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Intraoperative Ketamine to Reduce Postoperative Opioid Consumption in Chronic Pain Patients

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INTRAOPERATIVE KETAMINE TO REDUCE POSTOPERATIVE OPIOID

CONSUMPTION IN CHRONIC PAIN PATIENTS

by

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PERMISSION

Title	Intraoperative Ketamine to Reduce Postoperative Opioid Consumption in Chronic Pain Patients
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Abstract

Title: Intraoperative Ketamine to Reduce Postoperative Opioid Consumption in Chronic Pain Patients

Background: Typically, chronic pain patients have a predisposition for higher postoperative pain rating and a slower resolution of this pain. Ketamine, a potent anesthetic agent, works to inhibit the N-Methyl-D-aspartate (NMDA) receptors causing dissociative anesthesia. The NMDA receptors contribute to the pain felt after tissue injury and can cause increased pain perception. Ketamine binds to the NMDA receptors and blocks this effect reducing the patient's pain postoperatively.

Purpose: The purpose of this literature search is to provide an extensive review of the literature regarding ketamine administration and its effect on reducing postoperative pain and opioid requirements.

Process: A literature review was conducted using the PubMed, CINAHL, and Cochrane library databases which were accessed through the University of North Dakota's Health Sciences Library. Other pertinent literature was obtained by searching the reference lists of initially acquired articles. All research was evaluated extensively and applied to this paper or rejected due to substandard information.

Results: A review of the literature revealed case reports that supported the use of sub-anesthetic doses of ketamine for the purpose of reducing postoperative opioid consumption. Overall, the studies showed consistency between intraoperative ketamine administration and decreased opioid use and pain levels immediately following surgery. This was found to be consistent for patients with and without chronic pain.

Implications: Based upon the data compiled throughout this literature review one practice recommendation is definite: the administration of intraoperative sub-anesthetic doses of ketamine should be used as an adjunct for general and regional anesthesia to decrease postoperative pain.

Keywords: ketamine, postoperative, chronic pain, perioperative, opioid use and surgical

Intraoperative Ketamine to Reduce Postoperative Opioid Consumption in Chronic Pain Patients

Chronic pain is an epidemic in the United States, resulting in an increased number of prescribed opioids. As a result, medical professionals are being encouraged to decrease opioid prescriptions. Surgical pain often requires opioid administration for relief. Studies have shown that many patients who have been diagnosed with chronic pain are prescribed an opioid for pain relief. According to a study completed by Chapman, Davis, Donaldson, Naylor & Winchester (2011), chronic pain patients, in general, have a predisposition for higher postoperative pain rating and a slower resolution of this pain. The study states that chronic pain patients who have a surgical procedure and are currently prescribed an opioid experience markedly higher postoperative pain. Therefore, it is important for anesthesia providers to effectively manage postoperative pain in this patient population.

Ketamine was synthesized in 1962 from a series of phencyclidine derivatives (Mion, 2017). Researchers found it to be an excellent anesthetic that was short-acting and, unlike its phencyclidine precursors, the side effects were less potent and better tolerated (Mion, 2017). In 1964, ketamine use in humans was first attempted (Mion, 1017). Ketamine was patented in 1966 for human and animal use and officially approved for human use by the United States Food and Drug Administration in 1970. It was used as a field anesthetic during the Vietnam War. In 1971, subanesthetic doses of ketamine were shown to have analgesic properties with moderate side effects (Mion, 2017). Subanesthetic dose or "low-dose" ketamine is defined as a bolus of < 1milligram/kilogram (mg/kg) intravenous or a continuous intravenous infusion < 20 micrograms/kilogram/minute (mcg/kg/min) (Kaur, S., Saroa, R., & Aggarwal., 2015).

Ketamine, a potent anesthetic agent, works to inhibit the N-Methyl-D-aspartate (NMDA) receptors causing dissociative anesthesia (Vargo, 2012). The NMDA receptors contribute to the

pain felt after tissue injury and can cause increased pain perception (Vargo, 2012). Ketamine binds to the NMDA receptors and blocks this effect reducing the patient's pain postoperatively (Nagelhout & Plaus, 2014). Intraoperative ketamine use has been shown to reduce morphine use by 52% in the 48 hours following surgery (Vargo, 2012). According to Himmelseher and Durieux (2005), ketamine may also prevent opiate tolerance, allowing for smaller doses of opioids to be more effective. Ketamine's usefulness in the perioperative setting is promising, as it has been shown as an analgesic, anesthetic, and to decrease opioid requirements.

Purpose

The purpose of this independent project is to present a case report and provide anesthesia providers with evidence-based research regarding the effect of intraoperative ketamine on post-operative pain in the adult patient with chronic pain. Understanding the pharmacology of ketamine and the pathophysiology of chronic pain will enable anesthesia providers to make informed decisions regarding perioperative pain management.

Case Report

A 28-year-old, 99 kilogram, 160 centimeter female presented for a diagnostic laparoscopy. Past medical history included ovarian cyst and chronic pelvic pain. Past surgical history included cholecystectomy, cervix biopsy, colposcopy and ovarian cystectomy. The patient had an allergy to ketorolac and morphine, both of which caused a rash. Home medications included acetaminophen, ibuprofen, and naproxen. There was no history of anesthetic complications. Pre-operative vital signs were: blood pressure 126/82 mmHg, heart rate 83 beats per minute (BPM), respiratory rate 18/minute, temperature 36.7 degrees Celsius, and oxygen saturation 99% on room air. Pre-operative laboratory data included a negative urine pregnancy. An airway assessment revealed a Mallampati classification II pre-operatively, a

thyromental distance of fewer than three fingerbreadths, and full neck range of motion. The patient was given an American Society of Anesthesiologists physical status class II.

The patient was transported to the operating room (OR). Upon arrival to the OR, she was given 2 milligrams (mg) midazolam intravenously (IV). She was then assisted onto the operating table per OR staff. Standard monitors were applied, including a blood pressure cuff, pulse oximetry, and 5-lead EKG. Vital signs were stable.

The patient was pre-oxygenated via facemask with 100% oxygen. The patient was then induced intravenously through a 20-gauge intravenous catheter with 100 micrograms (mcg) of fentanyl, 60 mg lidocaine, 200 mg propofol, 60 mg rocuronium and 50 mg ketamine. A 7.0 mm cuffed endotracheal tube (ETT) was placed by direct laryngoscopy utilizing a Miller two blade. After intubation, tube placement was confirmed by bilateral breath sound auscultation, the presence of end-tidal carbon dioxide, and condensation within the tube. The tube was secured at 21 cm at the lip. The patient was placed on the ventilator on pressure controlled ventilation-volume guarantee mode with a respiratory rate of 10 breaths per minute, a tidal volume of 550 milliliters and positive end-expiratory pressure of 8 cm/H20. The anesthetic was maintained with sevoflurane with end-tidal concentrations of 1.8-2.4% throughout the case. A nasopharynx temperature probe was inserted for temperature monitoring, and a bispectral index monitor was applied to the forehead to monitor anesthetic depth.

Following induction, the patient was placed in supine position with arms tucked and pressure points padded. The patient received 2 grams of cefazolin IV prior to incision for post operative infection prophylaxis. Six mg of dexamethasone and 4 mg of ondansetron were given intravenously to prevent post-operative nausea and vomiting. A ketamine infusion was initiated at 10mcg/kg/min prior to incision. Another 100 mcg of fentanyl IV was given just prior to

incision for anticipated discomfort. Intra-abdominal pneumoperitoneum was established, and the patient was placed in Trendelenburg position. During the maintenance phase, the patient received 1200 milliliters of lactated ringers. No further fentanyl was administered during the case. Blood loss was estimated to be less than 50 milliliters. The non-depolarizing muscle relaxant was reversed with 0.6 mg of glycopyrrolate IV and 3 mg of neostigmine IV. The patient was extubated awake in the OR without difficulty.

The patient was transported to the post-anesthesia recovery unit (PACU). While in the PACU, the patient required an additional 75 mcg fentanyl intravenously. She was discharged home with a stated pain level of 1/10 to the abdomen and a prescription for oral 5 mg hydrocodone/325 mg acetaminophen.

Literature Search

According to Stillwell, Fineout-Overholt, Melnyk, and Williamson (2010), a literature search to answer a research question should be done using the Cochrane Library, PubMed and CINAHL databases as these will result in the strongest level of evidence. For this literature search, the Cochrane library, PubMed and CINAHL databases were accessed via the University of North Dakota's Health Sciences Library. The Cochrane Library, PubMed, and CINAHL databases were utilized because they contain medical, scientific, and nursing literature (Stillwell et al., 2010).

Keywords and Limits

Within the PubMed database, one search was conducted using Medical Subject Heading (MeSH) terms and the PubMed search builder. Using MeSH terms makes a search all-encompassing by finding all articles related to the concept. The first search utilized the MeSH term "ketamine." In the search results, there were several subheadings. From the subheadings,

therapeutic use was added to the PubMed search builder. The second search included the term "chronic pain," which yielded several more subheadings. From these subheadings, "prevention and control" was added to the PubMed Search builder. This resulted in eight articles. Five of these articles were specifically pertinent to the topic of interest.

The CINAHL database was searched next utilizing the CINAHL headings option for a more effective search. CINAHL headings are similar to MeSH terms in the PubMed database. The terms "ketamine" and "postoperative" were used resulting in 133 articles. To further narrow the results down to pertinent articles, the term "chronic pain" was added, which resulted in seven relevant articles. One final search was conducted in the CINAHL database utilizing the terms "chronic pain," "postoperative," and "opioid use." This search resulted in seven articles.

The terms "ketamine" and "chronic pain" were searched under the "title, abstract, keywords" on the Cochrane database resulting in six articles relevant to this topic. One final search in the Cochrane database utilizing the terms "ketamine" and "perioperative" resulted in three pertinent articles.

Additionally, three applicable articles were found by reviewing the reference list of research articles that had already been evaluated. The identification of key search terms as well as the use of controlled vocabulary within credible healthcare focused databases proved to be an effective and efficient literature search strategy.

After searches within the CINAHL and PubMed databases were completed, a total of 13 articles were saved and reviewed. A review of the literature will be presented in the following section.

Review of Literature

To evaluate the research on intraoperative ketamine use to decrease postoperative opioid requirements in chronic pain patients it is imperative to know and understand the pharmacology of ketamine and pathophysiology of chronic pain. The literature on these topics will be discussed first, followed by the role of ketamine in chronic pain.

Pain Physiology

According to the International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (Steeds, 2016). Pain is a subjective experience that results from both physical and psychological responses to injury and is difficult to measure (Steeds, 2016). It is the result of a complex interchange between signaling systems, modulation from higher centers, and the individual's unique perception (Steeds, 2016). According to Nagelhout and Plaus (2014), pain can be classified based on duration (acute or chronic) or underlying pathophysiology (nociceptive or non-nociceptive). Nociceptive pain is further differentiated into somatic or visceral pain. There are four processes associated with nociceptive pain: transduction, transmission, perception, and modulation. Non-nociceptive pain breaks down into neuropathic or idiopathic pain (Nagelhout & Plaus, 2014).

Acute pain.

Acute pain occurs due to a traumatic injury, surgery or acute illness, and the noxious stimulation it causes (Nagelhout & Plaus, 2014). It usually resolves as healing occurs and is responsive to pharmacological intervention and treatment of the underlying cause (Nagelhout & Plaus, 2014). It is often associated with nociceptive pain and begins with nociceptors (Nagelhout & Plaus, 2014).

Nociceptors are receptors in tissues specific to painful stimuli (Steeds, 2016). Activation of nociceptors initiates signaling systems (Steeds, 2016). The signaling systems transduce the noxious information into an electrical signal and send it to the central nervous system (Steeds, 2016). Nociceptors can be differentiated into two types: high-threshold mechanoreceptors and polymodal nociceptors (Steeds, 2016). High-threshold mechanoreceptors respond to mechanical deformation, while polymodal nociceptors respond to an array of mediators including hydrogen ions, cytokines, bradykinin, histamine, prostaglandins and leukotrienes (Nagelhout & Plaus, 2014; Steeds, 2016). These mediators activate and sensitize nociceptors. Nociceptors transmit their information along two types of nerve fibers: A-delta and C (Steeds, 2016). All pain fibers terminate in the dorsal horn, C fibers in lamina II (the substantia gelatinosa) and A-delta fibers in laminae I and V (Steeds, 2016). In these laminae, the A-delta and C fibers synapse with second-order neurons (Steeds, 2016).

Second-order neurons break down into three types: nociceptive specific, wide dynamic range and low threshold (Steeds, 2016). Nociceptive-specific second-order neurons respond selectively to high-threshold noxious stimuli and are found in laminae II and III (Steeds, 2016). Wide dynamic range second-order neurons respond to a variety of sensory stimuli and are located in laminae V and VI (Steeds, 2016). Low-threshold second-order neurons respond solely to innocuous stimuli (Steeds, 2016). These neurons cross the midline of the spinal cord and ascend in the anterolateral pathway of the spinothalamic tract to the thalamus where they then synapse with third-order neurons (Steeds, 2016). Third order neurons send projections to the cerebral cortex (Steeds, 2016). The pain signal is sent to the amygdala, the somatosensory areas of the cortex, the hypothalamus and the anterior cingulate cortex (Nagelhout & Plaus, 2014). These areas play various roles in the perception of pain (Nagelhout & Plaus, 2014).

Suppression of pain occurs through local inhibitory interneurons and descending efferent pathways (Steeds, 2016). Two important areas of the brainstem are involved in reducing pain, which is the final process of nociceptive pain, the periaqueductal grey, and the nucleus raphe magnus (Steeds, 2016). The periaqueductal grey surrounds the cerebral aqueduct in the midbrain and when stimulated, produces profound analgesia (Steeds, 2016). Anti-nociceptor neurons in the periaqueductal grey excite cells in the nucleus raphe magnus that then project down the spinal cord and block pain transmission by dorsal horn cells (Steeds, 2016). The nucleus raphe magnus consists of serotonin-containing neurons that, when stimulated, produces analgesia and block pain transmission (Steeds, 2016). Several neurotransmitters contribute to the inhibitory modulation of pain; these include enkephalin, glycine, norepinephrine, serotonin and gamma-aminobutyric acid (Nagelhout & Plaus, 2014).

Chronic pain.

Chronic pain is defined as pain that lasts longer than three months or beyond the normal healing time of an injury (Nagelhout & Plaus, 2014). The transition to chronic pain from acute pain occurs when peripheral damage and tissue inflammation switch to more prominent central nervous system mechanisms. Chronic pain is associated with peripheral and central sensitization. As previously described, in response to noxious stimuli, allogenic substances and neurotransmitters are released and enhance excitability of nerves. Constant excitation of these nerves can reduce pain thresholds and cause hyperalgesia. This process is termed peripheral sensitization (Nagelhout & Plaus, 2014).

Changes can also occur directly to nerve endings when nerve injury is present. These changes include the sprouting of new hyperexcitable nerve endings which fire ectopically or the formation of a neuroma, causing abnormal mechanosensitivity (Nagelhout & Plaus, 2014).

Regenerated and damaged nerves also have reduced thresholds, rendering them responsive to non-noxious stimuli (Nagelhout & Plaus, 2014).

Chronic pain is associated with chronic inflammation (Reddi & Curran, 2014). This chronic inflammation causes hyperexcitability and sensitization of second-order neurons in the dorsal horn (Reddi & Curran, 2014). Ongoing nociceptive input may cause an increase in excitability of neurons in the central nervous system (Reddi & Curran, 2014). This is known as central sensitization and may manifest as hyperalgesia or allodynia (Reddi & Curran, 2014). A central mechanism in the spinal cord, called "wind-up," may occur with repeated, prolonged and noxious stimulation (Reddi & Curran, 2014). Wind-up occurs with repeated activation of C fibers and is due to the action of glutamate at NMDA receptors (Reddi & Curran, 2014). Due to the ongoing nociceptive input, second-order neuron response to painful stimuli is amplified and may outlast the initial stimulus, also contributing to hyperalgesia. This also lowers the pain threshold outside the area of inflammation (Reddi & Curran, 2014).

Within the dorsal horn, inhibitory neurotransmitters are reduced, and excitatory synaptic connections are strengthened (Steeds, 2016). Output to the spinothalamic tract is increased as incoming axons develop ectopic activity (Steeds, 2016). This is all mediated via N-methyl-D-aspartate, neurokinins and nitric oxide (Steeds, 2016). The end result is a lowered sensory threshold and an enlarged receptive field (Steeds, 2016). Along with these excitatory neurotransmitters, others such as substance P and calcitonin-gene-related peptide, bind to their receptors and trigger up-regulation of second messengers (Nagelhout & Plaus, 2014). The up-regulation of second messengers produces hyperexcitability of N-methyl-D-aspartate receptors, also contributing to central sensitization and chronic pain (Nagelhout & Plaus, 2014).

N-methyl-D-aspartate Receptors

N-methyl-D-aspartate (NMDA) receptors are glutamate-gated cation channels with high calcium permeability (Nagelhout & Plaus, 2014). They are found at most excitatory synapses in the post-synaptic membrane of a neuron (Mion & Villevieille, 2013). These receptors are present on most cells of the central nervous system, especially those that participate in nociception (Mion & Villevieille, 2013). They are involved in signal transduction, learning, memory formation and pain (Mion & Villevieille, 2013). Full activation of NMDA receptors is both voltage and ligand-gated (Nagelhout & Plaus, 2014). NMDA receptors can have any variation of three different subunits; however, functional receptors are composed of two GluN1 and two GluN2 or GluN3 subunits (Mion & Villevieille, 2013). These subunits contain four hydrophobic segments in their central region, three of which are transmembrane with the fourth being the ionic channel of the receptor (Mion & Villevieille, 2013). Each receptor has an extracellular amino-terminal domain linked to an extracellular ligand binding domain (Vyklicky et al., 2013). This is then connected to a transmembrane domain which forms the ion channel (Vyklicky et al., 2013).

Activation of GluN1 and GluN2 subunits requires two molecules of glycine and two molecules of glutamate (Vytlicky et al., 2013). Other co-agonists that act on these subunits are D-serine, L-serine, D-alanine, and L-alanine (Vytlicky et al., 2013). Glutamate is the major excitatory neurotransmitter in CNS (Nagelhout & Plaus, 2014). It activates NMDA receptors by occupying two binding sites of GluN2 subunits (Vytlicky et al., 2013). Baseline glutamate levels are maintained by a glutamate uptake system and prevent substantial NMDA receptor activation at rest (Vytlicky et al., 2013). This leads to an influx of sodium and calcium and an efflux of potassium, causing depolarization and action potential (Vytlicky et al., 2013). NMDA receptors

are 5-10x more permeable to calcium than to sodium or potassium (Bennett, 2000). The influx of

calcium activates calcium-dependent enzymes and downstream signaling pathways. This can

lead to long-term changes in synaptic strength and cellular modifications (Zito & Scheuss, 2009).

NMDA channel closing is controlled by the rate of glutamate unbinding and receptor

desensitization (Zito & Scheuss, 2009).

Magnesium blocks NMDA receptor activation in a voltage-dependent manner (Nagelhout

& Plaus, 2014). At resting membrane potential, the receptor remains blocked (Nagelhout &

Plaus, 2014). With membrane depolarization, the magnesium block is relieved (Zito & Scheuss,

2009). At this time, any NMDA receptors with glutamate will open (Zito & Scheuss, 2009).

Coactivation of multiple synapses can overcome magnesium block (Zito & Scheuss, 2009).

NMDA receptor activation requires glutamate presence and binding along with depolarization of

postsynaptic membrane to unseat the magnesium (Bennett, 2000). Calcium influx into

postsynaptic cells activates signaling molecules in postsynaptic cells (Bennett, 2000).

Central sensitization occurs when glutamate released from C-nociceptors activate NMDA

receptors (Bennett, 2000). As previously discussed, activation of NMDA receptor by glutamate

released from C-fibers causes the spinal cord neuron to become more responsive to inputs,

including input from damaged or sensitized nociceptors and low-threshold mechanoreceptors,

contributing to the development of central sensitization and chronic pain (Bennett, 2000).

Excessive activation of NMDA receptors leads to excitotoxic cell death and plays a crucial role

in many acute and chronic neuro disorders (Vyklicky et al., 2013).

NMDA receptor antagonists can act at the agonist binding site, within the ion channel

pore or at specific modulation sites (Vyklicky et al., 2013). Competitive antagonists compete

with the agonist for the binding site but do not activate the receptor (Vyklicky et al., 2013).

Dissociative anesthetics act as a potent channel blocker (Vyklicky et al., 2013). Blockade of the ion channel is voltage and use-dependent which means the block of the channel requires previous receptor activation (Vyklicky et al., 2013). Inhibition by channel blockers is slow in onset and increases with the probability of channel opening (Nagelhout & Plaus, 2014).

Phosphorylation with phosphatase protein type I and cAMP-dependent protein kinase at the GluN1 subunit is responsible for long-term potentiation, hyperalgesia and opioid interactions with the NMDA receptor (Mion & Villevieille, 2013). Opioid receptors have been found to cause a dose-dependent activation of NMDA receptors on the surface of the same cells (Mion & Villevieille, 2013). Phosphorylation of NMDA receptors decreases the magnesium plug and calcium can enter the cell (Mioin & Villevieille, 2013). This leads to down-regulation and a blunted response of opioid receptors (Mion & Villevieille, 2013).

Ketamine

Ketamine was synthesized by Calvin Stevens in 1962 out of phencyclidine derivatives in search of the ideal anesthetic agent with analgesic properties (Mion, 2017). Phencyclidine was initially studied but was found to cause severe excitation, to the point of unmanageable (Mion, 2017). In 1964, the first dose of ketamine was administered to humans by doctors Corssen and Domino (Mion, 2017). This led to the first clinical study published in 1965, which described the dissociative anesthesia associated with ketamine administration (Mion, 2017). Ketamine became available in 1969 for human and animal use and officially approved by the United States Food and Drug Administration in 1970 (Mion, 2017). However, widespread use of ketamine was halted due to concerns about hallucinations and the arrival of Propofol on the market (Mion, 2017). Following the Vietnam War, ketamine abuse became a problem and ketamine was added to the class III substances list (Mion, 2017).

Much has been learned over the years through studies completed on ketamine, including much of what is known about NMDA receptors and their various roles. Ketamine is now being used to treat depression, as well as chronic pain (Mion, 2017).

Chemical make-up.

Ketamine is an arylcyclohexylamine derivative structurally related to phencyclidine (Barash et al., 2017). The chemical structure of ketamine is 2-(O-chlorophenyl)-2-(methylamino)cyclohexane hydrochloride (Nagelhout & Plaus, 2014). Ketamine contains a chiral center at the C-2 carbon of the cyclohexanone ring, creating two enantiomers: S(+)ketamine and R(-)ketamine (Barash et al., 2017). The S-enantiomer is more potent, has a shorter duration of action, and is cleared more rapidly than the R-enantiomer (Barash et al., 2017). Ketamine is a white crystalline powder that is partially water-soluble, slightly acidic with a pH of 3.5 to 5.5 and 7.5 pKa. (Nagelhout & Plaus, 2014).

Pharmacokinetics.

Ketamine is bioavailable by intravenous, intramuscular, transnasal, rectal, and oral routes (Barash et al., 2017). It is lipid soluble and not highly protein bound which allows for rapid uptake in highly perfused areas first (Barash et al., 2017). The onset of action after intravenous administration is 30 to 60 seconds and duration of 10 to 15 minutes (Barash et al., 2017). Ketamine is redistributed from the central nervous system to the peripheral tissues in 11 minutes, and total elimination from the body is 2.5 hours after intravenous administration (Barash et al., 2017). Ketamine is metabolized by cytochrome P-450 enzymes by demethylation to norketamine (Barash et al., 2017). Norketamine is one-third as active as ketamine (Barash et al., 2017).

Mechanism of action.

Ketamine works on NMDA, opioid, noradrenergic, nicotinic and muscarinic receptors (Miller et al., 2015). However, it is its non-competitive antagonist action on NMDA receptors that are responsible for its main pharmacological properties (Miller et al., 2015). Ketamine binds to an intrachannel site on the NMDA receptor referred to as the phencyclidine site (Miller et al., 2015). This binding decreases channel opening time (Barash et al., 2017; Mion & Villevieille, 2013). Ketamine prevents "windup," especially if the NMDA receptor was already opened by glutamate (Mion & Villevieille, 2013). It also works on a second site in the hydrophobic domain of the NMDA receptor to decrease the frequency of channel opening (Miller et al., 2015). By blocking these receptors, the medial thalamic nuclei, responsible for preventing afferent signals of pain perception to the thalamus and cortex, is depressed (Nagelhout & Plaus, 2014). NMDA-receptor antagonists suppress central sensitization (Bennett, 2000).

Ketamine's action on noradrenergic neurons causes inhibition of catecholamine uptake and leads to a hyperadrenergic state with increased release of norepinephrine, dopamine, and serotonin (Mion & Villevieille, 2013). This inhibition leads to prolonged synaptic action and an increased transfer of norepinephrine in the circulation (Mion & Villevieille, 2013). The hypnotic, psychic and analgesic effects of ketamine are partly due to this action (Mion & Villevieille, 2013). Ketamine affects CNS cholinergic neurons (Mion & Villevieille, 2013). It also acts on central nervous system cholinergic neurons by directly inhibiting nicotinic and muscarinic receptors (Mion & Villevieille, 2013). Of the opioid receptors, ketamine binds to mu, delta, and kappa but this is not believed to provide analgesia (Mion & Villevieille, 2013). The kappa opioid receptor involvement may be responsible for some of the psychic effects seen with ketamine (Mion & Villevieille, 2013).

Ketamine causes "dissociative anesthesia" due to a functional dissociation between thalamo-neocortical and limbic systems which allow sensory inputs to reach receiving areas but fail to be observed (Mion & Villevieille, 2013). It depresses neuronal function in the cerebral cortex and thalamus while simultaneously activating the limbic system (Mion & Villevieille, 2013).

Side effects and contraindications.

Ketamine affects the cardiovascular, central nervous, and respiratory systems (Nagelhout & Plaus, 2014). It increases cerebral blood flow and the cerebral metabolic rate of oxygen, thus increasing intracranial pressure (Nagelhout & Plaus, 2014). Because of this, ketamine is contraindicated in patients with increased intracranial pressure (Nagelhout & Plaus, 2014). Ketamine modifies electroencephalogram readings by decreasing alpha rhythm amplitude and the appearance of theta waves (Miller et al., 2015). It has also been found to cause a dose-dependent increase in the bispectral index (Nagelhout & Plaus, 2014). Due to its effects in the central nervous system, patients will exhibit a cataleptic state with nystagmus and pupil dilation (Miller et al., 2015).

Ketamine causes psychological reactions that may occur during awakening (Miller et al., 2015). These are often manifested as vivid dreaming, hallucinations, and extracorporeal experiences (Miller et al., 2015). They are secondary to depression of auditory and visual relay nuclei that leads to misinterpretation of auditory and visual stimuli (Miller et al., 2015). The incidence of these reactions can be reduced by administration of benzodiazepines (Miller et al., 2015; Nagelhout & Plaus, 2014).

Ketamine preserves protective airway reflexes and has bronchodilatory activity (Naglehout & Plaus, 2014). It has minimal effects on the central respiratory drive (Nagelhout &

Plaus, 2014). It does cause lacrimation and salivation through its action on cholinergic receptors (Nagelhout & Plaus, 2014).

Ketamine has cardiovascular stimulating effects related to direct stimulation of the sympathetic nervous system, causing an increase in pulmonary and systemic blood pressure, heart rate, and cardiac output, thereby increasing myocardial oxygen consumption (Miller et al., 2015). According to Miller et al. (2015), cardiovascular stimulation occurs after small dose ketamine infusion. Cardiodepression may also occur either pre-stimulation or post-infusion. Cardiodepression may precede stimulation if a large dose of ketamine is administered. It may also happen after repeated administrations when presynaptic catecholamine stores become depleted. Post-infusion, cardiodepression may be seen if cardiac output drops below pre-infusion cardiac output. Benzodiazepines may be helpful to prevent the stimulating effects (Miller et al., 2015).

Other side effects seen include increased intraocular pressure, potentiation of neuromuscular blocker and nausea and vomiting (Nagelhout & Plaus, 2014). According to Kaur, S., Saroa, R., and Aggarwal, S. (2015) ketamine-related adverse effects are uncommon in patients who have general anesthesia. Adverse effects are more likely to be seen in patients who receive bolus doses greater than 2 mg/kg, rapid administration or infusion rate greater than 2.5 mg/kg/min (Kaur et al., 2015).

Perioperative dosing.

Several completed studies have discussed the correct way to administer ketamine during surgery to decrease postoperative opioid requirements. Some studies focus on giving a bolus of ketamine at the beginning of surgery, some administer an infusion throughout, and others give

both a bolus and infusion. The one thing that is consistent is the dose of ketamine administered must be in a sub-anesthetic range to provide analgesic therapy.

According to Miller et al. (2015), ketamine administration in small doses decreases postoperative analgesic consumption by 33 percent. They state an infusion rate of 0.15-0.25 milligram/kilogram or a total dosage of 20-60 milligram perioperatively is adequate to provide this analgesic effect. An added benefit of decreased opiate use is reduced opiate side effects.

Remerand et al. (2009) conducted a randomized, double-blind, controlled clinical trial that included 154 patients undergoing total hip arthroplasty. In this study, patients were administered both a bolus and infusion of saline or ketamine. Patients who received the ketamine bolus and infusion intra-operatively were found to have decreases in all of the following post-operatively: morphine consumption at 24 hours, walking assistance at 30 days, and hip pain while at rest at 180 days.

A literature review conducted by Jougelet-Lacoste, La Colla, Schilling and Chelly (2015) concluded that low-dose intravenous ketamine reduces opioid consumption by 40% and lowers pain scores following surgery. Low-dose intravenous ketamine was defined as a bolus of < 1 mg/kg and/or an infusion of 1.2 mg/kg/hr. These clinical trials included a total of 2,482 patients with 1,403 who received ketamine. Jougelet-Lacoste et al. (2015) did not find any major complications when the ketamine was administered at sub-anesthetic doses.

Both Arikan, Aslan, Horasanh and But (2016) and Menigaux, Fletcher, Dupont, Guignard, Guerimund and Chauvin (2000) found that small-dose intraoperative ketamine decreased the amount of morphine required in the PACU and 24 hours after surgery. Another randomized, double-blind, controlled clinical trial looked at using a ketamine infusion, specifically, and found that these patients analgesia was effective in the post-operative period

(Kaur, Saroa & Aggarwal, 2015). These patients were given a 0.2 mg/kg ketamine bolus intravenously followed by an infusion of 0.1 mg/kg/hr for an open cholecystectomy. They found that intraoperative infusion of low-dose ketamine provided effective analgesia for the first 6 hours in the postoperative period. The opioid-sparing effect of ketamine was observed to be useful for narcotic-tolerant patients.

Loftus et al. (2010) conducted a randomized, double-blind controlled study, which showed a decrease in opiate usage for 48 hours following surgery. The main difference between this study and the ones previously listed is the inclusion criteria required that the patients had a history of chronic pain with daily opiate use. This study also found that ketamine may reduce pain intensity. These patients were given a 0.5 milligram/kilogram ketamine bolus intravenously followed by an infusion of 10 microgram/kilogram/hour infusion.

A systematic review completed by Himmelseher & Duriex (2005) was completed to examine the perioperative use of ketamine as an adjunct to general anesthesia and postoperative pain therapy. A total of 10 trials met inclusion criteria. Surgeries were described as being painful or less painful. A major visceral surgery was considered a painful surgery with a lumbar spine surgery being less painful. An initial bolus of 0.2 mg/kilogram intravenous ketamine for less painful surgeries and a bolus of 0.35 mg/kilogram for a painful surgery was administered prior to incision, followed by a 200-400 mcg/kilogram/hour infusion or a 0.1-0.2 milligram/kilogram bolus every 30 minutes was sufficient as an analgesic adjunct (Himmelseher, S. & Duriex, M., 2005).

Conclusion

In conclusion, the majority of recent research suggests perioperative ketamine use to be an excellent adjunct for postoperative analgesia and decreased opioid consumption. Ketamine

has been shown to supplement post-operative pain management in all patients, including chronic pain patients. In the aforementioned case study, ketamine was administered to a patient with a history of chronic pain throughout a laparoscopic surgery with minimal opioid requirement immediately post-operatively. It is impossible to state that the decreased post-operative opioid requirements are solely due to the ketamine administered, but the research supports this.

Literature supports intraoperative ketamine with sub-anesthetic dosing to be beneficial for all patients in decreasing post-operative opioid requirements. More research is needed to determine the ideal dose, but there does seem to be consistency with a ketamine bolus of less than or equal to 0.5mg/kg with or without an infusion.

Adequate pain management in patients with and without chronic pain is imperative in healthcare today. Multi-modal analgesia and decreasing opioid requirements in patients plays a considerable role in reducing opioid use overall. Anesthesia providers play a central role in pain management in many patients and would benefit from additional knowledge in ketamine administration.

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Appendix A

Intraoperative Ketamine to Reduce Postoperative Opioid Consumption in Chronic Pain Patients

Allyssa Wutzke, SRNA

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Introduction

- Chronic pain is an epidemic in the United States, resulting in an increased number of prescribed opioids. Medical professionals are being encouraged to decrease opioid prescriptions.
- Chronic pain patients who have a surgical procedure and are currently prescribed an opioid experience markedly higher postoperative pain.

(Chapman et al., 2011)

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Introduction continued

- NMDA receptors contribute to the pain felt after tissue injury and can cause increased pain perception.
- Ketamine binds to the NMDA receptors and blocks this effect reducing the patient's pain postoperatively
- Ketamine's usefulness in the perioperative setting is promising
  - It is an analgesic and an anesthetic
  - Decreases opioid requirements

(Nagelhout & Plaus, 2014)

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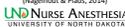
Case Information

- Diagnostic laparoscopy
- 29 year old female
- 99 kilogram – BMI 38.63
- ASA II
- Allergies to ketorolac and morphine

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Pre-operative Evaluation

- Past Medical History
  - ovarian cyst, chronic pelvic pain
- Surgical History
  - cholecystectomy, cervix biopsy, colposcopy, ovarian cystectomy
- Pre-op VS
  - BP: 126/82 HR: 83 RR: 18 T: 36.7C O2: 99% RA
- Pertinent labs
  - negative urine pregnancy
- Airway evaluation
  - Mallampati classification II, thyromental distance less than 3 fingerbreadths, full neck range of motion

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Anesthetic Course

- Pre-induction
  - 2mg midazolam IV

- Induction
  - 100mcg Fentanyl IV
  - 60mg Lidocaine IV
  - 200mg Propofol IV
  - 60mg Rocuronium IV
  - 50mg Ketamine (0.5mg/kg bolus) IV

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Anesthetic Course

- Maintenance
  - 1.8-2.4% Sevoflurane
  - 2 g Cefazolin IV
  - 6 mg Dexamethasone IV
  - 10 mcg/kg/min Ketamine IV infusion
  - 100 mcg Fentanyl with incision

- Emergence
  - 0.6 mg Glycopyrrolate IV
  - 3 mg Neostigmine IV
  - 4 mg Ondansetron IV

  1200mL LR total   EBL minimal

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PACU

- Patient complained of moderate pain and was given 75mcg Fentanyl IV.
- Patient was discharged home with 1/10 abdominal pain.
- No adverse effects noted while in PACU.

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Chronic Pain

- Chronic pain is defined as pain that lasts longer than three months or beyond the normal healing time of an injury
  (Nagelhout & Plaus, 2014)
- Acute pain turns into chronic pain when peripheral damage and tissue inflammation switch to more prominent central nervous system mechanisms.
- Changes can also occur directly to nerve endings when nerve injury is present.
  - Regenerated and damaged nerves also have reduced thresholds, rendering them responsive to non-noxious stimuli
- Chronic pain is associated with chronic inflammation.
  - Causing hyperexcitability and sensitization of second-order neurons in the dorsal horn
  (Reddi & Curran, 2014)

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Chronic Pain continued

- Central sensitization
  - Ongoing nociceptive input may cause an increase in excitability of neurons in the central nervous system
  - May manifest as hyperalgesia or allodynia
  - Wind-up occurs with repeated activation of C fibers and is due to the action of glutamate at NMDA receptors.
  (Reddi & Curran, 2014)
- NMDA receptors also contribute to central sensitization and chronic pain
  - Due to up-regulation of second messengers causing hyperexcitability of NMDA receptors
  (Steeds, 2015)

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NMDA Receptor

- N-methyl-D-aspartate (NMDA) receptors are glutamate-gated cation channels with high calcium permeability
- Found at most excitatory synapses in the post-synaptic membrane of a neuron
- Present on most cells of the central nervous system, especially those that participate in nociception
  (Mion & Villevieille, 2013)

- Magnesium blocks NMDA receptor activation in a voltage-dependent manner
  - At resting membrane potential, the receptor remains blocked. With membrane depolarization, the magnesium block is relieved
  (Nagelhout & Plaus, 2014)

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NMDA Receptor continued

- Glutamate is the major excitatory neurotransmitter in CNS
  - It activates NMDA receptors by occupying two binding sites of GluN2 subunits
  (Vytlicky et al., 2013)
  - NMDA receptor activation requires glutamate presence and binding along with depolarization of postsynaptic membrane to unseat the magnesium
  (Bennett, 2000)

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Ketamine

- Structurally related to phencyclidine
- Has two enantiomers: S(+)ketamine and R(-)ketamine.
- Ketamine is bioavailable by intravenous, intramuscular, transnasal, rectal, and oral routes
- Lipid soluble and not highly protein bound
  - Rapid uptake in highly perfused areas first
  - The onset of action after intravenous administration is 30 to 60 seconds and duration of 10 to 15 minutes
- Ketamine is metabolized by cytochrome P-450 enzymes by demethylation to norketamine

(Barash et al., 2017)

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Ketamine continued

- Works on NMDA, opioid, noradrenergic, nicotinic and muscarinic receptors
  (Miller et al., 2015)
- Binds to an intrachannel site on the NMDA receptor referred to as the phencyclidine site (this binding decreases channel opening time)
- It also works on a second site in the hydrophobic domain of the NMDA receptor to decrease the frequency of channel opening
  - By blocking these receptors, the medial thalamic nuclei, responsible for preventing afferent signals of pain perception to the thalamus and cortex, is depressed
  - NMDA-receptor antagonists suppress central sensitization
    (Miller et al., 2015)

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Ketamine continued

- Causes "dissociative anesthesia" due to a functional dissociation between thalamo-neocortical and limbic systems which allow sensory inputs to reach receiving areas but fail to be observed
  - It depresses neuronal function in the cerebral cortex and thalamus while simultaneously activating the limbic system
- Ketamine prevents "windup," especially if the NMDA receptor was already opened by glutamate

(Mion & Villevieille, 2013)

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Perioperative Dosing

- Miller et al. (2015) states ketamine administration in small doses decreases postoperative analgesic consumption by 33 percent
  - Infusion rate of 0.15-0.25 mg/kg or a total dosage of 20-60 mg perioperatively is adequate to provide this analgesic effect.
- Remerand et al. (2009) conducted a randomized, double-blind, controlled clinical trial
  - Included 154 patients undergoing total hip arthroplasty
  - Given both a bolus and infusion of saline or ketamine.
  - Patients who received the ketamine bolus and infusion intra-operatively were found to have decreases in all of the following post-operatively: morphine consumption at 24 hours, walking assistance at 30 days, and hip pain while at rest at 180 days.

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Perioperative Dosing continued

- A literature review conducted by Jougelet-Lacoste, La Colla, Schilling and Chelly (2015) concluded
  - low-dose intravenous ketamine reduces opioid consumption by 40%
  - lowers pain scores following surgery
  - Low-dose intravenous ketamine was defined as a bolus of < 1 mg/kg and/or an infusion of 1.2 mg/kg/hr
  - These clinical trials included a total of 2,482 patients with 1,403 who received ketamine
  - did not find any major complications when the ketamine was administered at sub-anesthetic doses

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Perioperative Dosing continued

- Studies by Arikan, Aslan, Horasanh and But (2016) and Menigaux, Fletcher, Dupont, Guignard, Guerimund and Chauvin (2000)
  - small-dose intraoperative ketamine decreased the amount of morphine required in the PACU and 24 hours after surgery.
- Kaur, Saroa and Aggarwal (2015) conducted a randomized, double-blind, controlled clinical trail
  - Patients were given a 0.2 mg/kg ketamine bolus followed by an infusion of 0.1 mg/kg/hr for an open cholecystectomy.
  - intraoperative infusion of low-dose ketamine provided effective analgesia for the first 6 hours in the postoperative period.
  - the opioid-sparing effect of ketamine was observed to be useful for narcotic-tolerant patients.

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Perioperative Dosing continued

- Loftus et al. (2010) conducted a randomized, double-blind controlled study
  - Showed a decrease in opiate usage for 48 hours following surgery
  - Inclusion criteria required that the patients had a history of chronic pain with daily opiate use
  - Found that ketamine may reduce pain intensity
  - Given a 0.5 mg/kg ketamine bolus IV followed by a 10mcg/kg/min infusion

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Perioperative Dosing continued

- A systematic review completed by Himmelseher & Duriex (2005)
  - Examined the perioperative use of ketamine as an adjunct to general anesthesia and postoperative pain therapy.
  - Surgeries were described as being painful or less painful. A major visceral surgery was considered a painful surgery with a lumbar spine surgery being less painful.
  - Bolus ranged from 0.2-0.35 mg/kg depending on anticipated pain of surgery followed by infusion of 200-400 mcg/kg/hr infusion or 0.1-0.2 mg/kg bolus every 30 minutes
  - These doses were deemed sufficient as an analgesic adjunct

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Recommendations

- Ketamine should be used to supplement post-operative pain management in chronic pain patients
- More research needed to determine ideal dosing
  - There does seem to be consistency in the current literature with a ketamine bolus of 0.2-0.5mg/kg followed by an infusion or hourly dosing
    - Minimal or no side effects noted in literature at these doses

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Conclusion

- Case Study
  - 0.5 mg/kg bolus given at induction followed by 10mcg/kg/min infusion perioperatively
  - Within the ranges noted above
- Literature supports sub-anesthetic dosing beneficial for chronic patients in decreasing post-operative opioid requirements.

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Thank You
Are There Any Questions?

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