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Residual Neuromuscular Blockade

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Keywords: residual neuromuscular blockade, post anesthetic care unit, train-of-four

For many decades anesthesia professionals have been aware that the use of neuromuscular blocking drugs (NMBDs) are associated with a risk of postoperative residual neuromuscular blockade (RNMB).1 Despite pharmacological and technological advances, the incidence of RNMB seen in the postoperative recovery areas can be as high as 31% of patients.2 Residual neuromuscular blockade may predispose patients to postoperative complications such as an increased risk of aspiration, airway obstruction, or attenuation of a hypoxic ventilatory response. Anesthetists should be vigilant and utilize proper monitoring techniques to assess the level of neuromuscular blockade and optimize the utilization of reversal agents.

Case Report

A 69-year-old, 157 cm, 79 kg female presented for a laparoscopic vs open cholecystectomy due to chronic cholecystitis originally diagnosed 2 years ago. Her current medical history was remarkable for hypertension for 20 years, non-insulin dependent diabetes mellitus for 8 years, hypothyroidism for 12 years, and obesity. Her surgical history included a hysterectomy, esophagogastroduodenoscopy, and thyroidectomy, all without anesthetic complications. Her medication regimen included hydrochlorothiazide 25 mg daily, lisinopril 10 mg daily, metformin 500 mg BID, glipizide 5 mg daily, levothyroxine 112 mcg daily, aspirin 81 mg daily, simvastatin 40...
mg daily, and pantoprazole 40 mg daily. Preoperative vital signs were as follows: blood pressure (BP) 137/63 mm Hg, heart rate 73/min, respiratory rate (RR) 14/min, SpO2 98%, and temperature 36.4°C.

The patient received midazolam 2 mg intravenously (IV) for anxiolysis and was taken to the operating room (OR). Upon arrival in the OR noninvasive monitors were placed and O2 10L/min was administered via face mask. General anesthesia induction commenced with fentanyl 100 mcg, propofol 140 mg, and rocuronium 40 mg. The trachea was intubated with a 7.0 mm cuffed endotracheal tube and respirations were controlled with mechanical ventilation set at 10/min with a tidal volume of 450 mL; ventilations were adjusted throughout the case to maintain an end-tidal CO2 between 35 and 40 mm Hg. General anesthesia was maintained with sevoflurane 2% expired concentration in a mixture of O2 1 L/min and air 1 L/min. Additionally, a total of 20 mg of rocuronium was administered throughout the procedure to maintain muscle relaxation with the goal of maintaining the train-of-four (TOF) response at one out of four twitches. Neuromuscular blockade monitoring was done with a standard peripheral nerve stimulator assessing the orbicularis oculi muscle.

Upon completion of the case, the nerve stimulator was repositioned to monitor the left ulnar nerve, at which point the patient exhibited a TOF of three out of four twitches. The neuromuscular blockade was antagonized with neostigmine 3 mg and glycopyrrolate 0.6 mg. The patient was breathing spontaneously, generating tidal volumes between 250 mL and 300 mL, and demonstrating sustained tetany to nerve stimulation at 100 Hz. Once awake and following commands, the patient’s trachea was extubated and she was taken to the post anesthesia care unit (PACU) while receiving O2 via simple face mask at 6 L/min. On arrival the patient’s SpO2 was 83%, BP 146/72 mm Hg, RR 21/min, and temperature 36.2°C. Equal but diminished bilateral breath sounds were auscultated. The patient was instructed to take deep breaths and was switched to a non-rebreather face mask delivering O2 at 15 L/min. Oxygen saturation improved to 94% but the patient continued to experience difficulty taking deep breaths. A portable chest X-ray was ordered and a BIPAP device was available. The chest X-ray was unremarkable and additional doses of neostigmine 2 mg IV and glycopyrrolate 0.4 mg IV were administered. Approximately fifteen minutes thereafter, the patient reported an improved ability to take deep breaths and was weaned to a nasal cannula at 2 L/min with SpO2 of 99%. The patient’s vital signs remained stable throughout her stay in PACU and she was discharged to the floor three hours later on room air.

Discussion

Residual neuromuscular blockade is most accurately defined as the presence of muscle weakness in the postoperative period after the intraoperative administration of a NMBD. Patients with adequate neuromuscular recovery should have the ability to breathe normally, maintain a patent upper airway, preserve protective airway reflexes, swallow, cough, smile, and talk. Most patients can demonstrate these actions when their TOF ratio is 0.9. However, some patients may show obvious weakness despite achieving TOF ratios.
>0.9, while others exhibit total recovery of muscle strength with TOF ratios <0.9. The inability to reliably exclude residual neuromuscular blockade when using conventional peripheral nerve stimulators creates the potential for inconsistency when assessing for RNMB.²

The actual incidence of RNMB is very difficult to quantify as the symptoms often go unrecognized or are blamed on other components of the anesthetic such as opioids, benzodiazepines or the presence of residual anesthetic gas. Multiple studies conducted over the past five decades have attempted to measure the incidence of RNMB and results have varied widely, with reported frequencies ranging from 2-64%.¹ A recent meta-analysis by Naguib et al³ looked at twenty-four studies including 3375 patients who received NMBD. The analysis showed that neuromuscular blockade antagonism was provided in 32.1% of patients. When studies utilizing intermediate acting NMBDs were analyzed, the incidence of TOF <0.7 was 12% and <0.9 was 41%.³ The authors concluded that there was a “continued high incidence of postoperative residual curarization reported from multiple academic centers” and despite advances in pharmacology and monitoring techniques the incidence of this particular postoperative complication has not decreased over time.³

The risks of RNMB are many and depending on the degree of the residual blockade can lead to severe complications. Multiple studies have shown that RNMB leads to weakness of the pharyngeal muscles and decreases the degree of muscle coordination involved in swallowing, thereby increasing the risk of aspiration in the PACU. Eikermann et al⁴ demonstrated evidence of inspiratory and expiratory airway obstruction even at a TOF ratio of 0.8, which is likely due to weakness of the upper airway dilator muscles. A study by Iragashi et al⁵ demonstrated that NMBDs impair the carotid body chemoreceptor function, which modulates the hypoxic ventilator response. It is likely that the incidence of these complications may be even greater in patients who receive perioperative adjunct medications such as opioids, benzodiazepines, volatile anesthetics, and induction agents in addition to NMBDs, all of which have been shown to affect physiologic functions.

The only way to decrease the incidence of RNMB and the associated complications is to identify the phenomenon prior to tracheal extubation. However, the standard peripheral nerve stimulator and other extubation criteria are not always adequate for this task. The subjective nature of the visual and tactile interpretation of the response to nerve stimulation creates inconsistencies in the evaluation process.¹ In fact, none of the frequently utilized clinical tests assessing RNMB, such as hand grip, leg lift, eye opening or head lift, have been experimentally proven to be reliable unless TOF ratios are <0.5.⁶ Even with the use of conventional peripheral nerve stimulators, clinicians are often unable to reliably identify residual neuromuscular blockade, as fade is difficult to subjectively detect when TOF ratios are between 0.4 and 0.9. There are commercially available quantitative tools that have been experimentally proven to better objectively assess the degree of neuromuscular blockade, which include: mechanomyography, electromyography, kinemyography, phonomyography, and acceleromyography. The universal adoption and utilization of these devices has been slow. The potential reasons are the lack of availability of the devices in the various institutions, the unwillingness by
providers to embrace a new technology, the financial cost to the institution, or limited knowledge of evidence based peripheral neuromuscular monitoring.

Although the patient in this case had an initial TOF of 3 out of 4 twitches and the neuromuscular blockade was antagonized with what was thought to be an adequate dose of neostigmine, it was likely insufficient to return the patient to baseline function. As well, it is possible that insufficient time was given to fully antagonize the NMBD. A study by Murphy et al\(^7\) demonstrated that on average, clinicians were ready to perform tracheal extubation eight minutes after administration of neostigmine, with mean TOF ratios of 0.67±0.2. According to Kim et al\(^8\), the median time required to reach a TOF ratio of 0.70 after administering neostigmine 0.07 mg/kg to a patient with TOF of 2 out of 4 twitches was 22.6 (8.3-57.4) min.

It is difficult to identify the exact reason for the respiratory distress demonstrated by this patient. However, it is likely the combination of the reasons stated above. Due to current clinical limitations, perioperative monitoring of evoked neuromuscular responses that guide the administration of reversal agents and proper documentation of responses should be the standard of practice when utilizing NMBDs.

References


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Diabetes Insipidus in a Patient Undergoing Pituitary Adenoma Resection

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Keywords: diabetes insipidus, perioperative, fluid therapy, pituitary tumor, desmopressin acetate

Pituitary adenomas are a unique class of intracranial neoplasms that represent 10-15% of intracranial neoplasms.1,2 “The prevalence of pituitary tumors is approximately 200 per million of the population”.1 75% of pituitary tumors secrete inappropriate amounts of pituitary hormones that disrupt hormone function and water metabolism.1 Diabetes insipidus is an indication of a deficiency in antidiuretic hormone (ADH) secretion.3 Decreased ADH secretion produces central diabetes insipidus (CDI) whereas renal tubular resistance to ADH is designated nephrogenic diabetes insipidus.4 Acquired CDI is present in only 2% of patients presenting for surgery.5 30% of patients undergoing pituitary surgery experience CDI postoperatively.3 The fluid and electrolyte imbalances that CDI produces need to be corrected immediately to prevent a dangerous situation.2 Central diabetes insipidus accounts for 0.5-31% morbidity in individuals undergoing pituitary surgery.6

Case Report

A 32-year-old, 172 cm, 70 kg female patient presented for a transsphenoidal resection of a pituitary adenoma and abdominal fat graft. Her past medical history included diabetes mellitus type II, gastroesophageal reflux disease, former smoker, depression, lumbosacral spondylosis, congenital spondylolisthesis, and spinal stenosis. Due to the pituitary tumor, she developed CDI & was being treated with desmopressin acetate (DDAVP). During the preoperative assessment, the patient revealed she was instructed to withhold her DDAVP the morning of surgery. The patient had remained NPO and was experiencing polyuria. She did not have any previous anesthesia history. Her preoperative blood pressure was 118/79 mmHg, heart rate 62/minute, respiratory rate 16/minute, temperature 36.5°C, and SpO2 was 99%. Medications for this patient included sitagliptin/metformin, bupropion, desmopressin acetate, and a birth control pill. Preoperative lab testing was completed several days prior to surgery and all values were within normal limits.

An 18-gauge peripheral intravenous (IV) catheter was placed and Lactated Ringers (LR) was initiated. Upon arrival to the operating room, standard monitors were applied and pre-oxygenation was initiated with 10 L/min of flow via facemask. She was given midazolam 2 mg. An arterial catheter was inserted for invasive blood pressure monitoring and frequent lab draws. An IV induction was performed with lidocaine 40 mg, fentanyl 100 mcg, propofol 150 mg, and rocuronium 43 mg. The trachea was intubated under directly laryngoscopy with a 7.0 cuffed oral endotracheal tube that was secured after placement was confirmed. The patient was placed on mechanical ventilation. General anesthesia was maintained with 1% sevoflurane in a mixture of oxygen and air, both at 1 L/min as well as a dexmedetomidine infusion at 0.4 mcg/kg/hr. A foley catheter was
placed to monitor urine output and a second peripheral IV catheter was placed. A 100 mg dose of hydrocortisone sodium succinate was administered. Fentanyl and rocuronium were administered intermittently. A phenylephrine infusion was used to treat hypotension with a goal mean arterial pressure of 65 mm Hg.

Fluid management was identified as a primary concern pre-operatively by the anesthesia team. It was determined that LR would be infused to cover her maintenance, deficit, third space loss, and estimated blood loss. A total of 1,400 mL of LR was administered. Urine output was replaced with 0.9% normal saline (NS). Her total urine output during the three-hour case was 2,675 mL. She received a total of 3,000 mL of 0.9% NS. A fluid warmer was used to keep the patient normothermic. Sodium, potassium, and glucose were monitored every 60 minutes throughout the case. Initial sodium was 145 mEq/L, potassium 3.6 mEq/L, and glucose 217 mg/dL. The final intraoperative sodium was 149 mEq/L, potassium 4.8 mEq/L, and glucose 210 mg/dL.

Upon completion of the case, the neuromuscular blockade was antagonized with neostigmine 3 mg and glycopyrrolate 0.4 mg. Once extubation criteria was met and the patient was following commands, the trachea was extubated and 4 L/min oxygen was administered via nasal cannula. The phenylephrine infusion was discontinued as the patient was hemodynamically stable. The patient was transferred to the recovery room where she received 1 mcg DDAVP IV.

Discussion

Central diabetes insipidus occurs due to a disruption in the hypothalamus-posterior pituitary axis (HPA) and is an indication of a deficiency in ADH secretion. Anatomical lesions involved in the disruption of the HPA include pituitary surgery & tumors such as pituitary adenomas. Pituitary adenomas can cause adrenal insufficiency, which leads to increased levels of ADH. Glucocorticoids are initiated due to adrenal insufficiency and inhibit the synthesis and secretion of ADH. Therefore, symptoms of CDI may become exposed upon initiation of glucocorticoid therapy.

The diagnosis of CDI is made primarily through clinical signs and symptoms as well as laboratory data. The diagnosis of CDI is confirmed with continued polyuria in the presence of hypernatremia and/or serum hyperosmolality. CDI manifests as polyuria, polydipsia, excessive thirst for cold water, fever, hypovolemia, and hypotension. Patients with untreated CDI secrete large amounts of urine at a rate of 2.5-3 mL/kg/hr. As a result urine becomes dilute. Diagnostic criteria for CDI includes a urine specific gravity < 1.005 and urine osmolality < 200 mOsml/kg H2O. The large volume of urine excretion results in an increase in serum sodium (≥ 145 mEq/L) and serum osmolality (≥ 295 mOsm/L).

Recent advancements and continuous improvements in surgical resection techniques of pituitary tumors presents unique challenges to the anesthesia professional, as it incorporates both endocrine and neurosurgical management. A review of literature concerning CDI associated with pituitary tumors revealed several factors involved in the
management and treatment of this phenomenon including use of IV ADH replacement and fluid therapy.

Antidiuretic hormone therapy should begin once the diagnosis of CDI is identified. The drug of choice for transient and chronic treatment of CDI is DDAVP, which is designed to minimize polyuria and polydipsia while simultaneously treating hypernatremia. Each dose of DDAVP is usually effective for 6-12 hours. Redosing should occur prior to the patient experiencing hyperosmolality and hypernatremia. A general guide to follow when to redose DDAVP consists of urine excretion ≥ 200-250 mL/hr with a urine osmolality < 200 mOsm/kg H2O or urine specific gravity < 1.005.

Historically, the choice of fluid therapy in this patient population was controversial. Recent data pertaining to fluid management is sparse. Mukherjee et al published a retrospective-prospective study in 2014 that was done to determine which perioperative IV fluid is best in the treatment of CDI. The findings support the use of hypotonic solution. Results were comparable in the retrospective & prospective groups. A number of patients receiving only 0.9% NS developed hypernatremia. Six of these patients subsequently died from cerebral infarcts that were attributed to their hypernatremia (Na > 150 mEq/L). Several patients receiving only 5% dextrose developed hyperglycemia and hyponatremia. No complications were experienced by those patients who received only 0.45% NS.

The patient in this report was diagnosed with CDI after presenting with polyuria, polydipsia, and excessive thirst for ice cold water. While the patient did receive 100 mg hydrocortisone succinate preoperatively for adrenal insufficiency, she did not receive DDAVP preoperatively or intraoperatively. She received LR and 0.9% NS for fluid management which may have contributed to her hypernatremia that persisted despite adequate volumes of IV fluids being administered. Arguably, her condition may have been optimized by prompt administration of IV DDAVP along with the use of 0.45% NS for fluid therapy. The patient was discharged home & returned to the clinic in 2 weeks. The surgeon reports that she remained in CDI, a finding that was not unexpected.

The incidence of CDI is rare and is generally not encountered by anesthesia professionals in the perioperative period. While planning the anesthesia care to be delivered to this patient population, it is imperative for the anesthesia provider to carefully select the type of IV fluids to be utilized. With the evidence that is available, 0.45% NS appears to be the fluid of choice to diminish water and electrolyte abnormalities. Early administration of DDAVP is crucial in treating polyuria and hypernatremia. Given that CDI is rare, little research exists and thus there is a gap in the literature. Additional research and case reports are needed to substantiate past evidence and hopefully enhance patient safety and improve patient outcomes.
References


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Acute Lung Injury after Cardiopulmonary Bypass

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Keywords: Acute lung injury, cardiopulmonary bypass, cardiothoracic surgery, pulmonary complication(s)

Acute lung injury (ALI) is a major complication of cardiopulmonary bypass (CPB). Major factors that contribute to CPB-induced ALI include atelectasis and pleural effusions, which occur in 60% of cardiac surgery patients.1,2 Additionally, embolic insults, prolonged CPB time, and CPB-induced systemic inflammatory response all contribute to the development of lung injury which results in impairment of gas exchange. Pre-existing medical conditions that increase a patient’s risk of developing ALI include a history of tobacco use and chronic obstructive pulmonary disease (COPD).1 Patients with postoperative lung injury have a longer intensive care stay and experience higher in-hospital mortality than those without injury.2
Case Report

A 52-year-old, 95.5 kg, 183 cm male with a 12-pack-year tobacco abuse history presented for aortic valve replacement. Pre-operative interview revealed a medical history of COPD, congestive heart failure, dyspnea on exertion, and bronchitis. The cardiac catheterization report revealed non-obstructive coronary artery disease with moderate pulmonary hypertension. Chest radiography showed no acute disease and echocardiogram revealed moderate aortic insufficiency with a left ventricular ejection fraction of 55%. Daily medications included metoprolol 50 mg by mouth (PO), furosemide 40 mg PO, budesonide/formoterol fumarate dihydrate 160-4.5 mcg inhaler, and albuterol HFA 90mcg inhaler, all of which were taken the morning of the scheduled surgery. Pre-operative assessment included lung auscultation of rhonchi with diminished breath sounds in the bases bilaterally. Oxygen saturation (SpO₂), as measured by pulse oximetry, was observed as 93% on room air. Pre-induction midazolam 2mg and fentanyl 50 mcg were administered intravenous (IV) push following the placement of a right forearm 18 gauge peripheral intravenous line (PIV). A left 20 gauge radial arterial line and right 9 French internal jugular double lumen venous catheter were placed in the pre-operative holding area with no complication. A warmed 0.9% normal saline intravenous infusion was initiated at 50 mL/hr.

After arrival to the operating room, Standard American Society of Anesthesiologists intra-operative monitoring guidelines were followed. Additionally, 12-lead electrocardiogram, arterial blood pressure, stroke volume variation, core temperature, urine output, and cerebral oxygenation were all continuously monitored. Pre-oxygenation was administered by facemask at 15 L/min. After the patient completed five tidal volume breaths, an end-tidal oxygenation of 90% and an SpO₂ of 98% were observed. Intravenous anesthetic induction included fentanyl 700 mcg, lidocaine 80mg, propofol 120mg, rocuronium 100mg, and phenylephrine 200 mcg. Tracheal intubation was atraumatic with the placement of a size 8.5 endotracheal tube (ETT) via direct laryngoscopy using a Miller 2 blade. Placement of the ETT was confirmed by positive ETCO₂ and equal breath sounds bilaterally. Volume control ventilation was set at a tidal volume of 480 mL with a respiratory rate of 12/min.

Anesthetic maintenance consisted of isoflurane at 1.2% with an oxygen flow of 2 L/min. Systolic blood pressure was maintained between 90-120 mm Hg using phenylephrine and nitroglycerin IV bolus amounting to 800 mcg and 240 mcg, respectively. Mechanical ventilation was held for approximately 15 seconds during sternotomy and resumed with previous volume control ventilation settings immediately after completion. Following sternotomy, heparin 27,000 units was administered IV and an aminocaproic acid 10 g intravenous bolus was followed by an infusion of 1.5 g/hr. The patient was cannulated and converted to CPB without complication after an activated clotting time of 456 seconds was achieved. Activated clotting time remained therapeutic and the total CPB time measured at 130 minutes. Immediately prior to separation from CPB, four 5-second lung recruitment breaths were administered at a positive end expiratory pressure (PEEP) of 30 mm Hg before reintroduction of ventilation and inhalational anesthetic at pre-bypass settings. Protamine 270mg intravenous infusion was administered after successful
weaning from CPB. Post-CPB vital signs were stable with SpO₂ of 97%. Neuromuscular blockade was not antagonized. After closure, cardiothoracic intensive care unit (CTICU) transfer was completed using manual bag ventilation without complications.

A four-day follow-up revealed continued CTICU admission, insertion of a pulmonary artery catheter and mechanical ventilation with pressure control settings of 38 mm Hg. Inverse inspiration to expiration ratio had been initiated resulting in an arterial oxygen partial pressure to fractional inspired oxygen (PF) ratio of 80 mm Hg. During three temporary volume control trials peak inspiratory pressures were recorded as 46-52 mm Hg. Chest radiograph confirmed placement of pulmonary artery catheter and showed bilateral pulmonary infiltrates. Pulmonary wedge pressures trended between 14-16 mm Hg with no evidence of left atrial hypertension.

Discussion

Multiple perioperative factors contribute to development of ALI after cardiothoracic procedures. These influences include complex interactions between present physiologic state, comorbidities, lifestyle choices, underlying surgical diagnosis, operative approach, and most importantly, their cardiopulmonary interaction with a mechanical ventilator. Current studies have exposed that aggressive tidal volumes may lead to intraoperative barotrauma causing tissue damage resulting in ALI. Preexisting pulmonary disease compiled with inflammatory mediator release and resulting atelectasis from cardiopulmonary bypass tremendously increase complications associated with ALI. During open heart surgery there are various interventions that can lower ALI risk: utilizing protective lung ventilation strategies, limiting CPB time, avoiding pulmonary ischemia, appropriate use of transfusion, and implementing anti-inflammatory adjuncts to pharmacological perioperative management.

Conventional tidal volumes provided during mechanical ventilation can be associated with a sustained plasma increase in inflammatory cytokines. In fact, tidal volumes greater than 700 mL and peak airway pressures greater than 30 cm H₂O are shown to be independently associated with the development of ALI. Appropriate management of intraoperative ventilation to prevent injury consists of providing lower tidal volumes with a decrease of 2 mL/kg of predicted body weight, lower peak inspiratory pressures decreased by 5 cm H₂O, and higher PEEP increased by 2 cm H₂O from the patient’s baseline. In addition to protective strategies for maintenance ventilator settings, studies have shown decreased ALI with the use of positive pressure recruitment after physical collapse of the lungs following CPB. In a randomized controlled trial by Serita et al. high-pressure recruitment maneuvers using an individualized weight-based inflation pressure of no greater than 45 mm Hg and held for 15 seconds resulted in improvement of oxygenation and lung compliance without hemodynamic instability. Amelioration of pulmonary sequela after recruitment maneuvers is thought to be a result of capitalizing on transient transpulmonary pressure increases to reopen alveoli that have suffered collapse. The re-inflation of alveoli thus decreases shunt fraction, ultimately improving hypoxemia. This is reflected clinically as improved PF ratio and oxygen saturation values.
Modifications to CPB can be implemented to prevent development and/or decrease the severity of lung injury following bypass. Apostolakis et al\textsuperscript{3} describes modifications including the utilization of heparin-coated circuits, use of ultra-filtration techniques, controlled hemodilution, and leukocyte depletion. The use of heparin-coated circuits and ultra-filtration techniques contribute to reduction in the observed activation of systemic inflammatory response syndrome and the scavenging of various pro-inflammatory cytokines. Abrupt hemodilution caused by the incorporation of priming solution in the bypass blood circuit can contribute to increased interstitial edema in vital organs, including the lungs. Reduction of priming volumes results in better hemodynamic ranges such as arterial blood pressure, cardiac index, and vascular resistance. Replacement of colloid for crystalloid or simple downgrade of priming solution volume may also contribute to a higher oxygen delivery by facilitating tissue perfusion. Current research has shown that entrapped leukocytes in the capillaries of the lungs have a large role in the inflammatory reaction after CPB. Some studies have shown reduced free radicals and preserved pulmonary function with depletion of leukocytes through circuit filtration.\textsuperscript{3} Production of destructive reactive oxygen species can result from transient ischemia and subsequent reperfusion of the lungs following CPB. Additionally, extra-pulmonary ischemia-reperfusion can add to lung injury. In aortic procedures, inflammatory mediators are produced with hepatosplanchnic ischemia-reperfusion, which contributes to pulmonary vascular permeability.\textsuperscript{8}

Transfusion-related lung injury, or TRALI, consists of a syndrome of hypoxia or bilateral pulmonary edema during or within six hours of blood product transfusion. Although thought to be related to systemic inflammatory response and antibody-mediated mechanisms, the exact etiology of TRALI is unknown. Prevention strategies surrounding transfusion include fresher products, washed components, and plasma primarily or exclusively from male donors, specifically avoiding multiparous women. Most importantly, however, the appropriate use of transfusion products is key to prevent unnecessary pulmonary consequences.\textsuperscript{4}

The role of pharmacological management in prevention of ALI can be overlooked due to focus on ventilation strategies and CPB technique. Adjunctive treatment of corticosteroid administration before initiation of bypass has been shown to inhibit the production of pro-inflammatory cytokines IL-6, IL-8, and TNF\alpha, thus improving post-operative values of the alveolar-arterial oxygen gradient, pulmonary vascular resistance, and extracellular lung water.\textsuperscript{6}

Early steps in preventing acute lung injury following cardiothoracic surgery are identifying patient-specific risk factors and formulating an individualized interdisciplinary intraoperative plan. In this case, the patient holds numerous risk factors including a history of tobacco use, congestive heart failure, chronic obstructive pulmonary disease, undergoing an aortic valve procedure via midline sternotomy, introduction of ventilation with large tidal volumes, and ultimately, exposure to CPB. Although recruitment strategies were performed upon separation from cardiopulmonary bypass, post-operative ICU follow-up implied diagnosis of ALI. In reviewing the
patient’s perioperative management, multiple factors may have contributed to this outcome. By implementing the previously discussed strategies and targeting each individual risk factor, the patient discussed may have experienced a better outcome.

References


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Dexmedetomidine for Procedural Sedation in Obstructive Sleep Apnea Patients

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Keywords: procedural sedation, obstructive sleep apnea, precedex

With an increasing number of invasive and non-invasive procedures done under procedural sedation the greatest risk patients face is airway compromise.¹ This risk increases when pre-anesthetic evaluation reveals certain risk factors for airway complications such as obesity and obstructive sleep apnea (OSA).¹² In addition, procedural sedation in high-risk patients can potentially have deleterious effects on the cardiovascular system, requiring the anesthesia provider to carefully select agents that leave the smallest anesthetic footprint possible to optimize outcomes. Dexmedetomidine preserves spontaneous respirations, promotes better hemodynamic stability, decreases opioid requirements and should be explored for moderate/deep procedural sedation of at risk patients.³
Case Report

A 61-year-old, 95 kg female with a body mass index (BMI) of 34.8 kg/m² presented with paroxysmal atrial fibrillation and was scheduled to undergo cryo electrophysiology catheter ablation. The patient demonstrated a Mallampati III airway classification, with visualization of the soft palate and base of the uvula only. Additionally, her inter-incisor gap was less than 4 cm, her atlanto-occipital joint mobility less than 35 degrees, and thyromental distance less than 6 cm. Her medical history was significant for obstructive sleep apnea, hypertension, hyperlipidemia, mitral valve regurgitation, pulmonary hypertension and non-insulin dependent diabetes mellitus. Her pre-operative blood pressure was 155/102 mm Hg and heart rate (HR) was 100/min atrial fibrillation. Medications administered the morning of surgery per surgeons request included lisinopril, aspirin and atenolol. The patient’s baseline 12-lead electrocardiogram (ECG) showed atrial fibrillation. A perioperative echo revealed a left ventricular ejection fraction of 50%.

The patient’s chart was reviewed and she was informed of the procedure for conscious sedation utilizing dexmedetomidine. Anesthetic risks and benefits were discussed and the patient consented to proceed as scheduled. Inside the operating room standard ASA monitors were applied. Non-invasive monitoring of ventilation was achieved utilizing capnography via placement of a nasal cannula administering oxygen at 3 L/min. The patient then received midazolam 1 mg and fentanyl 25 mcg intravenously (IV). Dexmedetomidine 100 mcg/mL (2 mL) was added to 50 mL of 0.9% sodium chloride injection constituting a final concentration of 4 mcg/mL. A loading dose of dexmedetomidine 1 mcg/kg was infused IV over 12 minutes followed by a maintenance infusion of 0.5 mcg/kg/hr (10.6 mL/hr).

Following the initial bolus infusion of dexmedetomidine a slight decrease in HR to 75/min atrial fibrillation was noted which resolved with administration of glycopyrrolate 0.1 mg IV. Blood pressure and HR remained within 20% of baseline with procedural burst pacing and isoproterenol administration by the surgical team being the exception. With surgeon-initiated synchronized cardio-versions at 200 joules a total of 50 mcg of fentanyl IV were administered for additional pain control. The patient maintained spontaneous ventilation with adequate respirations and carbon dioxide levels throughout the procedure. Upon successful conversion to sinus rhythm, protamine 50 mg IV was administered over five minutes to neutralize the anti-coagulant effects of heparin. At this point the dexmedetomidine infusion was discontinued and the patient opened her eyes after approximately 3 minutes.

Her post-operative blood pressure was 138/65 mm Hg, HR 63/min sinus rhythm, and SpO2 99% on room air. She was drowsy but able to follow commands with some assistance transferred herself from the operating room table to the stretcher. In the post anesthesia care unit the patient was breathing spontaneously, followed detailed commands and vital signs remained stable. There were no post-operative complications and the patient went home the next morning.
Obstructive sleep apnea (OSA) often is associated with obesity and is an independent risk factor for adverse respiratory events requiring airway intervention during procedural sedation. In the U.S. approximately 80%-95% of OSA cases remain undiagnosed and do not follow the “Pickwickian” stereotype, making it difficult to determine which patients might be at risk for OSA. Dexmedetomidine is an α-2 agonist generating a dose dependent sedation that resembles a natural sleep which does not cause respiratory compromise. Propofol and midazolam exert their effects via the γ-aminobutyric acid (GABA) receptor leading to depression of airway muscle reflexes and tone resulting in possible airway obstruction. These effects are often augmented by the presence of opioids and could pose a risk in patients predisposed to airway obstruction. The main goal is to maintain spontaneous ventilation and to avoid potential airway complications.

In a randomized controlled trial by Kaygusuz et al, respiratory effects of dexmedetomidine, propofol and fentanyl were compared during extracorporeal shockwave lithotripsy procedures. The study demonstrated that dexmedetomidine had minimal effects on respiratory rate, SpO2 values and unlike propofol did not cause apnea in spontaneously breathing patients when dosages had to be increased to maintain adequate sedation.

Adding to the efficacy and safety profile of dexmedetomidine is its ability to blunt sympathetic/hemodynamic responses in patients undergoing awake fiberoptic intubation (AFOI), a gold standard for managing potentially difficult airways. Dexmedetomidine decreases sympathetic outflow by reducing the release of norepinephrine, which leads to a sympatholytic effect decreasing heart rate and blood pressure. In a comprehensive review of literature conducted by Johnston and Rai, patients receiving dexmedetomidine consistently had less incidents of hypertension and tachycardia during AFOI. Another randomized controlled trial of 40 patients undergoing AFOI resulted in a mean HR increase of 1 and 14/min with dexmedetomidine and propofol control groups respectively. The most common dexmedetomidine side effects of bradycardia and hypotension were occasional and responsive to glycopyrrolate and fluid administration, although most often these resolved without intervention making the findings of the study only mildly significant. Dexmedetomidine also has demonstrated anti-anginal effects, as well as decreasing the myocardial oxygen demand, but caution should be exercised in patients with advanced heart block and severe ventricular dysfunction.

Scherrer et al conducted a large literature review to evaluate the association of obesity with sedation-related adverse events and found obese patients have a higher incidence of respiratory complications during procedural sedation requiring intervention by the anesthesia provider. Obese patients often exhibit an increased sensitivity to exogenous opioids, while midazolam with its depression of airway muscle tone can increase the frequency and duration of apneic events. Dexmedetomidine infusions resulted in a decrease in the mean total dose of midazolam and fentanyl required for sedation. A randomized controlled multicenter trial including 326 patients undergoing diagnostic and/or therapeutic procedures found that the percentage of patients not requiring any midazolam was as high as 54% in the dexmedetomidine groups compared to 3% for the
placebo. ³ Patients who required the barbiturate had a mean total dose of 0.9 mg versus 4.1 mg for the placebo group. ³, ⁸ For all surgeries performed fewer patients required rescue fentanyl administration 42.6% in the dexmedetomidine infusion (¹μg/kg) group, versus 88.9% in the placebo group. ⁸ It was also determined that the fentanyl dosages required were much higher in the placebo group at 144.4 μg versus 83.6 μg. ⁸

The patient in the case above had all the assessment findings of a potentially difficult airway, in addition to OSA and obesity. The respiratory implications associated with these conditions are considerable and therefore the decision was made by the anesthesia provider to utilize dexmedetomidine infusion to maintain spontaneous respirations. During the case glycopyrrolate was chosen to counter the decrease in heart rate seen with the bolus infusion of dexmedetomidine. The patient required no rescue midazolam to maintain adequate sedation, was calm, easily arousable and received a total of fentanyl 75 mcg IV for synchronized cardioversion. Upon discontinuation of dexmedetomidine the patient did not display any signs of delirium, was able to follow commands and move herself to the stretcher in approximately 3 minutes.

Currently approximately 200 million U.S. adults are classified as overweight or obese with 71-77% also having OSA. ¹ This patient population usually presents with a higher incidence of co-morbidities requiring absolute vigilance on behalf of the anesthesia provider to achieve optimal patient outcomes. The endeavor of maintaining spontaneous ventilation during procedural sedation, while achieving adequate analgesia/patient comfort presents a complex challenge, especially since these individuals often are much more sensitive to the respiratory-depressant effects of opioids and benzodiazepines. ¹ In patients with anticipated difficult airways, OSA and the morbidly obese, dexmedetomidine is gaining favor due to its unique ability of maintaining spontaneous ventilation, hemodynamic stability and establishing “cooperative sedation”. ¹-⁴, ⁸ Decreasing the need for opioids/benzodiazepines, as well as its anti-sialagogue properties make dexmedetomidine an excellent choice for procedural sedation. ¹, ³, ⁴, ⁵, ⁸

References


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### Anesthetic Considerations for Protamine Administration

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**Keywords:** protamine, protamine sulfate, anaphylaxis, anaphylactoid, vascular surgery

In the cardiovascular surgical population, protamine sulfate serves as the sole agent for reversal of heparin-induced anticoagulation. Although alternatives are being explored, it will likely retain preference despite the well-documented potential for adverse reactions up to and including death.1,2 Current literature estimates that protamine induced adverse reactions range from an incidence of 0.06% to 10.6%, making it one of the most common causes of life-threatening adverse reactions during cardiac surgery.1-4 It is likely that the pitfalls surrounding this modality will present a challenge for surgical patients, and their anesthesia practitioners, for years to come.

**Case Report**

A 78-year-old, 49 kg, 157.5 cm female presented with a non-healing left ankle ulcer and ischemic rest pain. She was scheduled to undergo angiography of the lower extremities with possible stenting for peripheral vascular disease. Pertinent medical history included Type II diabetes mellitus, myocardial infarction, congestive heart failure (CHF), and renal artery stenosis. Surgical history included a coronary artery bypass graft, as well as renal, femoral, and iliac stentings. Current medication regimen included felodipine, metoprolol, aspirin, atorvastatin, clopidogrel, and glimepiride. Baseline echocardiograph showed sinus rhythm with left ventricular hypertrophy (LVH), and a prolonged QT interval. Recent echocardiogram revealed mild dilation and LVH, with an ejection fraction estimated at 55%. Baseline hemoglobin and hematocrit were 10.5 g/dl and 31.5%, respectively, with a platelet level of 139,000 mcL.

Preoperatively, the patient reported anaphylaxis to penicillin, and denied allergies to latex or shellfish. She was a former smoker, and reported that she could climb a flight of stairs...
without difficulty. Breath sounds were clear and equal, bilaterally. Cardiac auscultation revealed an audible S3. Premedication with intravenous (IV) midazolam 1 mg was administered before invasive blood pressure monitoring was instituted.

General anesthesia was established with IV induction of propofol 80 mg and rocuronium 50 mg. Phenylephrine 20 mcg IV was required to maintain baseline hemodynamics before placing an oral endotracheal tube. General anesthesia was maintained with 1.3 - 1.8% expired sevoflurane, and a fresh gas flow totaling 2 L/min of an equal mixture of O2 and air. Mechanical ventilation mode was volume-control. Intravenous infusion of phenylephrine was started at 20 mcg/min to maintain a systolic blood pressure reading ≥140mmHg.

Shortly after incision, the surgeon requested initial heparinization. Over the 4-hour surgery, the patient received a total of 7000 units heparin IV with the last dose administered 3 hours before closure. Serial activated clotting time (ACT) measures were monitored with the iStat handheld (Abbot Point of Care Inc., Princeton, NJ) and corresponding celite cartridges, with a final ACT of 188 seconds. The surgeon requested reversal of heparinization with protamine sulfate 20 mg, which was administered over 4 minutes IV. Minutes after administration of protamine sulfate, the blood pressure decreased from 148/50 to 68/28 mmHg, with an increase in heart rate from low 50’s/min to mid 70’s/min (sinus rhythm). Peak inspiratory pressures were unchanged, as were lung sounds. Oxygen saturation remained at 99%.

The phenylephrine infusion was immediately increased to 120mcg/min with an additional bolus of 200 mcg, followed by a 500 mL bolus of lactated ringers. Blood loss was estimated at 50 ml. Ondansetron 4 mg and dexamethasone 4 mg were then administered for nausea prophylaxis. After 12 minutes, the vital signs returned to baseline values. Emergence and extubation occurred uneventfully. The patient was transferred to the recovery area in stable condition.

Discussion

Anesthesia professionals must be knowledgeable concerning the administration, immunologic implications, and anesthetic considerations associated with the use of protamine during surgery. It is a polycationic protein that is derived from the heads of salmon sperm. Protamine binds the negatively charged heparin molecule via an electrostatic interaction, which neutralizes heparin-induced anticoagulation.1,2,5,6 In the surgical setting, it is administered slowly according to the total amount of heparin given in a usual ratio of 1-1.3 mg protamine for every 100 units of heparin. The recommendation is to administer protamine no faster than 50 mg over 10 minutes.6 In addition to its reversal properties, it is also used to stabilize and delay the absorption of neutral protamine Hagedorn insulin (NPH) used by insulin-dependent diabetics.2 Adverse reactions associated with its administration may include a transient decrease in systemic blood pressure, anaphylaxis, and severe pulmonary vasoconstriction.2,5,6 Per Nussmeier et al6 protamine may cause an endothelial nitric oxide release, mast cell degranulation, and histamine release, depending on rate of infusion.
Since protamine is a non-human protein, it has antigenic potential, though the mechanism is not fully understood.² Severe systemic reactions can occur through both immunologic or non-immunologic mechanisms. Type I (IgE-mediated) hypersensitivity, or allergic anaphylaxis, usually occurs upon re-exposure to a specific antigen that causes the release of proinflammatory mediators. This has been reported to occur upon initial exposure in some cases.⁸ Conversely, anaphylactoid reactions occur via a non-immune mediated release of mediators from mast cells and/or basophils, or may result from direct complement activation. It can be difficult to differentiate between the two, since the latter presents with clinical symptoms similar to anaphylaxis.⁷

Recognizing a patient at risk for adverse reactions to protamine sulfate is of primary importance to anesthesia professionals. According to a systematic review conducted in 2008, the most common factor predisposing a patient to anaphylaxis was any exposure to NPH insulin, though fish allergy was also described as an independent risk factor.¹,²,⁴ Other unconfirmed factors include vasectomy, previous exposure via surgery, history of non protamine allergy, decreased LV function, and hemodynamic instability. Based on preoperative assessment, this patient possessed several risk factors for protamine sensitivity: multiple previous exposures to protamine following vascular procedures, penicillin allergy, and a previous diagnosis of CHF, which indicates impaired ventricular function. Of note, although our patient denied an allergy to shellfish, she did not explicitly deny allergy to vertebrate fish. Since shellfish are phylogenetically different from salmon, tolerance to the former does not exclude intolerance to the latter.² Therefore, it is possible that she may have had an additional, undiscovered risk factor.

In a 2011 retrospective study examining the utility of low-dose protamine (1.9±0.83 mg) to facilitate arterial sheath removal after peripheral endovascular intervention, there were no episodes of anaphylaxis or adverse reactions recorded in 166 cases.³ Compared to cardiac surgical cases where doses in excess of 300 mg upon completion of cardiopulmonary bypass are administered,³ this vascular patient received a relatively small dose of protamine sulfate, yet experienced a substantial drop in arterial blood pressure. This finding may suggest allergic sensitivity. Given the intraoperative setting, it was difficult to determine if there were any corresponding cutaneous manifestations. However, there was no tachycardia manifest in this beta blocked patient, and evidence of increased airway resistance, or wheezing to indicate severe anaphylaxis. In a systematic review analyzing prospective, intervention, and surrogate marker studies, researchers found that pretreatment with methylprednisolone 2 g, dexamethasone 20 mg, and/or diphenhydramine 50 -100 mg appeared to provide a net positive effect against hypotension in four separate studies.⁴ In this case, a small dose of dexamethasone was administered for nausea following heparin reversal, which may have simultaneously conferred protection against hypotension, if given earlier in the case.

Considerations for future practice should include thorough preoperative assessment of shellfish versus vertebrate fish allergy. All diabetic vascular patients should be asked if they have ever taken NPH insulin. In addition, in patients considered to be at risk, such as those with non protamine allergies or previous protamine exposure, it may be beneficial
to perform a skin test preoperatively to assess for the presence of antiprotamine antibodies, which mediate anaphylaxis.\textsuperscript{2} Several sources in the literature imply the utility of a test-dose (5 mg – 30 mg) of protamine sulfate to assess for tolerance before the full amount is given.\textsuperscript{2,6,8} Based on this patient’s reaction to a small dose of protamine, a larger dose given during a future procedure, without precaution, might prove to be catastrophic. Given the increasing national prevalence of cardiac and vascular interventions, it is very likely that anesthesia practitioners will encounter these issues related to protamine therapy.

Reference


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Cerebral Oximetry during Shoulder Surgery in the Beach Chair Position

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Keywords: cerebral oximetry, near-infrared spectroscopy, shoulder surgery, and beach chair position

Neurological injuries ranging from cognitive impairment and vision loss to stroke and death have been reported following the beach chair position (BCP); this may warrant the use of real-time, site-specific monitoring of oxygenation and perfusion at the level of the brain with cerebral oximetry.1-6 The mean arterial pressure (MAP) obtained during a non-invasive blood pressure (NIBP) measurement is an indicator of the average pressure during the cardiac cycle and has historically been the main parameter for ensuring adequate cerebral perfusion pressure (CPP). Patients in the BCP are often monitored to maintain MAPs greater than 65-70 mm Hg, but the minimum acceptable value to provide adequate cerebral perfusion is likely patient specific. Cerebral oximetry is a non-invasive monitor that may be useful in ensuring adequate cerebral perfusion and improve patient safety.

Case Report

A 52-year-old, 89 kg, 168 cm female presented for right total shoulder arthroplasty. Medical history included degenerative joint disease, fibromyalgia, anxiety, depression, controlled gastroesophageal reflux, and allergy-induced asthma. Patient was a current 1/3 pack per day cigarette smoker with concurrent marijuana use. Current medications included acetaminophen, amphetamine-dextroamphetamine, clonazepam, omeprazole, pregabalin, buproprion, trazadone, albuterol, cholecalciferol, and simethicone.

The patient received a supraclavicular and superficial cervical block preoperatively and was given midazolam 2 mg intravenously (IV) and fentanyl 100 mcg IV prior to the procedure. Forty minutes later, the patient was transported to the operating room, transferred to the operating room table, and electrocardiogram, NIBP, and finger pulse oximetry monitors were applied. The patient’s forehead was cleansed with alcohol, and the cerebral oximetry and bispectral index (BIS) monitors were applied. Baseline regional cerebral oxygen saturation (rSO2) measurements of 61% (left) and 56% (right) were obtained with the patient breathing room air in a supine position. Prior to induction her vital signs were: heart rate 88/min, blood pressure 138/86 (MAP 103) mm Hg, and a SpO2 of 95%.

The patient was pre-oxygenated via face mask at 10 L/min with cerebral oximetry values increasing to 70% (L) and 62% (R) respectively. Induction medications were administered IV and included: fentanyl 100 mcg, lidocaine 80 mg, propofol 150 mg, and rocuronium 30 mg. An endotracheal tube was placed, and after bilateral breath sounds were auscultated, she was placed on a mechanical ventilator with a respiratory rate of 12 and tidal volume of 580 mL. One hundred percent oxygen was delivered at 3 L/min and
sevoflurane was administered with end-tidal concentrations of 1.1-1.8 throughout the case.

The patient was repositioned into the BCP at approximately a 70-degree angle with her head padded and secured in a neutral position. The patient’s rSO₂ values remained above baseline (68/60%) throughout repositioning. The patient was placed on FiO₂ of 50% and remained there until emergence. End-tidal CO₂ was maintained at 32-35 mm Hg during the maintenance phase. The patient’s rSO₂ values never dropped below baseline for the remainder of the case. BIS readings were 36-46 during maintenance. One NIBP reading of 88/54 mm Hg (MAP 65 mm Hg) was recorded and treated with ephedrine 5 mg IV, resulting in a MAP > 70. Otherwise her MAP remained greater than or equal to 70 mm Hg throughout the surgery.

Near the conclusion of surgery, the patient was given glycopyrolate 0.4 mg IV and neostigmine 3 mg IV for reversal of paralysis. After decreasing the minute ventilation on the mechanical ventilator, the patient began to breath spontaneously and the anesthetic gas was discontinued. The total surgical time was 130 minutes. Once extubation criteria was achieved, the patient’s airway was suctioned and extubated without complication. Oxygen 4 L/min via nasal cannula was applied and the patient was transferred to the post anesthesia care unit (PACU). Upon arrival to the PACU, the patient answered questions appropriately. The post anesthesia evaluation on postoperative day 1 was unremarkable, and the patient was successfully discharged without complications on postoperative day 2. No neurological deficits were reported during the hospitalization, although no specific psychometric tests were performed.

Discussion

The BCP is often utilized for shoulder surgery to improve surgical exposure and minimize strain on the brachial plexus. However, the BCP can result in cerebral hypoperfusion due to both a decrease in blood pressure from vasodilatory effects of anesthetics and impeded blood flow if neutral alignment of the patient’s head and neck is not maintained. Even in healthy individuals, incidences of cerebral hypoperfusion can lead to neurological deficits. The BCP is associated with both slight impairments in cognitive functioning and severe neurologic deficits.

Currently employed monitors may not accurately detect cerebral hypoperfusion. When repositioned from supine to a 45-90 degree head of bed elevation, substantial hemodynamic changes including decreased blood pressure, cardiac index, and stroke volume can occur in both anesthetized and awake patients. Non-invasive blood pressure has historically served as the main parameter for ensuring adequate CPP. Autoregulation, which is the maintenance of constant cerebral blood flow during changes in arterial blood pressure, occurs in the intracranial arterioles and capillaries, necessitating the correction for blood pressure at the level of the brain. When the blood pressure cuff is placed on the upper arm, the difference between the MAP obtained from NIBP and cerebral pressure could easily be 25 mm Hg (approximately 1 mmHg for each 1.25 cm of height differential). Cerebral autoregulation was commonly thought to occur with a MAP
between 50-150 mm Hg but this assumption has been challenged.\(^1\) The lower limit of autoregulation is patient-specific, making the minimum acceptable MAP difficult to predict. A study by Drummond states that 70 mm Hg is the lower limit in supine, non-anesthetized patients and that hypertensive patients’ lower limits could be higher.\(^1\) A panel of experts on cerebral perfusion at the 2009 Anesthesia Patient Safety Foundation concluded that “blood pressure in the BCP should be adjusted to account for a hydrostatic gradient and the maximum reduction in blood pressure from baseline should be 30% after accounting for a hydrostatic gradient.”\(^1\)

It is essential for anesthesia providers to rapidly detect cerebral hypoperfusion and respond with an appropriate treatment such as administration of a vasopressor, increasing the FiO\(_2\), decreasing the respiratory rate to allow for an increase in end tidal CO\(_2\), and/or ensuring the patient’s head and neck remain neutral. Cerebral oximetry is a noninvasive, real-time method to indirectly estimate cerebral perfusion that involves near-infrared spectroscopy. The monitor displays left and right rSO\(_2\) measurements. A decrease in rSO\(_2\) by 20% or more from baseline and/or an absolute value below 50-55%, called a cerebral desaturation event (CDE), is described as a critical level for irreversible cell damage, which warrants investigation and treatment.\(^1\)\(^-\)\(^6\)

Numerous randomized controlled trials on the use of cerebral oximetry during major vascular surgeries have demonstrated that detection and treatment of CDEs results in improved patient outcomes.\(^2\)\(^,\)\(^4\) The benefit of cerebral oximetry during shoulder surgery in the BCP is a subject of ongoing debate. Several prospective, observational studies have been conducted examining the occurrence of CDEs by monitoring cerebral oximetry in the BCP and the incidence is quite variable. In a 51-participant study by Salazar et al., 18% of the patients placed in the BCP for shoulder arthroscopy with a regional block and general anesthesia experienced a CDE.\(^3\) “The patients averaged 1.89 CDEs with a mean desaturation from preoperative baseline of 32% with a minimum of 21% and a maximum of 62%.”\(^3\)\(^(p4031-4032)\) A 61-participant study by Murphy et al. found that 80.3% patients had a major CDE in BCP despite the use of a protocol to maintain SBP within 20% of baseline measurements.\(^5\) A 20-participant study by Moerman et al. found that 80% of participants had a CDE when the BCP was adopted and 30% of the participants had their absolute rSO\(_2\) value drop below 50%.\(^2\) A 53-participant study by Kocaoglu et al. found that nearly half of the patients had a CDE.\(^6\) There was a correlation between rSO\(_2\) and MAP values. Mean arterial pressure monitoring was found to be the most reliable method for detecting cerebral ischemia when cerebral oximetry was unavailable. However, CDEs still occurred when all the other monitors were at physiologic limits.

A 57-participant study by Triplett et al examined the relationship of CDE’s with both NIBP and the estimated temporal MAP (eTMAP), which was measured with arterial catheterization and leveling the transducer with the height of each patient’s temporal artery.\(^4\) Triplett et al. found that hypotension is not always present when a CDE occurs. Twenty-six of the 57 patients experienced 45 CDEs and there was no statistical correlation between the decrease in rSO\(_2\) during a CDE and the NIBP or eTMAP. Triplett et al. concluded that NIBP and eTMAP may not be reliable indicators of a CDE, but that rSO\(_2\) monitoring with cerebral oximetry may be a warranted addition.\(^4\)
The high prevalence of CDEs in the BCP and the rare but dramatic case reports of neurological damage support the need for more site-specific monitoring of brain perfusion. Although there is a lack of high quality evidence available, cerebral oximetry monitoring with near-infrared spectroscopy may be useful for ensuring adequate cerebral perfusion intraoperatively during beach chair positioning.

References


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**Prolonged Apnea in a Cirrhotic Patient receiving Remifentanil Infusion**

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**Keywords:** cirrhosis, remifentanil, delayed emergence, non-specific esterase, prolonged apnea

The liver provides homeostasis in multiple ways, one of which bears specific consideration for anesthesia practitioners. The metabolic functions of the liver bio-transforms most drugs, rendering them inactive.\(^1\) Cirrhosis is a progressive disease that decreases liver function and protein binding.\(^2\) Providing anesthesia for cirrhotic patients requires a sound pharmacological understanding of drug metabolism because certain medications can have prolonged effects on this patient population. Remifentanil is a unique opioid because unlike most narcotics which rely on hepatic enzymes for biotransformation, it is rapidly metabolized by non-specific esterase providing an ultra-short duration.\(^2\) Therefore, remifentanil’s ultra-short duration is beneficial for cirrhotic patients.\(^2\)
Case Report

A 37-year-old, 69 kg, 177 cm male patient presented to the emergency department after discharge five days prior. The patients’ symptoms and complaints included a 38.5°C fever with chills, weakness, diffuse abdominal tenderness on exam and straw-colored fluid from the right chest drain. Medical history was significant for cryptogenic cirrhosis and hydrothorax secondary to ascites. Surgical history included recent transjugular intrahepatic portosystemic shunt (TIPS), appendectomy, and cholecystectomy. Preoperatively, the patient’s laboratory results were consistent with liver failure. Significant values included white blood cell count 3.93, platelets 59,000/μL, prothrombin time 17.7 sec, international normalized ratio 1.4, aspartate aminotransferase 114 unit/L, alanine aminotransferase 92 unit/L, total bilirubin 3.9 mg/dL. The patient was scheduled for a subsequent TIPS procedure for treatment of persistent ascites and portal hypertension secondary to liver cirrhosis.

Premedication with midazolam 2 mg intravenously (IV) was administered, two units of fresh frozen plasma was infused IV, and the patient was transferred to the interventional radiology suite with two peripheral 20-gauge IV catheters. An additional peripheral 16-gauge IV was started in the patient’s right hand and normal saline solution was infused. A single dose unit of platelets was infused IV. Standard monitors were applied and the patient was pre-oxygenated with 10 L/min of oxygen. General anesthesia was induced with fentanyl 100 mcg, propofol 140 mg, lidocaine 80 mg, and cisatricurium 7 mg. Direct laryngoscopy was performed and a 7.5 mm cuffed endotracheal tube (ETT) was placed in the patient’s trachea. Ventilation was maintained at a rate of 10/min and tidal volumes of 550 mL to keep end-tidal carbon dioxide (ETCO₂) levels between 34-36 mm Hg. A radial 20-gauge arterial line was placed in the patient’s right wrist after induction. General anesthesia was maintained with sevoflurane 1.9% inspired concentration and remifentanil 0.1 mcg/kg/min. The TIPS procedure was completed in two hours without complications and the patient’s vital signs remained stable.

At the completion of the case, sevoflurane was turned off, remifentanil was discontinued, and the patient displayed four twitches on train-of-four stimulation with sustained tetany. Neuromuscular blockade was antagonized with neostigmine 3 mg and glycopyrrolate 0.6 mg IV. Twenty minutes after the remifentanil infusion was stopped the patient remained apneic and respirations were controlled by mechanical ventilation. The patient’s pupils were pinpoint, core body temperature was 36.5 °C, and ETCO₂ level was 44 mm Hg. The patient remained unresponsive to verbal and physical stimulation including jaw thrust, sternal rub, and oropharyngeal suctioning. Thirty-five minutes after the remifentanil was discontinued, the patient began to breath at a rate of 4 breaths/min with tidal volumes of 1200-1400 mL. Upon verbal instruction, the patient was able to open his eyes and lift his head. The patient was extubated without further complication and the patient continued to maintained respirations at 8-10/min and tidal volumes of 750 mL. The patient was returned to intensive care unit in stable condition.

Discussion

Cirrhosis is the result of chronic liver disease from a variety of causes including hepatitis, chronic alcohol and drug abuse, and biliary obstruction. More than 3 million Americans are
diagnosed with cirrhosis and it is a co-morbidity commonly encountered in anesthesia.² Cirrhosis adversely effects the pharmacokinetics of multiple anesthetic agents and anesthesia professionals should anticipate erratic responses to drug clearance.² Drug metabolism, elimination, protein binding, and volume of distribution are all affected by liver failure and have a significant effect on hepatic biotransformation.²

Most opioids are metabolized by phase I and II biotransformation and impaired liver function will result in prolonged response.¹ The patient in this case report had cryptogenic cirrhosis with laboratory values and symptoms that depict regressing liver failure. The anesthesia plan was to limit all drugs reliant on hepatic metabolism and use short acting opioids. Remifentanil is an opioid that agonizes μ-opioid receptor. Additionally, it is a peperidine derivative that is antagonized by naloxone.³ The chemical structure of remifentanil includes an ester side chain allowing rapid hydrolysis of the drug by both blood and tissue esterases and independence from hepatic biotransformation.³ This unique metabolism provides for a rapid onset of action and ultra-short duration, with average time of onset of one minute and recovery within 5-10 minutes.² Another unique property of remifentanil is that the duration of action does not accumulate with prolonged administration, which makes it an ideal analgesic for patients with reduced hepatic clearance functions.¹

Patients with atypical cholinesterase deficiency are not at risk for prolonged duration of action, as remifentanil trials have shown that it is not a substrate for pseudocholinesterase.³ Further research has shown that pharmacokinetics of remifentanil are not impacted by hepatic failure.³ After induction, a remifentanil infusion was started at 0.1mcg.kg/min and titrated to patient’s hemodynamic response and continued for duration of procedure. As a result, the literature supports the use of remifentanil in such cases.

Considerable research and data with remifentanil suggest that prolonged apnea is an atypical finding.⁴ In patients receiving remifentanil infusions for general anesthesia, the manufacturer reported only a 0.2% finding of prolonged respiratory depression greater than 10 minutes after discontinuation of the infusion.³ Nelson, Bretz, and Egan suggest that other causes of absence of spontaneous ventilation, such as remaining neuromuscular blockade, hypothermia, hypocarbia, and neurological impairment, be ruled out before opioid antagonists are used.⁴ Delayed return of ventilations may be due to a pharmacogenetic variant that has yet been evaluated and established.⁴ The prolonged emergence seen in this case was outside of what might be expected given remifentanils pharmacokinetic profile. The patient was normothermic, normocarbic, and neuromuscular blockade had been adequately reversed at the time that the infusion was discontinued. The patient began to spontaneously ventilate 35 minutes after remifentanil was discontinued at a rate of 4 breaths per minute and tidal volumes of 1200 mL/min.

The use of remifentanil alone is not sufficient for general anesthesia, so the administration of volatile agents, nitrous oxide and benzodiazepines are commonly used to obtain adequate levels of anesthesia for surgical procedures.² When used in conjunction with gases such as sevoflurane at 1 to 2% minimum alveolar concentration (MAC), remifentanil infusions can be run at lower levels, 0.2 to 0.25 mcg/kg/min.³ Sevoflurane is excreted from the body via exhalation but metabolism may be impaired in patients with liver failure and slightly prolonged.² Barak, Greenberg, and Danino reported a delayed emergence with the combined anesthetic of
midazolam, fentanyl and 2% MAC sevoflurane and treated the patient with an opioid antagonist until adequate patient respiratory response was achieved.\(^5\) The anesthesia plan included a dose of benzodiazepines preoperative and fentanyl and cisatricurium for induction. No further benzodiazepines or long acting narcotics were given and neuromuscular blockade was fully reversed. The small dose of versed and fentanyl and the length of the case, excluded these drugs from precipitating prolonged apnea in the patient.\(^2\)

In summary, patients with altered hepatic metabolism may require alternative methods of anesthesia to prevent prolonged respiratory depression. The chemical structure of remifentanil makes it an ideal narcotic for use with liver failure patients. Although remifentanil typically has a short duration of action, patients may still have delayed emergence with the additive effects of anesthesia. Patients with delayed awakening after remifentanil infusion may benefit from opioid reversal and avoidance of benzodiazepines regardless of case duration.

References


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The Impella Device for Unstable Ventricular Tachycardia Catheter Ablation

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**Keywords:** Impella device, ventricular tachycardia, Ventricular tachycardia ablation, unstable ventricular tachycardia, percutaneous left ventricular assist device

The Impella 2.5 device (Abiomed, Danvers, MA) is a percutaneous left ventricular assist device indicated to provide partial circulatory support during procedures not requiring cardiopulmonary bypass.\(^1\) Percutaneous catheter ventricular tachycardia (VT) ablation can be very difficult to complete when the patient has significant structural heart disease or advanced heart failure.\(^2\) The Impella improves hemodynamics during periods of stimulated VT that otherwise would not be possible due to patient instability. This paper will focus on the benefits of using the Impella device for a patient having a VT ablation.
Case Report

A 54-year-old male presented for a VT ablation after he received several shocks from his implanted cardioverter defibrillator (ICD). Past medical history included: myocardial infarction, status post percutaneous coronary intervention, dilated and ischemic cardiomyopathy, obstructive sleep apnea, diabetes mellitus type II, atrial fibrillation, paroxysmal ventricular tachycardia, congestive heart failure, previous ablation of ventricular arrhythmia, dual chamber ICD, renal insufficiency, and coronary artery disease. Current medications included: enalapril, aspirin, digoxin, warfarin, metformin, glipizide, amiodarone, simvastatin, spironolactone, metoprolol, and furosemide. Pertinent lab and diagnostic values included: Blood urea nitrogen (BUN) 21 mg/dL, creatinine 1.4 mg/dL, prothrombin time (PT) 16 seconds, international normalized ratio (INR) 1.3, and a left ejection fraction of 15%. Both the cardiovascular and pulmonary exams were normal.

An arterial line was placed in the right radial artery prior to induction of anesthesia. The electrocardiogram monitors, pulse oximeter, blood pressure cuff and cerebral oximetry monitors were applied. A pulse oximeter was also applied to the right great toe. The patient was given oxygen at 8L/min through the anesthesia mask for pre-oxygenation. Baseline cerebral oximetry was also established at 70% on the right and 66% on the left. An intravenous (IV) induction was then completed using milrinone 1mg IV, propofol 100mg IV, phenylephrine 200 mcg IV, fentanyl 100 mcg IV and rocuronium 50 mg IV. An 8mm endotracheal tube (ETT) was inserted after direct laryngoscopy using a Macintosh 4 blade. Placement was confirmed with auscultation and end tidal CO2 monitor tracing. Oxygen flows were then decreased to 2L/min. Sevoflurane was started and maintained throughout the procedure at inspired concentrations of 1-3%. An IV remifentanil infusion was also started at 0.1 mcg/kg/min for pain management. A left groin central venous catheter and a swan ganz catheter were placed by the electrophysiologist (EP).

The Impella device was then placed in the patient’s right groin and its flow was determined by the EP. Cardiac mapping was completed with the patient in NSR, after which VT was induced several times for mapping and ablation. In addition to hemodynamics, cerebral oximeter changes were used to guide the length of VT the patient could tolerate with decreases greater than 5% being reported to the EP. The lowest percentages recorded were 64% and 61% on the right and left respectively.

When the procedure was completed the Impella was removed and hemostasis was achieved. The inhalational agent and remifentanil drip were discontinued. No antagonism of muscle relaxants was administered; the patient emerged and was extubated after meeting ASA extubation criteria. Post-operatively, the patient was transported to the intensive care unit for monitoring.

Discussion

Sustained VT in patients with cardiomyopathy and advanced heart failure is potentially life threatening. An ICD is first line therapy for those patients presenting with structural heart disease and VT. About 20% of patients with an ICD for prevention of sudden cardiac death experience an episode of VT within 3-5 years after having the device inserted. Catheter ablation
is a successful treatment for VT, however, factors such as a large infarct area, poorly tolerated VT and a critical VT zone in difficult to ablate regions of the heart, increase the risk of hemodynamic instability.\(^3\) The addition of ventricular assist devices to support the failing ventricle has expanded treatment options for those patients with VT refractory to medications and an ICD.\(^2\) The Impella allows for more precise mapping due to more stable hemodynamics, as well as for the completion of procedures that would otherwise have failed due to patient intolerance.\(^2\)

The Impella 2.5/LD is a percutaneous left ventricular assist device. It is a microaxial pump that is capable of generating up to 2.5 L/min of flow that is inserted under fluoroscopic guidance through the femoral artery and positioned across the aortic valve in the left ventricle.\(^4\) A study by Lemaire et al.\(^4\) used the Impella device to support patients in cardiogenic shock. The patient population included both those who had been revascularized and those who had not. The results showed that 72% of patients recovered ventricular function with a 30 day mortality rate of 25%.\(^4\) Traditionally, significant reductions in the mortality of patients with cardiogenic shock had not been seen despite revascularization.\(^4\)

Short unstable episodes of VT and even longer periods of stable VT can have a negative cumulative effect. These can lead to progressively declining hemodynamics, end organ dysfunction and acute decompensated heart failure.\(^5\) The use of the Impella is intended to unload the left ventricle and maintain both cardiac output and systemic circulation during episodes of sustained VT.\(^5\) Cerebral oximeters can be used as a marker of end organ perfusion during VT mapping, as was shown in a study by Miller et al.\(^6\) When the Impella device was used for VT ablation, only 5% of patients desaturated below the pre-determined low saturation value of 55% versus a desaturation rate of 53% in patients without the support of the Impella.\(^6\)

Another study by Aryana et al.\(^7\) looked at clinical outcomes for unstable VT ablation in patients who were supported by the Impella device and IV inotropes compared to patients supported with IV inotropes alone. The study determined that those patients supported with both the Impella device and IV inotropes had shorter ablation times, shorter hospital stay, a reduction in 30 day re-hospitalizations, lower incidence of repeat ablation, and also a lower 30 day mortality.\(^7\) Furthermore, when the Impella was compared with an intra-aortic balloon pump (IABP), one study showed that the Impella allowed for both significantly longer duration of induced VT and had less early terminations of VT due to hemodynamic instability.\(^8\)

Research regarding the use of the Impella device for unstable VT ablation is still limited and there are many variables that have yet to be studied. Procedural outcomes are one area lacking in literature. Based on existing literature it can be determined that the use of the Impella device for VT ablations allows for a more hemodynamically stable procedure with less end organ deficits and less VT recurrence. Its minimally invasive insertion, low complication profile and significant patient benefits when compared to other techniques and devices makes the Impella device one that has great implications for heart failure patients.
References


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Anesthetic Management of 4-year-old with Bilateral Wilms Tumors

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Keywords: Wilms tumor, pediatric, anesthetic management

Wilms tumor (WT), also known as nephroblastoma, is the most common renal malignancy in children with approximately seven new cases per one million children per year.1 Congenital anomalies including Beckwith-Wiedemann syndrome, WAGR syndrome and Denys-Drash syndrome are seen in up to 10% of children diagnosed with WT.1 With hypertension occurring in 25-80% of patients with WT from elevated levels of renin, anesthetic management of these patients is known to be complicated throughout the perioperative period.2
Case Report

A 4-year-old female with history of febrile seizures presented with complaints of flank pain, hematuria, hypertension, tachypnea and tachycardia. Abdominal palpation revealed bilateral abdominal masses. Abdominal computed tomography (CT) scan was ordered and exposed bilateral renal tumors measuring 16 cm on the right and 4.5 cm on the left. Chest CT illustrated a small right pleural effusion. Suspected diagnosis of WT was made and the patient was admitted to the pediatric intensive care unit (PICU) for further evaluation.

Upon admission, the patient was started on: acetaminophen 15 mg every 6 hours, allopurinol 72 mg every 8 hours, amlodipine 2.5 mg every 12 hours, rocephin 1600 mg every 24 hours, furosemide 5 mg every 12 hours, lactulose 10 mg four times daily, oxycodone 3 mg every 3 hours, hydralazine 10.5 mg as needed, lorazepam 0.5 mg as needed. Preoperative labs were within normal limits with the exception of potassium 3.0 mEq/L.

The patient was scheduled for placement of a tunneled catheter for pre nephrectomy chemotherapy in interventional radiology (IR). The patient was tachycardic, hypertensive and anxious when the anesthesia team arrived in the PICU for preoperative assessment and transport to the IR suite; midazolam 2 mg was administered via the pre-existing 20 gauge peripheral intravenous catheter in the left forearm. In the IR suite, standard monitors were applied and O2 15 L/min was administered via facemask. Intravenous induction of anesthesia was achieved with fentanyl 50 mcg, propofol 40 mg and rocuronium 30 mg. Following rapid sequence induction (RSI), intubation of the trachea was successful on the second attempt with a 1.5 Wis Hipple blade and a 4.5 cuffed endotracheal tube.

Post-induction, the patient’s systolic blood pressure and SpO₂ dropped from 150 to 60 mm Hg and 98% to the low 80s respectively, with peak airway pressures > 30 cm H₂O. A lactated ringer’s intravenous (IV) fluid bolus of 20 mL/kg was given with minimal blood pressure improvement. A colloid IV fluid bolus of albumin of 10 mL/kg followed by epinephrine 10 mcg IV were given which resulted in improved hemodynamics. The patient was manually ventilated with O₂ 15 L/min, and given albuterol 4 puffs via the endotracheal tube with improvement of oxygen saturation to 90%.

The decision was made to perform a thoracentesis and relieve effusion pressure from patient’s right lung. There was immediate improvement in oxygenation and hemodynamics following the removal of 100 mL serosanguinous fluid. Anesthesia was maintained with 2.5% sevoflurane in O₂ 2 L/min. The patient remained stable throughout the remainder of the procedure. Neuromuscular blockade was antagonized with neostigmine 1 mg and glycopyrrolate 0.2 mg. The endotracheal tube was removed while the patient was on the procedure table. Oxygen 10 L/min was administered via facemask and the patient was transported to the PICU where she remained stable in the post-operative period.

Discussion

Patients with WT present a challenge to anesthesia providers regardless of surgical procedure. Tumor size, comorbidities, organ system involvement and patient functional state must be
considered when preparing the patient with WT for surgery. Tumor metastasis most commonly occurs in the lungs and leads to respiratory insufficiency in many patients. Ventilation management of patients with WT under general anesthesia should be focused on lung-protective strategies such as low tidal volume, high rate and positive end expiratory pressure. Elevated intra-abdominal pressures related to tumor size further inhibit respiratory function and may require rapid sequence induction for aspiration prevention.

Patients also commonly present with anemia, coagulation disorders and renal insufficiency, all affecting anesthetic management. Common congenital anomalies associated with WT include Beckwith-Weideman Syndrome (BWS), WARG syndrome and Denys-Drash syndrome. Patients with BWS may exhibit features such as macroglossia, midface hypoplasia, prominent mandible and cleft palate that may increase the likelihood of difficult airway. In addition, patients with BWS have cardiac anomalies and organ enlargement, primarily the kidneys and liver. It is imperative to assess cardiac, renal and hepatic function and adjust the anesthetic plan if any deviations from normal exist. Assess any chemotherapeutics the patient is receiving and potential adverse cardiac or respiratory effects.

Hypertension in patients with WT is believed to be due to elevated renin levels ultimately resulting in arteriolar vasoconstriction produced by angiotensin II. Hemodynamic instability in patients with WT is often seen with induction of anesthesia, tumor manipulation and surgical stimulus. Preoperative hypertension is often treated with angiotensin-converting enzyme inhibitors. Research discusses the avoidance of non-selective beta blockers due to probability of causing refractory hypotension in patients with WT. This hypotension results from tumor-secreted renin, which decreases vasodilation and blocks reflexive heart rate increases.

It is recommended that intraoperative management of acute hypertension be treated with sodium nitroprusside or esmolol and hypotension should be treated with intravascular fluid replacement and phenylephrine. During the procedure, the patient required phenylephrine boluses as well as intravascular volume replacement with both lactated ringer’s and albumin due to severe hypotension. When volume replacement and phenylephrine were insufficient to support the patient’s blood pressure, epinephrine 10 mcg boluses were administered intravenously.

The patient’s right renal tumor was 16 cm in size and in combination with a pleural effusion caused significant respiratory insufficiency prior to and following induction of anesthesia. Post-intubation, the patient had significant decreases in oxygen saturation and required albuterol and manual bag ventilation to improve oxygenation. Despite pharmacologic therapy, the patient continued to have increased PAPs > 30 mmHg and low tidal volumes of 3-4 mL/kg, which were expected. Initially, oxygenation minimally improved, yet significant improvements were noted following a thoracentesis with removal of 100 mL of serosanguinous fluid. Arterial blood gas analysis during this period showed pH of 7.3 mmol/L, CO₂ of 25 mm Hg and PO₂ of 155 mm Hg. Following thoracentesis, the patient’s ventilation improved with PAPs < 20 cm H₂O and tidal volumes improvement to 6-8 mL/kg. Minimal opioids are suggested for patients with WT in attempts to decrease or avoid respiratory compromise; epidural analgesia is often used in tumor resections or nephrectomy procedures. Our patient received fentanyl 50 mcg and hydromorphone 0.2 mg intravenously without compromise in respiratory status and the patient was successfully extubated at the end of surgery.
Pre-nephrectomy chemotherapy has become near standard of care for patients as reduced tumor size is associated with a decreased risk of tumor rupture from 33.3% to 6-8%. In addition, decreasing tumor size improves the chances that the surgical team can perform nephron-sparing surgery, which is known to reduce morbidity and mortality. Prior to resection, the patient had a right internal jugular vein tunneled catheter placed for chemotherapy administration in attempts to significantly reduce tumor size.

In addition to the aforementioned considerations, patients with WT often have coagulation disorders and present as a high risk for bleeding. Patients with WT present vast anesthetic challenges, regardless of surgical procedure. Comorbidities, metastasis and the nature of the tumor require astute intraoperative care.

References


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Awake Craniotomy Converted to General Anesthesia

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Keywords: Awake craniotomy, tumor resection, asleep-awake-asleep technique, scalp block, monitored anesthesia care, airway, hemodynamics, cerebral perfusion

Awake craniotomy is the preferred surgical approach used by neurosurgeons for brain tumor resections on or near eloquent areas. It allows immediate neurocognitive assessment during surgery while avoiding surgical injury. The eloquent cortex refers to areas in the brain that directly control important functions such as the primary motor and somatosensory cortex, Broca and Wernicke’s areas, and the primary visual cortex. Anesthesia for this procedure is dynamic as it requires thoughtful patient selection, varying states of sedation to ensure patient comfort and immobility, and a rapid wake-up for cortical testing, while the head remains fixated in a cranial stabilization device.

Case Report

A 59-year-old male (120 kg, 183 cm) presented for awake left temporal craniotomy for tumor resection following glioblastoma (GBM) diagnosis and worsening dysphasia. His medical history was significant for seizures, hypertension, and obstructive sleep apnea (OSA) with home use of continuous positive-airway pressure (CPAP). His significant surgical history included subtotal GBM resection at an outside facility five months prior, followed by chemotherapy and radiation therapy. On exam, he regarded the interviewer, had difficulty word finding, and was unable to follow commands. Due to the patient’s alteration in mentation, the anesthetic plan was made in coordination with the surgeon, anesthesia practitioners, the patient and spouse with an emphasis on a low threshold to convert from awake to general anesthesia (GA). In the preoperative area, the patient received midazolam 2 mg and famotidine 20 mg via an established 20-gauge peripheral intravenous (IV), and a 20-gauge arterial line was placed.

In the operating room, standard American Society of Anesthesiologist (ASA) monitors were applied, including bispectral index (BIS) monitor and oxygen via nasal cannula at 4 L/min. The patient was positioned right lateral, semi-recumbent, and the bed was turned 90 degrees from the anesthesia workstation. Infusions of dexmedetomidine 0.7 mcg/kg/hr and remifentanil 0.03 mcg/kg/min were initiated. An appropriate depth of sedation was achieved with spontaneous ventilation and a natural airway. Bladder temperature was monitored via an indwelling urinary catheter and a second 20-gauge peripheral IV was placed. The surgical team performed a scalp block and fixated the cranium via skull clamps in the desired surgical position. Following the surgeon’s request and prior to incision, the patient received dexamethasone, furosemide, mannitol, ceftriaxone, and vancomycin.

Two hours into the surgery, the patient remained adequately sedated with optimal oxygen saturations and hemodynamics. The dura was exposed and in preparation for cortical mapping, both dexmedetomidine and remifentanil infusions were discontinued. He awoke within 5 minutes and a functional neurologic assessment was performed. He was unable to respond
appropriately to questions, which was similar to his preoperative presentation. After 10-15 minutes of adequate mapping, the neurosurgeon requested the patient be re-sedated.

Both remifentanil and dexmedetomidine infusions were restarted. The patient complained of a headache, and despite reassurance and reorientation from the anesthetist, he attempted to move his upper and lower extremities. He received intermittent boluses of remifentanil 10-20 mcg and propofol 10-20 mg, which caused sedation, apnea and airway obstruction relieved with jaw thrust, airway adjuncts (oral airway and nasal trumpet) and mask ventilation. Due to the inability to render the patient comfortable without obstructing his airway, it was decided to convert to a GA. A bolus of propofol 50 mg was given and a laryngeal mask airway (LMA) #5 was properly placed. The patient maintained spontaneous ventilation with 0.5 MAC of sevoflurane, remifentanil infusion 0.01 mcg/kg/min and oxygen 2 L/min throughout the remainder of surgery, approximately 2.5 hours. At the end of the case, the patient was repositioned supine, head removed from fixation, and the head of bed was returned to the anesthesia workstation. Following ASA emergence standards, the LMA was safely removed. The patient’s neurological exam was unchanged from his preoperative assessment.

Discussion

The procedure is termed ‘awake craniotomy’ because during the 5+ hour long surgery, the patient is transitioned from various levels of consciousness throughout surgery to achieve surgical access, cortical mapping and surgical closure. Maintaining verbal contact with the patient while the surgeon is cortical mapping the extent of resection, is the most reliable monitor in protecting post-operative neurologic function. The varying depths of sedation maintains patient comfort and immobility, as well as enables successful execution of cortical mapping without compromising hemodynamics, ventilation, cerebral perfusion, the eloquent areas, or the surgical field. A compromised airway has deleterious effects of hypoventilation, hypoxia and hypercapnia. This triggers cerebral vasodilation and increases cerebral blood flow, which increases intracranial pressure (ICP) causing cerebral edema, impaired visualization and possible cerebral herniation. Maintaining a patent airway and adequate ventilation while the head is fixated, can pose a challenge for the neuroanesthetist, as it did in this case study.

To safely achieve varying levels of sedation for intraoperative success, careful patient selection is imperative. Patients with decreased mental capacity, a history of substance abuse, or a history of waking up violent from anesthesia are not candidates for awake craniotomy. Other exclusion criteria include patient refusal, inability to lay still for any length of time, and the inability to cooperate. The patient in this case study did meet the exclusion criteria due to decreased mental capacity. In the future, patients who meet the exclusion criteria should not undergo awake craniotomy. If after discussion with the surgeon and they request this approach, a low threshold for conversion to GA should strongly be considered.

A range of awake craniotomy techniques include local anesthesia via a scalp block, with or without monitored anesthesia care (MAC), to general anesthesia with the asleep-awake-asleep sequence, with or without establishing an airway with an LMA. Many approaches exist for anesthesia management for awake craniotomy, and one anesthetic technique does not prove superior to the others. A scalp block involves infiltrating 20-40 mL of local anesthesia, 0.5%
bupivacaine or 0.5% ropivacaine, along six nerves that innervate the sensory branch of the trigeminal nerve. The scalp block, in addition to the local anesthetic infiltration by the surgeon at the skull-pin sites, offers hemodynamic stability and decreases the stress response to painful stimuli. This can be done with or without premedication of fentanyl and midazolam for patient comfort. If effective, the scalp block can be the sole anesthetic for the remainder of the procedure provided the procedure can be completed within the timeframe for the effectiveness of the local anesthetic.

Another anesthetic technique is the asleep-awake-asleep (AAA) sequence, in which general anesthesia is induced with remifentanil and propofol bolus, after the patient is positioned lateral. One member of the anesthesia team fits the mask to ventilate the patient, then inserts the LMA facing the patient, while the other member ventilates. The AAA approach with an LMA allows for a depth of anesthesia that promotes sedation and analgesia during stimulating parts of the surgery like the scalp block, skull-pinning and incision, while avoiding hypoventilation and hypercarbia. Anesthesia is maintained with an infusion of propofol and remifentanil, and a 0.5 MAC of a volatile agent. Once the dura is uncovered, the infusions and inhalation agents are discontinued, the patient is woken up, the LMA is removed once extubation criteria is met, oxygen via nasal cannula is delivered and cortical mapping begins. Agents to treat hypertension and tachycardia, such as nicardipine, labetolol, metoprolol and esmolol should be readily available to control the hyperdynamic response to emergence, as well as treatment options for hypotension, with phenylephrine and ephedrine. Cortical mapping can induce focal or generalized seizures that are typically terminated with ice-cold saline on the field, however the anesthetist must be prepared to re-sedate and reinsert LMA following administration of antiepileptic drugs.

Upon completion of the cortical mapping and surgical resection, the patient is sedated and the LMA is reinserted, if necessary, to maintain ventilation for the remainder of the surgery. Infusions of remifentanil and propofol, or remifentanil and dexmedetomidine are restarted to achieve patient comfort and sedation.

In this case study, the surgery was initiated with sedation without airway manipulation, however he required an LMA after cortical mapping due to inability to achieve an adequate depth of sedation and analgesia without apnea and airway obstruction. Maintaining a low threshold for converting to GA and placing a supraglottic airway was imperative to maintaining his safety and surgical success. His history of OSA and increased BMI increased his risk for airway obstruction intraoperatively. As mentioned above, his declining mental capacity also increased his risks. In the future, early and careful collaboration with the neurosurgical team to identify the risks and benefits of awake craniotomy for high-risk patients is essential for a safe and successful surgery, as was demonstrated in this case report.

References

One-lung ventilation (OLV) is an essential anesthetic technique used to facilitate exposure during cardiac and thoracic surgeries by deflating one lung and ventilating the other. OLV can be accomplished via single-lumen endobronchial tubes (SLTs), bronchial blockers, or double-lumen tubes (DLTs).\(^1\,^2\) Although OLV was first achieved during the 1930s, Dr. Carlens is credited with the first development and use of DLT in 1950.\(^1\) In the 1960s, Dr. Robertshaw modified the DLT and subsequent revisions have resulted in our current models.\(^2\)

**Case Report**

A 61-year-old, 70 kg, 167 cm female with a lung neoplasm presented for right lower lobe wedge resection via video-assisted thoracoscopy (VATS) requiring OLV. Her medical history was significant for transient ischemic attack, hypertension, and systemic lupus erythematosus. Her home medications included clopidogrel, metoprolol, esomeprazole, and hydroxychloroquine. The patient’s prior anesthetics consisted of simple sedation with nasal cannula oxygen.

Physical examination revealed a Mallampati class II airway, thyromental distance of 5 cm, oral aperture of 3.5 cm, and adequate neck range of motion. The patient was premedicated with midazolam 2mg and transported to the operating room (OR). Upon arrival to the OR, standard monitors were placed and oxygen was administered via facemask. Anesthesia was induced intravenously with fentanyl 150 mcg, lidocaine 60 mg, and propofol 150 mg. After easy mask ventilation the patient was given succinylcholine 80 mg.
The student nurse anesthetist (SRNA) performed a direct laryngoscopy (DL) using a size 3 Macintosh blade with cricoid pressure and attained a Cormac-Lehane grade III view. This was deemed insufficient for placement of a DLT. The Certified Registered Nurse Anesthetist (CRNA) achieved the same view and the patient was again mask ventilated while a GlideScope (Verathon Inc., Bothell, WA) video laryngoscope (VL) was made ready. The SRNA obtained a Cormac-Lehane grade I view with the VL and unsuccessfully attempted to intubate the trachea with a 37 French (Fr) DLT. Despite several adjustments, neither the SRNA nor the CRNA could successfully intubate the trachea with the DLT. The patient was again mask ventilated while an 8.0 mm endotracheal tube (ETT) was readied. The SRNA successfully placed the ETT with the VL. However, the surgeon stated that the patient was not a candidate for a bronchial blocker.

Propofol 50 mg, midazolam 2 mg, dexamethasone 10 mg, and cisatricurium 2 mg were administered IV. A Cook Airway Exchange Catheter (AEC) – Double Lumen Extra Firm Soft Tipped with Rapid-Fit Adapter (Cook Medical Inc., Bloomington, IN) – was placed through the ETT, the ETT removed, then two unsuccessful attempts were made to place the 37 Fr DLT over the tube exchanger. The ETT was replaced over the tube exchanger and ventilations were controlled while a 35 Fr DLT was made ready. The SRNA successfully exchanged the 35 Fr DLT for the ETT and respiration was controlled by a mechanical ventilator. Proper DLT placement was confirmed by fiberoptic bronchoscopy. The case proceeded unremarkably with 97-100% SpO2 and general anesthesia was maintained with isoflurane 1% inspired concentration in a mixture of O2 1 L/min and air 0.5 L/min.

Upon completion of the surgery, neuromuscular blockade was antagonized with neostigmine 3 mg and glycopyrrolate 0.4 mg. The patient resumed spontaneous respirations with tidal volumes of 150-200 mL and appropriately followed commands. With an oropharyngeal airway in place, both the bronchial and tracheal cuffs of the DLT were deflated but no leak was detected. The AEC was placed down the tracheal lumen and the DLT removed. The patient maintained spontaneous ventilation and adequate SpO2 with O2 10 L/min. After monitoring the patient’s respiratory effort for one minute, the AEC was removed, the facemask applied, and tidal volumes of 200 mL noted. Oxygen was applied via a non-rebreather at 10 L/min and the patient was transferred to the post-anesthesia care unit (PACU) in stable condition.

Discussion

One-lung ventilation is most commonly accomplished using a DLT, as it facilitates rapid lung deflation and allows for independent intervention to either lung that is superior to bronchial blockers or SLTs. The initial choice of a 37 Fr DLT was deemed appropriate based on common sizing recommendations according to patient gender and height. The external diameter of a 37 Fr DLT is slightly larger than a standard 9.0 mm ETT and it is known that the larger size of DLTs may result in difficulty with initial tracheal intubation due to both maneuvering a larger tube in the oropharynx and passing the DLT through the glottic opening.

Appropriately sized DLTs should be 1-2 mm smaller than the patient’s left bronchus diameter to allow for inflation of the bronchial cuff. Selection of an inappropriately sized DLT can result in dislodgement or airway trauma and swelling. Brodsky and Lemmen’s study of 192 patients
determined that simple height and gender characteristics are insufficient for accurately predicting DLT sizing. More specific anthropometric data is necessary when selecting the correct DLT size.\textsuperscript{5} They found that the most accurate way to choose a DLT is to directly measure the left bronchial width (LBW) via chest radiography and utilize the largest DLT that will fit in the bronchus.\textsuperscript{5} However, the authors acknowledge that some 50\% of chest radiographs have an unclear view of the left bronchus therefore, the LBW must be ascertained via computed tomography or by the measurement of tracheal width (TW) followed by calculating LBW based on the equation $\text{LBW mm} = (0.45)(\text{TW mm}) + 3.3$ mm.\textsuperscript{5} Despite some researchers calling direct airway measurement the “gold standard” for DLT selection, others question if this optimal sizing results in improved patient outcomes.\textsuperscript{3,5} Time constraints of a busy OR may also preclude direct or calculated measurement of LBW.

The term difficult airway indicates that a trained anesthetist “experiences problems with (a) face mask ventilation of the upper airway, (b) tracheal intubation, or (c) both” and most anesthetists consider Cormack-Lehane grades III or IV with DL to be “difficult”.\textsuperscript{3} Both Brodsky and Merli et al. offer algorithms for difficult airway management when lung separation is required that delineates predicted versus unpredicted difficult airways.\textsuperscript{3,4} Although this patient was an unpredicted difficult airway, she was easily ventilated using the mask. This ability to maintain ventilation was crucial to ensure time to calmly problem-solve the situation, while the inability to ventilate would indicate the need for emergent intervention.

This case paralleled the unpredicted difficult airway algorithm devised by Brodsky.\textsuperscript{3} After failed intubation with DL, we ventilated via facemask and then proceeded to utilize the VL to place the ETT. We then exchanged the ETT for a DLT over the AEC and were able to continue with OLV. Both Brodsky and Merli et al. have similar algorithms that highlight salient points to ensure patient safety. First, always be prepared to wake the patient up in the event of a difficult airway in an elective surgery.\textsuperscript{4} Second, ensure the AEC is of sufficient length, fits through the DLT, and is inserted with the malleable tip in the lung.\textsuperscript{3,4} Finally, lung separation is absolutely indicated only in cases where one lung is infected or when there is trauma to the trachea or bronchus, therefore do not jeopardize patient safety for mere surgical preference.\textsuperscript{3,4}

Despite eventual successful tracheal intubation, always analyze what could have been done better or differently. Through retrospection and discussion with other anesthesia professionals any of the following alternatives may have lead to quicker intubation with DLT or ensured optimal patient safety. First, using a different blade for DL (perhaps a Macintosh size 4 or a Miller size 3) could have facilitated viewing the vocal cords and improved the Cormac-Lehane grade III view. However, difficult passage of the DLT appeared to be related to a small glottic opening and this maneuver may have wasted valuable time. Second, earlier selection of a smaller DLT may have resulted in tracheal intubation with DL or VL without using the tube exchanger. Third, laryngoscopy with DL or VL in concert with the AEC could have aided placement with the 37 Fr DLT. Fourth, lubrication of the outside of the DLT may have facilitated tracheal intubation at any point along the way. Fifth, tracheal intubation could have been accomplished by utilizing the fiberoptic bronchoscope with the patient either awake or asleep. Lastly, due to concern for airway edema, it may have been prudent to leave the tube exchanger in place for transportation to PACU thus aiding the ability to quickly re-intubate or for jet ventilation should the need arise.
The importance of readily available help, effective communication, and maintaining composure in a stressful situation cannot be overemphasized. This case epitomized selfless teamwork with all practitioners working together to care for the patient. It is also advisable for the anesthesia professional to be proficient in the use of the alternate techniques, such as the AEC, to attain tracheal intubation by practicing in simulation or choosing the AEC as the initial intubation method.

References


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Anesthetic Management of an Adult Patient with Transverse Myelitis

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Keywords: transverse myelitis, regional anesthesia, neuraxial anesthesia, autonomic dysreflexia, spinal cord inflammation, neuroimmunologic disorders

Transverse Myelitis (TM) is a rare inflammatory disorder that affects the spinal cord.1-3 Incidence of this rare condition is reported to be between 1-5 cases per million population each year.1-3 The spinal cord inflammation that occurs causes variable motor, sensory, and autonomic dysfunction that ranges in severity.1-3 The variability in presentation of TM requires anesthesia practitioners to be proactive and knowledgeable with preoperative assessments, intraoperative care, and postoperative evaluation.2

Case Report

A healthy, 70-year-old, 61 kg, 157 cm, female presented for a right knee medial unicompartmental arthroplasty. Her past medical history was significant for idiopathic transverse myelitis and osteoarthritis. The patient was not currently being treated for TM and had
no recent steroid use. Home medications included aspirin, fish oil supplement, and a multivitamin. Surgical history consisted of a laparoscopic cholecystectomy and cataract surgery with no anesthesia complications or problems with neuromuscular blockers. Preanesthesia physical assessment found baseline numbness in the 3rd toe on the right foot from idiopathic transverse myelitis. The surgeon requested an adductor canal peripheral nerve block for postoperative pain relief. Due to the presence of pre-existing nerve damage in the operative leg, it was decided to avoid a peripheral nerve block. The anesthesia plan consisted of a general anesthetic using narcotics for pain relief instead of a peripheral nerve block.

Upon entering the operating room, noninvasive monitors were applied. Oxygen was administered via the anesthesia circuit at 10 L/min for 3 minutes. Intravenous (IV) induction of general anesthesia was performed with lidocaine 100 mg and propofol 140 mg. After loss of the lash reflex, the eyes were taped and a size 4 laryngeal mask airway (LMA) was placed successfully. General anesthesia was maintained with sevoflurane expired concentration of 2% in O₂ 2 L/min. Boluses of fentanyl 25 mcg and hydromorphone 0.4 mg IV were used for pain control throughout the case. The patient received total opioid dosing of fentanyl 75 mcg and hydromorphone 0.4 mg IV. Postoperative nausea and vomiting prophylaxis was provided with ondansetron 4 mg, dexamethasone 8 mg, and famotidine 20 mg IV.

Vital signs remained stable throughout the case. Total tourniquet time was 36 minutes at 300 mm Hg to the operative limb. Upon conclusion of the surgery, the volatile anesthetic was discontinued, the LMA was removed, a 9.0 oral airway was placed, and the oropharynx was suctioned. Spontaneous respirations were maintained at 13/min and O₂ 8 L/min via facemask was administered. The patient was transferred to the post anesthesia care unit in stable condition and postoperative vital signs were as follows: blood pressure 143/54 mm Hg, heart rate 66/min, respiratory rate of 18/min, SpO₂ 99%, and temperature of 36.5°C. Postoperatively, the patient had adequate pain control with the use of opioids but experienced postoperative nausea and vomiting and along with numbness in the entire right foot. The patient was admitted for observation. She was discharged the next day with resolution of postoperative nausea and vomiting and the numbness in the right foot had returned to baseline.

Discussion

Transverse myelitis is a disorder of the spinal cord that is inflammatory in nature. It often involves the spinothalamic and pyramidal tracts, as well as the posterior columns and anterior fasciculi.2 Because there can be involvement of sensory and motor tracts, the signs and symptoms of TM can include sensory deficits. It may also present as muscle weakness and paralysis, which can be symmetrical or asymmetrical depending on the lesion.1-3 Autonomic dysfunction can occur which commonly causes bowel and bladder dysfunction.1-3 Patients often have allodynia in the lower back and lower limbs along with altered sensation.2

The cause of acute transverse myelitis (ATM) is often idiopathic, but can be associated with infectious processes or autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus.1-3 There are cases in the literature of ATM occurring after epidural, spinal, and general anesthesia, but no direct causal relationship has been found.3,4 Little evidence is available regarding treatment, but initially ATM should be treated with high dose intravenous
steroids. Other treatment options include: plasmapheresis, immunosuppressive agents, and immunoglobulin therapy. The progression and outcomes of the disease are variable and range from good recovery to permanent disability. The patient in this case was diagnosed with idiopathic TM and experienced isolated sensory involvement of the right lower extremity that consisted of pain and numbness. The patient continued to experience residual symptoms of numbness in the 3rd toe on the right foot at the time she presented to surgery.

When a patient presents for surgery with transverse myelitis, the anesthesia professional must consider preoperative baseline function, risk for autonomic dysreflexia, and the potential for interactions with neuromuscular blocking agents. Preoperative assessment of a patient with transverse myelitis, whether acute or chronic, must be thorough with proper documentation of baseline sensory deficits, motor function, and autonomic dysfunction. Inquire about current treatments of TM and medical management, which may include steroid therapy or immunosuppressive agents. Steroid replacement intraoperatively and postoperatively may be needed. Additional laboratory testing to evaluate blood counts, renal function, and liver function should be performed if the patient is taking immunosuppressive medications. In this case, the patient reported no complications from past surgeries or problems even when neuromuscular blocking agents were used.

General anesthesia is often the anesthetic of choice due to neurological involvement at the spinal cord level and possible exacerbation of the disease. Neuraxial anesthesia has the potential to worsen transverse myelitis and other pre-existing neurological signs and symptoms, so the use of this technique is debatable. Because of this knowledge, the option of using a spinal anesthetic for this case was not presented to the patient. Regional anesthesia is recommended to be considered only if the benefits outweigh the risks in a particular situation. After discussing the risks and benefits of the adductor canal nerve block, the patient did not want to risk causing further neurological damage and chose to avoid regional anesthesia.

Patients with transverse myelitis are sensitive to non-depolarizing neuromuscular blockers and can have an exaggerated potassium release with the use of succinylcholine due to an upregulation of acetylcholine receptors in the skeletal muscle. The use of succinylcholine and non-depolarizing neuromuscular blockers were avoided in this case with the appropriate use of an LMA rather than endotracheal intubation.

Early stages of transverse myelitis may cause acute spinal shock and autonomic dysreflexia. Autonomic dysreflexia is an uncontrolled activation of the sympathetic nervous system and is always a concern in these patients. The anesthesia professional must be prepared to treat hypertension with vasodilators, bradycardia with anticholinergics, and other possible cardiac dysrhythmias that can occur in response to surgical stimuli. The sympathetic outflow during autonomic dysreflexia is uncontrolled and hypertension can become so severe that intracranial hemorrhage can occur if not treated and managed appropriately.

In this case, the new numbness in the right foot after surgery was concerning, but it could not be explained by neuraxial or regional anesthesia because those anesthesia techniques were avoided. It is known that nerve injuries after tourniquet use are common because of the pressure on the nerves and ischemia that occurs because of the tourniquet. Nerve damage can occur from direct pressure on the nerves and ischemia.
pressure, which can cause postoperative deficits, but often heals over time as the damage to the nodes of Ranvier and myelin are repaired by the body.\textsuperscript{5} The new sensory deficit in this patient postoperatively could not be explained by anesthesia since peripheral and neuraxial anesthetics and neuromuscular blocking agents were avoided.

Patients with transverse myelitis are at an increased risk for exacerbation of symptoms, autonomic dysreflexia, and altered response to neuromuscular blocking medications. A thorough preoperative evaluation, as well as, vigilant monitoring throughout the intraoperative and postoperative period are required to ensure proper management of possible sensory, motor, and autonomic dysfunction. Baseline neurological function documentation must be precise and specific in order to allow for a proper risk and benefit analysis to create an individualized (or optimized) anesthetic plan for the proposed procedure.

References


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\textbf{Successful Resuscitation during a Metopic Cranioplasty}

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\textbf{Keywords:} Craniosynostosis, cranioplasty, pediatric craniotomy, pediatric blood loss, pediatric anesthesia

Craniosynostosis is the premature fusion of one or more cranial sutures resulting in an abnormally shaped skull. Affecting one in 2100-2500 children, craniosynostosis can cause hydrocephalus with increased intracranial pressure (ICP), visual changes and may accompany other anomalies.\textsuperscript{1} Children often undergo a cranioplasty between 3 and 12 months of age.\textsuperscript{2,3} Metopic cranioplasty involves opening the metopic suture which runs from the nose to the sagittal suture.\textsuperscript{4} A multi-specialty team performs a frontal craniotomy with cranial vault remodeling and orbital advancement. Rapid, extensive blood loss is common so anesthesia practitioners must be prepared to respond quickly and appropriately.\textsuperscript{5}
Case Report

This 11-month-old male presented for a metopic cranioplasty. His preanesthetic evaluation revealed a 10.4 kg infant with unremarkable medical, surgical and family histories. His estimated fluid deficit was 280 mL. Electrolytes, complete blood count and coagulation studies were within normal limits 6 days earlier, including a hematocrit (HCT) of 33%.

Standard monitors were placed and an inhalation induction performed with 8% sevoflurane and oxygen 5 L/min. Two 22-gauge peripheral intravenous (IV) catheters for the infusion of plasmalyte and lactated ringer’s (LR) solutions and a 22-gauge left radial arterial catheter were placed. Cefazolin 300 mg IV, cisatracurium 1 mg IV, lidocaine 10 mg IV and propofol 25 mg IV were given and the trachea intubated. Just prior to incision, cisatracurium 2 mg IV and morphine 3 mg IV were given. Point of care arterial blood gas (ABG) and electrolyte values were within normal limits and the patient’s HCT was 32%.

Over the next 2 hours, blood loss was replaced with boluses of packed red blood cells (PRBCs) matching the estimated loss. Arterial systolic pressures declined to approximately 50 mm Hg several times and were treated with crystalloid boluses, a total of 250 mL of PRBCs, 2 IV doses of ephedrine totaling 25 mg and epinephrine 50 mcg IV.

Approximately 3 hours into the procedure, the arterial tracing suddenly dampened significantly. Drapes were dropped and chest compressions initiated. Doses of epinephrine totaling 100 mcg were given and chest compressions were stopped after approximately 10 seconds. It was then discovered that one of the IV access sites was no longer functional. The HCT at this time was 18%. After attempts by multiple anesthesia practitioners to gain additional IV access, a pediatric general surgeon inserted a right subclavian central venous catheter. Placement was difficult, presumably due to hypovolemia, vasoconstriction and epinephrine but was confirmed by radiography. During this time, an additional PRBCs 200 mL, 5% albumin 200 mL and calcium gluconate 200 mg IV were given.

After a discussion of these events between the plastic surgeon and the parents, the procedure was resumed. The HCT was 42% and an ABG revealed a pH of 7.21 but was otherwise unremarkable. Coagulation studies included a PT of 22.7 seconds, PTT of 42.8 seconds, INR of 2.0 and a platelet count of 91,000. Fresh frozen plasma (FFP) 150 mL and 3 platelet boluses totaling 100 mL were given. During the platelet boluses, the sinus rhythm converted to a right bundle branch block which converted back to a sinus rhythm when the bolus was stopped. After the FFP and platelet transfusions, all ABG values were within normal limits except the HCT which was noted to be 25%. Because stimulating the myocardium with blood product boluses through the central line was considered the possible etiology of the dysrhythmia, PRBCs 150 mL were transfused through a peripheral line.

Upon completion of the procedure, the sedated and intubated patient was transported to the pediatric intensive care unit. Total EBL was 525 mL; urine output was 25 mL. The patient had received plasmalyte 475 mL, LR 600 mL, 5% albumin 200 mL, FFP 150 mL, platelets 100 mL, and PBRCs 600 mL. Total surgical time was just over 6 hours.
Discussion

Anesthetic management of cranioplasty patients is challenging for even highly experienced practitioners. Hypovolemia accounts for 12% of cardiac deaths in children with 50% of these due to underestimated blood loss. Children undergoing craniofacial reconstruction lose 0.5 - 4 blood volumes. Those who are less than 10 kg, less than 18 months of age, have craniofacial syndromes, or known increased ICP carry an even higher risk of extensive blood loss. Other risk factors for major blood loss include surgery times greater than 5 hours and revision procedures.

To minimize the risk of dilutional coagulopathy and thrombocytopenia, the North American and European guidelines for intraoperative administration of fluid and blood products during pediatric craniofacial surgery include goal-directed replacement of blood loss with plasma, platelets and PRBCs at a 1:1 ratio when losses exceed 20% of the patient’s estimated blood volume. Although point of care or laboratory-guided interventions are optimal, blood loss is often too sudden and heavy for the anesthesia practitioner to obtain a specimen and wait for results before administering fluid boluses and blood products. After approximately 250 mL of blood loss (30% of the 830 mL estimated blood volume), the first coagulation studies were evaluated and goal-directed therapy began. FFP 15mL/kg, platelets 10 mL/kg and PRBC 15 mL/kg were then transfused.

To prepare for major blood loss, fluid warmers with blood transfusion tubing and compatible IV fluids were set up preoperatively. Cross-matched units of PRBCs totaling 500 mL were at the bedside and checked per the blood bank protocol before the incision was made. When several minutes of rapid and heavy blood loss occurred and the patient’s hemodynamic status began to deteriorate, additional anesthesia providers were readily available to assist with resuscitation. Although hypothermia and acidosis can worsen the hemostatic picture, the patient was normothermic throughout the procedure and the only documented period of acidosis lasted less than 30 minutes.

Other interventions have been shown to decrease the need for blood products in pediatric cranioplasty patients. The antifibrinolytic agent tranexamic acid (TXA) prevents the conversion of plasminogen to plasmin thus preventing fibrinolysis. In a clinical trial at Children’s Hospital, Boston, craniosynostosis patients receiving a loading dose of 50 mg/kg over 15 minutes and an infusion of 5 mg/kg intraoperatively had less intraoperative and postoperative blood loss and a reduced need for transfusions. TXA cannot always eliminate the need for transfusions, but can reduce a patient’s exposure to multiple blood products and lower the risk of postoperative adverse events. Also, point of care testing with transfusion algorithms such as TEG® and ROTEM® can more accurately guide the use of blood products than standard laboratory testing.

The need to include dependable, large-bore IV access that allows for rapid fluid and blood product boluses in the anesthesia management plan is widely recognized. Although a 20-gauge peripheral IV catheter or larger can obviously provide greater access, this size catheter can be difficult to place in children less than 1 year of age. Placement of a central venous line before beginning the cranioplasty could have been beneficial, especially considering that a peripheral IV line was lost during resuscitation. However, in this facility where many of these cases are performed and adverse events rarely seen, routine preparation for fluid management and
monitoring includes 2 peripheral IV catheters and an arterial line. Although this complies with published guidelines, placement of a central venous line has been suggested not only for dependable access, but also for central venous pressure directed volume replacement, more efficient delivery of vasopressors and management of venous air emboli.\(^3,^8\)

Patients undergoing craniosynostosis repairs could benefit from these interventions described in the literature. This patient may have had less perioperative blood loss if TXA had been given. Losing IV access during resuscitation heightened the anxiety level of the practitioners. While awaiting central venous line placement, emergent medications and blood products were administered via the patient’s existing peripheral IV lines, further illustrating the importance of IV access. The anesthesia practitioners at this facility are considering using point of care testing with transfusion algorithms for all cases with associated risks for extensive blood loss. Transfusion of blood products in this patient could have been more goal-directed with this technology.

Because of the preparation, vigilance and rapid responses of the anesthesia and surgical teams, this patient was discharged from the ICU in the usual time period for these procedures and was home after the usual length of stay with no apparent anesthesia or surgical complications. The patient was evaluated 2 weeks after discharge and according to his plastic surgeon, was healing well and continuing to show no signs of adverse outcomes related to his perioperative events.

References


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Management of Extraordinary Risk Factors in Pheochromocytoma Resection

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Key words: pheochromocytoma, risk factors, anesthesia, management, hemodynamics

A pheochromocytoma is a rare, catecholamine-secreting tumor originating from the chromaffin cells of the adrenal medulla.1,2 The clinical manifestations result from the release of epinephrine and norepinephrine into the circulation.1 Elevated catecholamine levels precipitate tachycardia, diaphoresis, and headache.1 Hypertension is present in 80% of those diagnosed.1 Definitive treatment includes surgical removal and is complicated due to periods of extremes in blood pressure and heart rate.2-4 Minimizing the dangerous fluctuations in blood pressure is challenging, at best. This case study reviews evidence-based risk factors that potentiate instability during resection.

Case Report

A 54-year-old, 72 kg, 163 cm female presented for removal of a 12.3 x 10.5 x 11.4 cm pheochromocytoma on the left adrenal gland. Medical history was significant for essential hypertension, hyperlipidemia, type II diabetes mellitus, and non-specified tachyarrhythmia. Pharmacologic management for one month prior to surgery included doxazosin 2 mg, metoprolol 50 mg, and diltiazem 240 mg orally one time per day. Preoperative blood pressure (BP), mean arterial pressure (MAP), and heart rate (HR) were 147/89 mm Hg, 108 mm Hg, and 73/min, respectively. Baseline 12-lead electrocardiogram depicted normal sinus rhythm with left ventricular hypertrophy and T-wave abnormalities. Additionally, a 2-dimensional echocardiogram and cardiac catheterization were unremarkable, as were key laboratory studies (complete blood count, comprehensive metabolic panel, hemoglobin A1C). Twenty-four hour urinary analysis revealed norepinephrine levels greater than 4,000 nmol.

Midazolam 2 mg and fentanyl 100 mcg were administered intravenously (IV) to facilitate left radial arterial line placement in the preoperative holding area. Anesthesia was induced with propofol 180 mg, lidocaine 50 mg, rocuronium 50 mg, and fentanyl 100 mcg IV. Mask ventilation with oxygen at 8 L/min and 2% end tidal isoflurane was performed for 4 minutes. Additional fentanyl 250 mcg and metoprolol 5 mg IV were administered in response to BP elevations to 220/100 mm Hg during the induction. Laryngoscopy was performed when BP reached 150/90 mm Hg. Following tracheal intubation, a right internal jugular venous catheter was placed. Anesthesia was maintained with oxygen at 1 L/min, air at 1 L/min, and isoflurane at 1.1-2.9% expired concentration. Intraoperative analgesia was maintained with a remifentanil infusion, which was titrated within a dose range of 0.08 – 0.5 mcg/kg/min.

Total surgical time was longer than anticipated due to involvement of the tumor into the spleen and distal pancreas. Blood pressure ranged from a high of 325/114 mm Hg during intense resection to a low of 78/43 mm Hg upon culmination of venous ligation. Surgical manipulation ceased during episodes of hypertension. Both a nitroprusside infusion (dose range 0.5-20 mcg/kg/min) and a nicardipine infusion (dose range 1 – 15 mg/hour) were utilized with attempts...
to maintain the BP < 150/90 mm Hg. An esmolol infusion was titrated (dose range 50 – 250 mcg/kg/min) to maintain the HR < 100/min.

The surgical procedures performed included splenectomy, distal pancreatectomy, and complete removal of the tumor. Prior to venous ligation, intravascular volume was expanded with 2.5L of lactated ringer’s solution in anticipation of a reduction in MAP; anti-hypertensive infusions were discontinued during this time. The remifentanil infusion was titrated downward, and discontinued. Following ligation, systemic hypotension ensued; MAPs ranged from 53 to 65 mm Hg. Phenylephrine 80 mcg IV boluses were administered and a norepinephrine infusion (dose range 2-20 mcg/min) initiated to restore MAP above 65 mmHg. Additionally, vasopressin 1 unit IV was required for noted refractory hypotension. IV fluid for the case totaled 3.8L. Estimated blood loss was 200 ml. When hemodynamic stability was achieved, hydromorphone 1 mg IV was administered. A low normal blood pressure of 96/63 mm Hg was obtained upon conclusion of the surgery. Emergence was uneventful and the patient was extubated.

Discussion

The goals of preoperative care, specifically establishing normotension and sinus rhythm, as well as intraoperative anesthetic management during pheochromocytoma surgery, have been well established. Pharmacologic management typically begins 7-21 days prior to surgery in the form of selective or nonselective alpha antagonists, namely phenoxybenzamine, prazosin, or doxazosin. Beta-blockers are commonly used for treatment of hypertension and tachyarrhythmias, however independent use should be avoided since unopposed alpha-adrenergic stimulation can lead to vasoconstriction and hypertensive crisis. Management during surgery is focused on minimizing extremes in BP and HR. In this case, anesthetic management was tailored towards avoiding these extremes. Attempts were made to diminish the sympathetic responses during periods of high stimulation, such as laryngoscopy, incision, tumor manipulation, as well as curtail hypotensive episodes after adrenal vein ligation and tumor removal.

Despite adequate preoperative preparation, it is not uncommon to encounter periods of instability intraoperatively. This case highlights the importance of recognizing the patient at risk for the development of severe hemodynamic instability during adrenalectomy. Current literature describes multifactorial risk factors ‘beyond the expected’ for intense hemodynamic instability. They include:

- Pharmacologic BP management with selective alpha antagonists
- A preoperative MAP > 100 mmHg
- Twenty-four hour urinary analysis indicating high levels of metanephrine and norepinephrine
- Large tumor size
- Open procedures (versus minimally invasive)

It has been noted that preoperative preparation with selective alpha antagonists is associated with higher incidence of intraoperative systolic blood pressure (SBP) > 200 mm Hg, compared to those receiving non-selective alpha antagonists. These medications are competitive inhibitors of the alpha1 adrenergic receptor, so their effects can be overcome by large surges of catecholamines secreted by the tumor, leading to an increased number of hypertensive events.
The preoperative preparation for the patient presented in this case included doxazosin, a selective alpha antagonist. The large surges in catecholamines may have prevented the competitive inhibition at the receptor sites and contributed to the overwhelming periods of hypertension.

A preoperative regimen insufficient in lowering the MAP to less than 100 mm Hg is associated with severe hypertension intraoperatively; it underscores the importance of pre-surgical hemodynamic optimization. In this case, the preoperative MAP was 108 mm Hg. Perhaps this patient would have benefitted from additional pharmacologic interventions prior to surgery.

Twenty-four hour urinary analysis indicating high levels of metanephrine and norepinephrine (greater than 880 nmol/day) is associated with a seven times greater incidence of intraoperative hemodynamic instability when compared to levels less than 880 nmol/day. This is due to the effects of catecholamines on the vascular endothelium which leads to damage and reduced vessel compliance. Moreover, tumor manipulation and adrenal vein ligation independently cause an excessive release of catecholamines, exacerbating the problem. Tumors that primarily secrete norepinephrine (versus epinephrine) release catecholamines more continuously, and at a higher rate, than those primarily secreting epinephrine. In this situation, the patient demonstrated twenty-four hour urinary norepinephrine levels > 4,000 nmol.

Tumor size greater than 3-4 cm is associated with more frequent episodes of hypertension, greater than 30% above baseline, and hypotension, which requires vasopressor administration. This may be a consequence of surgical tumor manipulation time, which creates more time for catecholamine release, versus smaller tumors. Administration of vasopressors is necessary due to the precipitous decrease of circulating catecholamines when a hormonally-active tumor is removed. When compared to laparoscopic procedures, open procedures are associated with more episodes of SBP greater than 200 mm Hg and an increased need for vasopressors after tumor removal.

The benefit of identifying risk factors for hemodynamic instability above and beyond the expected allows for an intense, aggressive and individualized care plan. Standard guidelines do not suffice. This case demonstrates that although ‘standard pharmacologic management’ was utilized, it was not sufficient in minimizing cardiovascular instability. The initiation of IV anti-hypertensive agents prior to anesthesia induction may have attenuated the resultant hypertensive crisis during critical periods of stimulation. A more liberal dose of IV lidocaine or initiation of an IV magnesium sulfate infusion may have diminished the sympathetic responses to laryngoscopy, incision, and tumor manipulation. Utilization of nicardipine, nitroprusside, esmolol, and remifentanil infusions during the maintenance phase were paramount in mitigating the hypertensive and tachycardic responses to tumor manipulation. This demonstrated polypharmacology and massive dosing ranges which were necessary for the management of this case. A shorter-acting calcium channel blocker, such as clevidipine, may have been superior to nicardipine, however lack of availability precluded its use in this situation. It was also determined postoperatively that adding an assessment of stroke volume variation may have guided fluid administration more appropriately and mitigated the profound hypotension following tumor resection that necessitated vasopressors. Since estimated blood loss was 200 ml, it was determined to have an insignificant contribution to the hemodynamic changes following venous ligation.
The significant cardiovascular instability that was observed during this case appeared to be a result of numerous preexisting extraordinary risk factors associated with catecholamine secreting tumors. Knowledge of these risk factors guided the complex anesthetic management and required multifaceted pharmacologic techniques. Clearly the importance of an individualized and advanced pre anesthesia assessment cannot be underestimated. In retrospect however, additional advanced monitoring modalities and selecting anesthetic agents with differing mechanisms of action may have allowed for a more timely and precise control of the wide swings in blood pressure and a greater understanding of the physiologic deviations that occurred. Staying abreast of the most current evidence based information related to the anesthetic management of pheochromocytoma is emphasized.

References


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Posterior Spinal Fusion and Perioperative Visual Loss

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Keywords: prone position, posterior spinal fusion, perioperative vision loss, ischemic optic neuropathy, hypotensive management

Scoliosis is characterized by a lateral curvature of the spine. The incidence of scoliosis is 1-3% in adolescents with 70% of scoliosis cases being idiopathic in nature. Surgical correction is indicated when the curvature measures between 40-50°. Anesthetic management of these cases presents unique challenges including prone position, length of surgery, significant blood loss, and total intravenous anesthetic (TIVA) to allow for spinal cord monitoring. Due to these challenges, patients have a high risk of ischemic optic neuropathy, the leading cause of perioperative visual loss (POVL).

Case Report

A 15-year-old, 84.4 kg, 170 cm male presented for a posterior spinal fusion for a T10-L3 idiopathic scoliosis with a 58° Cobb’s angle. His past medical history included: exercise-induced reactive airway disease, recent upper respiratory infection, and a body mass index (BMI) of 29.1 kg/m². The patient’s medications included albuterol and vitamin supplementation. Physical examination was unremarkable except for his BMI and an in situ 20 gauge peripheral intravenous catheter (PIV).

Anesthetic induction was accomplished via a combined mask/intravenous (IV) technique with 250 mg propofol and 4 LPM nitrous oxide 2 LPM oxygen mix. The trachea was intubated as an 18 gauge PIV and 20-gauge arterial line were placed and capped in preparation for positioning. The patient remained on 3% sevoflurane and 2 LPM of oxygen after intubation, with stable vital signs. After the patient was placed in the prone position, sevoflurane was discontinued, air was mixed into the fresh gas flow, and propofol and sufentanil infusions were started at 200 mcg/kg/min and 0.2 mcg/kg/hr respectively. The arterial line was transduced and demonstrated severe hypotension. The propofol infusion was reduced to 150 mcg/kg/min and a 500 mL fluid bolus was administered; sufentanil was continued despite the hypotension in an effort to achieve therapeutic analgesic concentrations prior to skin incision. The patient remained mildly hypotensive for 17 minutes until the initial incision was made. Evoked potentials remained at baseline during the mild hypotension and the patient produced 125 mL of urine.

During the case, pulse pressure variation (PPV) was monitored by the Intellivue MP monitor (Koninklijke Philips N.V., Best, The Netherlands) and was treated with 250 mL crystalloid boluses when variation was greater than 15%. PPV correlated to blood loss throughout the case. The propofol was titrated between 150-200 mcg/kg/min in response to neuromonitoring information and mean arterial pressure (MAP). After surgical insertion of pedicle screws, a computed topography (CT) scan with an O-arm (Medtronic, Minneapolis, MN) was performed. During the scan the patient was placed on 2 LPM of oxygen (1.0 FiO₂) and ventilation was held. Post CT scan, an alveolar recruitment maneuver was performed. The patient’s MAP decreased
significantly to approximately 30 mm Hg which required rapid administration of 1.5 L of crystalloid, 5 mg of ephedrine IV, and 250 mL of available red blood cells (RBCs); the propofol was decreased to 100 mcg/kg/min and sufentanil was discontinued. Upon examination of the surgical field it was determined that the patient lost an estimated 700 mL of blood during the scan due to inadequate hemostasis resulting in 12 minutes of hypotension.

Case intake/output totals were 5500 mL of crystalloid, 750 mL of cell-saver, an estimated blood loss (EBL) of 1800 mL and total urine output of 900 mL during the 7 hour and 22 minute surgery. The patient was extubated at the end of the procedure, intact neurologically, and transferred to the Post-Anesthesia Recovery Unit (PACU). After he met the facility’s PACU discharge criteria he was transferred to the inpatient surgical care unit and discharged home 3 days later.

Discussion

Perioperative visual loss (POVL) is a rare and unpredictable complication associated with spine, cardiac, and head-neck surgeries with ophthalmic complications reported in less than 0.028-0.2% of spine surgeries. The most common cause of POVL is reported to be ischemic optic neuropathy (ION). The POVL study group performed an analysis of those POVL cases caused by ION and identified both univariate and multivariate risk factors. The univariate risk factors included: male sex, anesthetic duration, EBL, and hypotension less than 40% of baseline for greater than 30 minutes. Their multivariate regression analysis identified male sex, obesity, anesthetic duration, and lower amounts of colloid as a percent of total non-blood replacement as risk factors.

The POVL practice advisory recommends maintaining blood pressure within 24% of baseline, monitoring of CVP in high risk patients, avoiding pressure on the eyes, monitoring hemoglobin and hematocrit, offers no opinion on vasopressor use, and does not advise for preoperative consultation with a neuro-ophthalmology. This particular patient met many of these risk factors, he was: overweight (borderline obese), male, anesthetic duration was > 6.5 hours, he received no colloid, and had a significant amount of blood loss. Additionally, the patient experienced two periods of significant hypotension for a total time of 29 minutes.

Conceptually, ocular perfusion pressure is the difference between MAP and IOP so a reduction in MAP or an increase in IOP can decrease perfusion, possibly resulting in ION. Intraocular pressure (IOP) was not measured during the case, however several factors placed this patient at risk for high IOP. It has been demonstrated that IOP and time in the prone position are linearly correlated and that increased IOP is related to positive fluid balance. This patient received a significant amount of crystalloid (65 mL/kg) and had anesthesia for >7 hours. These factors combined place this patient at high risk of POVL; however, he did not develop any such symptoms. In a retrospective study by the POVL study group they identified the above stated risk factors. The information from the POVL Study Group and the Practice Advisory for Perioperative Visual loss one is made to believe that many factors that cause POVL are under the anesthesia practitioners’ control.
However, when evaluating the subject from a neuro-ophthalmic perspective one finds a much different opinion. The reason lies in the complexity of the pathogenesis. In a review article written by Hayreh\(^6\) he identifies non-arteritic anterior ION (NA-AION), commonly referred to as “ION” in the anesthesia literature, as having many predisposing factors. Among these he includes the extreme variation of arterial anatomy (particularly the posterior ciliary arteries), absent or small cup, and nocturnal hypotension. He describes the pathogenesis of NA-AION as beginning far in advance of symptoms with short periods of hypoxia to the optic nerve head caused by nocturnal hypotension, axonal swelling, asymptomatic disc edema, compression of the capillaries in the crowded disc and an ensuing deleterious cycle.\(^6\) Theoretically, the stage is set for catastrophe; a short episode of hypotension would trigger a repeat of the previously stated cycle and significant visual loss would occur. To support such a claim he refers to the increase in pharmacologic anti-hypertensive use and the rising incidence of NA-AION.\(^6\) A further review of the neuro-ophthalmic literature and one will find a competing hypothesis stating that it is not a disease of arterial insufficiency but of venous insufficiency.\(^7\) This hypothesis asserts that venous congestion creates a compartment syndrome within the vulnerable optic nerve, from which most blood drains via the central retinal vein within the optic nerve.\(^7\) However, what both theories share is the belief that NA-AION is not unilaterally caused by any one event under anesthetic control.\(^6,7\)

The practice advisory states that practitioners should, “consider informing patients [who are high risk]... that there is a small, unpredictable risk of perioperative visual loss”\(^3\). “Unpredictable” being the key phrase, as this condition is characterized as an insidious process that develops over time and may not principally be caused by intraoperative management.\(^6,7\) As can be seen with this case, the patient did not develop NA-AION in spite of his significant hypotension, large amounts of crystalloid, lack of colloid, prolonged prone time, and large blood loss.

References

Tranexamic Acid versus ε-Aminocaproic Acid in Cardiac Surgery

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Keywords: antifibrinolytic, epsilon-aminocaproic acid, tranexamic acid, cardiac surgery, cardiopulmonary bypass

According to the centers for disease control, there are approximately 51.4 million inpatient surgeries performed annually, over a million of which are cardiovascular surgeries.1 The administration of antifibrinolytics for cardiac surgery is common to reduce post-operative bleeding, to reduce blood component administration and to reduce the need for surgical re-exploration. Lysine analogs, tranexamic acid (TXA) and ε-aminocaproic acid (EACA) are used frequently in cardiac surgery for bleeding prophylaxis. This case report describes the anesthesia care of a patient undergoing three-vessel coronary artery bypass graft with a focus on the efficacy and safety of TXA versus EACA.

Case Report

A 68-year-old, 182.9 cm, 81 kg male presented with three-vessel coronary artery disease. The patient had taken oral metoprolol 50 mg, and atorvastatin 20 mg, the morning of surgery. Co-existing diseases included hypertension, glaucoma and dyslipidemia. An echocardiogram demonstrated an estimated ejection fraction of 55-60%. Preoperative hemoglobin and hematocrit (H/H) were 12.3 g/dL and 36.7% respectively. Preoperative vital signs were: blood pressure 133/79 mm Hg, heart rate 71/min, SpO2 98% and respiratory rate of 18/min. A 20 gauge intravenous catheter was placed in the patient’s left forearm. Lidocaine 1% skin wheal at the (right radial) insertion site and SQ infiltration optimized patient comfort during an arterial line insertion before induction. Midazolam 2 mg intravenous (IV) was administered prior to transfer to the operating room.

Upon arrival in the operating room, standard monitors were applied. The patient was pre-oxygenated for 5 minutes at 8 L/min delivered via facemask. Fentanyl 100 mcg and lidocaine 80 mg IV were administered. General anesthesia was induced with propofol 100 mg and ketamine 50 mg IV. Adequate mask ventilation with an oral airway was confirmed and rocuronium 50 mg IV was administered. Direct laryngoscopy was performed using a Macintosh 3.5 blade yielding a grade 1 view of the vocal cords. An 8.0-cuffed oral endotracheal tube was placed through the vocal cords without difficulty. Placement was confirmed with positive chest rise, positive breath sounds and positive end-tidal CO2. Mechanical ventilation was initiated and anesthesia was maintained with 1 MAC of isoflurane. A right central venous catheter and pulmonary artery catheter were placed in sterile fashion without difficulty.

The patient was placed in the supine position with all pressure points padded and bilateral upper extremities flexed less than ninety degrees. Bilateral lower extremities were positioned and
prepared for vein harvesting. Next, a trans-esophageal echocardiogram was performed, vancomycin 1 gm and cefazolin 2 gm IV were initiated and EACA 5 gm IV was administered (followed by an infusion of 1 gm/hr). Prior to sternotomy, fentanyl 500 mcg IV was administered. The left internal mammary artery and vein grafts were isolated without difficulty. Heparin 25,000 units IV was administered. During cannulation, systolic blood pressure (SBP) was 90-100 mmHg. While on cardiopulmonary bypass (CPB), anesthesia and mean arterial pressure (>60 mmHg) were maintained by the perfusionist. Adequate relaxation was maintained with rocuronium. Norepinephrine and epinephrine IV infusions were on standby. The patient’s blood sugar was controlled via IV insulin protocol.

Upon warming, midazolam 3 mg IV was administered. During decannulation, SBP remained between 90-110 mm Hg. Once the patient was off CPB, cefazolin 2 gm and protamine 250 mg IV were slowly administered. Albumin 5% one liter and autologous blood 325 mL IV were administered at the conclusion of the case. A total of EACA 10 gm IV was administered throughout the case. Total surgical time was 6 hours. The patient was transferred in stable condition to the intensive care unit with monitors and manual bag ventilation. The patient’s postoperative hemoglobin and hematocrit were 9.6 g/dL and 28.7% respectively. The administration of blood components in the postoperative period was not required.

Discussion

There are significant coagulation alterations, which occur with CPB. The use of CPB promotes accelerated thrombin generation, platelet dysfunction and enhanced fibrinolysis.2 As a result; fibrin is consumed by plasmin in a hyperfibrinolytic state, which can lead to an increased blood loss.2 Bleeding in cardiac surgery can be due to the surgical procedure, comorbidities, medications and coagulation defects that occur from CPB.3 Therefore, the goal of antifibrinolytic therapy is to reduce pathologic fibrinolysis related to CPB, ultimately leading to reduced blood loss, reduced blood component transfusions and reduced surgical re-exploration.

There are two main classes of antifibrinolytic agents: protease inhibitors and lysine analogs. Aprotinin (AP), a serine protease inhibitor, binds directly to the active site of free plasmin and reduces fibrinolytic activity. Aprotinin was removed from worldwide markets in 2008 due to an increased risk of death in cardiac surgical patients participating in The Blood Conservation Using Antifibrinolytics in a Randomized Trial.3,4 The most popular alternative to AP is EACA. Greilich et al suggest EACA is comparable to AP in reducing fibrinolysis and blood loss in primary, isolated coronary artery bypass graft surgeries.5 However, Koul et al demonstrated a 12% decrease in operative site bleeding in patients who were treated with AP versus EACA.6 Although the patients in the AP group received more fresh frozen plasma, there was no significant difference in the transfusion rates of packed red blood cells (PRBC) for either medication. Most importantly, there were no differences in morbidity and mortality rates between the patients.6 Therefore, Koul et al concluded EACA was a safe and cost-effective antifibrinolytic in place of AP for patients undergoing a variety of cardiac operations.6

Lysine analogs, TXA and EACA, competitively block the lysine binding sites on plasminogen, preventing the binding of fibrin and fibrinogen, ultimately decreasing fibrinolysis. Makhija et al studied the efficacy and safety of lysine analogs in thoracic aortic surgery. Efficacy was analyzed
based on intraoperative and postoperative blood loss, perioperative blood component administration and time for chest closure (hemostasis). Mean blood loss, total PRBC and blood component requirements were comparable between both medication groups. Although there was more blood loss observed with TXA use, this was not statistically significant. Makhija et al concluded EACA and TXA were both effective in reducing perioperative blood loss and transfusion requirements in patients undergoing thoracic aortic surgery. Safety was analyzed based on the incidence of thrombosis, neurologic dysfunction (seizure or stroke), renal dysfunction, duration of mechanical ventilation and death. Makhija et al concluded significant renal injury and increased possibility for renal failure were associated with EACA, while increased risk for seizure was associated with the administration of TXA.

Falana et al studied the efficacy and safety of TXA versus EACA in cardiovascular surgery. Efficacy was analyzed based on massive perioperative bleeding; chest tube drainage greater than 1500 mL in any 8-hour period after surgery, perioperative transfusion of 10 or more units of PRBCs, reoperation for bleeding or death from hemorrhage within 30 days. Safety was analyzed based on the incidence of thromboembolic events, postoperative renal dysfunction, seizure and 30-day all-cause mortality. Falana et al concluded there were no differences in the efficacy and safety outcomes between TXA and EACA on cardiovascular surgical bleeding. However, TXA is more potent and 40 times more expensive than EACA. The cost of TXA and EACA for cardiac surgery (in 2013) at their institution was $145.25 and $3.66 respectively. Therefore, Falana et al suggest that EACA may be more cost effective compared to TXA for reducing cardiovascular surgical bleeding.

Raghunathan et al compared the clinical value of TXA with EACA when used in high-risk cardiac surgery. Efficacy was analyzed based on any massive bleeding, bleeding from chest tubes, massive transfusions, death from hemorrhage, reoperation for bleeding and 30-day all-cause mortality. Safety was analyzed based on incidences of infarction, deep vein thrombosis or pulmonary embolism, respiratory failure, cardiac shock, renal failure and blood components administered. Raghunathan et al concluded that there were no significant differences in overall safety and efficacy between TXA and EACA. Based on “clinical value” analysis, which is a function of clinical outcomes, costs, satisfaction with care and functional status, EACA exceeds that of TXA. Therefore, given the rising numbers of cardiac surgeries in the United States, Raghunathan et al suggest that EACA should be the choice for antifibrinolytic therapy for high-risk cardiac surgeries.

Evidence based practice maximizes the safety of our patients. The case presented here is consistent with literature findings and supports the use of EACA as a safe, efficacious and cost effective alternative. However, there are side effects associated with antifibrinolytic administration, such as seizures and renal complications. The routine administration of antifibrinolytic agents in low risk cardiac surgery should be reevaluated, especially in patients with seizure and renal disorders. Most importantly, the risks and benefits should always be considered when choosing between TXA and EACA for antifibrinolytic therapy.
References


Mentor: Kären Embrey, CRNA, EdD

A Multi-modal Approach to Intraoperative Management of Chronic Pain

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Keywords: chronic pain, neuropathic, perioperative, glutamate

In 2011 the Institute of Medicine of the National Academies estimated 100 million Americans suffer from chronic pain, more than those suffering from diabetes, heart disease, and cancer. Despite medical management, patients may continue to have inadequate pain relief and thus require surgical intervention. Chronic pain syndromes may have varying etiologies which pose perioperative challenges. This case report reviews several pharmacologic strategies for a patient with chronic pain that are distinct from treatment of acute nociceptive pain.
Case Report

A 68-year-old female (61 kg, 168 cm) presented with chronic lower back pain radiating to the right lower extremity with ipsilateral intermittent numbness, tingling, and weakness. Skin color and temperature changes were observed in the affected extremity. Radiographic studies confirmed lumbar spinal stenosis and spondylolisthesis at lumbar vertebrae level L4-5. The patient was diagnosed with degenerative disc disease and complex regional pain syndrome. Home medications included diazepam, duloxetine hydrochloride, hydrocodone, magnesium, morphine, and pregabalin. Despite this regimen and previous lumbar laminectomy and spinal fusion of L5-S1 the patient continued to have severe pain. A direct lateral interbody fusion of the lumbar vertebrae level L4-5 was planned.

On arrival to the preoperative area the patient received gabapentin 900 mg orally. An 18 gauge peripheral intravenous (IV) catheter was placed following 1% lidocaine 0.25 mL subcutaneous infiltration. Premedication included ranitidine 50 mg and glycopyrrolate 0.2 mg IV. In the OR suite standard monitors were placed and oxygen at 10 L/min via anesthesia mask was administered. Vital signs were obtained and preoxygenation/denitrogenation continued for 2 minutes. Induction of general anesthesia commenced with lidocaine 60 mg, propofol 100mg, methadone 5 mg, and ketamine 50 mg IV. Bag-mask ventilation was established and rocuronium 50 mg IV was administered. Video laryngoscopy with cervical spine immobilization was performed. A 7.0 endotracheal tube was inserted and placement confirmed. Mechanical ventilation was initiated with volume control, respiratory rate 12/min, tidal volume 500 mL, and FiO2 0.5. Anesthesia was maintained with desflurane 0.5 MAC and propofol at 75 mcg/kg/min IV. A second 18 gauge peripheral IV and a radial arterial line were placed. The patient was positioned in right lateral decubitus position with pressure points padded maintaining the spine in neutral position. Dexamethasone 10 mg IV, magnesium sulfate 2 gm IV, and cefazolin 1 gm IV were administered prior to incision. A neurophysiologist monitored somatosensory evoked potentials and electromyography throughout the case.

The patient received 3 L of normosol-R IV and output included 50 mL of estimated blood loss and 1500 mL of urine. At surgical closure, the propofol infusion was discontinued and within 30 minutes the ventilator setting was changed to pressure support. Acetaminophen 1000 mg IV was administered at that time. Once in the supine position, neuromuscular train of four was reassessed and reversal agents were administered including neostigmine 4 mg and glycopyrrolate 0.8 mg IV. A laryngotracheal anesthetic of 4% lidocaine (160 mg) was administered topically (to the cords around the endotracheal tube). Desflurane was discontinued, oxygen flow was increased to 15 L/min, and ondansetron 4 mg IV was administered. Spontaneous ventilations were observed as regular, unlabored, and 12 to 18/ breaths per minute. The case duration was approximately four hours, after which the patient was extubated fully awake. Prior to transport from the operating room the patient denied having pain. In the recovery room the patient received methocarbamol 500 mg IV. After one hour in the PACU the patient’s pain was reported to be 3/10 without the administration of additional opioids.
Discussion

Neuropathic pain is due to a “primary lesion or dysfunction in the nervous system\(^2\)\(\text{p476}\),” and is a significant feature of chronic regional pain syndrome (CRPS).\(^2\) The International Association for the Study of Pain defines CRPS as chronic pain disproportionate to any inciting event associated with alterations in at least one of the following categories: sensory, vasomotor, motor, and/or trophic. The pathophysiology of chronic pain syndromes is complex and remains an area of ongoing research, yet what is understood has helped to guide pharmacological strategies. Glutamate, the central nervous system’s main excitatory neurotransmitter, has been identified as a key factor to the development of central sensitization. In chronic pain states, there is an up-regulation of second messengers such as protein kinase and phospholipase which can hyperexcite receptors.\(^3\) The following medications utilized in this case were directed at attenuating glutamate release.

Gabapentin, a second-generation antiepileptic, inhibits neuronal excitation and stabilizes nerve membranes to minimize the ectopic firing of pain pathways.\(^3\) Gabapentin blocks presynaptic voltage-gated calcium channels in the central nervous system and prevents the release of excitatory neurotransmitters.\(^3\) In a randomized, double-blind, placebo-controlled study of 100 patients Pandey et al\(^4\) exhibited that preemptive gabapentin reduced opioid consumption and pain severity after single-level lumbar discectomy. A statistically significant reduction of both pain scores utilizing the Visual Analogue Scale and postoperative fentanyl requirements were observed with a preemptive dose of gabapentin preoperatively.

Ketamine is a noncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist that inhibits glutamate release.\(^3\) Loftus et al\(^5\) conducted a randomized prospective, double-blind placebo-controlled trial with opiate-dependent patients undergoing lumbar spine surgery. Intraoperative ketamine significantly reduced opioid requirements and pain scores postoperatively. The investigators recruited patients with a history of chronic low back pain and randomized 101 patients into one of two groups. The treatment group of patients with chronic pain received 0.5mg/kg of ketamine on induction followed by an infusion of 10 mcg/kg/min. The investigators demonstrated a 37% reduction in opiate consumption in the acute postoperative period.\(^5\) Additionally PACU and 6 week post-operative pain scores were statistically reduced by 26.7% and 26.2% respectively with the use of intraoperative ketamine.\(^5\)

Among the many physiologic actions of magnesium, it also functions as a non-competitive NMDA antagonist. Levaux et al\(^7\) performed a randomized, controlled trial examining the use of magnesium sulfate (MgSO\(_4\)) in the setting of lumbar spine surgery. The treatment group received 50 mg/kg of MgSO\(_4\) over 30 minutes before induction. The study showed a statistically significant reduction of opioid analgesic requirement with the administration of magnesium. Side effects of magnesium administration may include hypotension and prolonged neuromuscular blockade. The treatment group receiving MgSO\(_4\) did not experience excessive hypotension, however delayed recovery from neuromuscular blockade was evident. An additional 20 minutes to achieve 4 out of 4 train of four responses after the administration of rocuronium was observed.\(^9\) Despite these findings, the investigators recommend MgSO\(_4\) can be used safely as an adjunct for pain management with close monitoring of neuromuscular relaxation and appropriate attention to timing.
Methadone, a synthetic racemic mixture opioid, has been used to treat opioid addiction, severe acute pain, chronic cancer pain, and neuropathic pain. The l-isomer (R-methadone) binds to opioid receptors and the d-isomer (S-methadone) antagonizes NMDA receptors and inhibits the uptake of serotonin and norepinephrine. Gottschalk et al designed a prospective, randomized, single-blinded study to compare the efficacy of a continuous sufentanil infusion versus a single dose of methadone 0.2 mg/kg IV intraoperatively in patients experiencing multi-level thoracolumbar spine surgery. Patients receiving methadone reported a statistically significant decrease in postoperative pain and had lower opioid requirements at 48 hours. The investigators attributed this to methadone’s antagonism at the NMDA receptors, rather than to its opioid agonist action. Methadone’s elimination half-life varies from 15 to 60 hours, up to 130 hours in some patients thus its use for outpatient surgery is discouraged.

Chronic pain is far reaching and can be disruptive to the physical, psychological, social, and economic well-being of an individual. Management of chronic pain with opioid mono therapy predisposes patients to opioid tolerance, central sensitization, and hyperalgesia following surgery. This discussion focused on the use of gabapentin, ketamine, magnesium, and methadone; however other non-opioid adjuvants were also utilized to achieve optimal patient comfort including intravenous acetaminophen, dexamethasone, and methocarbamol. This case review demonstrates that the utilization of a multi-modal pain management strategy can result in successful outcomes for chronic pain patients in the immediate perioperative period.

References


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Laryngospasm with Laryngeal Mask Airway

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Keywords: anesthesia, airway, laryngospasm, laryngeal mask airway (LMA)

Vagal stimulation of the superior laryngeal nerve can result in the life threatening reflex known as a laryngospasm. The cause of airway obstruction is the contraction of the intrinsic laryngeal muscles causing the glottis to close. With prolonged laryngospasm hypoxemia will result, leading to bradycardia and asystole. In a Scandinavian study of over 130,000 anaesthetics administered, the overall incidence of laryngospasm was 0.78%. Greater risk was identified in children with asthma or airway infections or those undergoing oesophagoscopy or hypospadias repair, and adults undergoing anal surgery. It is essential that providers are trained in recognition and treatment of laryngospasm.

Case Report

A 29-year-old, 66 kg, 150 cm, Hispanic female presented for a right lumpectomy of a breast abscess. She had no known drug allergies and was taking no medications. Her medical history included the right breast abscess, a recent diagnosis of hypothyroidism and occasional headaches. The patient’s surgical history consisted of an incision and drainage of the right breast abscess. Baseline vital signs were: SpO2 99% on room air, blood pressure was 126/71 mm Hg, respirations were 14/min, heart rate was 99/min, and her temperature was 36°C. The airway exam was unremarkable. In the holding room, midazolam 2 mg and glycopyrrolate 0.2 mg were administered via a 20 gauge intravenous (IV) catheter.

In the operating room, noninvasive monitors were applied. Oxygen 10 L/min via facemask was administered. An IV induction was performed using lidocaine 80 mg and propofol 150 mg. A size 4 laryngeal mask airway (LMA; Teleflex Inc., San Diego, CA) was placed without difficulty in the hypopharynx. Breath sounds and end-tidal carbon dioxide (ETCO2) were confirmed. Sevoflurane 3% inspired concentration was initiated in a mixture of O2 1 L/min and air 1 L/min to maintain general anesthesia with a minimum alveolar concentration of 1. The LMA was secured midline with tape. Spontaneous ventilation returned approximately 3 minutes after induction and intermittent doses of fentanyl 25 mcg were administered to total 100 mcg for the entire case. Assessment of ventilation was monitored continuously utilizing a precordial stethoscope positioned at the base of the patient’s neck and ETCO2 monitoring.

After the incision was made a high-pitched sound was auscultated through the precordial stethoscope. Upon further assessment, it was noted that the LMA was no longer midline, but rotated slightly. An attempt was made to reposition the LMA back to midline. At that time, spontaneous ventilation was lost as evidenced by absence of ETCO2 and lack of auscultated air movement through the precordial stethoscope. Sevoflurane was immediately increased to an inspired concentration of 8% and O2 was increased to 10 L/min. Attempts to administer positive pressure ventilation via the LMA proved unsuccessful and the patient experienced a transient decrease in SpO2 to 80%. The LMA was removed and propofol 150 mg IV was administered as a
bolus. Manual mask ventilation was successful and SpO₂ returned to 96%. Spontaneous respirations returned and sevoflurane was decreased to 3% inspired concentration. Due to the brevity of the procedure it was decided to continue administration of sevoflurane via facemask. Emergence from anesthesia and transport to the post anesthesia care unit was uneventful.

**Discussion**

This case highlights the risk of laryngospasm in the unsecured airway, specifically when using a LMA. A review of the literature concerning laryngospasm reveals multiple contributing factors to this complication and various methods for treatment. While more prevalent in children, adult laryngospasm results in 23% of critical postoperative respiratory events.²

The trigeminal, glossopharyngeal, and vagus nerves provide the afferent pathways that innervate the mucosal surfaces of the nasopharynx to the vocal cords. Secretions, blood, gastric fluid, pressure, and even temperature changes can stimulate this reflex arc. Stimulation can trigger coughing, bronchospasm, apnea, and vocal cord closure.² The cause of airway obstruction is the result of contraction of the intrinsic laryngeal muscles, specifically the lateral cricoarytenoid, the thyroarytenoid, and the cricothyroid muscles.³ Failure to correct a laryngospasm can result in hypoxia, eventually leading to bradycardia and asystole. Negative-pressure pulmonary edema can also result in the patient who has respiratory effort against a closed glottis.³ The negative intrathoracic pressure created by this respiratory effort causes the alveoli to fill with fluid from the pulmonary capillary bed, resulting in noncardiogenic pulmonary edema.³

Supraglottic devices, specifically the LMA, have risks and benefits. Advantages of the LMA include reduced cardiovascular response to placement, less coughing on emergence, protection of the airway from blood and surgical debris, decreased risk of bronchospasm in the asthmatic patient, and reduced incidence of laryngospasm after removal. Some of the main contraindications for the use of LMAs are: morbid obesity, intestinal obstruction, hiatal hernia, and a full stomach; all of which increase the risk of aspiration of gastric contents. Complications associated with the use of LMA include sore throat from placement, and laryngospasm because of the unprotected airway.³

Orliaguet et al⁶ discusses the various methods that have been proposed to treat laryngospasm. Techniques include airway manipulations such as chin lift and jaw thrust, continuous positive airway pressure, and administration of 100% O₂. Pressure at the laryngospasm notch is another proposed method of treating laryngospasm.⁷ Cessation of stimulation and clearing the airway of secretions are also indicated.³-⁵ If these interventions fail to resolve the laryngospasm, increasing the depth of anesthesia with an IV agent should take place.⁵ Continued laryngospasm dictates the use of IV succinylcholine 0.5mg/kg, unless there is a contraindication for its administration, such as muscular dystrophy or history of malignant hyperthermia. If no IV access is available, succinylcholine 4 mg/kg may also be given. Failure to ventilate the patient effectively after these interventions necessitates intubation.³

The patient undergoing breast biopsy, as depicted in the case study, was an appropriate candidate for the use of a LMA. The factors that predisposed the patient to laryngospasm, at the time of the event, were dislodgement of the LMA with potential irritation to the vocal cords and inadequate
depth of anesthesia at the time of incision. Initial interventions to remove the offending stimulus, and provide positive pressure ventilation by face mask followed current recommendations. The second line intervention, administering propofol, was appropriate to rapidly increase the depth of the anesthetic.\(^3\) Succinylcholine was not needed in this case, as the laryngospasm was relieved after propofol administration. While the assumption was made that this patient experienced a laryngospasm, visualization of closed vocal cords never took place. The patient could have been experiencing a bronchospasm; this differential diagnosis may have necessitated intubation.\(^5\)

In conclusion, a suspected laryngospasm, induced by an attempt to re-seat a dislodged LMA, was successfully treated with a bolus of propofol administered to increase the depth of anesthesia and continuous positive airway pressure via face mask. The literature discussed contributing factors of laryngospasm as well as treatments. In the case presented, quick identification and action was taken to relieve the suspected laryngospasm. Although the treatment could have included a short acting paralytic, the steps taken were appropriate when compared with the literature. The resulting outcome was restoration of ventilatory exchange with no negative outcomes for the patient.

References


Mentor: Ashlee Z. Chafin, CRNA, MSN
Hypotension and Epidural Analgesia: Does Body Mass Index Matter?

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Keywords: obesity, labor epidural analgesia, hypotension, anesthesia, obstetrics

Introduction

Obesity rates in the U.S. are on the rise and this epidemic impacts all areas of healthcare, including obstetrics. This study investigates whether parturients with a body mass index (BMI) ≥ 40 kg/m² experience a greater degree of hypotension and conversion to emergency cesarean section (CS) after labor epidural analgesia (LEA) placement, compared to parturients with BMI 20–25 kg/m². The study results advance the knowledge on whether anesthesia practitioners should adjust practice to best care for morbidly obese parturients.

Methods

A retrospective cohort study of women who received LEA placement from January 1, 2014 through December 31, 2014 at a large, academic medical center was completed. Institutional review board approval was obtained. Study inclusion criteria were as follows: women aged 18 to 30 admitted for labor or induction of labor, gestation ≥38 weeks, and BMI 20–25 kg/m² or ≥ 40 kg/m². Women with multi-fetal pregnancies, pre-eclampsia, and eclampsia were excluded. The subject’s baseline systolic blood pressure (SBP) and diastolic blood pressures (DBP) were recorded. This was defined as the first blood pressure recorded prior to LEA placement. After LEA placement, the subject’s SBP and DBP were recorded at 5-minute intervals for the first 15 minutes, then at 10-minute intervals until the anesthesia practitioner left the room. Hypotension was defined as a 20% decrease in SBP or DBP from baseline. Persistent hypotension was defined as a 20% decrease in any 3 readings and sustained hypotension as a 20% decrease in at least 5 readings. Prior to analysis an α < 0.05 was set. SPSS software (SPSS Version 20; SPSS Inc., Chicago, IL) was used to analyze data.

Results

There were 148 subjects who met study inclusion criteria, 71 in the BMI 20-25 kg/m² group and 77 in the BMI ≥40 kg/m² group. Chi-Squared Tests were run to determine whether a correlation between the two groups and persistent systolic hypotension (PSHo), persistent diastolic hypotension (PDHo), sustained systolic hypotension (SSHo), or sustained diastolic hypotension (SDHo) was present. Additional tests were run to see if there was a correlation between PSHo, PDHo, SSHo or SDHo and conversion to CS, and if the morbidly obese had an increased rate of conversion to CS. A correlation was found between the morbidly obese group and SSHo, BMI ≥40 15.5% vs. BMI 20-25 kg/m² 6.8% (p=0.021). There was also a correlation between PSHo and conversion to CS, PSHo 30.8% vs. no PSHo 11.1% (p=0.043).
Discussion

The study findings did not show a strong correlation between morbid obesity and hypotension following LEA placement leading to CS. The BMI $\geq 40$ kg/m$^2$ group was the only group that had an increased incidence of SSHo. However, this did not lead to an increased rate of CSs. Using G*Power analysis (G*Power Version 3; Heinrich-Heine-Universität, Düsseldorf) it was determined that future studies would need a sample size of 220 with 110 in each BMI group. The small sample size is a limitation of this study. Therefore it is hard to establish strong correlations within the limited data and cannot be generalized to the population as a whole.

Mentor: Kelli Pryor, CRNA, DNP

Liposomal Bupivacaine: A Revolution in Post-Operative Analgesia and Outcomes

Meagan Stark, MS
Florida Gulf Coast University

Keywords: liposomal bupivacaine, analgesia, postoperative, anesthetics

Introduction

Post-operative pain management is transitioning to a multimodal approach. The degree of post-operative pain is clinically and economically significant.\(^1\)\(^-\)\(^9\) Inadequate pain control results in delayed patient discharge and delayed patient satisfaction, both of which are vital components for Centers for Medicare and Medicaid Services reimbursement.\(^3\) With the passing of the Affordable Care Act in 2010 there is an ever increasing need for safe, cost-effective and high quality care.\(^3\)

Infiltration of local anesthetics at the surgical site is commonly utilized to decrease post-operative pain and narcotic usage.\(^1\),\(^2\),\(^4\)-\(^12\) The introduction of liposomal bupivacaine for wound infiltration provides up to 96-hours of post-operative analgesia.\(^1\),\(^2\),\(^4\)-\(^12\) Providing up to 96 hours of post-operative analgesia leads to decreased narcotic consumption and decreased length of stay; both critical components of patient associated costs.\(^1\),\(^2\),\(^6\)-\(^9\) The increased efficacy of liposomal bupivacaine for post-operative pain relief delivers improved patient satisfaction and patient outcomes.\(^1\),\(^2\),\(^4\)-\(^12\)

Traditionally, opioids have been the mainstay for post-operative pain management whether administered orally, intravenously, or through a patient controlled analgesia (PCA) system.\(^1\),\(^2\),\(^4\)-\(^12\) A retrospective analysis concluded that 55% of post-operative patients required treatment for vomiting, nausea, or constipation following opioid administration, all common adverse events associated with narcotic usage.\(^1\) Adverse effects of narcotics can lead to hospitalization and can also increase the length of stay and cost of a patient’s hospitalization.\(^2\),\(^4\)-\(^12\) Effective post-operative pain management is transitioning to a multimodal approach due to its complex and multifactorial underlying basis.\(^1\),\(^2\),\(^4\)-\(^12\) The multimodal approach, which includes liposomal bupivacaine, is aimed at decreasing opioid usage and utilizing non opioid analgesics.\(^1\)
Bupivacaine HCl, a local anesthetic, is traditionally used to decrease post-operative pain, however it is limited by its maximum duration of action of up to 24 hours. Liposomal bupivacaine, has been proven to provide up to ninety-six hours of post-operative pain relief due to its unique pharmacokinetic properties. Liposomal bupivacaine is an effective method to reduce opioid administration and consumption amongst post-operative patients. Decreased opioid consumption from the use of liposomal bupivacaine leads to decreased length of stay, decreased hospitalization costs, decreased morbidity and mortality from opioid consumption, and higher patient satisfaction.

Methodology

Evidence-based Practice Model
The PICO format was utilized to formulate the clinical question being investigated. The following parameters included: P(Patient Population)= In surgical patients age 18 or older, I(Current Intervention)= can the use of liposomal bupivacaine, C(Comparison)= as compared to bupivacaine HCl, O(Outcome)= lead to decreased opioid usage, longer duration of post-operative analgesia, decreased morbidity and mortality, and higher patient satisfaction.

Purpose
The purpose of this review is to examine and evaluate the efficacy of liposomal bupivacaine for prolonged postoperative analgesia. The clinical question that guided this review include: Can the use of liposomal bupivacaine lead to longer duration of post-operative analgesia, decreased narcotic consumption, decreased morbidity and mortality, and higher patient satisfaction?

Search Terms
Liposomal bupivacaine, analgesia, postoperative, anesthetics

Search Methods
Electronic database search included ScienceDirect, PubMed, Cochrane Library, MEDLINE from years 2010-2015. Electronic data bases including PubMed, Science Direct, Cumulative Index to Nursing and Allied Health Literature (CINAHL), DynaMed, Cochrane Database and Google Scholar were searched via the internet for the most current and highest levels of evidence published within the last five years.

Levels of Evidence
The primary evidence utilized included four randomized control trials (Level II evidence), one cohort study and one meta-analysis providing Level I evidence.

Literature Review
Quercia and Coleman showed that over 80% of patients reported having pain that was moderate, severe, or extreme for two weeks post-operatively. Local anesthetics are commonly utilized to provide post-operative analgesia. The duration of action of bupivacaine HCl and traditional local anesthetics is limited to an average of seven hours or less, whereas liposomal bupivacaine has been proven to provide analgesia for up to seventy-two hours and thereby decreasing narcotic utilization by 45%.
Efficacy
Liposomal bupivacaine’s unique mechanism of action provides a longer duration of action as evidenced by decreased pain scores and decreased opioid consumption up to 96 hours postoperatively. McAlvin et al determined that liposomal bupivacaine provided a sensory block of up to 240 minutes on the sciatic nerve as compared to 120 minutes provided by bupivacaine HCl.

Golf et al calculated the adjusted mean of the area under curve (AUC) of the numeric rating scale (NRS) pain intensity scores. The research shows the pain intensity scores of the liposomal bupivacaine 120-mg group to be significantly lower in comparison to the placebo group 24 hours postoperatively. The authors also determined that 31.5% of the patients who received 120-mg liposomal bupivacaine were pain free 48 hours postoperatively compared to 19.1% who received placebo.

Haas et al states cumulative pain scores for those receiving liposomal bupivacaine at each study dose were all significantly lower than those receiving bupivacaine HCl 72 hours postoperative excisional hemorrhoidectomy. Gorfine et al conducted a randomized control trial (RCT) and measured pain intensity scores by the area under the curve of the numerical rating score. Gorfine et al determined that the pain scores were significantly lower in the group receiving liposomal bupivacaine compared to the placebo group. The authors also determined that 59% of patients in the liposomal bupivacaine group remained opioid free at 12 hours and 28% at 72 hours postoperatively versus 14% at 12 hours and 10% at 72 hours following excisional hemorrhoidectomy.

Bramlett et al conducted an RCT showing mean cumulative pain scores at rest were significantly lower $P<0.05$ at numerous time points in the group receiving liposomal bupivacaine. Additionally, the research shows patients treated with 532-mg liposomal bupivacaine had lower cumulative pain scores at each time interval from postoperative day 1 through day 5. Bramlett et al collected patient blood samples for pharmacokinetic assessment and determined that it took 60 hours longer for the plasma level of bupivacaine to reach 0 mg/ml. These cumulative pain scores along with blood sample analysis provide strong evidence to support liposomal bupivacaine’s hypothesized longer duration of action.

Dosage Dependent
Research findings suggest that there is a strong correlation between the dosage of liposomal bupivacaine administered and the efficacy achieved. Bramlett et al researched four different doses of liposomal bupivacaine administration in total knee arthroplasty and found that with the highest dose of administration, 532-mg, there was a statistically significant difference in the pain rating scores as compared to plain bupivacaine. The research shows a dose-response trend between the four groups of liposomal bupivacaine administration.

Ilfeld utilized a cohort study and determined peripheral nerve block duration lasted longer for doses above 40 mg of liposomal bupivacaine. Ilfeld disclosed that the responses to this study had high variability and the need for future, larger clinical trials for confirmation of the dose-dependent responses. Haas et al conducted an RCT comparing three increasing doses of
liposomal bupivacaine and found the highest dose of 266 mg provided the lowest amount of opioid consumption postoperatively. Additionally, the research shows that cumulative pain scores were significantly lower ($P<0.05$) with each dose of liposomal bupivacaine versus plain bupivacaine.6

**Decreased Opioid Consumption**

Cohen10 conducted a Phase IV cohort study on patients undergoing open colectomy and determined the multimodal analgesia group consisting of a 266 mg single dose administration of liposomal bupivacaine via wound infiltration, consumed significantly less ($P=0.025$) opioids (57 mg) per patient as compared to the opioid analgesia group that consumed 115 mg.

Three out of the four RCTs reviewed showed a decrease in total opioid consumption postoperatively.4,7,10 Gorfine et al7 determined 72 hours post-operative hemorrhoidectomy, the mean total amount of opioid consumption was 22.3 mg for the bupivacaine extended-release 300 mg group in comparison to 29.1 mg in the placebo group. The authors determined the average time until first opioid use was 1.2 hours in the placebo group compared to 14.3 hours in the liposomal bupivacaine group.7 Patient satisfaction is of clinical importance because it is a crucial and key component in CMS reimbursement.3

Smoot et al11 concluded the total amount of opioid consumption was significantly lower in the group that received liposomal bupivacaine vs bupivacaine 24 hours and 48 hours postoperative mammoplasty. Golf et al4 concluded the liposomal bupivacaine group deferred 7.2 hours until first opioid consumption compared to 4.3 hours with the placebo group. Golf et al4 also determined the liposomal group consumed fewer opioids ($P=0.0077$) through 24 hours compared to the placebo group.

**Decreased Opioid Related Adverse Events**

Opioids are a mainstay in postoperative pain management but they are not without adverse events.2,3 Common adverse events associated with opioid usage include nausea, respiratory depression, vomiting, constipation, all of which can contribute to longer PACU recovery time, increased healthcare costs, and longer length of stay.4

Haas et al6 conducted a double-blind RCT for post-hemorrhoidectomy pain management with 266-mg liposomal bupivacaine. There was a 31% reduction in the incidence of opioid related adverse events with the 266-mg liposomal bupivacaine group compared with the bupivacaine HCl group.6 Golf et al4 concluded 58% of the liposomal bupivacaine 120 mg group experienced one or more adverse event while in the placebo group, 65% of the population experienced one or more adverse event postoperative bunionectomy.

Cohen’s10 cohort study concluded the average total cost of hospitalization was $11,850 in the opioid group versus $8,766 in the multimodal group for patients undergoing open segmental colectomy with anastomosis. The authors also concluded the average length of hospital stay was 59% shorter, 4.9 days versus 2 days, in the multimodal group.9 The author concluded that the multimodal analgesia group had 72% less opioid related adverse event, $P=0.0027$ in comparison to the IV PCA opioid group.9 Surdam et al12 concluded the average length of stay was 2.36 days.
for the liposomal bupivacaine group versus 2.65 days for the group receiving a single shot femoral nerve block.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design</th>
<th>Surgery</th>
<th>Major Findings</th>
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<tbody>
<tr>
<td>Bramlett 2012</td>
<td>RCT</td>
<td>Total Knee Arthroplasty</td>
<td>Patients treated with 532-mg liposomal bupivacaine had lower cumulative pain scores at each time interval from postoperative Day 1 through Day 5. After 144 hours, the plasma bupivacaine concentration was 0 mg/mL for the 532-mg liposomal bupivacaine dose, whereas it only took 84 hours after plain bupivacaine administration for the plasma bupivacaine concentration to reach 0 mg/mL.</td>
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<tr>
<td>Cohen 2012</td>
<td>Cohort</td>
<td>Colectomy</td>
<td>Average cost of hospitalization $8,766 in liposomal bupivacaine group vs. $11,850 in PCA group Average total opioid consumption postoperatively was significantly less in the liposomal bupivacaine group (57 mg) compared to the PCA group (112 mg)</td>
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<tr>
<td>Golf 2011</td>
<td>RCT</td>
<td>Bunionectomy</td>
<td>Pain intensity scores of the liposomal bupivacaine group were significantly lower (123.9) in comparison to the placebo group (146) 24 hours postoperatively 31.5 % of the patients who received 120-mg liposomal bupivacaine were pain free 48 hours postoperatively compared to 19.1% who received placebo</td>
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<tr>
<td>Gorfine 2011</td>
<td>RCT</td>
<td>Hemorrhoidectomy</td>
<td>More patients in the liposomal bupivacaine group remained opioid free at 12 hours (59%) and 72 hours (28%) postoperatively versus 14% at 12 hours and 10% at 72 hours Pain intensity scores were significantly lower in the group receiving liposomal bupivacaine (141.8) vs. the placebo group (202.5)</td>
</tr>
<tr>
<td>Haas 2012</td>
<td>RCT</td>
<td>Hemorrhoidectomy</td>
<td>Cumulative pain scores were significantly lower with liposomal bupivacaine at each dose compared to bupivacaine HCl 72 hours post-op. Median time to first opioid use was 19 hours for liposomal bupivacaine vs. 8 hours for bupivacaine HCl. Incidence of opioid-related adverse events was 4% for liposomal bupivacaine vs. 35% for bupivacaine HCl.</td>
</tr>
<tr>
<td>Smoot 2012</td>
<td>RCT</td>
<td>Mammoplasty</td>
<td>Total amount of opioid consumption was significantly lower 24 hours and 48 hours postoperatively in the group that received liposomal bupivacaine</td>
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Table 1. Recent Literature regarding the use of liposomal bupivacaine
Conclusions

The use of liposomal bupivacaine is only approved by the FDA for intraoperative injection during hemorrhoidectomy and bunionectomy.\textsuperscript{1,2,9} Liposomal bupivacaine was approved by the FDA in 2011 for intraoperative injection only despite research dating from 1994 suggesting its benefits for use in epidurals and regional anesthesia management.\textsuperscript{9}

This literature review is intended to provide an introduction and state of inquiry regarding the use of liposomal bupivacaine for future practice. The underlying themes found throughout the various research articles included but are not limited to efficacy, dosage dependency, decreased opioid consumption, and decreased adverse events due to opioid usage. This literature review provides strong evidence towards the benefits of liposomal bupivacaine. Limitations for this literature review include the numerous ongoing larger clinical trials of liposomal bupivacaine and therefore lack of available results. All of the articles utilized concluded that their findings are suggestive and significant but require further investigation through larger clinical trials. The authors are optimistic towards the trends shown throughout their research and the hope for future incorporation into clinical practice. There were inconsistencies in the literature regarding dose dependency. Despite these findings, there is an overall theme that the use of liposomal bupivacaine provides for prolonged analgesia as compared to plain bupivacaine and placebo groups. These inconsistencies were disclosed by the researchers and in a majority of the research articles, the researchers all state the need for further extensive and larger clinical trials to solidify the findings.

Liposomal Bupivacaine: A revolution in post-operative analgesia and outcomes provides significant evidence through the utilization of RCTs, meta-analysis, and cohort studies to create a state of inquiry for the future use of liposomal bupivacaine. Furthermore, liposomal bupivacaine can provide a basis for practice change and how it will influence anesthesia practitioners by providing safe, cost effective, and quality patient care.

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**Mentor:** Ann Miller, CRNA, DNP

**Cannabinoid System: A Safer Chronic Pain Management Approach**

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**Keywords:** marijuana, cannabinoids, medical, chronic pain, opioids

**Introduction**

The treatment of chronic pain has become a widening area of concern regarding increase use and dependency of prescription opioids. Between 1999-2010, prescription opioid overdose mortalities in the United States nearly doubled.\(^1\) Overdoses occur with 60% of patients holding valid prescriptions, but the improper use of narcotics has demonstrated lethal side effects.\(^1\) The increase may be attributed to growth in access to pain clinics, affording better screening of chronic pain conditions; however, increased prescribing of opioids has correlated with a significant rise in opioid analgesic overdoses.\(^1\) Therefore, an escalating need for an alternative treatment of chronic pain exists with medical cannabis.\(^2\) Currently viewed as a public health epidemic, prescription opioid abuse can safely be alleviated by generating further awareness of
medical cannabis while easing government restrictions and rescheduling cannabis control status to aide further research.

Tracing back 5000 years, cannabis has been a religious and medicinal choice for the treatment of pain.³ Egyptian relics from the 16th century B.C. appear to depict medicinal benefit of cannabis for neuralgia, headache, and toothaches.⁴ In second century China, cannabis resin was mixed with wine and used with success as an anesthetic to perform major surgical procedures.⁴ During the 1840’s United States Cavalry Army Physician, William O’Shaughnessy proposed the use of cannabis in the West for analgesic treatment of various ailments after witnessing India’s medicinal practices.² In 1854, Eastern Medicine was adopted, placing marijuana on the U.S. Dispensary list and legally prescribed by physicians to treat pain, vomiting, convulsions, insomnia, headaches, anorexia, and sexual dysfunction.⁵ By the late 19th century cannabis-based preparations began to be manufactured and marketed by Burroughs-Wellcome & Co., Bristol-Myers Squib, Parke-Davis in England and North America by Eli Lilly to treat many conditions.³

In 1936, increasing debate over the use of marijuana was stigmatized through the ideology of negative effects with no clinical or scientific merit.³ The movie production of, “Reefer Madness” discredits marijuana’s therapeutic properties, while persuading families to warn their children about its use and implying devastating psychoactive behaviors that would lead to societal chaos.⁵ Following the Marijuana Stamp Tax Act in 1937, the use of cannabis was criminalized by the government with no scientific data that discredited cannabis as a therapeutic agent.² Moreover, the American Medical Association’s objection to the criminalization of cannabis was not recognized.² Before 1937, cannabis was part of more than 2000 different pharmaceutical products prescribed by physicians and dispensed in drug stores throughout the United States including preparations intended for neuralgia.⁶ In 1942, after 88 years of therapeutically treating patients, cannabis was removed from the U.S. Dispensary list and deemed to have no therapeutic implications.³ Despite removal from the U.S. Dispensary, cannabis has been widely used as an alternative therapeutic adjunct in the treatment of chronic pain through personal choice despite its illegal status.

In 1970, the Food & Drug Administration (FDA) passed the Controlled Substance Act which labeled cannabis with Schedule I Status stating no therapeutic value.⁴ Although, to overturn this directive, chairman of the National Commission on Marijuana and Drug Abuse, Raymond P. Shafer implored that cannabis be re-legalized regarding misconceptions of the intangible therapeutic benefits cannabis exhibits, only to be ignored.² Unbeknownst to the general public, marijuana and its derivatives have been prescribed by the government for three decades with the only approved route of administration considered to be smoking cannabis cigarettes grown by the U.S. government.² Through the Compassionate Care Act, participants have been able to receive government marijuana cigarettes to successfully treat unmanageable chronic pain; therefore the validity of cannabis to hold no therapeutic value is erroneous.² In 1980, the Compassionate Care Act was enacted to allow the government bodies to issue medical cannabis to patients with unrelieved and chronic pain. While embracing current research and understanding the factual therapeutic implications surrounding the drug, new methods of chronic pain management can reduce opioid overdose mortalities.
Regardless of government led treatments utilizing cannabis, reversal of its drug status remains stagnant. Political and societal agendas against cannabis have become accepted and the impact of twentieth century biased propaganda is still evident today with conservative generational negative perceptions; despite an extensive history of therapeutic values. In 1964, Israeli scientists, Raphael Mechoulam and Gaoni identified Tetrahydrocannabinol (THC) as a primary psychoactive ingredient of cannabis at the Hebrew University of Jerusalem and they identified preferential binding at cortical receptors throughout the brain. In the late 1980s and early 1990s, the presence of two G-protein coupled receptors (GPCRs) named Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) were identified, thus providing physiologic significance to cannabis. To further solidify cannabinoid receptor potential, the endogenous ligand Arachidonic Acid-derived mediators, Anandamide (AEA) and 2-arachidonogyl-glycerol (2-AG) were identified in the early 1990s and deemed in 1995 as Endocannabinoids. Thus, AEA and 2-AG were found to modulate CB1 and CB2 sites respectively with small degrees ligand variability upon each receptor to decrease nocioception.

**Methodology**

*Evidence-based Practice Model*

The PICOT format was used to formulate a clinical question that would guide the search criteria. In chronic pain management patients (P), how does medical cannabis alone (I) and in conjunction with opioids (C), attenuate pain (O), throughout chronic pain management (T).

**Purpose**

The intent of this literature review is to provide evidence related to the use of cannabis. Alternative approaches to safely treat chronic pain warrants substantial recognition by practitioners and legislative bodies.

**Search Terms**

Marijuana, cannabinoids, medical, chronic pain, opioids

**Search Models**


**Levels of Evidence**

Results of a Randomized, double-blind, placebo-controlled, crossover design study, a Multicenter, open-label, follow-on study, and a Phase 1a study advocated for therapeutic management of pain through the Endocannabinoid System with cannabis.

**Literature Review**

To evaluate the efficacy of cannabis as an adjunct to the treatment of Chronic Neuropathic Pain, Wilsey and colleagues evaluated cannabis dosing utilizing vaporized cannabis, Eissenberg calculated efficacy of THC metered dosed inhaler, and Hoggart and associates examined a sublingual spray. Two studies evaluated cannabis dosing utilizing vaporized cannabis, THC
metered dosed inhaler, and one implemented a sublingual spray. These trials enrolled male and female participants 18 years of age and older composed of heterogeneous collection of chronic pain conditions including causalgia, diabetic neuropathy, idiopathic peripheral neuropathy, post-herpetic neuralgia, brachial plexopathy, lumbosacral radiculopathy, central neuropathic pain, multiple sclerosis, thalamic pain, complex regional pain syndrome, lumbosacral radiculopathy, pelvic neuropathic pain, pain related to spinal cord injury, post-herpetic neuralgia, and diabetic neuropathy.

In a study conducted by Wilsey and colleagues, the administration of low and medium dose vaporized cannabis was evaluated for its efficacy in neuropathic pain reduction while avoiding cognitive and psychomotor effects. As a result, 21 of 37 (57%) study subjects (95% CI: 41-71%) exposed to low dose vaporized cannabis demonstrated reduction in pain intensity compared to 22 of 36 participants (61%) of participants exposed to medium dose vaporized cannabis (95% CI: 45-75%); however, better tolerance to cognitive and psychomotor effects were noted in low dose cannabis with effective cumulative dosing. Through a similar trial performed by Eisenberg and colleagues, a portable metered-dose THC inhaler was utilized to mitigate chronic neuropathic pain. In this study, inhalation of 3.08% THC by 8 subjects provided 45% reduction of pain intensity. In contrast, Wisley et al demonstrated inhalation of vaporized 10.3 mg THC attributed to a 31% reduction of pain intensity and increasing the dose to 28.2 mg THC produced an equal analgesic response that remained stable, but with a decreased tolerance to side effects.

Utilizing a different method of administration, Hoggart and colleagues establish the efficacy of Tetrahydrocannabinol/Cannabidiol (THC/CBD) sublingual spray for treatment of Chronic Peripheral Neuropathic Pain (CPNP). Of 234 participants with at least 30% reduction in pain provided as clinically significant, 50% displayed cumulative reductions of pain over time, providing evidence to support sustained long-term benefits, safety, and tolerability of continued THC/CBD spray to treat CPNP. Corresponding with similar results, these studies validate the efficacy and tolerance of low dose vaporized cannabis inhalation, THC inhalation device, and oromucosal spray as medicinal methods for cannabis administration for chronic neuropathic pain management.

Confirming through two laboratory rat studies Romero et al and Wilson-Poe, use of cannabinoids decreased the degree of hind paw pressure nociception and promote anti-nociception in the dorsal root ganglion (DRG) respectively. Romero and colleagues established efficacy in peripheral anti-nociceptive, inflammatory, and non-inflammatory effects with endocannabinoids through mechanical hind paw pressure tests. This study demonstrated adrenergic receptor activation of DRG via anandamide and N-palmitoylethanolamine (PEA) inhibition induces hyperpolarization, producing substantial desensitization. With similar results demonstrating attenuation of nociception, Wilson-Poe and associates authenticated systemic concomitant administration of THC enhances the anti-nociceptive effect of morphine through bidirectional mechanisms in ventrolateral periaqueductal grey matter. This evidence suggests cannabinoids enhance anti-nociception and limits neurotoxicity in morphine administration.

Lucas verifies the relationship between the cannabinoid system, endocannabinoid agonists, and neuromodulators in the attenuation of pain through vanilloid receptors with concomitant administration of reduced opioid requirements. Moreover, Lucas validates the ability of
cannabinoid-centered drugs used by 21 patients utilizing smoked cannabis containing THC 9.4% for chronic pain reduced pain and improved sleep. Further reported through Lucas, evidence has demonstrated cannabinoids ability to prevent development of central nervous system depression, tolerance, and withdrawal from opioids via serotonergic agonistic properties increasing serotonin levels while decreasing impulsiveness and cravings. Therefore, an alternative opioid treatment exists for practitioners to safely prescribed cannabis with minimal side effects.

Endocannabinoid System Research
The past three decades has revealed a significant process which cannabinoids function in homeostatic regulation. The Endocannabinoid System (ECS) plays a significant role in physiologic regulation with implications towards modulation of central and peripheral nervous, immune, gastrointestinal, and, cardiovascular systems while modulating the degrees of nocioception. Analgesic sites of action for cannabinoids have been identified at brain, spinal cord, and peripheral levels. Fine and Rosenfeld describes the ECS as an ancient lipid signaling system, modulating neuronal functions, inflammatory processes, and is involved in the etiology of certain human diseases such as crohn’s disease, atherosclerosis, and osteoarthritis in mammals. Moreover, Fine and Rosenfeld theorize the ECS is able to down regulate stress-related signals which produce chronic inflammation.

CB1 distribution has been well established in the brain with high concentrations located in the hippocampus, cortical regions, cerebellum, and the basal ganglia. Moreover, receptors are absent from the brain stem which demonstrates lack of opioid side effects, thus placing cannabinoid-based drugs advantageously over opioid treatments. CB2 receptors serve a beneficial role in immune function and inflammation. Modulations of CB2 receptors produce a decrease in release of pro-inflammatory mediators, which may represent abnormalities in the ECS in chronic pain patients. According to Fine and Rosenfeld, the ECS is intimately involved with tissue healing in the presence of inflammatory conditions, thus displaying significance in prevention and treatment of inflammatory mediated pain.

As a CB ligand, AEA produces effects similar to THC, but at CB1 receptors providing anti-nociceptive effects. Further, Aggarwal and Carter indicate that neurons in the rostroventral medulla and periaqueductal gray substances are involved in the brain-mediated analgesic effects of cannabinoids which provide anti-nociception. As cited in Fine and Rosenfeld, cannabinoids produce additive analgesic efficacy as kappa opioid receptors agonists. Therefore, cannabis may provide a therapeutic synergistic opportunity to improve pain management treatments. Additional studies have demonstrated the function through CB2 receptors in the DRG and spinal cord sensory neurons with nociceptive integration. Reported through Fine and Rosenfeld rodent models demonstrate both systemic and intrathecal administration of CBD suppresses chronic inflammatory and neuropathic pain without the development of tolerance, suggesting that cannabinoids may efficaciously treat chronic pain without increased dosing.

Cannabis Prescribing
Since the classification of cannabis as a Schedule I drug, suggesting it has no therapeutic medical value, a misunderstanding was created of potential medicinal benefits. However, since the 1980s, smoking U.S. government grown cannabis cigarettes has been prescribed to selective individuals through the Compassionate Care Act. Although, concerns remain regarding correct
dosing and possible interactions with other medications. The FDA has not rescheduled cannabis to recognize its medicinal value given a suggested lack of government control.\(^3\) A well-regulated State program can ensure proper quality production of cannabis while eliminating potential contaminants.\(^6\) Standardized quality control medicinal cannabis programs can be established as they have been implemented in Holland, Canada, and Israel without significant adverse effects.\(^2\)

In an analysis of 13 states which have legalized cannabis, patient-hospital contacts related to illicit drug use were reduced after legal risks of cannabis possession decreased.\(^3\) The safety profile of cannabinoids is high with no risk of overdose death and no end-organ damage that requires routine laboratory monitoring.\(^5\) Cannabis has no known lethal dose and if implemented in chronic pain treatments, thousands of opioid related deaths could be prevented.\(^2\) Furthermore, there is limited ability to develop tolerance to cannabis and the safety profile of cannabinoids remains a persuasive strength to augment research despite federal limitations.\(^2\)

Available research data indicates most patients can receive therapeutic dosing of 5 grams per day with minimum adverse effects while decreasing pain effectively.\(^2\) When used in conjunction with opiates, cannabinoids can lead to a greater cumulative relief of pain that may result in a reduction of opiate consumption while reducing adverse effects.\(^3\) According to Fine and Rosenfeld,\(^4\) preclinical and clinical data indicates cannabinoids administered together are more effective at ameliorating neuropathic pain than the use of single agent alone. While not reported as a panacea, the use of cannabis as an analgesic agent as any other medication must be based on clinical judgment. Pain management practitioners should become informed about the most current literature, clinical guidelines, and embrace scientific process that continues to document therapeutic effects of cannabis. By utilizing science and current evidence rather than societal and political stigma, alternative advancements in treating chronic pain can be made available.

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<th>Articles</th>
<th>Description and Study Design</th>
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<tr>
<td>Wilsey et al. (2013)</td>
<td>Randomized, double-blind, placebo-controlled, crossover design study utilizing low-dose vaporized cannabis in the treatment of neuropathic pain. Objective was to formulate adequacy of pain attenuation at medium (3.53% THC) to low-dose (1.29% THC) cannabis while attenuating adverse cognitive and psychoactive effects of cannabis.</td>
<td>21 of 37 (57%) of participants exposed to low dose (95% CI: 41-71%) vaporized cannabis demonstrated reduction in pain intensity in contrast to 22 of 36 (61%) of participants utilizing medium dose vaporized cannabis (95% CI: 45-75%); however, better tolerance to cognitive and psychomotor effects were noted in low dose cannabis with effective cumulative dosing.</td>
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<td>Eisenberg et al. (2014)</td>
<td>Phase 1a study, a portable cannabis metered-dose THC inhaler was utilized to mitigate Chronic Neuropathic Pain. Objective of this study was to explore the pharmacokinetics, safety, tolerability, efficacy, and ease of use of a novel portable thermal-metered-dose inhaler.</td>
<td>Inhalation of 3.08% THC utilized by 8 subjects provided 45% reduction of pain intensity. In contrast, inhalation of vaporized 10.3 mg THC attributed to a 31% reduction of pain intensity and increasing the dose to 28.2 mg THC produced an equal analgesic response that remained</td>
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<td>Study</td>
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<td>Hoggart et al. (2015)</td>
<td>Multicenter, open-label, follow-on study to assess the long-term efficacy, tolerance and safety of THC/CBD oromucosal spray in the management of Chronic Peripheral Neuropathic Pain.</td>
<td>234 participants with at least 30% reduction in pain provided as clinically significant, subjects displayed 50% cumulative improvements in pain with time. Study provided evidence to support sustain long-term benefit, safety, and tolerability of continued THC/CBD spray utilized to treat Peripheral Neuropathic Pain.</td>
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<td>Romero et al. (2013)</td>
<td>To determine whether the CB1 and CB2 agonists anandamide and N-palmitoyl-ethanolamine (PEA), respectively, induce peripheral anti-nociception in male Sprague-Dawley rats.</td>
<td>Study established efficacy in peripheral antinociceptive, inflammatory, and non-inflammatory effects with endocannabinoids AEA and PEA through mechanical pressure tests. The activation of adrenergic receptors inhibits excitation of the DRG through the activation of alpha1 and beta adrenoceptors which induces hyperpolarization with desensitization of the DRG with concomitant administration of morphine and cannabinoids.</td>
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<tr>
<td>Wilson-Poe et al. (2013)</td>
<td>Objective of trial was to establish association between anti-nociception in the periaqueductal gray matter between morphine and cannabinoid synergism utilizing male Wistar rats.</td>
<td>Systemic administration of THC enhances the anti-nociceptive effect of morphine through bidirectional mechanisms in ventrolateral periaqueductal grey matter. Evidence suggests cannabinoids enhance anti-nociception and limits neurotoxicity in morphine administration. Data indicates combined opioid/cannabinoid therapy can be efficacious in patients already undergoing opioid therapy.</td>
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**Conclusion**

Cannabinoids have been exemplified through research that cannabis is significantly safer than opioids with extensive applicability in chronic pain management. If cannabis was not removed from the U.S. Pharmacopeia, it may have spared thousands of lives lost to opioid toxicity. Thus, the U.S. Drug Enforcement Administration may consider implementation of scientific evidence.
to provide rationale and legitimacy to current regulations surrounding cannabis’s current Schedule I Status. The ECS efficacy has been demonstrated over many studies which validate the importance of cannabinoid lipid-based signaling systems and demonstrates significant potential towards alleviation of pain. In spite of a large body of political objection against medical cannabis, the need for alternative multi-targeted approaches to address intractable chronic pain is essential. The greatest harm of cannabis is based on its illegal status with associated stigma which has left therapeutic research at paucity, leaving patients to experience adverse effects of opioids that diminish pain marginally in chronic pain conditions.

Consequently, the known lethal effects of opioids provide a legitimate argument for alternative effective analgesic treatments through medical cannabis to decrease morbidity and mortality. The evidence supports the utilization of cannabis alone and in conjunction with opioids to attenuate chronic pain. Further research will expand current evidence which supports cannabis’s efficacy in chronic pain management.

References

Mentor: Ann Miller, CRNA, DNP

The Pediatric Perioperative Experience with Music Therapy

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Keywords: Pediatric anesthesia, pediatric music therapy, postoperative pain control, analgesia, music therapists, cardiac surgery, induction anxiety, perioperative anxiety

Introduction

Approximately 3 million pediatric patients undergo anesthesia and surgical procedures each year. Fifty to seventy-five percent of children experience extreme anxiety during the perioperative period that can manifest as inappropriate and disruptive behavior, noncompliance, and traumatic events. The goal of the perioperative experience in the pediatric population is to alleviate anxiety, pain, and hemodynamic instability. Traditionally, pharmacological and behavioral interventions have been implemented to control pediatric behavior, pain, and anxiety. In an effort to provide a decreased perception of pain, anxiety, and an increase in safe and effective care, trends involving therapies that avoid pharmacological interventions are currently being addressed. Studies indicate promising results with music therapy in reducing perioperative anxiety and hemodynamic instability. Music therapy modalities such as music therapists are being studied, in addition to specifically examining different types of music which may impact diverse age groups in the perioperative period. Also, research is examining if there are specific age groups that respond more favorably to a certain genre of music.

Purpose

The purpose of this review is to determine the effectiveness of music therapy on pediatric pain, anxiety, and hemodynamic parameters in the perioperative setting. In addition gaps in the literature will be discussed to provide direction for future research.

Music therapy is defined as the utilization of music therapists, personal playlists, instrumentation, and interactive musical modalities to alleviate pain and anxiety in the pediatric population. Music therapy is utilized in the perioperative setting, which includes the preoperative holding period, the intraoperative experience, and postoperative recovery. Additionally, music therapy has been utilized in the immediate critical care setting in specific situations in which the patient is delivered directly to the unit intubated from surgery. The literature supports a wide age range of pediatric patients experiencing music therapy but a specific age group was difficult to analyze due to the lack of literature.
Methodology

Evidence-Based Practice Model
The clinical question was expressed through the use of a PICO statement. In pediatric patients during the perioperative period (P) does the utilization of music therapy (I) compared to no music therapy (C) decrease surgical stress, parental separation anxiety, and utilization of pharmacological agents? (O).

Search Terms
Pediatric anesthesia, pediatric music therapy, postoperative pain control, analgesia, music therapists, cardiac surgery, induction anxiety, perioperative anxiety

Search Models
An electronic database search was conducted utilizing EBSCOHost, PubMed, ELSEVIER, Google Scholar, Cochrane Database and CINAHL. Inclusion criteria were peer-reviewed journals published in English, full-text, and within the last ten years. Populations examined included pediatric patients undergoing outpatient surgical services, inpatient surgical services in addition to hospital stays, and sedation procedures. Healthy ASA I and ASA II patients, male and female, ages ranging from infant to age 18 were included in this review. Patients excluded were those born premature, chronic illness, obesity, and use of continuous medications that prevented the potential impact of music therapy.

The literature review conducted was from the most recent and valid sources including CINAHL, EBSCOhost, Elsevier, PubMed and Sage Journals. The majority of the evidence examined was between the years 2006-2013. However, pediatric music therapy is an area that needs additional study as there is limited literature in this topic, and studies conducted farther than 8 years were reviewed. The broadness of time creates a documentation of data that can be replicated for validity purposes in addition to constructing a foundational literary framework in which to base further studies. Furthermore, it highlights gaps in evidence that may need further investigation and research.

Levels of Evidence
Studies examined and found applicable for analysis were appraised for their level of evidence based on its design. Randomized control trials by the rank of I were analyzed according to levels of evidence, Rank II being non-randomized control trials, experimental designs such as correlational or comparative studies qualifies as a rank III, and opinion pieces as being rank of IV. Six randomized control trials were addressed to include the following: one literature review, one cross-sectional design, one feasibility study, and one dissertation were analyzed.

Literature Review

Pediatric Hemodynamic Parameters
Music therapy has been linked to positive outcomes for surgical patients acting on autonomic function stimulating the pituitary gland, endorphin release, and facilitating a biological reduction in the amount of catecholamines. The effects of music on cardiac hemodynamic parameters were examined immediately after cardiac surgery in pediatric patients. Hemodynamic stability
Cardiac surgery increases hemodynamic instability due to the invasiveness, length of surgery, risk of infection, and complexity. An estimated 70-80% of pediatric patients entering the ICU following surgery experience elevated anxiety levels in conjunction with physical stress on their already compromised body. Pediatric physiological stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. Cortisol is released as a response from the HPA axis to compensate for changing cardiovascular and inflammatory responses. The study assessed 79 pediatric patients undergoing cardiac surgery, where classical music was played for 30 minutes and vital signs including heart rate, SpO2, systolic and diastolic blood pressure, mean blood pressure, temperature, and respiratory rate, were recorded immediately prior and immediately after the music therapy. Hemodynamic parameters were significantly altered with music therapy, with a reduction in heart rate ($P=0.04$) and respiration rate ($P=0.02$).

Calcaterra et al examined physiological changes in the pediatric patient in outpatient surgeries. Calcaterra et al found that pediatric patients respond to music therapy physiologically even in the absence of conscious reaction. A rise in glucose is linked to stress-induced hyperglycemia, which is a temporary condition that is caused by insulin resistance and up regulated hepatic gluconeogenesis. Stress-induced hyperglycemia also causes an increased susceptibility to infection. A difference was noted in rises in serum glucose ($P<0.001$) with the music group’s levels plateauing as compared to the non-music group, whose levels consistently rose during the postoperative period. Sympathetic nervous system responses were lowered by a decrease in both systolic and diastolic blood pressure in the music group during anesthesia emergence as compared to the non-music group ($P=0.09$, and $P=0.003$). Also noted was a reduction in sweat gland activity, skeletal muscle tension, and gastric acidity in the postoperative period following outpatient day surgery with pediatric patients.

Behavioral distress can be indicative of the patient acting out through behaviors such as facial affect, level of engagement, eye contact, and level of participation in the perioperative setting. The hospital experience can be a terrifying place for a child and can cause disruption between a child’s psychological ability to cope as indicated by altered vital signs such as heart rate, blood pressure and decreased oxygen saturation. These hemodynamic changes indicate that a child is undergoing a stress-induced physiological response in the perioperative period in which music therapy could have positive outcomes. Music therapy can also create a cooperative and positively engaged child in addition to positive hemodynamic changes.

**Music Genres**

The genre of music and the impact music has on pediatric neuroendocrine and sympathetic responses have also been examined. Calcaterra et al applied three different types of music, including baroque, romantic, and classical to determine what differences the music selection made in the pediatric population. A music genre that had an upbeat tempo prompted an arousal effect whereas meditative music such as romantic and classical tended to induce a positive relaxing effect that was calming for pediatric patients. Balan et al utilized Indian classical music to determine if venipuncture was reported to be less stressful than no music and the use of EMLA cream. While music therapy did not prove to be more efficacious than EMLA cream, the
results were comparable and concluded that EMLA cream or music therapy could be utilized for blunting venipuncture pain control. Kain et al. evaluated the use of soft classical music for induction. Results positively correlated with non-stimulating musical types as an appropriate choice for induction.

**Invasive Procedures**

Invasive procedures in the pediatric patient are stress inducing and can often be a traumatic experience. Noguchi examined the relationship between child anxiety and invasive procedures which were previously based on observational methods and not from a tool the child could utilize to self-report their level of anxiety or pain. Therefore, Noguchi utilized traditional methods of observation and an Observational Scale of Behavioral Distress (OSBD) tool in which the pediatric patient could indicate if their anxiety was altered. Musical stories were presented during painful injection and interactively played with the child to alleviate anxiety. Pediatric patients reported less pain on injection during the music interaction (SD 2.79) as compared to no music (SD 2.55). The study also utilized The Observational Scale of Behavioral Distress, which was reported to have lower anxiety outcomes than the control group who had no music. Children who received 4-6 vaccines reported less pain when listening to music than the control group who received 4-6 vaccines.

**The Use of Music Therapists**

Kain et al. explained that music therapists who utilized singing familiar songs with the pediatric patient, for example, singing the “Wheels on the Bus,” allowed the pediatric patient to feel a higher sense of control, familiarity, and acceptance of surgery. Music therapists also encouraged interactive music expression to decrease the anxiety level the child is feeling and physical release through the use of hand motions and utilizing instruments.

Kain et al. stated a high level of importance of how the music therapists design their plan to play music. Music therapist’s purpose is to plan receptive music listening, improvisation and song writing to alter a patient’s mood. Kain et al. implemented the utilization of two music therapists with the same training and showed two different musical styles. One therapist who utilized a specific musical style had greater success with separation anxiety from parents then the music therapist who utilized a different musical style, with a ($P=0.025$). The results signify the therapist technique is just as important as having a therapist present.

Music therapists provide essential distraction techniques which allow the patient to have a positive experience and help orient the child to the evolving surroundings of the perioperative suite. The music therapists are able to gauge the child’s anxiety level, state of awareness, understand past medical procedures, and integrate those factors into a custom plan to alleviate anxiety.

Increased perioperative anxiety results in increased analgesic requirements and delayed discharges. Providing the therapist utilize proper therapeutic techniques that correlate to the children’s psychological and cognitive development, children experienced much less postoperative psychological discomfort, resulting in decreased hospital stays and higher satisfaction rates.
Induction
Mask induction has proved to be the most anxiety producing time for the pediatric patient. Studies examined different modalities that reduce pediatric anxiety and facilitate positive coping mechanisms throughout the perioperative period. Kain et al. evaluated the role of the anesthesiologist working with the child exclusively in combination with soft classical background music. The environment was dimmed and quiet for induction. Pediatric patients that received these interventions were significantly less anxious ($P=0.03$) than the control group. Additionally, compliance upon entering the OR and anesthesia mask induction was as much higher than the control group ($P=0.000$ versus $P=0.003$).

The Effects of Music on Postoperative Pain
Calcaterra et al. examined the effects of music on postoperative pain by the pain gate control theory. In this theory, music alters pain pathways in the pediatric patient and therefore their perception of pain. Pain is influenced by the perceived level of control, the perception, and the emotional state of the patient. Non-pharmacological methods need to be utilized to aid in the treatment of postoperative pain.

Music also acts as a distracting tool. According to Bradt, there is a tendency to underutilize pain medication administration in pediatric patients postoperatively. A music therapist worked with children ages 8-19 recovering from orthopedic surgery created resonance between live music equaling the child’s pain. Results positively correlated music therapy and a reduction in pain intensity which lasted after the music was discontinued. Music also enhanced the pediatric patients’ feeling of wellbeing and control in the second music session ($P=0.005$).

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<th>Articles</th>
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<th>Results/Conclusion</th>
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<tr>
<td>Hatem, Lira, Mattos, (2006)</td>
<td>In this randomized control trial, classical music was played for 30 minutes. Vital signs including heart rate, systolic and diastolic blood pressure, mean blood pressure, respiratory rate, temperature and SpO2, were recorded immediately prior and immediately post music therapy.</td>
<td>Statistically significant results were noted when utilizing the facial pain scale, and the objective parameters HR and RR ($P&lt;0.001$, $P=0.04$, $P=0.02$)</td>
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<tr>
<td>Calcaterra, Ostuni, Bonomelli, Mencherini, Brunero, Zambaita, , , Pelizzo, (2014)</td>
<td>The randomized control trial examined how specific music therapies impacted pediatrics postoperatively through random assignment to a control group or intervention group in pediatric day care surgery</td>
<td>Physiologically, a difference in serum glucose ($P&lt;0.001$) with the music group’s levels plateauing and as compared to the non-music group, whose levels consistently rose during the postoperative period. Diastolic and systolic BP decreased, along with glucose, gastric acidity</td>
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<td>Balan, Bavdekar, and Jadhav, (2009)</td>
<td>In this randomized control trial pediatric patients undergoing venipuncture were randomly assigned to a local</td>
<td>Both modalities alleviated pain on insertion and both can be utilized with equal validity and trust of effectiveness.</td>
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anesthetic group or a music therapy group to determine if music therapy proved to have better pain control benefits than the local anesthetic

| Kain, Caldwell-Andrews, Krivutza, Weinberg, Gaal, Wang, and Mayes (2004)¹ | This randomized control trial utilized music therapists and how they interact with the pediatric population in the perioperative period, in which anxiety levels were measured at specific stages. | The use of a music therapists did significantly help in areas of (a) holding area and (b) OR entrance, but not (c) mask induction or (d) until anesthesia adequately induced. Music therapist allowed the child to feel in control of their situation. |

**Conclusions**

The research validates music therapy decreases sympathetic responses to pain and stimulation, alleviates fear, anxiety, and provides an alternative to pharmacological interventions. Music therapy programs implemented nationally could ensure quality of care by consistently decreasing pediatric anxiety and benchmarking a standardized national expectation to the public. Music therapy programs also increase safety standards by increasing pediatric compliance with bedside procedures and creates a cost effective, safe environment by decreasing pharmacological administration and interventions.

Gaps in the literature point towards a generalized study trend in which ranges of age are examined with broad musical types. Additional research can address establishing relevancy between age groups and specific types of music. An increased knowledge of how music affects different age groups could serve hospital systems desiring to implement music therapy across the country. An increase in research would also further validate and prove the effectiveness of music therapy and the pediatric perioperative environment for safe quality care.

**References**

Cannabis Therapy in Patients with Rheumatoid Disease

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Keywords: cannabis, neuropathic, pain, inflammatory, rheumatoid

Introduction

Historically, many neurological diseases were classified as autoimmune or inflammatory. Multiple sclerosis was viewed as a neuroinflammatory disease which affects the central nervous system. It is theorized multiple sclerosis has an autoimmune component that leads to neurodegeneration in addition to the inflammation process.¹ The neuro-autoimmune mediated degradation occurs at the axons of the central nervous system’s nerves; the axons are demyelinated.² Along with inflammation, the demyelination leads to the signs and symptoms of multiple sclerosis. There is a multitude of empirical evidence supporting cannabis for the treatment of chronic pain caused by inflammatory pathways, autoimmune processes, or neurodegeneration. Current research has focused on the symptoms of multiple sclerosis and treatment with cannabis therapy.¹,² At the turn of the century, the National Academies Institute of Medicine reported the prevalence of multiple sclerosis as 1 in 1,000 in the United States.² The prevalence of multiple sclerosis suggests there are over 400,000 Americans with the disease.

The variability of symptoms associated with multiple sclerosis leads to treatment with a variety of modalities. Multimodal pharmacological treatment of rheumatoid diseases includes steroids, benzodiazepines, muscle relaxants, tranquilizers, anti-depressants, narcotics, non-steroidal anti-inflammatoryatories, and immune system suppressants.³ Initial disease symptoms may at first present as mild or vague and fail to be properly diagnosed: cognitive impairment, difficulty concentrating, inattention, or poor memory.⁴ Other common symptoms include color blindness, double or blurry vision, and muscle weakness; symptoms may progress to tremors, uncoordinated movements, balance problems, or trouble walking.⁴ Treatment of multiple...
sclerosis’ symptoms, especially muscle spasticity, are limited by medication side-effects. Serpell et al cited that the treatments of multiple sclerosis are not regularly effective across the patient population.

The illegal use of cannabis to self-treat multiple sclerosis and other rheumatoid diseases has been in use by 10-15% of patients for decades. A study by Stuchiner et al found multiple sclerosis patients who reported higher scores on the Patient Determined Disease Steps and more disabling symptoms on the Multiple Sclerosis Impact Scale were statistically more likely to use cannabis, as evidenced by $P<0.001$. The reported severe symptoms include fatigue, numbness, tingling, pain, heat sensitivity, and muscle spasms. The study shows patients with severe multiple sclerosis symptoms were more disabled and their quality of life more negatively impacted than non-cannabis users. This symptomatology is substantiated by Serpell et al who reports that half of multiple sclerosis patients suffer from spasticity or its associated symptoms.

Other chronic diseases associated with inflammation or neurodegeneration may also benefit from cannabis therapy; chronic inflammation, deep pain associated with cancer or sciatica, and neuropathy pain due to insulin-dependent diabetes mellitus. Rossi et al suggested the cannabinoid receptors have an effect on and regulate the immune and nervous systems. Cannabinoid receptors effect neuronal transmission and change immune cell activity during inflammation. Within the spinal cord, glial cell activity and stimulation have been shown to be affected by cannabis with a subsequent decrease of cytokines: interleukin-1beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).

**Methodology**

The PICO format was utilized to focus the literature search and refine the topic of clinical significance. In patients afflicted by chronic pain due to a rheumatoid disease (P), how does the utilization of cannabis or cannabidiol (I), compared to non-treatment (C), provide symptomatic relief and contribute to decreased pain levels, spasticity, and insomnia. (O).

Multiple online electronic databases were investigated for the current literature. Databases searched included Pubmed, DynaMed, ScienceDirect, and Cochrane Library, with the keywords: “cannabis, neuropathic, pain, inflammatory, rheumatoid, and disease.” Synonyms, boolean operators, and mixed combinations of the keywords were utilized to expand or reduce the number of article results. Variations of the keywords were employed. Initial inclusion criteria was restricted to English language, online peer-reviewed articles from 2010 to 2015. Articles relating to human trials and animal models were included. Through the use of reference pages in two article reviews, additional primary source articles were obtained.

After analysis of the search results, primary source articles used in the literature review included three randomized controlled trials with consenting human participants and nine studies in animal models. The twelve articles were based on the Joanna Briggs Institute of Evidence and Grades of Recommendation and were the highest levels of empirical evidence retrieved during the literature search. The animal models were level III, non-randomized, case-controlled studies. The studies included level II human studies, randomized control trials, which have the least amount
of bias in the hierarchy of evidence. All three human trials found statistically significant results in comparison to placebo.

**Literature Review**

**Efficacy**

The efficacy of cannabis and cannabinoid receptor agonists in relation to pain and symptom alleviation in various disease settings is progressing. The two researched outcomes were pain relief and the mitigation of disabling symptoms of rheumatoid diseases, specifically, multiple sclerosis. Nine of the reviewed articles compared cannabis treatment to a control group.\(^2,^3,^5-^11\) Spasticity related to multiple sclerosis was evaluated in three research articles.\(^2,^8,^12\)

Corey-Bloom et al\(^8\), Serpell et al\(^2\) and Ware et al\(^3\) evaluated the response of treatment resistant neuropathic pain to cannabis treatment in humans.\(^2\) Ware et al studied multiple concentrations of tetrahydrocannabinol (THC) in smoked cannabis and found 9.4% THC decreased the average pain scores significantly as compared to placebo or other less concentrated THC doses.\(^3\) Corey-Bloom et al\(^8\) studied pain resistant to conventional treatment with opioids and found a positive correlation between cannabis and pain relief. According to Corey-Bloom et al\(^8\), participants who smoked cannabis with 4% THC reported an average decrease in pain scores of 2.74 (\(P < 0.001\)) compared to placebo; observational pain decreased on average of 5.28 (\(P = 0.008\)) more than placebo when evaluated by researchers. Continuous use of oral cannabis therapy for intractable neuropathic pain compared to placebo was reported as efficacious in an ongoing study for two years.\(^2\)

Two randomized controlled trials and one animal model evaluated the efficacy of cannabis treatment versus placebo in regards to symptomatic reduction of spasticity.\(^2,^8,^12\) Corey-Bloom et al\(^8\) concluded smoked cannabis with 4% THC reduced patient treatment-resistant spasticity when compared to placebo. Serpell et al\(^2\) evaluated a current pharmaceutical, Sativex, which contains THC and cannabidiol, which was found to be superior over placebo.\(^2\) De Lago et al\(^12\) conducted research in an animal model that evaluated multiple sclerosis symptoms; cannabis significantly improved (\(P < 0.0001\)) motor coordination and neurological disability.

Two research studies reported specifically on participants’ quality of sleep and ease of sleep.\(^2,^3\) Ware et al\(^3\) reported participants fell asleep with more ease, quickly, and had less interruptions in their sleep than those taking a placebo, as evidenced by \(P < 0.05\).\(^3\) In the second study reviewed, rates of uninterrupted sleep increased and participants experienced an increase in self-rated sleep quality 59% of the time.\(^2\) In addition to treating spasticity in multiple sclerosis or assisting in sleep quality, research has evaluated the associated inflammatory pathways.

Inflammatory pathways have an effect on rheumatoid disease states. Animal trials have expanded research of cannabis therapy to inflammation and have shown cannabis reduces inflammation.\(^9,10,12\) Jackson et al\(^9\) stated cannabis weakened inflammation mediated by the immune system, decreased hypersensitivity to pain, and had a positive effect on microRNA which attenuated pro-inflammatory pathways. Kozela et al\(^10\) identified certain cytokines with pro-inflammatory activity that are suppressed by cannabinoids: TNF-\(\alpha\), IL-1\(\beta\), IL-2, IL-6, IL-12, and IFN-\(\gamma\). A study by de Lago et al\(^12\) suggested a selective cannabinoid-1 receptor agonist
reduced inflammation in an animal model. The same study showed progression of multiple sclerosis in mice was slowed and the associated disability was reduced.\textsuperscript{12}

In addition to decreasing inflammation, cannabis has been studied for effects on attenuating neurodegeneration in diseases.\textsuperscript{1} Three animal studies focused on induced pain of differing neuropathic etiologies; they showed positive results in the treatment of existing pain and decreasing the progressive development of neuropathic pain.\textsuperscript{5,6,11} In a 2010 study by Toth et al\textsuperscript{5} research looked at cannabinoid receptor agonists in the treatment of diabetic neuropathic pain. A cannabinoid receptor-1 and -2 agonist decreased allodynia and hypersensitivity to heat in comparison to control group.\textsuperscript{5} The authors also projected cannabis therapy could prevent the development of diabetic associated neuropathic pain by preventing microglial cell proliferation.\textsuperscript{5} Gunduz et al\textsuperscript{11} applied the cannabinoid receptor effects on allodynia and hyperalgesia to an animal study for pain related to nerve injury. Chronic neuropathic pain caused by injury, for example, sciatica pain, had a positive response to cannabis therapy as evidenced by a decreased observation of physiologic pain characteristics.\textsuperscript{11} Lastly, an animal study stated cannabis therapy was efficacious in the treatment of osteoarthritis compared to placebo.\textsuperscript{6} In the animal model, Burston et al\textsuperscript{6} found decreased pain behavior by administering a cannabinoid receptor-2 agonist systemically and via spinal.

\textit{Safety}

An efficacious drug or compound has an obligation to be proven safe before human consumption. There were no deleterious effects on vital signs during smoked inhalation administration of cannabis with 4\% THC.\textsuperscript{8} The authors of two randomized controlled trials reported no events where hypotension, hypertension, bradycardia, or tachycardia required medical attention.\textsuperscript{3,8} Ware et al\textsuperscript{3} further reported laboratory blood chemistry values and renal function did not change significantly when compared to placebo.\textsuperscript{3}

Adverse side effects have been documented, however, the most common side effects reported were headache, dizziness, and fatigue.\textsuperscript{2} Ware et al\textsuperscript{3} reported no serious safety concerns or the finding of unexpected side effects from the administration of cannabis in comparison to placebo. Safety concerns by Ware et al\textsuperscript{3} reported three occasions where participants described being “high” or euphoric while smoking 9\% THC three times a day. Over the two-year study by Serpell et al\textsuperscript{2} the frequency of side effects did not increase and tolerance to cannabis therapy did not occur. Burston et al\textsuperscript{6} also reported no effects of tolerance to cannabis were detected in an animal model. The reports of side-effects from cannabis therapy to treat chronic illnesses could potentially be confounded by the associated symptoms of the chronic diseases themselves or polypharmacy therapy already in use by participants.

Corey-Bloom et al\textsuperscript{8} suggested long-term studies to evaluate the efficacy of lower dosed cannabis and associated cognitive side effects. The acute cognitive side effects of cannabis therapy with 4\% THC have been studied; future studies are required to assess the potential long-term effects.\textsuperscript{8} The acute cognitive side effects of cannabis were not detrimental enough to cause harm.\textsuperscript{8} Patients’ cognitive functioning were found to remain within a normal range for the respective age group and level of education, although there was a decrease from baseline.\textsuperscript{8} Coordination and cognitive function were measured by scoring a timed walk; there was no significant
correlation between timed walk scores of patients in the control group or cannabis therapy group.8

<table>
<thead>
<tr>
<th>Articles</th>
<th>Spasticity</th>
<th>Pain</th>
<th>Side-effects</th>
<th>Limitations</th>
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| Serpell, Notcutt, & Collin, 2012² | Sativex over placebo has been demonstrated in patients with intractable peripheral neuropathic pain and spasticity | Sleep quality 59% ‘good’ or ‘very good’; undisturbed sleep increased. | Sativex has enhanced efficacy and tolerability relative to other cannabis preparations. Cannabinoil may modulate s/s ‘dizziness’, ‘fatigue’ and ‘headache common
Neither was long-term Sativex treatment associated with an increasing incidence of AEs. AEs leading to permanent cessation of Sativex developed in 25 patients (14 %). | The tolerability and efficacy data support its continuous use for periods approaching 2 years. -did not develop tolerance to Sativex with long-term treatment. |
<p>| Ware et al., 2010³               | Participants with refractory pain for which conventional therapies had failed. The average daily pain intensity was significantly lower on 9.4% tetrahydrocannabinol cannabis than on placebo. | A total of 248 mild and six moderate adverse events (fall,2 increased pain,1 numbness,1 drowsiness1 and pneumonia1) were reported during the trial. No serious or unexpected adverse events were reported. | Number of participants. Short time period of study. Studies with higher potencies and flexible dosing strategies are needed to explore dose–response effects Clinical studies using inhaled delivery systems, such as vaporizers, are needed. |                                                                                               |
| Toth et al., 2010⁵               | Cannabidiol provided at the onset of diabetes and prior to identified neuropathic pain limited the development of later neuropathic pain and prevented increases in microglial | selective targeting with either CB2 selective agonists may play a role in the prevention of neuropathic pain states if treatment could be delivered at the time of neural injury or disease. |                                                                                                 |                                                                                               |</p>
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<tr>
<th>Study</th>
<th>Methodology</th>
<th>Findings</th>
<th>Implications</th>
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<tr>
<td>Burston et al., 2013&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Animal Study. Level III evidence.</td>
<td>Density, tactile allodynia/thermal hypersensitivity can be ameliorated with CB1 and CB2 receptor agonists</td>
<td>Future human studies may assist in the further assessment of the roles of cannabinoids in chronic pain prevention and alleviation</td>
</tr>
<tr>
<td>Cain et al., 2011&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Animal Study. Level III evidence.</td>
<td>Attenuated the development and maintenance of pain OA behavior, not observe any evidence of tolerance to the effects of repeated systemic administration</td>
<td>Our clinical and preclinical data support the further investigation of the potential of CB2 receptor agonists for the treatment of pain associated with OA, in particular at earlier stages of the disease</td>
</tr>
<tr>
<td>Corey-Bloom et al., 2012&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Human study. Level II evidence.</td>
<td>Smoked cannabis was superior to placebo in symptom and pain reduction in participants with treatment-resistant spasticity. Treatment reduced pain scores on a visual analogue scale by an average of 5.28 points more than placebo (p = 0.008). Stated improved pain control decrease average 2.74 points. p &lt;0.001</td>
<td>Provides the rationale to consider clinical trials for the evaluation of deep pain and the analgesic potential of cannabinoids to treat pain in Sickle Cell Disease. Due to ischemia, reperfusion, and development of neuropathy.</td>
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- density.
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<tr>
<th>Jackson, Nagarkatti, &amp; Nagarkatti, 2014&lt;sup&gt;9&lt;/sup&gt; Animal Study. Level III evidence.</th>
<th>Attenuate cell-mediated inflammation and subsequent hypersensitivity. Seen by footpad swelling, tissue injury, and histopathological cell infiltration. -microRNA that negatively targets proinflammatory pathways associated with autoimmunity, i.e. multiple sclerosis.</th>
<th>range for their age group and level of education</th>
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<tbody>
<tr>
<td>Kozela et al., 2011&lt;sup&gt;10&lt;/sup&gt; Animal Study. Level III evidence.</td>
<td>Cannabidiol, non-psychoactive cannabinoid, ameliorates clinical signs in mice. -slows axonal damage and inflammation at the spinal cord. -decreases proliferation of inflammatory immune cells. Cannabinoids suppress the production of proinflammatory cytokines including TNF-α, IL-1β, IL-2, IL-6, IL-12 and IFN-γ.</td>
<td>No effect on healthy mice spinal cords. No sedation. Approved in mixture with THC for multiple sclerosis pain and spasticity under the drug name Sativex</td>
</tr>
<tr>
<td>Gunduz et al., 2011&lt;sup&gt;11&lt;/sup&gt; Animal Study. Level III evidence.</td>
<td>Cannabinoid agonist, has been shown to exert antiallodynic and antihyperalgesic effect in nerve injury-induced neuropathic pain-chronic neuropathic</td>
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pain due to injury, like sciatica.

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<tr>
<th>de Lago et al., 2012&lt;sup&gt;12&lt;/sup&gt;</th>
<th>reducing neurological disability and improving motor coordination p &lt; 0.0001</th>
<th>A cannabinoid agonist reduced their neurological disability and the progression of the disease. This effect was exerted through the activation of CB1 receptors, which would exert a positive influence in the reduction of inflammatory events</th>
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**Conclusion**

Cannabis therapy and the associated cannabinoid receptor agonists have been evaluated in three randomized, placebo control trials in humans. The human trials in this review are level II in the hierarchy of evidence and represent the highest level of evidence for single studies. A conflict of interest in the study by Serpell et al<sup>2</sup> was disclosed; the funding for the study on Sativex was provided by GW Pharma Ltd through research grants. Each of the three human trials found statistically significant results in favor of cannabis therapy for treatment of chronic neuropathic pain or intractable spasticity.<sup>2,3,8</sup>

The animal trials in this literature review provide strong evidence to support future human trials. One of the animal studies were of level II evidence with statistically significant results in favor of cannabis therapy over placebo.<sup>5</sup> The remaining animal studies in the review were level III evidence, which is indicative of well-conducted controlled studies. Interestingly, upon critical examination of the animal trials, no single gender was used throughout the animal studies.<sup>6,7,9-12</sup>

There were limitations to the human studies; one such limitation was the different routes of cannabis administration. Oral and inhalational routes were utilized. Another mode of administration, vaporization, may present an alternative to smoking for the use of cannabis delivery.<sup>3</sup> Correlations made between the studies may come into question if a consistent mode of administration is not employed.

The inconsistent modes of cannabis administration between studies weakens the research if correlations cannot be made. The most efficacious, safe, and efficient mode of administering cannabis requires further research. In addition to finding the most effective route for cannabis therapy in treating certain disease states, finding the lowest efficacious dose with the fewest side effects or adverse events should be a priority for future human research studies.

Another limitation suggested by researchers was the limited number of cannabinoid receptor agonists evaluated and the respective doses.<sup>5</sup> Toth et al<sup>5</sup> also proposed different agonists and doses which may have different side-effect profiles than those reported in the study. The
limitations stated by Toth et al\textsuperscript{5} may extend to other studies. In order to assess dose titration and patient response to cannabis therapy, short time periods of studies could be extended beyond weeks or months. In addition to extended trials, there would be a benefit to expanding the number of participants for a larger sample size.

The prevention of developing neuropathic pain or neuron degeneration has been determined to improve outcomes for patients with chronic diseases. A study found there is potential for using cannabis as a preventative measure in disease treatment.\textsuperscript{5} Toth et al\textsuperscript{5} advised future human studies could improve upon assessing cannabis therapy and the prevention of neuropathic pain in diabetics.\textsuperscript{5} Burston et al\textsuperscript{6} also proposed further evaluation of early cannabinoid-2 receptor therapy for the treatment of osteoarthritis.

The empirical evidence supports cannabis for the treatment of chronic pain caused by inflammatory pathways, autoimmune processes, or neurodegeneration. Animal studies have played a key role in evaluating the different mechanisms by which cannabis works. Future long term studies with human participants will forward cannabis research for patients with rheumatoid disease, neuropathic pain and autoimmune processes for safe, quality and effective pain management.

References


**Mentor:** Ann Miller, CRNA, DNP

**Editorial**

*The following is a guest editorial from Julie A. Pearson, CRNA, PhD, who has served as Associate Editor for the ISJNA since its inception.*

It is hard to believe that it has been more than 14 years since the inaugural issue of the International Student Journal of Nurse Anesthesia was published. The journal was the brainchild of Ronald Van Nest (founding Editor). While on faculty at Georgetown University Ron utilized case reports as a course requirement in an effort to develop the writing skills of the students. He felt it was wasteful to simply grade the assignments and file them. The assignment consolidated efforts that students put forth to meet both didactic and clinical requirements. The students wrote about a case for which they had provided anesthesia. Students initially wrote a single case report. Eventually an additional case report assignment was added the subsequent semester so the students had the opportunity to improve and utilize the skills they learned writing the first case report. The initial case reports were basic, requiring significant faculty guidance to relate the clinical scenarios, develop a coherent writing style and comply with proper manuscript and reference formatting.

The first step to the journal was when these assignments were collated, copied and distributed to all members of the class. This desk top published journal eventually advanced from the program level to a national level and all nurse anesthesia programs were invited and encouraged to participate. This project was presented to the Dean of the School of Nursing at Georgetown who realized the potential and agreed to fund the publication, including cost of a graphic artist to design the cover, printing, and distribution to all of the nurse anesthesia programs throughout the United States. Two issues were published and distributed the first year. Corporate funding was provided by Baxter Healthcare over the next five years which paid for the printing and distribution.
Increasing inquiries about subscriptions prompted us to explore the possibility of posting the journal on the internet. AANA accommodated this request. Issues beginning with Volume 5, Number 1 from 2006 are available on the AANA website.

Many thanks to those of you who have contributed over the years as authors, mentors, reviewers and editors. A special thanks goes out to Ronald Van Nest for his vision to start this Journal.

Julie A. Pearson, CRNA, PhD

Thank you Julie for your unwavering support of the ISJNA!

Sincerely,

Vicki C. Coopmans, CRNA, PhD
Editor

“The International Student Journal of Nurse Anesthesia is produced exclusively for publishing the work of nurse anesthesia students. It is intended to be basic and introductory in its content. Its goal is to introduce the student to the world of writing for publication; to improve the practice of nurse anesthesia and the safety of the patients entrusted to our care.”

To access prior issues of the ISJNA visit the following link: www.aana.com/studentjournal
MISSION STATEMENT
The International Student Journal of Nurse Anesthesia is produced exclusively for publishing the work of nurse anesthesia students. It is intended to be basic and introductory in its content. Its goal is to introduce the student to the world of writing for publication; to improve the practice of nurse anesthesia and the safety of the patients entrusted to our care.

ITEMS ACCEPTED FOR PUBLICATION
Case reports, research abstracts, evidence-based practice (EBP) analysis reports, and letters to the editor may be submitted. These items must be authored by a student under the guidance of an anesthesia practitioner mentor (CRNA or physician). The mentor must submit the item for the student and serve as the contact person during the review process. Items submitted to this journal should not be under consideration with another journal. We encourage authors and mentors to critically evaluate the topic and the quality of the writing. If the topic and the written presentation are beyond the introductory publication level we strongly suggest that the article be submitted to a more prestigious publication such as the AANA Journal.

ITEM PREPARATION & SUBMISSION
Student authors prepare case reports, abstracts, EBP analysis reports, and letters to the editor with the guidance of a mentor. Only students may be authors. Case and EBP analysis reports must be single-authored. Abstracts may have multiple authors. Mentors should take an active role in reviewing the item to ensure appropriate content, writing style, and format prior to submission.

The original intent of this journal was to publish items while the author is still a student. In order to consistently meet this goal, all submissions must be received by the editor at least 3 months prior to the author’s date of graduation.

PEER REVIEW
Items submitted for publication are initially reviewed by the editor. Items may be rejected, or returned to the mentor with instructions for the author to revise and resubmit prior to initiation of the formal review process. All accepted submissions undergo a formal process of blind review by at least two ISJNA reviewers. After review, items may be accepted without revision, accepted with revision, or rejected with comments.

General guidelines
1. Items for publication must adhere to the American Medical Association Manual of Style (AMA, the same guide utilized by the AANA Journal and such prominent textbooks as Nurse Anesthesia by Nagelhout and Plaus). The review process will not be initiated on reports submitted with incorrect formatting and will be returned to the mentor for revision. Please note the following:
   a. Use of abbreviations is detailed in Section 14. Spell out acronyms/initialisms when first used. If you are using the phrase once, do not list the acronym/initialism at all.
   b. Instructions regarding units of measure can be found in Section 18. In most cases The International System of Units (SI) is used. Abbreviations for units of measure do not need to be spelled out with first use. Some examples: height/length should be reported in cm, weight in kg, temperature in °C, pressure in mm Hg or cm H₂O.
   c. In general, first use of pulmonary/respiratory abbreviations should be expanded, with the following exceptions: O₂, CO₂, PCO₂, PaCO₂, PO₂, PaO₂. Please use SpO₂ for oxygen saturation as measured by pulse oximetry.
   d. Use the nonproprietary (generic) name of drugs - avoid proprietary (brand) names. Type generic names in lowercase. When discussing dosages state the name of the drug, then the dosage (midazolam 2 mg).
   e. Use of descriptive terms for equipment and devices is preferred. If the use of a proprietary name is necessary (for clarity, or if more than one type is being discussed), give the name followed by the manufacturer and location in parenthesis:
      “A GlideScope (Verathon Inc., Bothell, WA) was used to . . . .”

Please note, TM and ® symbols are not used per the AMA manual.
2. Report appropriate infusion rates and gas flow rates:
   a. When reporting infusion rates report them as mcg/kg/min or mg/kg/min. In some cases it may be appropriate to report dose or quantity/hr (i.e., insulin, hyperalimentation). If a mixture of drugs is being infused give the concentration of each drug and report the infusion rate in mL/min.
   b. Keep the gas laws in mind when reporting flow rates. Report the liter flows of oxygen and nitrous oxide and the percent of the volatile agent added to the gas mixture. Statements such as “40% oxygen, 60% nitrous oxide and 3% sevoflurane” do not = 100% and are thus incorrect. For example, “General anesthesia was maintained with sevoflurane 3% inspired concentration in a mixture of oxygen 1 L/min and air 1 L/min”.

3. Only Microsoft Word file formats will be accepted with the following criteria:
   a. Font - 12 point, Times New Roman
   b. Single-spacing (except where indicated), paragraphs separated with a double space (do not indent)
   c. One-inch margins
   d. Place one space after the last punctuation of sentences. End the sentence with the period before placing the superscript number for the reference.
   e. Do not use columns, bolds (except where indicated), or unconventional lettering styles or fonts.
   f. Do not use endnote/footnote formats.

4. Do not use Endnotes or similar referencing software. Please remove all hyperlinks within the text.

5. Avoid jargon.
   a. “The patient was reversed’ - Did you physically turn the patient around and point him in the opposite direction? “Neuromuscular blockade was antagonized.”
   b. The patient was put on oxygen. "Oxygen was administered by face mask."
   c. The patient was intubated and put on a ventilator. “The trachea was intubated and respiration was controlled by a mechanical ventilator.
   d. The patient had been on Motrin for three days. “The patient had taken ibuprofen for three days.”
   e. Avoid the term “MAC” when referring to a sedation technique - the term sedation (light, moderate, heavy, unconscious) sedation may be used. Since all anesthesia administration is monitored, the editors prefer to use specific pharmacology terminology rather than reimbursement terminology.

6. Use the words “anesthesia professionals” or “anesthesia practitioners” when discussing all persons who administer anesthesia (avoid the reimbursement term “anesthesia providers”).

7. References
   a. Again, the AMA Manual of Style must be adhered to for reference formatting.
   b. All should be within the past 8 years, except for seminal works essential to the topic being presented.
   c. Primary sources are preferred.
   d. All items cited must be from peer-reviewed sources – use of internet sources must be carefully considered in this regard.
   e. Numbering should be positioned at the one-inch margin – text should begin at 1.25”.

8. See each item for additional information.

9. Heading for each item (Case Report, Abstract, EBPA Report) must adhere to the following format:

   Title (bold, centered, 70 characters or less)
   [space]
   Author Name (centered, include academic credentials only)
   Name of Nurse Anesthesia Program (centered)
   [space]
   Anticipated date of graduation (italics, centered, will be removed prior to publication)
   E-mail address (italics, centered, will be removed prior to publication)
   [space, left-justify from this point forward]
   Keywords: (‘Keywords:’ in bold, followed by keywords (normal font) that can be used to identify the report in an internet search.)
**Case Reports**

The student author must have had a significant role in the conduct of the case. The total word count should be between 1200 – 1400 words. References do not count against the word count. Case reports with greater than 1400 words will be returned to the mentor for revision prior to initiation of the review process. The following template demonstrates the required format for case report submission.

**Heading** (see #9 above in General Guidelines)  

A brief introductory paragraph of less than 100 words to focus the reader’s attention. This may include historical background, demographics or epidemiology (with appropriate references) of the problem about to be discussed. It is written in the present tense. Although it is introductory, the heading word ‘Introduction’ is not used. Be certain to cite references in this section, especially statistics and demographics pertaining to your topic.

**Case Report** (bold, 400-500 words)  

This portion discusses the case performed in 400 words or less, and is written in the past tense. Do not justify actions or behaviors in this section; simply report the events as they unfolded. Present the case in an orderly sequence. Some aspects need considerable elaboration and others only a cursory mention.

- Patient description: height, weight, age, gender.
- History of present illness
- Statement of co-existing conditions/diseases
- Mention the current medications, generic names only. (Give dosage and schedule only if that information is pertinent to the consequences of the case.)
- **Significant** laboratory values, x-rays or other diagnostic testing pertinent to the case. Give the units after the values (eg. Mmol/L or mg/dL).
- Physical examination/Pre-anesthesia evaluation - **significant** findings only. Include the ASA Physical Status and Mallampati Classification only if pertinent to the case.
- Anesthetic management (patient preparation, induction, maintenance, emergence, post-operative recovery).

Despite the detail presented here it is only to help the author organize the structure of the report. Under most circumstances if findings/actions are normal or not contributory to the case then they should not be described. Events significant to the focus of the report should be discussed in greater detail. The purpose of the case report is to set the stage (and ‘hook’ the reader) for the real point of your paper which is the discussion and teaching/learning derived from the case.

**Discussion** (bold, 600-800 words)  

Describe the anesthesia implications of the focus of the case report citing current literature. Describe the rationale for your actions and risk/benefits of any options you may have had. This section is not merely a pathophysiology review that can be found in textbooks. *Relate the anesthesia literature with the conduct of your case noting how and why your case was the same or different from what is known in the literature.* Photographs are discouraged unless they are essential to the article. Photos with identifiable persons must have a signed consent by the person photographed forwarded to the editor via first class mail. Diag must have permission from original author. This is the most important part of the article. In terms of space and word count this should be longer than the case presentation. End the discussion with a summary lesson you learned from the case, perhaps what you would do differently if you had it to do over again.

**References** (bold)  

A minimum of 5 references is recommended, with a maximum of 8 allowed. No more than 2 textbooks may be included in the reference list, and all references should be no older than 8 years, except for seminal works essential to the topic. This is also an exercise in evaluating and using current literature.

**Mentor:** (bold, followed by mentor name and credentials in normal text)  

_E-mail address_ (italics, will be removed prior to publication)
Research Abstracts
Research abstracts are limited to 500 words. References are not desired but may be included if considered essential. Note that this abstract is different from a research proposal. This abstract reports the outcome of your study. Use the same format described for the case report with the exception of the section headings:

Heading (see #9 above in General Guidelines)

Introduction (bold)
A brief introductory paragraph including purpose and hypotheses.

Methods (bold)
Include research design and statistical analyses used

Results (bold)
Present results – do not justify or discuss here.

Discussion (bold)
Discuss results

References (bold)
Not required, but a maximum of 5 references is allowed.

Mentor: (bold, followed by mentor name and credentials in normal text)
E-mail address (italics, will be removed prior to publication)

EBP Analysis Reports
Evidence-based practice analysis reports are limited to 3000 words. Please do not include an abstract. The report should provide a critical evaluation of a practice pattern in the form of a clinical question about a specific intervention and population. The manuscript should:

1. Articulate the practice issue and generate a concise question for evidence-based analysis. A focused foreground question following either the PICO or SPICE format should be used.
2. Describe the methods of inquiry used in compiling the data.
3. Critically analyze the quality of research reviewed and applicability to different practice settings.
4. Draw logical conclusions regarding appropriate translation of research into practice.

The same general format guidelines apply with the exception of the section headings as below. Please note that text books and non-peer reviewed internet sources should be avoided, and sources of reference should be less than 8 years old unless they are seminal works specifically related to your topic of inquiry:

Heading (see #9 above in General Guidelines)

Introduction (bold)
Briefly introduce the reader to the practice issue or controversy, describe the scope or significance or problem, and identify the purpose of your analysis. Describe the theoretical, conceptual, or scientific framework that supports your inquiry.
Methodology
Include the format used for formulating the specific question you seek to answer, search terms and methods used, and levels of evidence.

Literature Analysis
Review and critique the pertinent and current literature, determining scientific credibility and limitations of studies reviewed. Your synthesis table would be included in this section. Your review and discussion of the literature should logically lead to support a practice recommendation. Subheadings may be used if desired.

Conclusions
Summarize the salient points that support the practice recommendation and make research-supported recommendations that should improve the practice issue, while also acknowledging any limitations or weaknesses

References
A minimum of 8 references is recommended, with a maximum of 12 allowed.

Letters to the Editor
Students may write letters to the editor topics of interest to other students. Topics may include comments on previously published articles in this journal. Personally offensive, degrading or insulting letters will not be accepted. Suggested alternative approaches to anesthesia management and constructive criticisms are welcome. The length of the letters should not exceed 100 words and must identify the student author and anesthesia program.

AMA MANUAL OF STYLE

The following is brief introduction to the AMA Manual of Style reference format along with some links to basic, helpful guides on the internet. The website for the text is http://www.amamanualofstyle.com/oso/public/index.html. It is likely your institution’s library has a copy on reserve. http://www.docstyles.com/amastat.htm#Top http://healthlinks.washington.edu/hsl/styleguides/ama.html

Journal names should be in italics and abbreviated according to the listing in the PubMed Journals Database. The first URL below provides a tutorial on looking up correct abbreviations for journal titles; the second is a link to the PubMed where you can perform a search. http://www.nlm.nih.gov/bsd/viewlet/search/journal/journal.htm http://www.ncbi.nlm.nih.gov/pubmed

The International Student Journal of Nurse Anesthesia (ISJNA) is not listed in the PubMed Database. For the purpose of citing the ISJNA in this Journal use “Int Student J Nurse Anesth” as the abbreviation. The titles of text books are also printed in italics. Please pay close attention to ensure correct punctuation.

Journals
Note there is a comma after the first initials until the last author, which has a period. If there are six or less authors cite all six. If there are more than six authors cite only the first three followed by “et al.” Only the first word of the title of the article is capitalized. The first letters of the major words of the journal title are capitalized. There is no space between the year, volume number, issue number, and page numbers. If there is no volume or issue number, use the month. If there is an issue number but no volume number use only the issue number (in parentheses). The pages are inclusive - do not omit digits.

Some journals (and books) may be available both as hard copies and online. When referencing a journal that has been accessed online, the DOI (digital object identifier) or PMID (PubMed identification number) should be included (see example below).
Journal, 6 or fewer authors:

Journal, more than 6 authors:

Texts
There is a difference in citing a text with one or more authors from a text with one or more editors. Texts that are edited give credit to the authors of the chapters. They must be annotated and the inclusive pages of the chapter are noted. Texts that are authored do not have different chapter authors, the chapter is not cited by heading but the inclusive pages where the information was found are cited, unless the entire book is cited.

Text:

Chapter from a text:

Each chapter was written by a different author. Note the chapter’s author gets the prominent location. The chapter title is cited; “editor” is abbreviated in a lowercase. The word “edition” is also abbreviated and in lower case. The inclusive pages of the chapter are cited.

Electronic references
Only established, peer-reviewed sources may be referenced. Please do not reference brochures or informational websites where a peer-review process cannot be confirmed. Authors are cautioned to not copy and paste from these without full credit and quotation marks where appropriate. Electronic references are cited using the following format:

Author (or if no author, the name of the organization responsible for the site). Title. Name of journal or website. Year;vol(issue no.):inclusive pages. doi: or URL. Published [date]. Updated [date]. Accessed [date].

For online journals, the accessed date may be the only date available, and in some cases no page numbers.

Examples:


ACADEMIC INTEGRITY
Issues of academic integrity are the primary responsibility of the author and mentor. Accurate and appropriate acknowledgement of sources is expected. Any violation will be cause for rejection of the article.

“Plagiarism is defined as the act of passing off as one's own the ideas, writings, or statements of another. Any act of plagiarism is a serious breach of academic standards, and is considered an offense against the University subject to disciplinary action. Any quotation from another source, whether written, spoken, or electronic, must be bound by quotation marks and properly cited. Any paraphrase (a recapitulation of another source's statement or idea in one's
own words) or summary (a more concise restatement of another's ideas) must be properly cited.”
http://grad.georgetown.edu/pages/reg_7.cfm

HOW TO SUBMIT AN ITEM
Manuscripts must be submitted by the mentor of the student author via e-mail to INTSJNA@aol.com as an attachment. The subject line of the e-mail should be “Submission to Student Journal”. The item should be saved in the following format – two-three word descriptor of the article_author’s last name_school abbreviation_mentor’s last name_date (e.g. PedsPain_Smyth_GU_Pearson_5.19.09)

REVIEW AND PUBLICATION
If the editor does not acknowledge receipt of the item within one week, assume that it was not received and please inquire. Upon receipt, the Editor will review the submission for compliance with the Guide to Authors. If proper format has not been following the item will be returned to the mentor for correction. This is very important as all reviewers serve on a volunteer basis. Their time should be spent ensuring appropriate content, not making format corrections. It is the mentor’s responsibility to ensure formatting guidelines have been followed prior to submission.

Once the item has been accepted for review the Editor will send a blinded copy to a Section Editor, who will then coordinate a blinded review by two reviewers who are not affiliated with the originating program. The reviewers recommend publication to the Section Editor or make recommendations for changes to be addressed by the author. The Section Editor will return the item to the Editor, who will return it to the mentor for appropriate action (revision, approval to print). If the article is returned to the author for repair it is usually to answer a specific question related to the case that was not clear in the narrative or it asks the author to provide a reference for a statement. Every effort is made to place the returned article in the earliest next issue.

The goal is for all articles submitted by students to be published while the author is still a student. Therefore, deadlines must be met and the entire process must be efficient. If an item is not ready for publication within 3 months after the student author has graduated it will no longer be eligible for publication. For this reason it is recommended that case reports be submitted at least 4-6 months prior to the student author’s anticipated graduation date.

Mentors of the papers may be asked to serve as reviewers of case reports by student authors from other prog and will be listed as contributing editors for the issue in which the item is published.

PHOTOS
Photos of students for the front cover of the Journal are welcome. Include a legend describing the activity and who is in the photo and identify the photographer. Only digital photos of high quality will be accepted via email to INTSJNA@aol.com. There must be a follow up hard copy signed by all present in the photo, as well as the photographer/ owner of the original photo, giving consent to publish the photo. Mail that consent to:

Vicki C. Coopmans, CRNA, PhD
Webster University
470 E. Lockwood Ave. Suite 15
St. Louis, MO 63119
SUBMISSION CHECK LIST

___ AMA Manual of Style and other format instructions are adhered to.
___ Total word count not exceeded (1400 for case report, 500 for abstract, 3000 for EBPA).
___ The item is one continuous Word document without artificially created page breaks.
___ Verbatim phrases and sentences are quoted and referenced.
___ All matters that are not common knowledge to the author are referenced.
___ Generic names for drugs and products are used throughout and spelled correctly in lower-case.
___ Units are designated for all dosages, physical findings, and laboratory results.
___ Endnotes, footnotes not used.
___ Jargon is absent.

Heading
___ Concise title less than 70 characters long
___ Author name, credentials, nurse anesthesia program, graduation date and email are included.
___ Five Keywords are provided

Case Report
___ Introduction is less than 100 words.
___ Case Report section states only those facts vital to the account (no opinions or rationale)
___ Case report section is 400-500 words and not longer than the discussion.
___ Discussion section is 600-800 words.
___ Discussion of the case management is based on a review of current literature
___ Discussion concludes with lessons learned and how the case might be better managed in the future.

Abstract
___ The 500 word count maximum is not exceeded.
___ Abstract reports the outcome of your study.
___ Includes Introduction, Methods, Results, and Conclusion sections.

EBPA Report
___ The 3000 word count maximum is not exceeded.
___ A critical evaluation of a practice pattern in the form of a precise clinical question about a specific intervention and population is presented.
___ A focused foreground question following either the PICO or SPICE format is used.
___ Includes Introduction, Methodology, Literature Analysis, and Conclusion sections.

References
___ AMA Style for referencing is used correctly.
___ Reference numbers are sequenced beginning with one and superscripted.
___ References are from anesthesia and other current primary source literature.
___ All inclusive pages are cited, texts as well as journals.
___ Journal titles are abbreviated as they appear in the PubMed Journals Database.
___ Number of references adheres to specific item guidelines.
___ Internet sources are currently accessible, reputable, and peer reviewed.

Transmission
___ The article is sent as an attachment to INTSJNA@AOL.COM
___ The file name is correctly formatted (e.g. PedsPain_Smyth_GU_Pearson_5.19.09)
___ It is submitted by the mentor with cc to the student author
___ The words "Submission to Student Journal" are in the subject heading.