5-25-2019

Prevention of Postoperative Nausea and Vomiting with Subhypnotic Doses of Propofol

Chelsea L. Lingle

Follow this and additional works at: https://commons.und.edu/nurs-capstones

Recommended Citation
https://commons.und.edu/nurs-capstones/191

This Independent Study is brought to you for free and open access by the Department of Nursing at UND Scholarly Commons. It has been accepted for inclusion in Nursing Capstones by an authorized administrator of UND Scholarly Commons. For more information, please contact zeinebyousif@library.und.edu.
PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING WITH SUBHYPNOTIC DOSES OF PROPOFOL

By
Chelsea L. Lingle

Bachelor of Science in Nursing, North Dakota State University, 2015

An Independent Study
Submitted to the Graduate Faculty
of the
University of North Dakota
in partial fulfillment of the requirements
for the degree of
Master of Science

Grand Forks, North Dakota
December 2019
SUBHYPNOTIC DOSES OF PROPOFOL

PERMISSION

Title
Prevention of Postoperative Nausea and Vomiting with Subhypnotic Doses of Propofol

Department
Nursing

Degree
Master of Science

In presenting this independent study in partial fulfillment of the requirements for a graduate degree from the University of North Dakota, I agree that the College of Nursing and Professional Disciplines of this University shall make it freely available for inspection. I further agree that permission for extensive copying or electronic access for scholarly purposes may be granted by the professor who supervised my independent study work or, in her absence, by the chairperson of the department or the dean of the School of Graduate Studies. It is understood that any copying or publication or other use of this independent study or part thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of North Dakota in any scholarly use which may be made of any material in my independent study.

Signature________________________

Date__________________________
Abstract

**Title:** Prevention of Postoperative Nausea and Vomiting with Subhypnotic Doses of Propofol

**Background:** Postoperative nausea and vomiting (PONV) is one of the most common adverse effects of anesthesia. It delays time to discharge and increases post anesthesia care unit (PACU) lengths of stay, ultimately leading to increased patient and hospital costs. In addition to its anesthetic properties, propofol demonstrates antiemetic effects. Total intravenous anesthesia (TIVA) with propofol has become an accepted method to reduce PONV in high-risk patients. More recently, subhypnotic doses of propofol have been administered in combination with inhaled volatile anesthetics to prevent PONV. Current evidence and clinical practice support the administration of subhypnotic doses of propofol to effectively reduce PONV.

**Purpose:** The purpose of this independent project is to present a successful case report in which combined intravenous-volatile anesthesia (CIVA) was used in a case with a patient who was at high-risk for PONV and provide a thorough literature review of evidence-based literature on subhypnotic doses of propofol as a prophylactic treatment for PONV.

**Process:** A thorough literature review was conducted using PubMed and CINAHL databases. The databases were accessed online through the University of North Dakota’s Health Sciences Library. All literature was selected and evaluated extensively based on preset inclusion criteria.

**Results:** The literature review confirmed that CIVA is an effective method to reduce PONV. The evidence shows CIVA reduces PONV as effectively as TIVA. Combined intravenous-volatile anesthesia does not increase time to extubation and has not shown to have hemodynamic implications when compared with other anesthetic methods.

**Implications:** Subhypnotic propofol infusions can be used in combination with inhaled volatile anesthetics to reduce PONV, which can decrease PACU stays, hospital costs, and increase
patient satisfaction. The utilization of both intravenous propofol and inhaled volatile anesthetics yields many benefits discussed in the literature review.

**Keywords:** Postoperative nausea and vomiting, propofol, propofol infusion, subhypnotic propofol, inhaled volatile anesthetics.
Prevention of Postoperative Nausea and Vomiting with Subhypnotic Doses of Propofol

Postoperative nausea and vomiting (PONV) is a common adverse effect experienced with anesthesia. Sources report around one in three patients undergoing general anesthesia experience PONV; this rate increases to eight in ten when the patients are considered high risk (Butterworth, Mackey & Wasnick, 2013; Nagelhout & Elisha, 2018; Sizemore & Grose, 2018; Shaikh, Nagarekha, Hegade, & Marutheesh, 2016). High-risk patients include female gender, young or middle-aged, non-smokers, or individuals with a history of motion sickness (Sizemore & Grose, 2018; Nagelhout & Elisha, 2018; Butterworth et al., 2013; Shaikh, et al., 2016). Certain types of procedures and medications may also increase the risk of PONV. Nitrous oxide, opioids, volatile anesthetics, longer procedural time, abdominal, gynecological, urological, and intracranial procedures have been reported to increase a patient’s risk for PONV (Nagelhout & Elisha, 2018). Postoperative nausea and vomiting can increase the length of hospital stays and expenses for both the patient and hospital. It may also increase post-operative surgical complications in patients who cannot tolerate increased intra-abdominal, intrathoracic, intraocular pressures, or increased blood pressure and heart rate (Nagelhout & Elisha, 2018). For these reasons, it is important to establish the most effective means to decrease the incidence of PONV.

Dipravan, is the common brand name for propofol in the United States. It is a sedative-hypnotic medication used frequently in the induction and maintenance of anesthesia since 1977 (Robinson & Toledo, 2012). Other agents commonly used for induction and maintenance of anesthesia are inhaled volatile anesthetics agents, sevoflurane, desflurane, and isoflurane (Nagelhout & Elisha, 2018; Butterworth, Mackey & Wasnick, 2013). These inhaled anesthetics have been a mainstay of anesthesia for several decades. Both propofol and volatile inhaled
anesthetics offer a rapid onset and speedy recovery from an anesthetic state (Butterworth, Mackey & Wasnick, 2013; Nagelhout & Elisha, 2018).

In the early postoperative period the amount of exposure to volatile anesthetics has been implicated as the primary cause for PONV (Kawano et al., 2014). Opioids have also been linked to postoperative nausea and vomiting (Nagelhout & Elisha, 2018). The chemoreceptor trigger zone (CTZ) is located in the area of postrema in the 4th ventricle of the brain; it communicates with structures in the vomiting center to initiate vomiting and has been shown to be sensitive to stimulation from substances such as opioids (Nagelhout & Elisha, 2018). Seratonin type 3 and dopamine type 2 receptors are dominant in the CTZ, although the exact mechanism of propofol’s antiemetic properties remains undetermined, it has been shown to be a weak serotonin antagonist (Erdem et al., 2009; Gan et al., 1997; Nagelhout & Elisha, 2018). It has been discussed whether propofol is a dopaminin antagonist however, two studies have shown otherwise (Erdem et al., 2009). Erdem et al. (2009) noted propofol does decrease synaptic transmission in the olfactory cortex, which decreases glutamate and aspartate release, which may contribute to its antiemetic properties. Some have even suggested propofol may directly depresses the CTZ and vagal nuclei which are strongly linked to nausea and vomiting (Erdem et al., 2009).

Evidenced based research has clearly shown that propofol decreases PONV. However, a clear guideline for the administration of propofol to most effectively utilize its antiemetic properties has not been developed. This guideline should be supported by extensive evidence based literature and clinical experiences. In the following pages a case report of a high-risk PONV patient having a routine laparoscopic cholecystectomy under CIVA will be presented. Additionally, a literature review on propofol’s antiemetic properties will follow.
Purpose

The purpose of this independent project is to present a case report of successfully using CIVA on a high-risk patient to prevent PONV. Additionally, this paper will provide anesthesia practitioners with current evidence-based research found in the literature supporting CIVA and subhypnotic doses of propofol as prophylactic treatment for PONV. Therefore, providers may effectively use this method to decrease PONV which in turn increases patient satisfaction, decreases PACU times and ultimately hospital and patient costs.

Case Report

A 38-year old, 152.4 centimeter, 83.3 kilogram, female with symptomatic cholelithiasis presented for a laparoscopic cholecystectomy. Her medical history included mild persistent asthma, gastroesophageal reflux disease, upper gastrointestinal bleed, bipolar 1 disorder, obesity (body mass index 35.8), head trauma, seizures, eating disorder, anxiety, depression, hyperlipidemia, and substance abuse. She had a history of smoking tobacco with a 7.5 pack-years history, however she ceased smoking in 2012. Surgical history included cesarean section, skin graft, carpal tunnel release, upper endoscopy, tendon repair, bladder repair, open rotation internal fixation, osteotomy, bunionection, dilation and curettage, and laparoscopic gastric bypass. She had reported a significant history of PONV with previous surgical procedures. Current medications included omeprazole, oxycodone, fluconazole, fluticasone, albuterol, and mirtazapine. Allergies included tramadol, droperidol, ketorolac, latex, melatonin, nitrous oxide, metoclopramide, and vancomycin. Her reaction to tramadol was angioedema and she had a history of a rash with droperidol. All other reactions were unknown.

Her airway assessment revealed the patient had full neck range of motion, adequate thyromental and hyoid mental distances, and a mallampati II. Preoperative vital signs were
respiratory rate 16 breaths per minute, heart rate 94 beats per minute, blood pressure 116/74 mmHg, oxygen saturation of 100% on room air, and temperature of 36.4 degrees Celsius. Bilateral breath sounds were clear to auscultation. Auscultation of heart tones noted a regular rate and rhythm, no click, rub, or murmur appreciated. She had been NPO 8 hours prior to surgery. No pre-operative labs were drawn. She was classified as an American Society of Anesthesiologists (ASA) physical status three. Her PONV score was four per Apfel’s simplified scoring system.

A 20-gauge intravenous catheter (IV) was placed utilizing ultrasound in the right forearm in the preoperative holding room and lactated ringer’s crystalloid solution was initiated. The patient was transported to the operating room (OR) via transport cart. In the OR, the patient was transferred from the transport cart to operating table with assistance from staff. A pulse oximeter was placed on the patient’s right pointer finger and midazolam 2 milligrams (mg) IV was administered. A noninvasive blood pressure cuff was placed on the patient’s left upper arm and a three lead EKG was placed on the patient for continued heart monitoring throughout the case. The patient was pre-oxygenated with 100% oxygen at 10 liters for 2 minutes via tight fitting face mask. For induction the patient was given 1% lidocaine 50 mg IV, fentanyl 100 micrograms (mcg) IV, and Propofol 170 mg IV. Once eyelid reflex was lost, eyes were carefully taped closed to prevent corneal abrasions. The ability to mask ventilate was verified by the presence of end tidal carbon dioxide, adequate tidal volume readings on the ventilator, chest rise, and fogging in the mask. The patient was then given 30 mg of rocuronium IV. Sevoflurane was administered, via mask, at a minimum alveolar concentration until ventilation became easier. A grade 1 view on the Cormack-Lehane classification was achieved by direct laryngoscopy with a MAC 3 blade. A 7.0 endotracheal tube (ETT) was atraumatically placed. Placement was confirmed with
fogging in the tube, chest rise, presence of ETCO2, and bilateral breath sounds. The ETT was secured with tape. The patient was ventilated via volume-controlled ventilation with tidal volumes of 500 milliliters, respiratory rate of 10 breaths per minute, and positive end-expiratory pressure of 5 cmH2O. Fresh gas flow was blended with 1 liter of air to 1 liter of oxygen. A nasopharyngeal temperature probe, and BIS monitor were placed. Sevoflurane was administered at 0.5-0.8 minimum alveolar concentration (MAC) and was titrated to a BIS reading of 40-60. An intravenous propofol infusion was initiated immediately after intubation at a rate of 70 mcg per kilogram per minute (mcg/kg/min). The patient received Ancef 2 grams IV for surgical incision infection prophylaxis. Additional fentanyl 100 mcg IV was given in increments of 50 mcg for analgesia throughout the case, for a total of 200 mcg. Prior to incision dexamethasone 4 mg IV was administered, and Zofran 4mg IV was administered 30 minutes prior to end of procedure for PONV prophylaxis. One liter of lactated ringers was administered in total for the procedure. Once wound closure began, the sevoflurane was discontinued. The patient had 2 out of 4 twitches on the train of four monitor and was given glycopyrrolate 0.6 mg and neostigmine 4 mg, which yielded successful reversal of motor blockade. Upon closure of the fascia, the propofol infusion was discontinued, the oropharynx was suctioned and the the nasopharyngeal temperature probe and eye tapes were removed. After dressings were placed, the patient was able to open her eyes and follow commands. Her tidal volumes were approximately 380 mL with a regular breathing pattern. The ETT was removed without complication; she was placed on 3L oxygen via nasal cannula, and her oxygen saturation remained 98% or greater. All monitors were removed; the patient was transferred back to the transport cart with assistance from OR staff and transported to post-anesthesia care unit (PACU). Procedure length was approximately 40 minutes and anesthesia time was just over an hour. No delay in extubation was noted due to the CIVA.
technique. The patient reported no nausea and did not vomit in PACU, in fact she reported feeling less nauseated then prior to the procedure. Overall, the patient’s PACU stay was short and uneventful.

**Literature Search**

**Databases**

PubMed was used to conduct this literature search because it houses millions of works in the biomedical and life science field. Thus, a good choice for medical providers. CINHAL was also briefly searched as it is comprised of nursing and biomedical journals. However, no additional useful results were found through this database, only duplicates.

**Terms**

A total of three searches were conducted utilizing the Medical Subject Heading (MeSH) within the PubMed database. First, “Postoperative nausea and vomiting,” “propofol,” and “anesthesia” were searched as MeSH terms using the Boolean connector “AND.” This search yielded 17 items, of these results one article was used. In an attempt to refine the search the MeSH terms were changed slightly to “Postoperative nausea and vomiting,” “anesthesia, inhalation,” and “propofol.” This resulted in 15 articles, three of which pertained to the topic. The search was then broadened by searching two of the MeSH terms, “postoperative nausea and vomiting” and “propofol,” while still using “AND” as a connector. Forty-two articles resulted, and one new article was found.

**Limits and relevant articles**

All searches were limited to articles published within the last five years. This ensured current evidence-based information was reviewed. Only full text articles available in English were used. A total of five articles were found from these searches. The search was widened to a 10 year
time frame to find additional high quality research. Two articles were found with this method. Due to the limited number of useful articles generated through these searches the reference section within the articles were reviewed. One of the articles was cited in half of the works. The article was outside the search limit of “within five years”; however, it was pertinent to the topic. In total three articles were found cited in multiple works. In all, seven articles were found using MeSH terms in PubMed and an additional three articles were found in the reference section of the original articles. A total of ten articles were found and utilized in this review.

**Literature Review**

Combined subhypnotic propofol with volatile anesthetic has been found to decrease PONV and is as effective as total intravenous anesthesia (TIVA) (Kawano et al., 2014; Lai et al., 2017; Lai et al., 2018). Patients who receive the combined intravenous-volatile anesthesia (CIVA) technique do not have an increase in vomiting or a need for rescue medication post-operatively for nausea when compared to TIVA (Kawano et al., 2014; Lai et al., 2017; Lai et al., 2018). In order to understand CIVA one must understand the pathophysiology and causative factors for PONV. It is also essential to understand the pharmacodynamics of both propofol and inhaled anesthetics, as both possess benefits and risks to the patient. However, the benefits may be exploited and the risks minimized with the CIVA technique. In the pages to follow PONV and the pharmacodynamics of propofol and inhaled anesthetics are discussed. The pharmacologic discussion is not comprehensive as this would be beyond the scope of this independent project. Finally, a thorough literature review of subhypnotic doses propofol and the beneficial outcomes will follow.
Postoperative Nausea and Vomiting

Nausea is defined as an uncomfortable feeling of a need to vomit without the act of vomiting (Shaikh, Nagarekha, Hegade, & Marutheesh, 2016). The expulsion of gastrointestinal contents upward through the mouth is defined as vomiting (Shaikh, Nagarekha, Hegade, & Marutheesh, 2016). Post-operative nausea and vomiting is when a patient experiences one or both of these phenomena during the postoperative period (Nagelhout & Elisha, 2018; Shaikh, Nagarekha, Hegade, & Marutheesh, 2016). Substantial effort has been made by anesthesia providers to decrease PONV, in an effort to increase patient satisfaction and decrease hospital and patient costs. However, it remains one of the most prevalent adverse effects to patients undergoing anesthesia. In fact, it is the second most common complaint after pain in the postoperative period (Shaikh, Nagarekha, Hegade, & Marutheesh, 2016). Post-operative nausea and vomiting can lead to incision site stress, bleeding, fluid and electrolyte disturbances, cardiovascular stress, and aspiration (Nagelhout & Elisha, 2018). Post-operative nausea and vomiting can also lead to increased PACU times and admission to the hospital for outpatient procedures, both of which increase hospital and patient costs.

Patient characteristics which have been proven to increase the risk for PONV include female gender, history of PONV, motion sickness, nonsmoker, and younger than 50 years of age. Anesthetic risk factors include general anesthetics, use of inhaled anesthetics, postoperative opioid consumption, and duration of anesthesia over one hour. Furthermore, certain procedures carry a high risk for PONV, including gynecological, urological, intracranial and laparoscopic procedures (Butterworth, Mackey & Wasnick, 2013; Nagelhout & Elisha, 2018; Shaikh, Nagarekha, Hegade, & Marutheesh, 2016).
Apfel’s risk assessment tool is a frequently used preoperative assessment tool to evaluate the risk of PONV (Nagelhout & Elisha, 2018, p.1161). The tool ranges in scores from 0 to 4 based on how many of the following risk factors are present: female gender, nonsmoker, history of motion sickness or PONV, and intended post-operative opioid use. Generally, with two risk factors it is considered best practice to administer two antiemetic medications. If three or more risk factors are present further preventative measures should be taken, traditionally TIVA has been used. If the patient has two risk factors it is associated with around a 40% incidence of PONV. If three risk factors are present roughly a 60% incidence of PONV exists, and if four risk factors are present approximately an 80% incidence of PONV occurs (Naglehout & Elisha, 2018; Butterworth, Mackey & Wasnick, 2013; Shaikh, Nagarekha, Hegade, & Marutheesh, 2016).

The pathophysiology of PONV is complex and involves many different pathways and receptors. The primary pathways involved include the chemoreceptor trigger zone (CTZ), the vagal mucosal pathway in the gastrointestinal system, neuronal pathways from the vestibular system, reflex afferent pathways from the cerebral cortex, and midbrain afferents. Stimulation of these afferent pathways can stimulate vomiting. This occurs through cholinergic (muscarinic), dopaminergic, histaminergic, and serotonergic receptors. These pathways send input to the “vomiting center” within the reticular formation in the brainstem. The nucleus tractus solitarius, also located in the brainstem, receives input and interacts in the process of nausea and vomiting. Furthermore, Neurokinin-1 (NK-1) receptors in the postrema area have been associated with the processes of vomiting. The CTZ is located outside the blood brain barrier and is in contact with cerebrospinal fluid which forms a link between substances in the blood and the vomiting reflex centers of the brain. Thus, the vomiting reflex can be triggered when causative substances within the blood stimulate the CTZ. The vomiting center may also be triggered by the gut, oropharynx,
pain, hypoxemia, and hypotension. Once the vomiting center is stimulated the efferent signals travel via the glosopharyngeal, hypoglossal, trigeminal, accessory, and spinal segmental nerves. Vomiting occurs and the abdominal muscles contract against a closed glottis which increases intra-abdominal and intrathoracic pressures. The pyloric sphincter contracts and the esophageal sphincter relaxes. Antiperistalsis occurs in the esophagus which leads to forward and upward movement of GI contents (Nagelhout & Elisha, 2018; Shaikh et al., 2016).

**Inhaled Volatile Anesthetics**

To fully appreciate the CIVA technique a provider must understand the value of inhaled volatile anesthetics. Total intravenous anesthesia is an established method which utilizes propofol without inhaled volatile anesthetics in an effort to prevent PONV (Nagelhout & Elisha, 2018). The addition of inhaled anesthetics has the potential to enhance many anesthetic plans.

Commonly used inhaled anesthetics include nitrous oxide, sevoflurane, desflurane, and isoflurane. The exact mechanism of action of inhaled anesthetic agents is largely unknown. A current accepted hypothesis states inhaled anesthetics work on multiple different ion and/or voltage gated channels in the brain. The GABA receptor chloride channel may be one of these sites of action. Glycine, opioid, serotonin, acetylcholine, and alpha 2 receptors have also been implicated in the mechanism of action for these agents. Specific biophysical and structural studies implicate halogenated inhaled anesthetics act on ion-gated sodium and potassium channels (Nagelhout & Elisha, 2018; Butterworth, Mackey & Wasnick, 2013).

**Nitrous oxide.**

Nitrous oxide is a simple inorganic compound; it is colorless, odorless and a relatively inexpensive anesthetic agent. Minimum alveolar concentration cannot be achieved with nitrous
oxide alone, so it is commonly used in combination with other inhalation agents. This gas has many potential benefits with administration. Nitrous oxide exerts the second gas effect, which increases the partial pressure of the second gas in the alveoli resulting in a more rapid uptake. Furthermore, Nitrous oxide is a N-methyl-D-aspartate (NMDA) receptor antagonist. Antagonism of the NMDA receptor has been proven to provide analgesia and neuronal protection. However, no anesthetic drug is ideal; nitrous oxide has the potential to stimulate the sympathetic nervous system, can directly depress myocardial contractility, and increase pulmonary vascular resistance. It has been shown to increase cerebral blood flow and volume leading to increased intracranial pressure and increase cerebral oxygen consumption. Lastly, nitrous oxide diffuses rapidly into a cavity more quickly than air diffuses out, which may lead to expansion in cases that have, or at risk of, air embolism, pneumothorax, ect. (Nagelhout & Elisha, 2018; Butterworth, Mackey & Wasnick, 2013).

**Isoflurane, sevoflurane and desflurane.**

Inhaled anesthetics: isoflurane, sevoflurane, and desflurane are halogenated ethers with fluorine atoms and are widely used in clinical practice (Nagelhout & Elisha, 2018). These inhaled anesthetics have the ability to produce amnesia and unconsciousness at less than a MAC of gas primarily by acting on synaptic transmission in the central nervous system (Nagelhout & Elisha, 2018). At concentrations greater then 1.0 MAC immobility occurs by blunting ascending impulses on the spinal cord central pattern generators (Nagelhout & Elisha, 2018). Volatile agents decrease CMRO$_2$ and increase CBF especially if administered at concentrations greater then 1.0 MAC, which may make administration ideal in neuroprotective situations.

The effect on the cardiovascular system is a dose-dependent decrease in cardiac output, MAP, and cardiac index (Nagelhout & Elisha, 2018). The literature also notes that volatile
agents have cardio-protective effects mediated by the adenosine triphosphate-sensitive potassium channels in cardiac myocytes (Kawano et al., 2014; Naglehout & Elisha, 2018). These same channels are present in vascular smooth muscle promoting coronary vasodilation (Nagelhout & Elisha, 2018). According to Kawano et al. (2014), when volatile agents are used in cardiac procedures they decrease troponin, decrease cardiac events, and enhance left ventricular function.

Volatile anesthetics have been shown to decrease the incidence of intraoperative awareness and may attenuate the cough reflex by decreasing agonists affinity to nicotinic acetylcholine receptors at the vagal afferent neurons in the brain (Kawano et al., 2014; Lai et al., 2018). Lastly, it has been hypothesized that propofol may increase secretions, Lai et al. (2017) found that sevoflurane effectively attenuates this response by chloride secretion indirectly inhibiting potassium voltage-gated channel subfamily Q member 1 (KCNQ1) in the trachea and salivary gland.

**Propofol**

Propofol has been used as a sedative and hypnotic agent since 1977 (Robinson & Toledo, 2012). It is a 2, 6-diisopropyl phenol and is prepared as a 1% solution in a lipid emulsion that includes soybean oil, glycerol, and purified egg lecithin. Propofol is highly lipid soluble. When administered as a bolus it has a quick onset because this property which leads to rapid distribution of the drug to well-profused tissues such as the brain where it produces its pharmacological effect. It then rapidly redistributes to less well-profused tissues where it exhibits no action leading to rapid reawakening (Naglehout & Elisha, 2018).

Propofol is metabolized in the liver by the CYP2B6, UTHP4, and CYP2C6 pathways and less than 1% is eliminated unchanged in the urine. Patients with cirrhosis of the liver show no
change in metabolism. Age, however, does affect the dosing of propofol, with elderly requiring lower doses and children requiring higher doses relative to body weight due to volumes of distribution. The elimination and half-life is 1-2 hours; however, with prolonged infusion propofol accumulates in tissues that become saturated with the drug leading to potential increased elimination times (Nagelhout & Elisha, 2018).

Propofol’s main mechanism of action occurs via the γ-aminobutyric acid (GABA) and the GABA<sub>A</sub> glycoprotein receptor complex. γ-aminobutyric acid, a major inhibitory neurotransmitter in the central nervous system, directly binds with the GABA<sub>A</sub> receptor and increases the affinity of endogenous GABA to the receptor site. The GABA<sub>A</sub> receptor is a ligand gated ion channel receptor; when GABA binds to the receptor, chloride ions move through the channel and into the cell. The cell then becomes hyperpolarized and inhibits cell excitation (Nagelhout & Elisha, 2018).

Propofol may be avoided in some cases as hemodynamics could be affected by the administration of propofol. A decrease in mean arterial pressure, metabolic rate, and cerebral vasoconstriction are seen with standard dosing. Another concern maybe in cerebral cases as a dose-dependent decrease can be seen in cerebral blood flow, cerebral metabolic rate of oxygen consumption, intracranial pressure, intraocular pressure and cerebral perfusion pressure (Nagelhout & Elisha, 2018).

With the administration of a standard induction dose of propofol respiratory depression does occur affecting tidal volume more than respiratory rate, and creates apnea. These effects appear to be due to a decreased sensitivity to carbon dioxide in the respiratory center. However, propofol does possess some benefits to the respiratory system as it does not cause histamine release and it does produce some bronchodilation (Nagelhout & Elisha, 2018). Propofol does not appear
to affect the hypoxic pulmonary vasoconstriction mechanism whereas, inhaled anesthetics do in a dose dependent fashion (Kawano et al., 2014). Other benefits to using propofol include reduced post-operative pain and neuroendocrine stress response, which allows proper ventilation and stable hemodynamics (Kawano et al., 2014).

The exact mechanism of propofol antiemetic properties is largely unknown. It had been hypothesized that it possessed antidopaminergic effects; however, two studies have disproven this theory (Erdem et al., 2009). It does decrease synaptic transmission in the olfactory cortex, which decreases glutamate and aspartate release this may contribute to the antiemetic properties of propofol (Erdem et al., 2009). Furthermore, in prolonged infusions, it has been shown to decrease the concentration of serotonin in the area postrema which may also contribute to the antiemetic properties (Gan, 1997). Some literature has even suggested propofol may directly depress the CTZ and vagal nuclei, which are strongly linked to nausea and vomiting (Erdem et al., 2009).

**Antiemetic Effects of Subhypnotic Doses of Propofol**

This thorough literature review yielded adequate evidence to support providers using subhypnotic doses of propofol for its antiemetic properties. Several studies found no difference in rates of PONV in patients who were administered CIVA versus TIVA. In addition, they found that both CIVA and TIVA methods of anesthesia decreased PONV when compared to inhalational volatile anesthetics alone (Kawano et al., 2014; Lai et al., 2017; Lai et al., 2018). Valid studies showed no delay in time to extubation and no significant hemodynamic changes when the CIVA technique was utilized (Lai et al., 2018; Lai et al., 2017, and Kawano, et al., 2014). The benefits of CIVA on PONV is clear in the immediate postoperative period. However, there is less evidence that it reduces post discharge nausea and vomiting in the first 24-hour
period. In fact, both TIVA and CIVA have not been shown to reduce post-discharge nausea and vomiting (Lai et al., 2018; Lai et al., 2017, and Kawano, et al., 2014).

**CIVA**

Kawano et al. (2014) studied three groups of patients with different primary anesthetics: a propofol maintenance, a sevoflurane maintenance, and a CIVA group. The propofol group was maintained with an IV infusion, at a rate of 4-8 mg/kg/hr and the CIVA group was maintained with a propofol IV infusion of 2mg/kg/hr and sevoflurane at fixed rates of approximately 0.5 MAC concentrations. Both the CIVA and propofol group had reduced PONV when compared to the sevoflurane group. There was no significant difference between the CIVA and propofol groups.

Celik et al. (2014) compared subhypnotic propofol and dexamethasone for prevention of PONV in patients undergoing laparoscopic cholecystectomy. A group received 1 mg/kg/hr infusion of Propofol, a second group received 8 mg dexamethasone, and the control group received 10% intralipid infusion. All groups were maintained with 1-2.5% sevoflurane. No difference was seen between the propofol and dexamethasone group and both groups had decreased PONV compared to the control group in the immediate postoperative period.

Lai et al., (2017) and Lai et al. (2018) compared patients receiving CIVA to patients recieving TIVA anesthetics in a randomly controlled study. Propofol for the TIVA group was adjusted to maintain BIS 40-60. The CIVA group was administered fixed rate 1% sevoflurane and the propofol infusion was titrated to BIS 40-60. The results showed no significant difference of PONV between TIVA and CIVA groups.

Erdem et al. (2008) compared dexamethasone and subhypnotic propofol to dexamethasone alone. The Propofol was infused at 20 mcg/kg/min after 1 mg/kg induction dose.
Dexamethasone was administered at 0.15 mg/kg to both groups. The study was performed in pediatric patients undergoing tonsillectomy. The patients who received both subhypnotic infusion of propofol and dexamethasone had less PONV than those who received dexamethasone alone.

Erdem et al. (2009) also studied subhypnotic infusions of propofol in pediatric patients during tonsillectomy. Two groups were compared one group received 15 mcg/kg/min propofol infusion after 1 mg/kg induction dose and 0.2 mg/kg tropisetron (max dose of 5 mg). The second group received 0.2 mg/kg of tropisetron alone. Both groups were maintained with sevoflurane nd nitrous oxide. In the immediate postoperative period the subhypnotic propofol-tropisetron group experienced significantly less PONV than the tropisetron alone group.

**Bolus dose of Propofol**

Studies have shown that a single subhypnotic dose of propofol can be administered as a bolus after an inhalational anesthetic to decrease PONV (Song, et al., 1998; Borgeat, Wilder-Smith, Saia, & Rifat, 1992; Naghibi, Kashefi, Azarnoush, & Zabihi, 2013). Naghibi, Kashefi, Axarnoush and Zabihi (2013) found that 30 mg IV of propofol administered 15 minutes before the end of the procedure effectively reduced PONV in the first six hours after maintenance of an anesthetic with isoflurane. Song, Whitten, White, Yu, and Zarate (1998) administered a propofol bolus of 0.5 mg/kg IV at the time of skin closure after maintenance with either desflurane or sevoflurane. The group with sevoflurane as a maintenance anesthetic and 0.5 mg/kg propofol at time of skin closure had significantly lower rates of PONV when compared to the desflurane and propofol group. However, this is the only study found during this literature review that showed delayed times to extubation, 2-4 minutes, with the administration of propofol. Regardless of the delay in time to extubation, time to readiness to discharge was significantly less in the
sevoflurane-propofol group. This finding is consistent with findings of subhypnotic doses either bolus at the end of the procedure or an infusion in combination with a volatile anesthetic. However, it has been found that maintenance IV infusions of propofol more effectively prevent PONV than IV boluses at the end of the procedure (Erdem et al., 2008, Gan et al., 1997).

Propofol has been shown to have positive effects in the pediatric population as well. Children commonly undergo procedures associated with high risk PONV such as myringotomy, tonsillectomy and adenoidectomy. Erdem et al. (2008) and Erdem et al. (2009) found that subhypnotic infusions of propofol effectively reduces PONV in children. The studies used propofol infusion of 1mg/kg/hr IV with 1.0-2.5% sevoflurane.

**Plasma concentrations.**

For propofol to have an antiemetic effect, plasma concentrations must be at least 343 ng/mL; a bolus of 10 mg IV followed by 10 mcg/kg/min IV infusion will achieve this level (Gan et al., 1997). If one induces with propofol 1.5 mg/kg IV and administers a continuous infusion of 200 mcg/kg/hr IV the plasma concentration will be well above 343 ng/mL. This dosing may be seen when doing a TIVA. With this dosing regimen, the plasma concentration level will remain above the necessary level for antiemetic properties for 170 minutes after the infusion is discontinued (Kawano et al., 2014).

**Synergist effects of propofol.**

When using the CIVA technique sevoflurane may be the best choice for a volatile anesthetic. Propofol has more effective antiemetic properties when used in combination with sevoflurane vs. desflurane (Song, Whitten, White, Yu, & Zarate, 1998). Propofol has also been shown to have synergistic effects with commonly used antiemetics such as tropisetron, a 5HT3 antagonist. Postoperative Nausea and Vomiting is decreased more significantly when propofol
and tropisetron are used in combination than when tropisetron is used alone (Erdem et al., 2009). Dexamethasone, another commonly used antiemetic, also decreases PONV at greater rates when combined with subhypnotic doses of propofol than when used alone. (Erdem et al., 2008; Celik et al., 2015).

**Additional anesthetic considerations.**

Subhypnotic doses of propofol are most effective at preventing early PONV (Kawano et al., 2016; Erdem et al., 2009). Some providers may have concerns about the delayed time to extubation or hemodynamic instability with this technique; however, research has shown this method does not increase time to extubation (Lai et al., 2018; Lai et al., 2017). In addition, subhypnotic doses of propofol have not been shown to significantly affect hemodynamics (Gan et al., 1997).

Sevoflurane has been shown to be the most effective inhaled anesthetic used with the CIVA technique. Using inhaled anesthetics have shown to decrease secretions and attenuate cough reflex which may be mediated through vagal afferent neurons in the brain. Sevoflurane also has agonist activity at nicotinic acetylcholine receptors. These may contribute to positive use of sevoflurane. Another inhaled anesthetic highly linked to PONV is nitrous oxide. Previously nitrous oxide may have been avoided in someone with PONV. Bhakta et al. (2016) found that propofol infusions in combination with nitrous oxide reduced PONV compared to nitrous oxide and isoflurane alone. Suggesting if nitrous oxide use is desired a propofol infusion can decrease the risk of PONV in these cases. Research has shown patients who receive CIVA are ready to go home sooner than those receiving volatile anesthetics alone (Song, Whitten, White, Yu, & Zarate, 1998).
Discussion

The patient presented in this independent project was at high risk for PONV. She was a young female, nonsmoker, with a history of PONV, with intended use of opioids postoperatively undergoing general anesthesia for a laparoscopic procedure. CIVA was utilized as a prudent choice for a patient centered anesthetic plan. The intraoperative course and short PACU stay were uneventful. The patient did not experience any PONV and expressed satisfaction with the care she received.

The literature search yielded sufficient evidence to conclude that CIVA and subhypnotic doses of propofol safely reduce PONV. Additional research and clinical trials are needed to conclude the most effective dosing of propofol in combination with inhaled volatile anesthetics to reduce PONV. Research to determine the best combination of multimodal antiemetics with CIVA is also needed.

Anesthesia providers need to determine the most effective way to prevent PONV in mild to high-risk patients and implement guidelines for best clinical practice in the management of PONV. The development of these finding should be a high priority as PONV is a common occurrence with identifiable risk factors that can lead to increased lengths of stay for patients, as well as increase costs. CIVA and subhypnotic doses of propofol show promising results and should be considered a potential solution to the problem of PONV.

Conclusion

In conclusion, it is important to establish the most effective way to prevent PONV as it is a common, costly, and unpleasant adverse effect of anesthesia. The use of propofol as an antiemetic is widely accepted. Traditionally, TIVA has been used for high-risk PONV patients. However, with the current literature review, it seems CIVA is as effective at preventing PONV
and allows providers to use inhalation agents that have beneficial cardiovascular, respiratory, and neurological effects. This information should be considered when choosing a patient-specific anesthetic technique.
References


Prevention of Postoperative Nausea and Vomiting with Subhypnotic Doses of Propofol
Chelsea Lingle, SRNA

Introduction
- Combined Intravenous Volatile Anesthesia (CIVA)
  - "Background Propofol" or subhypnotic doses of propofol
  - Traditionally TIVA has been used however current literature review suggests CIVA is as effective at prevention of PONV
- PONV is a common adverse effect of anesthesia
  - 1 in 3 experience PONV
    - High risk 8 in 10 experience PONV
  - Second most common complaint in PACU


Case Information
- Laparoscopic cholecystectomy
  - 38 year old
  - Female
  - 83.3 kg, 5 ft
  - ASA 3

Pre-operative Evaluation
- Medical history: mild persistent asthma, GERD, upper GI bleed, bipolar I disorder, obesity, head trauma, seizures, eating disorder, anxiety, depression, hyperlipidemia, substance abuse
- Surgical history: cesarean section, skin graft, carpal tunnel release, upper endoscopy, tendon repair, joint arthroplasty, open reduction internal fixation, otoplasty, bronchotomy, dilation and curettage, and laparoscopic gastric bypass
- Current medications: unprivate, zolmitriptan, flurbiprofen, flucortasone, albuterol, and metronidazole
- Allergies: tiamadol, droperidol, loradexa, lakes, melittin, nitrous oxide, metaproterenol, and vancomycin (reactions largely unknown by patient)

Pre-operative Evaluation
- Pre-op VS: HR 94, BP 116/74, RR 16, Sats 100% on RA, 36.4 degrees C
- Pertinent Labs/ EKG/chest X-ray/evaluation unremarkable
- Airway evaluation: Full neck ROM, adequate TM and HM distances, malampati II
- Apfel’s simplified scoring system: 4
**Anesthetic Course**

- Standard non-invasive monitors used
- Combined Intravenous Volatile anesthesia
  - Propofol 70 mcg/kg/min, sevoflurane titrated to desired anesthetic depth
- Sedation: 0.5 mg of 1% lidocaine, 100 mcg fentanyl, 170 mcg propofol, 34 mcg rocuronium
- Maintenance: 160 mcg fentanyl (increments of 50 mcg), Decadron 4 mg (prior to skin incision), Zofran 4 mg (withins closure), total 1 L LR
- Emergence: 8 mg glycopyrrolate and 4 mg neostigmine, Propofol and sevoflurane discontinued

**Intraoperative Issues**

- Intraoperative course was uneventful
  - Hemodynamically stable, sat >94%, paralysis maintained, mechanically ventilated
- 40 mins of procedural time, ~1 hr anesthesia time
- No delayed time to extubation
- No hemodynamic concerns

**PACU**

- Short uneventful PACU stay
- No PONV
  - Pt reported improvement in nausea
  - Satisfied with anesthetic care

**Propofol at subhypnotic doses for prophylaxis of PONV**

- PONV is the second most common complaint in PACU
- PONV can lead to incision site stress, bleeding, fluid and electrolyte disturbance, cardiovascular stress, and aspiration
- PONV increases PACU and can lead to admissions for outpatient procedures
- Also increases costs for patients and facilities

**Propofol at subhypnotic doses for prophylaxis of PONV**

- Antiemetic Properties of Propofol are largely unknown
  - Two studies have disproven antiemetic effects
  - Current research suggests:
    - Decreases synaptical transmission in the olfactory cortex which leads to decreases in glutamate and serotonin
    - Decreases concentrations of serotonin in the area postrema
    - Some suggests it may directly depress C12 and vagal nuclei

(Cohen et al., 2016; Cohen et al., 2017; Koo et al., 2014; Li et al., 2017; Lu et al., 2016)

**Propofol at subhypnotic doses for prophylaxis of PONV**

- CVA decreases PONV as effective as TVA
- No delay in time to extubation
- No significant hemodynamic changes
- CVA is most effective at decreasing PONV in the immediate post-operative period (first 24 hrs)
- Subhypnotic propofol drip increases the effects of dexamethasone and serotonin antagonists
- Subhypnotic propofol effective as dexamethasone
- IV infusions of propofol more effectively prevent PONV

(Cohen et al., 2016; Cohen et al., 2017; Gen et al., 2017; Iwase et al., 2016; Lee et al., 2015; Li et al., 2016; Wang et al., 2016)
Propofol at subhypnotic doses for prophylaxis of PONV

- Dosing of CIVA or background propofol
  - Kawano et al. (2014) IV propofol infusion 2 mg/kg/hr sevoflurane at 0.5 MAC
  - Lei et al. (2017) and Lei et al. (2018) sevoflurane fixed at 1%, propofol titrated to 0.5-1.0 MAC
  - Celik et al. (2014) used 1 mg/kg/hr with 1-2.5% sevoflurane
  - Eden et al. (2008) used 1 mg/kg/hr with sevoflurane 1.25%
  - Eden et al. (2009) used 15 mcg/kg/min with sevoflurane

- Benefits to subhypnotic doses of propofol
  - Effectively decreases PONV
  - Readiness to discharge time is decreased when subhypnotic doses of propofol are utilized
  - Save time and money for facility and patients
  - Increase patient satisfaction

Recommendations

- Continuous Propofol infusions should be used for patients at high risk of PONV
- If cardiovascular protective effects or other effects of inhalation agents are desired combined intravenous-volatile anesthesia can effectively be used to prevent PONV
- To utilize CIVA technique a minimum propofol dose of 10 mg bolus followed by 10 mcg/kg/min infusion and sevoflurane should be used.

Conclusion

- CIVA is as effective as TIVA at reducing PONV
- Further research is needed to show the most effective way to combine volatile anesthetics and propofol to reduce PONV