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EXAMINING THE EFFECTS OF KETAMINE ON REDUCING THE

INCIDENCE OF OPIOID-INDUCED HYPERALGESIA

IN THE PERIOPERATIVE PHASE

A Major Paper Presented

by

Marie Rahme

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EXAMINING THE EFFECTS OF KETAMINE ON REDUCING THE INCIDENCE OF OPIOID-INDUCED HYPERALGESIA IN THE PERIOPERATIVE PHASE

by

Marie Rahme

A Major Paper Submitted in Partial Fulfillment

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Abstract

Pain in the postoperative period is a serious issue that can have a negative physical and emotional impact on patient outcomes. Complications from postoperative pain can have detrimental outcomes for patient's health and wellbeing as well as the increased economic burden of continued treatment. Better management of pain in the perioperative phase can result in improved patient outcomes, fewer postoperative complications, and increased patient satisfaction. Although opioids are the mainstay of treatment in the perioperative period for pain management, abnormal pain responses such as hyperalgesia may be induced by administration of opioids. The purpose of this systematic review is to examine the effect of ketamine on reducing the phenomenon of opioid-induced hyperalgesia. After a comprehensive literature search, the PRISMA Statement was used to frame this systematic review and elevate the validity of the results by providing transparency and clarity of the findings. The theoretical framework that guided this systematic review was Melzack and Wall's (1965) Gate Control Theory of Pain which encompassed the physiologic and emotional responses of pain. Studies incorporated in this systematic review were critically appraised to evaluate reliability of randomized control trials. Variables such as intraoperative doses of opioids, intraoperative ketamine doses, postoperative pain scores, postoperative opioid consumption, and evidence of hyperalgesia were evaluated and put into tables for comparison. The results of this systematic review support the use of ketamine in decreasing postoperative opioid consumption, decreasing postoperative pain scores, and decreasing the incidence of opioid induced hyperalgesia.

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EXAMINING THE EFFECTS OF KETAMINE ON REDUCING THE INCIDENCE OF OPIOID-INDUCED HYPERALGESIA IN THE PERIOPERATIVE PHASE

Background/Statement of the Problem

The phenomenon of pain is a multifaceted problem that millions of Americans endure. Pain involves not only a physical response to an injury that occurs, but an emotional and psychological response as well. Failure to recognize all aspects of pain and only focus on physical manifestations may lead to inadequate management of symptoms. Approximately 40% of Americans struggle with chronic pain and pain is one of the most common reasons for individuals to seek medical treatment in this country (Flood, Rathmell, & Shafer, 2015). Bottemiller (2012) estimated that medical expenses related directly to medical or surgical pain management along with indirect costs of lost workdays and decreased productivity cost Americans approximately $635 billion per year. These staggering statistics reveal the importance for health care providers to understand the complexity of pain so that they may be better equipped to treat it.

Pain in the postoperative period is a serious issue that can have a negative impact on patient outcomes. Poorly managed pain in the perioperative phase can result in pathologic conditions such as deep vein thrombosis, pulmonary embolism, pneumonia, and impaired wound healing (Apefelbaum, Chen, Mehta, & Gan, 2003). Pain can also result in emotional and psychological complications such as demoralization, insomnia, and patient dissatisfaction (Apefelbaum et al., 2003). These postoperative complications can result in extended length of stay in the hospital, hospital readmissions, as well as the economic burden of continued treatment (Apefelbaum et al., 2003). Better management of pain in the perioperative phase can result in better patient outcomes, fewer postoperative complications, and increased patient satisfaction.

Opioids are a common class of drug that many health care providers utilize to medically manage pain symptoms on a chronic outpatient basis, in the hospital setting, or during the perioperative phase in surgical patients. There are many risks associated with opioid use including physiological side effects, such as euphoria, respiratory depression, constipation, miosis, bradycardia, and urinary retention (Flood et al., 2015). Some untoward effects of opioids with chronic use include physical and psychological dependence, tolerance, and hyperalgesia (Bottemiller, 2012). Opioid tolerance is defined by Mauermann et al., (2015) as "desensitization to opioid effect requiring more opioid to reach the same effect" (p. 460). Mauermann et al., (2015) also define opioid-induced hyperalgesia as "an increase in pain sensitivity induced or aggravated by opioids" (p. 460). Since these two phenomena have a similar clinical presentation, it is imperative for health care providers to differentiate between them because with tolerance, an increase in opioid dosage will alleviate painful symptoms whereas with opioid-induced hyperalgesia, an increased dose of opioids will intensify painful symptoms. The occurrence of hyperalgesia after abrupt discontinuation of chronic opioids is well-documented; however, recent research has indicated that high dose opioids for even a short period of time, such as during the perioperative phase, can induce hyperalgesia (Bottemiller, 2012).

Treatment options for tolerance include increasing the dose of opioids and using a multimodal approach to pain management to produce analgesia (Flood et al., 2015). Treatment of opioid-induced hyperalgesia is still being researched, but many studies point to N-methyl-D-aspartate (NDMA) antagonists such as ketamine as being a viable option to manage this phenomenon (Bottemiller, 2012).

Reduction in postoperative complications, such as opioid-induced hyperalgesia may result in improved patient outcomes and better patient satisfaction. The purpose of this systematic review is to determine the possible effects that ketamine has on the occurrence of opioid-induced hyperalgesia in adult surgical patients.

A review of the literature will be presented next.

Literature Review

A literature search was conducted using the following key words: “pain”, “hyperalgesia”, “opioid-induced hyperalgesia”, “ketamine”, “fentanyl”, “remifentanil”, “sufentanil”, “prevention”, and “treatment”. The databases and websites used included MEDLINE, PubMed, CINHAL, and Google Scholar. These sources provided relevant research articles produced within the past 19 years for use within this review of the literature.

Physiology of Pain

Pain is a complex phenomenon that is experienced, and described differently, based on an individual’s perception of it. Pain is usually precipitated by a noxious stimulus that creates an unpleasant sensation in the individual experiencing it. This unpleasant sensation sometimes acts as a necessary protective mechanism to warn the body against danger.

The human body is equipped with pain receptors called nociceptors located throughout the entire body with the exception of the brain (Helms & Barone, 2008). These nociceptors are free nerve endings that sense pain at the site of the harmful stimulus and transmit information through an afferent pathway beginning in the dorsal horn of the spinal cord and then traveling to the thalamus in the brain (Pandharipande & McGrane, 2017). The limbic system and cerebral cortex also play a role in pain interpretation and perception because pain is both an emotional and physical phenomenon (Helms & Barone, 2008).

Pain involves the four phases of transduction, transmission, modulation, and perception that make up the process of nociception, or the pain experience. Transduction begins at the site of injury where the release of chemical mediators of pain respond to a

noxious stimulus by converting the chemical information to sensory information (Flood et al., 2015). Chemical mediators of pain such as histamine, substance P, bradykinin, acetylcholine, leukotrienes, and prostaglandins are released by the damaged tissues (Flood et al., 2015). These chemical mediators can cause a variety of physiological reactions, such as inflammation at the site of the injury (Helms & Barone, 2008). Often it is the inflammation itself that causes the sensation of pain and leads to the requirement of analgesic medications to alleviate painful symptoms.

Transmission of chemical signals involves the pain signal moving from the peripheral nervous system toward the central nervous system (Flood et al., 2015). There are thought to be two types of nerve fibers that aid in pain transmission and sensation along this afferent pathway: A_δ fibers and C fibers (Helms & Barone, 2008). A_δ fibers are large fibers, myelinated fibers responsible for what Helms and Barone (2008) describe as "first pain" or acute pain. The A_δ fibers facilitate a fast response to a stimulus for the individual experiencing the pain. According to Helms and Barone (2008), the C fibers are responsible for the "second pain" or the constant, prolonged, aching pain that remains after the initial tissue injury.

Modulation of pain involves the release of inhibitory or excitatory neurotransmitters that affect the way pain impulses reach the central nervous system. Releasing certain inhibitory neurotransmitters such as endogenous opioids like enkephalins, endorphins, serotonin, and norepinephrine can fully or partially block the transmission of pain signals to the brain. These inhibitory neurotransmitters can also prevent the release of some of the excitatory chemical mediators of pain such as substance P, leading to decreased pain perception (Flood et al., 2015).

Perceptions of Pain

Acute and Chronic Pain. Although there are many causes and descriptive characteristics of pain, pain is usually separated into two categories; acute pain and chronic pain. Acute pain is referred to as the initial pain that stimulates the sympathetic nervous system's fight or flight response. It usually decreases in severity over time and provides a warning that an injury has occurred (Helms & Barone, 2008). Helms and Barone (2008) describe chronic pain as sustained pain that lasts longer than what constitutes as a normal healing time for an illness or injury. The concept of chronic pain is poorly understood and difficult to manage (Helms & Barone, 2008). This can be due to a variety of factors including the differences in how different populations experience and describe pain.

Sex-based Differences in Pain Perception. Many differences exist in how pain is described and reported based on patient demographics such as sex. Current literature describes sex-based differences in pain reporting, in fact Helms and Barone (2008) note that women report pain more frequently than men and with greater intensity. For instance, chronic pain disorders such as fibromyalgia and migraines are found to be more prevalent in female populations than men (Helms & Barone, 2008; Paller, Campbell, Edwards, & Dobs, 2009). This could be due in part to recent research suggesting that brain activity in men and women vary during painful experiences (Paller et al., 2009). In their review on sex-based differences in pain perception and treatment, Paller et al., (2009) described differences seen between men and women on magnetic resonance imaging (MRI). In patients diagnosed with irritable bowel syndrome (IBS) experiencing mild rectal distension, MRI studies showed that this pain activated the left thalamus and

ventral striatum of the brain in men, whereas in women, this painful stimulus deactivated areas of the amygdala and mid-cingulate (Paller et al., 2009). Men experienced greater activation of the insula compared to females during anticipation of pain (Paller et al., 2009).

Background. The limbic system in the brain is involved with the behavioral and emotional response to pain and contains the hypothalamus, insula, ventral striatum, amygdala, and hippocampus (Hall, 2016). The ventral striatum in the basal ganglia of the brain contains the nucleus accumbens which is involved in dopamine secretion and reward pathways (Hall, 2016). This area of the brain has been shown to be activated during anticipation of or experience of pleasant events, but the significance of activation during painful events in men is poorly understood (Paller et al., 2009). Jensen et al., (2003) hypothesized that activation of the ventral striatum during painful experiences may be due to anticipation of pain cessation. The amygdala is a part of the limbic system involved learning and subconscious behavior awareness that allows humans to appropriately express anxiety and fear (Hall, 2016). The mid-cigulate is a component of the paralimbic region and receives inputs from the amygdala (Jensen et al., 2003). Paller et al., (2009) inferred that deactivation of these areas in the brain as seen on MRI in the female population may be due to greater familiarity with pelvic pain in women. The insula is part of the limbic system involved in relaying sensory information regarding reactions to pain and processing emotions (Jensen et al., 2003). Sex-based differences in activation and deactivation of these areas of the brain may contribute to differences in the processing of actual or anticipated painful stimuli in men and women (Paller et al., 2009).

Age Related Differences in Pain Perception. Helms and Barone (2008) also compared pain perception in children to pain perception in the elderly. These researchers note that it is often a misconception that infants and children do not experience pain due to their immature nervous systems. On the contrary, pain can be experienced by fetuses as young as 24 weeks gestation because their central nervous system is usually formed and functioning by that time (Mathew & Mathew, 2003; Helms & Barone, 2008). Nociceptive impulses in infants travel to the spinal cord through unmyelinated fibers rather than the myelinated fibers utilized by adults for pain transmission (Mathew & Mathew, 2003). Infants also have higher concentrations of substance P than adults (Mathew & Mathew, 2003). This suggests that infants may experience more pain than adults due to their lower nociceptive threshold.

Pain experienced by infants and children during the developing years may have long-term behavioral and psychological consequences and may also increase perceptions of pain as children grow older (Helms & Barone, 2008). Negative long term effects of pain in neonates have been demonstrated in many studies and include Alzheimer's disease, depression, anxiety, and hyperalgesia (Correa et al., 2018). These potential detrimental effects are related to damage to the peripheral and central pain pathways during neurodevelopment. In their prospective interventional case control study, Gajbhiye, Rao, and Singh (2018) aimed to compare the analgesic effects of breast feeding and oral sucrose in full term, healthy, breastfed, vaginally delivered newborns. Their study included 150 newborns who were separated into three groups: group I, n=50 (control), group II (interventional), n=50, and group III (interventional), n=50. There were 74 male and 76 female newborns included in this study. These newborns were

observed during administration of a painful, intramuscular hepatitis B vaccine. Newborns in group I were treated as the control group and received their vaccination without intervention while sitting on their mother's lap. Newborns in group II were given 1 ml of 25% oral sucrose two minutes prior to administration of the vaccine and were also held on their mother's lap during vaccination. Newborns in group III were breastfed two minutes prior to vaccination and were also given the vaccine while on their mother's lap. The neonate's pain was evaluated using a Premature Infant Pain Profile (PIPP) scale which has been accepted to be a reliable and valid tool used to quantify pain in infants (Duhn & Medves, 2004). PIPP examines variables such as gestational age, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow to measure pain in infants. Cry time was also measured and calculated for 30, 60, 90, and 120 seconds after vaccination. PIPP scores were considered the primary outcome of this study. The mean PIPP scores were significantly lower ($p < 0.0001$) in infants in group III who were breast fed, compared to those group II who were given oral sucrose or group I who was given no intervention. The duration of cry time was lower in group III compared to groups I and II; however, the results were not significant ($p > 0.05$). The results of this research suggest that infants not only experience pain, but that breast feeding provides superior analgesia to oral sucrose in decreasing pain with intramuscular injection of a vaccine (Gajbhiye, Rao, & Singh, 2018).

The elderly population is also not well understood when it comes to pain management. In their 2008 review of the physiology of pain, Karp, Shega, Marone, and Weiner (2008) note that elderly individuals rely more on C fibers, or delayed, "second pain" sensations, rather than A_δ fibers, or fast "first pain" sensations, which younger

adults utilize for pain transmission. This delayed response to pain causes older adults to have a slower response to painful stimuli and is thought to be related to physiologic changes associated with aging in the density of myelinated Aδ fibers (Karp et al., 2008). A seminal study by Chakour, Gibson, Bradbeer, and Helme (1996) studied this phenomenon in their randomized control trial where they explored age related changes in pain perception in 30 healthy adults. Fifteen young adults between 20-40 years old (mean age: 26.1 years) and fifteen elderly adults over the age of 65 (mean age: 74.1 years) participated in this study. Researchers measured thermal thresholds of pain, mechanical thresholds of pain, and reaction times before, during, and after a radial compression block was performed. Pain was inflicted using a CO2 laser to provoke a thermal stimulus in the subjects. Chakour et al., (1996) performed a radial compression block using two 1.3 kg weights that were suspended in order to impair myelinated Aδ fibers while keeping C fiber function intact. Their procedure examined three different testing periods: pre-block, block, and post-block where they measured temperature threshold, mechanical sensory threshold, thermal pain threshold, and reaction times. Efficacy of the block was proven through testing temperature thresholds. The results showed that regardless of age, all subjects lost cold sensation and retained warm sensation after the block, although there was a trend in the elderly group that suggested they had an increased thermal threshold. Chakour et al., (1996) found a significant difference in the elderly group's description of pain where they used words such as "hot, burning, or stinging" (p. 148) which are commonly associated with C fiber activation during all three testing periods. They found that prior to the block and after the compression block the young group used words such as "sharp and pricking" (p. 148)

which are associated with A_δ fiber activation and during the compression block, they used words associated with C fiber activation. Reaction times were measured by asking participants to press a button with their dominant hand when they felt the stimulus from the CO2 laser. Pre and post-block, the mean results of reaction times for the young group was <600 milliseconds (ms) and during the block the mean results were 1,600 ms. The older adults had a mean reaction time of 1,100 ms pre and post-block and a mean reaction time of 2,100 ms during the block (Chakour et al., 1996). The results supported the hypothesis that young adults rely heavily on Aδ fibers for pain transmission and had quicker response times compared to the elderly patients who were found to rely more on C fibers for pain transmission and had slower response times (Chakour et al., 1996).

Although pain transmission may be delayed in older adults, pain intensity does not decrease with age as is often believed. This was described by Helms and Barone (2008) as altered and atypical reactions and descriptions of pain from the elderly population. These atypical reactions and descriptions of pain can manifest as delirium due to diminished cognitive abilities related to aging. Gagliese and Melzack (2003) performed a randomized control trial to examine differences in pain intensity and quality in elderly chronic pain patients compared with young chronic pain patients. These researchers evaluated 565 randomly selected participants over a 5-year period. Participants were assigned to two groups based on age with one group younger than 60 years old and one group older than 60 years old. In order to reduce confounding variables, participants from each group were equally matched regarding diagnoses, pain location, sex, and duration of pain, resulting in a total of 278 individuals participating in this study (Gagliese & Melzack, 2003). Data was measured in the younger group

(n=139; mean age = 42.93) and elderly group (n=139; mean age = 70.12) utilizing the McGill Pain Questionnaire (MPG) which is a widely used, valid, and reliable tool consisting of 20 adjectives to describe different components of pain (Gagliese & Melzack, 2003). Patients were also asked to rate their highest pain using the Numerical Rating Scale (NRS-H), usual pain (NRS-U), and lowest pain (NRS-L) levels over the past week on a Numerical Rating Scale (NRS). A Pain management index (PMI) was also created for each patient to compare the potency of analgesic medication these patients receive with their highest pain scores to examine if these patients receive adequate analgesia (Gagliese & Melzack, 2003). Elderly patients were found to have lower sensory scores and used fewer descriptors of pain using the MPQ in comparison to the young patients. There were, however, no significant differences in pain scores when using the NRS (Gagliese & Melzack, 2003). These results suggest that although pain quality may decrease with age, pain intensity remains the same (Gagliese & Melzack, 2003).

Opioid Receptors

Opioid receptors are a group of G-coupled protein receptors that exist within the central nervous system at presynaptic and postsynaptic sites. These sites are located in the amygdala, corpus striatum, and hypothalamus of the brain, periaqueductal gray matter, rostral ventral medulla (RVM), locus ceruleus in the brainstem, and the substantia gelatinosa in the dorsal horn of the spinal cord, and in the periphery (Flood et al., 2015). G-coupled proteins are intracellular proteins that are involved in transmission of signals. When G-proteins are bound to guanine diphosphate (GDP) they are inactivated, or “off”, and when G-proteins are bound to guanine triphosphate, they are activated, or “on”

(Flood et al., 2015). Agonism of the opioid receptor by endogenous or exogenous opioids causes a conformational change and activation of the G-coupled protein receptor. This causes the GDP to be exchanged for GTP resulting in inhibition of adenylyl cyclase and a reduction of intracellular cyclic adenosine monophosphate (cAMP) (Pathan & Williams, 2012). Decreased cAMP within the cell results in hyperpolarization of the cell, activation of intracellular potassium channels, and inhibition of intracellular calcium channels, resulting in reduction in release of excitatory neurotransmitters and therefore, reduced pain perception (Pathan & Williams, 2012).

There are four major opioid receptors that aid in decreasing nociception: mu_1, mu_2, kappa, and delta. Mu_1, kappa, and delta receptor activation are involved in producing supraspinal analgesia, while mu_2 receptor activation produces spinal analgesia. Consequences of activating Mu_1 receptors may cause euphoria and miosis while activation of Mu_2 receptors may induce respiratory depression (Flood, et al., 2015). Activation of kappa receptors produce dysphoria, sedation, and miosis and activation of delta receptors may cause urinary retention, constipation, and respiratory depression (Flood, et al., 2015). Mu_1 and kappa activation through analgesics provide low abuse potential for those medications while Mu_2 and delta activation may be responsible for the high abuse potential in certain opioids (Flood, et al., 2015).

Endogenous opioids such as enkephalins, endorphins, and dynorphins as well as exogenous opioid medications can act as ligands and activate these opioid receptors resulting in decreased transmission of pain signals. As endogenous or exogenous opioids bind to these receptors, calcium influx is prevented, and hyperpolarization of potassium channels occurs. This inhibits the release of chemical mediators of pain, such

as substance P, which has been implicated in inducing a painful response (Flood et al., 2015).

Opioid receptors are also involved in regulating signals in N-methyl-D-aspartate (NMDA) receptors, which are found in nerve cells (Jamero, Borghol, Vo, & Hawawini, 2011). The NMDA receptor acts as the receptor for the neurotransmitter, glutamate, which is also released when individuals are exposed to painful stimuli. The activation of NMDA receptors causes increased sensitivity to pain and perception of pain while also decreasing the effectiveness of opioid receptors (Jamero et al., 2011).

Treatment of Pain: Opioid Analgesia

Opioid receptors exist throughout the body in order to dampen pain signals through their activation by endogenous or exogenous opioids. Once a painful stimulus has warned the body against danger, there is no reason for the individual to remain in pain because the pain is no longer serving a useful purpose (Flood et al., 2015). There are many pharmacological and nonpharmacological therapies to remedy painful symptoms, depending on the type of pain the patient is experiencing. Regardless of the method, the goal of treatment is to alleviate pain or at least make it tolerable for the patient to achieve and maintain a comfortable quality of life.

Classification of Opioids. Opioids can be classified as naturally occurring compounds, semi-synthetic compounds, or synthetic compounds and classified as an opioid agonist, agonist-antagonist, or antagonist based on their effect at the opioid receptor (Pathan & Williams, 2012). Naturally occurring opioid agonists include opioids such as morphine and codeine. Semi-synthetic opioid agonists include oxycodone, heroin, dihydromorphone, and buprenorphine while synthetic opioid agonists include

medications like methadone, fentanyl, and analogues of fentanyl such as remifentanil, alfentanil, and sufentanil. The synthetic compounds can be further separated into four different groups: morphanian derivatives, diphenylheptane derivatives, benzomorphan derivatives, and phenylpiperidine derivatives, which include fentanyl and its analogues (Pathan & Williams, 2012). Whether endogenous, naturally occurring, semi-synthetic, or synthetic, most opioid agonists exert the majority of their effects on the mu receptors with some having effects on kappa and delta receptors as well (Flood et al., 2015).

Morphine. Morphine is a naturally occurring opioid agonist that is recognized as the prototype opioid agonist which all other opioids are derived from and compared to (Flood et al., 2015). It is thought that as early as 3000 B.C. the active extract *P. somniferum* from the opium poppy was being utilized for analgesic properties (Pathan & Williams, 2012). Morphine was first isolated as the active compound in the opium poppy in 1806 by a German pharmacist and soon after was chemically manipulated to develop semi-synthetic and synthetic opioid agonists (Pathan & Williams, 2012). Morphine exerts its effects predominantly on the mu receptors producing analgesia, even at low doses, as well as euphoria, sedation, respiratory depression, dry mouth, and pruritis (Flood, 2015).

Morphine can be administered intravenously (IV), intramuscularly (IM), or by mouth (PO) but is usually administered IV in the perioperative period. The onset of morphine after IV administration is delayed compared to that of synthetic opioids such as fentanyl and its analogues. The peak effects of IV morphine occur in 15 to 30 minutes after administration and duration can last 1-4 hours, whereas the peak effects of fentanyl

occur within 2-3 minutes and the duration is much shorter lasting only 30-45 minutes (Pathan & Williams, 2012).

Fentanyl. According to Casserly and Alexander (2017), fentanyl is one of the most prevalently used opioids intraoperatively. Fentanyl is a synthetic derivative of the opioid morphine but is about 100 times more potent than morphine (Casserly & Alexander, 2017). Its highly lipophilic nature allows the drug to be rapidly distributed to highly perfused tissues and organs within the body and more slowly distributed to muscle and fat (Casserly & Alexander, 2017; Pandharipande & McGrane, 2017). The onset of action of fentanyl is about 3 to 5 minutes, but it can have a longer half-life depending on whether it is administered as a bolus dose or as an infusion during or after a procedure (Casserly & Alexander, 2017). Due to its context-sensitive half-life, infusions are not preferred for use in short surgical cases due to its potential for inducing lengthy sedation (Casserly & Alexander, 2017).

Sufentanil. Sufentanil is an analogue of fentanyl that is about 10 times more potent than fentanyl and 1000 times more potent than morphine (Flood et al., 2015). Its onset after IV administration is almost immediate with peak effects occurring in less than 5 minutes and duration lasting about 30 minutes (Nagelhout & Plaus, 2014). Sufentanil is used intraoperatively for a variety of surgical procedures and has been shown to prolong analgesia and induce less respiratory depression compared with both fentanyl and morphine resulting in earlier emergence from anesthesia and earlier extubation (Flood et al., 2015).

Remifentanil. Remifentanil is a derivative of fentanyl that is also frequently used for opioid analgesia intraoperatively. It is about one to two times stronger than fentanyl

but is similar in the sense that it is also highly lipophilic and can be rapidly distributed to tissues and organs (Casserly & Alexander, 2017). Some of the advantages of remifentanil compared to fentanyl are its shorter onset of action of 1 to 2 minutes and its shorter half-life and context-sensitive half time, regardless of whether it is administered as a bolus or an infusion, making it the preferred opioid for short surgical procedures (Casserly & Alexander, 2017; Pandharipande & McGrane, 2017).

Opioids in the Perioperative Phase

In patients undergoing surgical procedures, pharmacological pain management is standard practice. Patients in the perioperative phase, a term encompassing the preoperative, intraoperative, and postoperative phases, typically receive opioid analgesia throughout their surgical experience (Pandharipande & McGrane, 2017). In addition to pain control, opioids provide benefits during induction of anesthesia to attenuate the hemodynamic response to direct laryngoscopy and endotracheal intubation (Gurulingappa, Aleem, Awati, & Adarsh, 2012). During direct laryngoscopy and endotracheal intubation, patients experience a reflexive tachycardia and hypertension that may be detrimental to patients with preexisting cardiac disease (Gurulingappa et al., 2012). Opioids have been shown to attenuate the sympathetic response to direct laryngoscopy and endotracheal intubation by increasing parasympathetic tone and blunting airway reflexes during induction of anesthesia (Gurulingappa et al., 2012; Pathan & Williams, 2012). In their randomized control trial, Gurulingappa et al., (2012) compared the effects of fentanyl, lidocaine, and a placebo of normal saline on the cardiovascular response to direct laryngoscopy and endotracheal intubation. Their subjects included 75 male and female, ASA I patients, between the ages of 20 and 60

years old, undergoing a routine elective surgical procedure. Group one received 4 mcg/kg of fentanyl, group two received 1.5 mg/kg of lidocaine, and group three received a placebo of normal saline during induction of anesthesia to examine which drug would provide the greatest hemodynamic stability during direct laryngoscopy and endotracheal intubation. Gurulingappa et al., (2012) concluded that the incidence of tachycardia and hypertension in the lidocaine and placebo groups were significantly greater ($p < 0.05$) than that of the fentanyl group. Although lidocaine also provided some attenuation of the reflexive tachycardia and hypertension observed with direct laryngoscopy and endotracheal intubation, fentanyl offered a more reliable hemodynamic stability during induction of anesthesia (Gurulingappa et al., 2012).

Although opioids have benefits during the perioperative phase such as providing analgesia and maintaining hemodynamic stability direct laryngoscopy, endotracheal intubation, and surgical manipulation of the patient, opioids may be associated with adverse effects such as decreased level of consciousness, respiratory depression, muscular rigidity, pruritis, nausea, vomiting, urinary retention, and hyperalgesia (Pathan & Williams, 2012). Different pharmacodynamic properties of natural, semi-synthetic, and synthetic opioids produce a variety of effects. Flacke et al., (1985) performed a double-blind randomized control trial comparing the use of morphine, meperidine, fentanyl, and sufentanil in 60 healthy adult patients undergoing general anesthesia for elective procedures. Patients were split into four groups and equipotent doses of these four opioids were administered to these patients during the perioperative phase. Variables such as histamine release, catecholamine concentrations, hemodynamic data including incidence of tachycardia, and respiratory depression were examined.

Researchers found that use of narcotics such as morphine and meperidine correlated with significant increases in catecholamine levels, histamine release, and incidence of tachycardia when compared with the groups that received fentanyl and sufentanil. Respiratory depression was markedly increased in the postoperative phase in patients who received morphine and occurred least in the group that received sufentanil (Flacke et al., 1985).

Fleischman et al., (2010) performed a retrospective study examining the efficacy of a protocol change from morphine to fentanyl for out-of-hospital analgesia for emergency medical services (EMS) in Multnomah County, Oregon. A total of 718 patients, ages 13-99 years old were chosen for this research study. Researchers aimed to compare the differences in pain scores on a numerical rating scale (NRS) of 0-10, as well as to compare and assess the incidence of adverse side effects of morphine and fentanyl. Some parameters examined included respiratory rate less than 12 breaths per minute, pulse oximetry less than 92%, requirement of intubation, systolic blood pressure less than 90 mm Hg, nausea or vomiting, decrease in Glasgow Coma Scale score, and requirements of naloxone administration (Fleischman et al., 2010). Three hundred fifty-five patients in the study received morphine prior to the protocol change and 363 received fentanyl after the protocol change. There was no significant difference in pain scores when equivalent doses of fentanyl and morphine were given (Fleischman et al., 2010). There was a low rate of negative effects (0.8% to 7.3%) resulting from either fentanyl or morphine administration. The most common adverse effect experienced by patients in this study was nausea which occurred 7% of the time in patients receiving morphine compared to 3.8% incidence of nausea when fentanyl was administered. Other adverse

effects measured that were previously mentioned occurred 0.5% to 2.3% of the time in both groups (Fleischman et al., 2010). Fleischeman et al., (2010) concluded that both fentanyl and morphine were efficacious at treating pain with a low rate of adverse events and statistically significant differences were not observed in their study.

Quantifying Pain for Best Treatment

Pain can be quantified using different scales and methods depending on whether the target population is able to verbalize and describe their pain. Capabilities of self-reporting pain can be multifactorial, depending on variables such as age, developmental capability, and condition of the patient. Determinants of the appropriate pain scale that health providers may use to quantify pain is dependent on the age of the patient and whether the patient is able to self-report pain.

Williamson and Hoggart (2005) performed a review of three scales that are commonly used to quantify pain in patients who are capable of self-reporting pain in order to examine the reliability and validity of these scales. The scales included in the review are the visual analogue scale (VAS), numerical rating scale (NRS), and verbal rating scale (VRS) (Williamson & Hoggart, 2005). The VAS can be used in cognitively intact individuals to visually describe their pain on a 10 cm linear scale with 100 mm markings, with different descriptors of pain along the scale ranging from 'no pain' to 'worst pain imaginable' (Williamson & Hoggart, 2005). The score is determined after the patient marks where their pain lines on the scale, with a higher score being indicative of more pain (Williamson & Hoggart, 2005). The pain scale that is most commonly used in clinical practice for individuals capable of describing their pain is the NRS, which quantifies pain on an 11 point scale where pain is given a rating of 0 to 10. A score of 0

is indicative of no pain and 10 describes the worst pain imaginable (Williamson & Hoggart, 2005; Helms & Barone, 2008). The VRS is a pain scale also used by individuals capable self-reporting pain. The VRS involves rating pain on a scale of zero to three to describe the level of pain. This four-point scale quantifies the intensity of pain by assigning the adjectives to describe pain levels: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain (Williamson & Hoggart, 2005). Lara-Munoz, Deleon, Feinstein, and Wells (2004) performed a study aimed at examining the efficacy of the VAS, VRS, and NRS. They conducted this prospective, clinometric study with 30 individuals using sound to produce painful stimuli. Tones of 1000 Hz with different intensities were administered and pain levels were recorded on the VAS, VRS, and NRS to explore if the results correlated among these three different scales (Lara-Munoz et al., 2004). The results of the study indicate that all three pain scales are reliable and valid, however; the VRS was shown to be the least sensitive of these tools and the VAS and NRS displayed equal sensitivity (Lara-Munoz et al., 2004). The NRS was shown to be easiest to use tool while the VAS was the most difficult to use tool (Lara-Munoz et al., 2004).

Individuals who cannot self-report pain due to cognitive impairment, sedation, anesthesia, or critical physiologic condition prove to be difficult to assess for pain. There are different scales available such as the Behavioral Pain Scale (BPS) and the Critical Care Observation Tool (CPOT) which use indicators such as facial expression, limb movement, and ventilator compliance to assess and treat assumed pain in these populations (Kampo et al., 2013; Pandharipande & McGrane, 2017). The CPOT is frequently used in critically ill individuals who are incapable of self-reporting pain. It

allows critically ill patient's pain to be quantified by assessing four components, including facial expression, body movements, ventilator compliance, and muscle tension that may be observable to healthcare professionals and indicate pain in this population (Khanna, Pandey, Chandralekha, Sharma, & Pangasa, 2018). This tool can also be modified for use in critically ill, spontaneous breathing patients by substituting the category of ventilator compliance with vocalization (Khanna et al., 2018). Khanna et al., (2018) performed a prospective observational study to examine the efficacy of the CPOT in 180 critically ill, mechanically ventilated, sedated adults in the intensive care unit (ICU) by comparing the CPOT scores to hemodynamic changes in arterial blood pressure and heart rate during painful procedures. Researchers obtained baseline CPOT scores and vital signs while patients were at rest and then three times per day during endotracheal suctioning and patient repositioning, which were assumed to be painful procedures. Khanna et al., (2018) found that during these painful procedures, there was a significant ($p < 0.001$) increase in baseline systolic and diastolic blood pressures, but no significant rise in heart rate. These cardiovascular changes correlated with CPOT scores, indicating that the CPOT was an accurate and reliable tool that may be used in patients who are unable to self-report pain (Khanna et al., 2018).

When patients are under general anesthesia in the operating room, anesthesia providers may struggle to identify and quantify pain during the surgical procedure. Patients under general anesthesia may display a variety of physiologic responses to pain such as increased blood pressure, increased heart rate, and increased respiratory rate (Kampo et al., 2013). Despite recognizing these hemodynamic changes, it may be difficult for the anesthesia provider to distinguish between inadequate depth of anesthesia

and pain during the intraoperative period. In order to assist anesthesia providers in making this distinction, Kampo et al., (2013) created the Anesthetized Patient Pain Scale (APPS) and examined its efficacy by using a cerebral state monitor (CSM) to also assess depth of anesthesia in their prospective study. The APPS is a pain assessment tool that quantifies pain in anesthetized patients by accounting for hemodynamic, physiologic, and behavioral changes that may occur intraoperatively (Kampo et al., 2013). The APPS measures cardiovascular responses to pain such as blood pressure, heart rate, and respiratory rate along with behavior responses to pain such as facial expression, muscle tension, and body movement. In order to quantify pain, a score from 1-3 is given to each category. A minimum possible score of 6 indicates no pain, scores of 7-8 indicate moderate pain, scores of 9-12 indicate moderate-severe pain, and a maximum possible score of 18 indicates severe pain (Kampo et al., 2013). The CSM is a device that utilizes electroencephalogram (EEG) waves to monitor depth of anesthesia (Kampo et al., 2013). CSM readings of 0-10 indicate a comatose state, 10-40 indicate deep anesthesia, 40-60 indicate adequate depth of anesthesia, 60-80 indicate light anesthesia, and 90-100 indicate an awake patient (Kampo et al., 2013). Kampo et al., (2013) included 250, healthy orthopedic patients with no known comorbidities to participate in their prospective study. All of these subjects underwent general anesthesia for their surgical procedure. Their findings indicated that out of the 250 participants, 150 of those had adequate depth of anesthesia as demonstrated by CSM scores; however, 68.7% of those patients APPS scores still indicated moderate to severe pain. Researchers treated intraoperative pain with 30-50 mcg fentanyl and then re-evaluated pain scores using the APPS. Their results showed a statistically significant ($p < 0.001$) difference in intensity

of pain after fentanyl administration while using the APPS and CSM intraoperatively. This indicates that the APPS may be an effective tool for assessing intraoperative pain while used in conjunction with the CSM to help minimize complications postoperative pain (Kampo et al., 2013).

Abnormal Pain Perception

Disorders of pain perception such as hyperalgesia and allodynia can occur when the C fibers, which are responsible for the second or prolonged pain, are overstimulated (Flood et al., 2015). Hyperalgesia is defined by Helms and Barone (2008) as "a heightened pain response to a stimulus that is painful" (p. 43). Primary hyperalgesia is defined by Flood et al., (2015) as hyperalgesia that occurs at "the original site of injury" (p. 205) and secondary hyperalgesia as the pain that occurs "in the uninjured skin surrounding the injury" (p. 205). Allodynia is defined by Helms and Barone (2008) as "pain from a stimulus that does not normally produce pain, such as touch" (p.43). These two disorders of intensified pain perception are attributed to the central sensitization phenomenon (Helms & Barone, 2008; Flood et al., 2015).

Central sensitization of the nociceptors occurs due to overstimulation of the C nerve fibers which damages these nerve fibers resulting in an increased sensitivity to painful stimuli (Flood et al., 2015). Conditions such as chronic pain are associated with prolonged release of inflammatory mediators which overstimulates C fibers, leading to disordered pain perception. With an acute painful process, once the inflammatory process resolves, the nerve fibers are able to return to their original state with a normal threshold for painful stimuli (Flood et al., 2015).

Opioid-Induced Hyperalgesia Versus Tolerance

Background. Opioids, such as fentanyl and its analogues sufentanil and remifentanil, have been believed to induce hyperalgesia, which has long been confused with acute and chronic tolerance to these medications (Lee & Yeomans, 2014). Tolerance to opioids is defined by Mauermann et al., (2015) as "desensitization to opioid effect requiring more opioid to reach the same effect" (p. 460). These authors further define opioid-induced hyperalgesia as "an increase in pain sensitivity induced or aggravated by opioids" (Mauermann et al., 2015, p. 460). This differentiation is important because with tolerance, an increase in opioid dosage will alleviate painful symptoms whereas with opioid-induced hyperalgesia, an increased dose of opioids will intensify painful symptoms.

Evidence of Hyperalgesia Versus Tolerance. In a randomized control trial, Guignard et al., (2000) found that intraoperative remifentanil increased pain scores and morphine requirements within the first 24 hours postoperative. They studied 50 adult patients undergoing major abdominal surgery, who all received general anesthesia with the volatile anesthetic desflurane, as well as a remifentanil drip. Participants were then separated into two groups, with one group receiving high dose remifentanil and low concentration of desflurane to maintain sedation, and the other group received low dose remifentanil and high concentration of desflurane to maintain sedation. Guignard et al., (2000) found that the group receiving high dose remifentanil reported significantly higher pain scores in the 24-hour postoperative period and required opioids earlier and more frequently than the group receiving low dose remifentanil. At this time, these researchers attributed this phenomenon to acute opioid tolerance, but suggested that further research was needed into the phenomenon of opioid-induced hyperalgesia and the involvement of

the NDMA receptor. Guignard et al., (2000) noted that it was difficult to differentiate between tolerance and hyperalgesia in their patient population but found the patients in their study did not report lower pain scores despite increasing doses of opioids in the postoperative period, which is consistent with hyperalgesia.

Fletcher and Martinez (2014) performed a systematic review and meta-analysis of 27 randomized control trials (RCTs) which included a total of 1494 patients in an attempt to explore the potential consequences of different doses of intraoperative opioids on patient's perceptions of pain intensity in the postoperative phase. Fletcher and Martinez (2014) conducted this systematic review in accordance with the Prisma Statement and the Cochrane Collaboration's recommendations for assessing risk of bias in the RCTs they selected. The authors asserted that this was the first quantitative systematic review and meta-analysis to examine the impact of opioid-induced hyperalgesia in the postoperative phase (Fletcher & Martinez, 2014). The primary outcome of this systematic review was to investigate acute pain at rest 24 hours postoperatively as reported by patients using the numerical rating scale (NRS). Secondary outcomes were identified as opioid consumption in the 24-hour postoperative period, pain intensity as reported by patients on a NRS at 1 hour and 4 hours postoperatively, and incidence of hyperalgesia measured after the operation. Fletcher and Martinez (2014) measured and quantified the phenomenon of primary and secondary hyperalgesia regarding surgical wounds of these patients, describing primary hyperalgesia as the measurable pain threshold experienced close to the wound, and secondary hyperalgesia as allodynia extending around the wound.

Fletcher and Martinez (2014) evaluated RCTs conducted between 1994 and 2013 that included adults and children receiving opioids for a variety of different surgical procedures. The investigators identified their control group as patients receiving low dose opioids intraoperatively and the experimental group as receiving high dose opioids intraoperatively. Fletcher and Martinez (2014) found that at 1 hour, 4 hours, and 24 hours postoperatively, the experimental group reported higher pain scores in the 17 of the RCTs (863 patients). They acknowledged that they were unable to differentiate between tolerance and hyperalgesia when looking at total opioid intake in 24 hours, making the validity of their results questionable. Five of the RCTs (471 patients) they examined explored the phenomenon of primary and secondary hyperalgesia. No significant difference was found in secondary hyperalgesia between the experimental and control groups, but the incidence of primary hyperalgesia was found to be more pronounced in the experimental group (Fletcher & Martinez, 2014). Despite insufficient evidence, Fletcher and Martinez (2014) suggest that lower dose intraoperative remifentanil administration can aid in more positive perceptions of pain postoperatively.

Mauermann et al., (2015) recognized a gap in the literature regarding opioid-induced hyperalgesia relating specifically to fentanyl administration. They performed a prospective, double-blind RCT examining this issue. Since a great deal of literature already acknowledges that remifentanil induces hyperalgesia in multiple animal and human studies Mauermann et al., (2015) sought to examine the effect of fentanyl on acute pain, hyperalgesia, and allodynia in healthy adults. Researchers defined healthy adults as having ASA scores of I or II and BMI between 18 to 25 kg/m^2. They excluded

individuals who had a substance abuse history, psychiatric disorders, known or suspected liver/kidney disease, and sleep apnea (Mauermann et al., 2015).

Mauermann et al., (2015) obtained written informed consent from 21 healthy male volunteers, 20-39 years old, who were separated into two groups using a virtual coin toss which ensures randomization of these groups. Both groups were familiarized with the NRS pain scale for purposes of participating in this RCT. One group received high dose fentanyl (10µg/kg) and one group received low dose fentanyl (1µg/kg) which were administered in a consistent way using the same medication pump for all subjects.

Two models were used to elicit a pain response: Intradermal Electrical Stimulation (IES) and Cold Pressor Pain (CPP). Mauermann et al., (2015) describes the ability of IES to measure a hyperalgesic response by activating the C fibers, previously described by Helms and Barone, through electrical stimulation of needles in the arm. Allodynia was assessed by researchers using a cotton swab on the arm. Acute pain response was measured in this study using CPP, which involves subjects holding their arm in ice water and measuring the time in seconds it took for the subject to remove their arm from the ice water. Opposite arms were used in this RCT in order to maintain validity of results (Mauermann et al., 2015).

Mauermann et al., (2015) found that the group receiving high dose fentanyl experienced lower levels of acute pain four to six hours after administration as compared to the group receiving low dose fentanyl. However, the group treated with high dose fentanyl had a greater incidence of hyperalgesia than the group treated with low dose fentanyl. There was no significant difference between the groups when reporting incidence of allodynia (Mauermann et al., 2015). Researchers concluded that more

research needed to be performed on this topic because this is one of the first studies to show opioid-induced hyperalgesia from fentanyl in healthy subjects.

Treatment and Prevention of Opioid-Induced Hyperalgesia

Researchers have recognized opioid-induced hyperalgesia as a phenomenon existing within the concept of abnormal pain perception; however, treatment modalities and prevention of it are still being researched. N-methyl-D-aspartate (NMDA) receptors, which are found in nerve cells, are believed to be connected with hyperalgesia and the "functionality of opioid receptors" (Jamero et al., 2011) because they acts as receptors for the excitatory neurotransmitter, glutamate, which is released when individuals are exposed to painful stimuli. The activation of NMDA receptors causes increased sensitivity to pain and perception of pain while also decreasing the effectiveness of opioid receptors (Jamero et al., 2011). NMDA antagonists such as ketamine can block the NMDA receptor, which in turn has been thought to decrease hyperalgesic responses by many researchers.

Ketamine. Ketamine is a noncompetitive N-methyl-d-asparate (NMDA) receptor antagonist and derivative of phencyclidine (PCP) that causes dissociative anesthesia, amnesia, and analgesia (Flood et al., 2015). Primary uses of ketamine involve its use as an induction agent for anesthesia as well as an adjuvant medication for multimodal pain control in the perioperative period (Nagelhout & Plaus, 2014). Activation of the NMDA receptor through binding to glutamate is thought open a cation channel, causing an influx of calcium, which in turn causes upregulation of second messengers such as cAMP (Nagelhout & Plaus, 2014). Activation of the NMDA receptor has been linked to disorders of pain such as hyperalgesia, phantom limb pain, and neuropathic pain

(Nagelhout & Plaus, 2014; Urman et al., 2016). Ketamine prevents activation of the NMDA receptor by suppressing the presynaptic release of the excitatory neurotransmitter, glutamate (Flood et al., 2015; Nagelhout & Plaus, 2014). By blocking the NMDA receptor, ketamine may prevent cations from entering the channel, reducing central sensitization and chronic pain states (Urman et al., 2016).

Célèrier et al., (2000) were one of the first groups of researchers to examine the effects of ketamine on opioid-induced hyperalgesia. They performed a randomized crossover trial to test fentanyl's effect on inducing hyperalgesia in rats. They also studied the effects of ketamine administered alone and in conjunction with fentanyl on nociceptive threshold in these rats. Célèrier et al., (2000) performed two sets of experiments on six groups of adult male Sprague-Dawley rats who all weighed the 350-400g. All rats being the same weight and same species added to the validity of the results. Researchers conducting this RCT thoroughly described the consistency in handling the rats and the controlled environment of these rats in the weeks leading up to the experiment as well as the randomization of the rats (Célèrier et al., 2000).

The first set of experiments Célèrier et al., (2000) conducted involved splitting the rats into six groups with 8-12 rats per group. The control group was given a placebo of saline while the five experimental groups were given subcutaneous weight-based doses of fentanyl every fifteen minutes at 20µg/kg, 40µg/kg, 60µg/kg, 80µg/kg, and 100µg/kg for five days. The researchers examined the long-lasting effects of fentanyl on the rats' pain threshold based on the fentanyl dose received (Célèrier et al., 2000). They measured these results using a modified version of the Randall-Selitto tool known as a paw pressure vocalization test which applies a constant pressure to the hind paw of the rat until they

squeak. Célèrier et al., (2000) found that on day zero, the increased dose of fentanyl provided the rats with increased analgesia for the acute pain experienced. Conversely, in days 1-5, researchers found that the rats that received higher doses of fentanyl had a hyperalgesic response.

In the second set of experiments, Célèrier et al., (2000) tested the pain threshold of the rats of one group that were pretreated with ketamine prior to administration of the four consecutive doses of 60µg/kg of fentanyl for five days. The control group was treated with ketamine and saline which provided no analgesic effect to the rats when administered without opioids (Célèrier et al., 2000). Researchers found that the addition of ketamine with the middle range dose fentanyl enhanced the analgesic effect and prevented fentanyl-induced hyperalgesia (Célèrier et al., 2000). Though these results yielded a positive outcome for prevention of hyperalgesia with ketamine, it is difficult to generalize the results for humans due to the fact that rats participated in the study. The small sample sizes of rats included in the study also undermine the validity of the results and further research should be performed on humans before recommendations can be made.

Hadi, Al Ramadani, Daas, Naylor, and Zelko, (2010) performed a prospective, double blind, randomized control trial to determine if intraoperative ketamine combined with opioids, compared with intraoperative opioids, alone would provide better postoperative pain control for patients after a spinal fusion. The authors examined these effects on 30, ASA I-II, healthy male and female patients and divided them into two groups (n=15). Group 1 (G1) was given a remifentanil infusion at a dose of 0.2 mcg/kg/min and group 2 (G2) was given a remifentanil infusion at a dose of

0.2mcg/kg/min plus a ketamine infusion at a dose of 1 mcg/kg/min. Hadi et al., (2010) recorded and compared intraoperative vital signs, including mean arterial pressure (MAP) every five minutes for each patient as well first pain scores, time (minutes) to first dose of postoperative opioid, and total consumption of opioids (morphine) within the first twenty-four hours after surgery. The intraoperative heart rate and MAP were significantly higher ($p < 0.05$) in G2, compared with G1. The mean time to first postoperative opioid consumption for G1 was 19.5 ± 3.2 minutes compared to G2 which had a mean time of 22.9 ± 3.5 minutes, indicating a significantly ($p < 0.05$) later time to first opioid in G2 compared with G1. The number of patients who reported pain after surgery in G1 was 13/15, while G2 had 5/15 patients report pain after surgery which were significant results ($p < 0.05$). Opioid consumption for the first 24 hours postoperatively were 60mg of morphine in G1 and 45mg of morphine in G2, indicating significantly ($p < 0.05$) lower doses of postoperative morphine consumption in the group who received low dose intraoperative ketamine with remifentanil. Hadi et al., (2010) concluded that their results showed benefits to utilization of intraoperative ketamine in reducing pain scores and opioid consumption in the postoperative period and suggested that ketamine may be considered a routine anesthetic for spinal fusions in the future.

In 2011, Forero, Chan, and Restrepo-Garces performed a retrospective case report on one patient's experience with chronic lower back pain. They described the patient as a 52-year-old male with chronic pain issues lasting more than 20 years. His pain was first treated conservatively with medical management and then with surgical intervention where he received an L5-S1 laminectomy. He continued to experience back pain and was again treated conservatively with different analgesic medications for another eleven

years before he finally received an intrathecal pain pump (ITP). The ITP delivered opioid analgesics with different medications such as morphine and hydromorphone at varying doses throughout the years. Pain relief was still not achieved despite all interventions and treatment modalities. He finally underwent a spinal cord stimulation (SCS) procedure five years after the ITP was placed, however, his pain persisted. In October of 2008, the patient complained of a new onset of burning and excruciating (9/10 on NRS) systemic pain and severe nausea. The integrity of the ITP was examined through fluoroscopy and an invasive surgical exploration; however, the pump was intact, and no malfunction was appreciated. The patient then began experiencing severe leg spasms in addition to the generalized aches and burning sensation and received no relief with increasing, high dose opioids. Physicians suspected opioid toxicity and opioid-induced hyperalgesia and they administered an intrathecal dose of ketamine. According to the case report, one minute after administering this ketamine bolus, the patient reported resolution of all painful symptoms. A maintenance infusion of intrathecal ketamine along with a low dose opioid, 25% of the dose he was previously receiving, was started with sustained relief of painful symptoms for this patient (Forero et al., 2011).

Although Forero et al., (2011) formulated thoughtful research in attempts to explore ketamine's role in reversal of opioid-induced hyperalgesia, the results cannot be easily generalized because they are describing one patient's experience. This patient had specific attributes as he was a middle-aged male with many unknown factors such as race, weight, and comorbidities which could all impact the results in different populations. This case study also only evaluates intrathecal opioid and ketamine use,

whereas all of the RCTs performed in humans describe intravenous use of opioids and ketamine. It is unclear how the results would vary based on the route of administration.

This review of the literature has produced information regarding the effects of ketamine as a potential treatment to reduce the incidence of opioid-induced hyperalgesia; however, there is still a great deal of research to be done on the subject before recommendations can be made for implementing treatment modalities for patients in the perioperative phase. This topic is relevant in not only aiding in proper treatment of patients, but also educating healthcare providers in recognizing differences between opioid tolerance and opioid-induced hyperalgesia. Ongoing and prospective research of this topic will guide practice changes for the future.

The theoretical framework that guided this research project will be presented next.

Theoretical Framework

The theoretical framework that guided this systematic review was the Gate Control Theory of Pain which evolved over time into the Neuromatrix Theory of Pain.

Specificity Theory of Pain

Throughout history there have been many pain theories proposed to describe the complex nature of pain and pain perception. French philosopher, Rene Descartes, proposed the Specificity Theory of Pain as early as 1644 (Helms & Barone, 2008). He suggested that pain is a sensation produced by peripheral nerve impulses as a result of injury and that peripheral pain receptors transmit pain via a straight line channel to the brain (McAllister, 2014). Descartes viewed pain sensation and perception as a phenomenon that directly correlates with the extent of the injury. This early Cartesian pain theory does not account for differences in pain perception among diverse populations or for phenomena such as chronic pain and phantom limb pain.

Gate Control Theory of Pain

Canadian psychologist Ronald Melzack and British neuroscientist Patrick Wall recognized the shortcomings of Descartes' Specificity Theory of Pain and proposed the Gate Control Theory of Pain in 1965 which encompassed the physiologic as well as emotional responses of pain (Melzack & Wall, 1965). Melzack first realized that pain was both a physiologic and psychological phenomenon while working toward his Ph.D. at McGill University in the 1950s, studying phantom limb pain (McAllister, 2014). The Gate Control Theory of Pain suggests that a nerve gate exists in the spinal cord to allow or prohibit pain signals to reach the brain. If the gate is open, the nerve impulses are able to reach the brain and the sensation of pain is perceived (Melzack & Wall, 1965). Conversely, if the gate is closed, nerve impulses do not reach the brain, resulting in

decreased pain perception (Helms & Barone, 2008). The Gate Control Theory of Pain shifted the focus away from the outdated Cartesian view of pain as a strictly peripheral process to the central nervous system as a major regulator of pain perception (Melzack & Wall, 1965).

According to the Gate Control Theory, A nerve fibers and C nerve fibers are responsible for the transmission and sensation of pain along an afferent pathway from the spinal cord to the brain. The pain impulses travel to the substantia gelatinosa in the dorsal horn of the spinal cord where the gate is located, and it will either block or facilitate pain impulses to the brain (Melzack & Wall, 1965; McEwen & Wills, 2014).

Wind-up Phenomenon

The Gate Control Theory relates directly to the central sensitization phenomenon which can lead to abnormal processing of sensory information, resulting in hyperalgesia (Dickenson, 2002). Dickenson (2002) described how after a tissue or nerve injury, calcium channels within the spinal cord become activated. These active calcium channels are responsible for the release of the excitatory neurotransmitter glutamate in the A and C nerve fibers. NMDA receptors become activated when glutamate is released causing the wind-up and central sensitization phenomena (Dickenson, 2002).

Melzack and Wall describe this wind-up phenomenon in the Gate Control Theory as repeated and persistent stimulation of the C fibers, causing an intensified pain response (Melzack & Wall, 1965). Helms and Barone (2008) make an analogy to describe this phenomenon by comparing it to winding up a child's toy; the more the toy is wound up, the faster and longer it will run. The wind-up phenomenon is thought to be a major factor in the abnormal pain response, hyperalgesia (Dickenson, 2002).

Neuromatrix Theory of Pain

In 1999, Melzack and Walls evolved the Gate Control Theory of Pain into the Neuromatrix Theory of Pain as a new and improved pain theory to clarify the unanswered questions within the Gate Control Theory regarding "chronic pain issues, sex-based differences, stress effects, and the effects of previous pain experiences" (Melzack & Wall, 1965). The Neuromatrix Theory expands on the Gate Control Theory's idea that the central nervous system is more than just a passive receiver of pain signals from the peripheral nervous system (McAllister, 2014). According to the Neuromatrix Theory, each person has a unique "body-self neuromatrix" which is composed of neurons affected by all aspects of the individual including their "physical, psychological, and cognitive makeup, as well as his or her experience" (Helms & Barone, 2008). The Neuromatrix Theory shifts the idea that the sensation of pain is elicited from the peripheral site of tissue damage to a more abstract concept that involves the central nervous system, composed of the brain and spinal cord, as the main producer of pain responses (McAllister, 2014).

Clinical Relevance of the Gate Control Theory

The Gate Control Theory of Pain has been used as a theoretical framework for many research studies because of its high potential for generalizability regarding its applicability towards many different types and perceptions of pain. It can be used to frame current pain research in different populations regarding age, gender, and disease processes contributing to painful experiences.

Lane and Latham (2009) conducted a qualitative review of different studies detailing the gaps in current literature regarding acute and chronic pain control using heat

and cold therapy in children. Their nursing study references the Gate Control Theory while discussing the mechanism of heat and cold therapy. They found that superficial heating and cooling of tissue with ice packs or hot packs can stimulate thermoreceptors deep within the tissues that can close the pain gate in the spinal cord and reduce pain perception. Lane and Latham (2009) found that their ice packs work best on targeting A nerve fibers and the hot packs works best on targeting C nerve fibers as pain control strategies. Heat works best on the C nerve fibers because it promotes vasodilation while decreasing the sympathetic nervous system's response of releasing pain provoking neurotransmitters such as bradykinin and prostaglandin as described in the Gate Control Theory (Lane & Latham, 2009). Use of the Gate Control Theory in regard to treatment and prevention of children's acute and chronic pain is an example of the generalizability of this pain theory.

Ngamkham, Holden, and Wilkie (2011) provide another example of utilization of the Gate Control Theory of Pain in their comparative, secondary data analysis examining the differences in pain patterns among 762 adult outpatients with cancer. The Gate Control Theory framed their study as they analyzed cancer pain as a multidimensional experience that differs from patient to patient regarding quality, location, and intensity of pain. This pain theory acknowledges the complexities in pain perception including its "sensory, affective, cognitive, and behavioral dimensions" (Ngamkham et al., 2011, p. 229).

The Gate Control Theory of Pain has changed not only the way healthcare providers and researchers think about pain perception, but also the way pain is prevented and treated. It is now believed that premedication with analgesic medication will keep

the gate closed for longer, allowing fewer pain impulses to travel along the afferent pathway to the brain (McEwen & Wills 2014). Keeping the gate closed will allow fewer nerve impulses to reach the brain and the key focus of pain therapy involves preventing pain before it happens to help keep the gate closed. The concepts of pain management and prevention outlined in Gate Control Theory have shaped the way pain is currently recognized and treated across a variety of patient populations suffering from different types of pain.

The wind-up phenomenon described by Melzack and Wall (1965) is directly involved in central sensitization because it leads to an amplified and abnormal pain perception known as hyperalgesia, resulting from overstimulation of C fibers. Initially, when opioids are administered, they act as agonists on opioid receptors which activate G-proteins, leading to inhibition of adenylyl cyclase and decreased cAMP, which produces analgesia (Flood et al., 2015). Although the exact mechanism is still unclear, it is now recognized that in high doses, opioids can induce a hyperalgesic pain response by damaging C fibers through activation of the NMDA receptor by the release of glutamate and activation of adenylyl cyclase which increases pronociceptive activity by increasing levels of cAMP (Hayhurst & Durieux, 2016). The Gate Control Theory of Pain and Neuromatrix Theory of Pain will be used to shape this systematic review by examining the potential treatment and reduction of opioid-induced hyperalgesia, caused by the central sensitization and wind-up phenomena, through the use of the NMDA antagonist, ketamine.

Next, the methodology of this systematic review will be presented and discussed.

Methods

Purpose

The purpose of this systematic review is to examine the effect of ketamine, on reducing the phenomenon of opioid-induced hyperalgesia. Further research of this topic will lead to clinical changes in the way pain is treated and prevented in the perioperative phase.

Search Strategy

A comprehensive literature search was conducted using databases and websites including MEDLINE, PubMed, CINHAL, Up-to Date, and Google Scholar. Current research regarding the effect of ketamine on opioid-induced hyperalgesia was found after performing a search for the keywords, “physiology of pain”, “hyperalgesia”, “opioid-induced hyperalgesia”, “fentanyl”, “remifentanil”, “ketamine”, “prevention”, and “treatment”. The initial comprehensive search of current literature yielded over 150 potential articles on this topic from these databases. Studies were then limited to include publications written in English within the past 18 years. Further narrowing of the search provided articles that examined the use of ketamine on adult subjects (over the age of 18) regarding treatment or prevention of opioid-induced hyperalgesia.

PRISMA Statement

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement was used to frame this systematic review. The PRISMA Statement incorporates a 27-item checklist and flow diagram aimed at improving the quality of the systematic review by providing the reader with transparency and clarity of the studies examined for purposes of this review (Hutton et al., 2015). By ensuring meticulousness of the findings of this systematic review, validity of the results were elevated. The

PRISMA checklist (Appendix A) and flow diagram (Appendix B) enhanced this systematic review by addressing limitations and risk of bias within the studies used for this review (Moher et al., 2017).

Inclusion/Exclusion Criteria

Inclusion criteria for this systematic review included meta-analysis, systematic reviews, and randomized control trials conducted over the past 18 years that examine the use of ketamine in male or female adult patients, over the age of 18, undergoing surgery. The phenomenon of hyperalgesia must be measured within the immediate postoperative phase.

Articles examined in this systematic review included patients who are relatively healthy, with no severe or moribund comorbidities, which is measured for the purposes of this review on the American Society of Anesthesiology (ASA) scoring system. ASA scores of I indicate a completely healthy patient with no comorbidities. ASA scores of II indicates the patient has a mild systemic disease or includes any individual who smokes. ASA score of III indicates presence of a severe systemic disease that is not imminently incapacitating or any morbidly obese patient regardless of age. ASA scores of IV indicates that the patient has comorbidities that are incapacitating or an immediate threat to their life. ASA scores of V indicate severe systemic disturbances within a patient who is not expected to live more than 24 hours without surgical intervention (Daabiss, 2011). Patients must be ASA score of I-III to be included in this study.

Exclusion criteria for this systematic review included any studies involving the pediatric population and studies that were more than 18 years old. Other exclusion criteria involved using articles that explore the use of other NMDA antagonist

medications such as memantine, amantadine, methoxetamine, nitrous oxide, and dextromethorphan in managing opioid-induced hyperalgesia (Jamero et al., 2011). Using this inclusion and exclusion criteria, six randomized control trials were chosen in performing this systematic review.

Data Collection

The randomized control trials that were chosen for this systematic review were appraised and relevant data was collected and analyzed. In order to examine the effects of ketamine on reducing opioid-induced hyperalgesia in adult surgical patients in the perioperative period, tables were created for ease of comparison and analysis of different variables in each study (Table 1 and Table 2). Table 1 reports data regarding demographics of the studies, while Table 2 reports results of the outcomes measured in the studies. Variables being examined have been collected and organized into the tables. Some of these outcomes being reported include pain scores at designated times throughout the postoperative period, quantity of analgesic medication used in the PACU, and time to first postoperative opioid consumption. Evidence of hyperalgesia has been measured and reported as well.

Table 1

Data Collection Sheet #1

Study Title

Aim	
Design	
Sample	
ASA Score	
Methods	
Outcomes Measured	

Table 2

Data Collection Sheet #2

Study Title

Intraoperative Opioid & Ketamine Doses	
Postoperative Pain Score	1 hour – (pain score) 6 hour – (pain score) 24 hour – (pain score)
Evidence of Hyperalgesia	
Time to First Postoperative Opioid Administration (min)	
Postoperative Analgesic Consumption	

Critical Appraisal Tool

Critical appraisal of the studies used for this systematic review were performed using the Critical Appraisal Skills Programme (CASP). The CASP appraisal tool

involves the use of multiple checklists that examines the usefulness and validity of the studies chosen for this systematic review. Utilizing CASP checklists (Figure 1) to evaluate the relevance and reliability of randomized control trials used for this systematic review promotes trustworthiness of the findings (CASP, 2017).

Figure 1: *CASP Randomized Control Trial Checklist* (CASP, 2017)

1. Did the trial address a clearly focused issue?	YES	CAN'T TELL	NO
2. Was the assignment of patients to treatments randomized?	YES	CAN'T TELL	NO
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	YES	CAN'T TELL	NO
4. Were patients, healthcare workers, and personnel 'blind' to treatment?	YES	CAN'T TELL	NO
5. Were groups similar at the start of the trial?	YES	CAN'T TELL	NO
6. Aside from the experimental intervention, were the groups treated equally?	YES	CAN'T TELL	NO
7. How large was the treatment effect?			
8. How precise was the estimate of the treatment effect?			
9. Can the results be applied in your context?	YES	CAN'T TELL	NO
10. Were all clinically important outcomes considered?	YES	CAN'T TELL	NO
11. Are the benefits worth the harm and cost?	YES	CAN'T TELL	NO

Data Synthesis & Cross Study Analysis

The results from relevant studies have been evaluated, analyzed, and presented using multiple tables to display the findings. Data was gathered, and placed into a table for comparison, and a cross study analysis was performed (Table 3). This cross study analysis evaluated the relationship between the dose of intraoperative opioids, whether or not ketamine was administered and at what dose, pain scores at different points in the

postoperative period, evidence of hyperalgesia, time to first postoperative opioid administration, and total dose of postoperative opioid consumption within 24 hours. Recommendations for future practice changes have been made based on statistically significant findings within the research.

Table 3

Cross Study Analysis

Study	Intraoperative Opioid & Ketamine Doses	Evidence of Hyperalgesia	Results

Next, the results will be discussed.

Results

The previously mentioned inclusion and exclusion criteria as well as the PRISMA flow diagram (Appendix B) aided in the selection of five articles for purposes of this systematic review. Initial searches yielded a total of 41 articles for potential use in this systematic review. After reviewing the articles while referencing the PRISMA checklist (Appendix A) to ensure quality of the selected articles as well as relevance to the topic of this systematic review, 8 were selected for further appraisal. Closer examination of these articles with the outlined inclusion and exclusion criteria and CASP checklist (Appendix E) produced a total of 5 articles that incorporated the multifaceted outcomes investigated to compile relevant, strong, and valid evidence for this systematic review.

Joly et al., (2005) conducted a double-blind RCT to examine if high-dose remifentanil can induce hyperalgesia and assess the preventative effects of intraoperative ketamine on remifentanil-induced hyperalgesia in healthy adults undergoing major abdominal surgery. Researchers hypothesized that patients receiving high dose intraoperative remifentanil would have an increased nociceptive threshold, which would be indicative of hyperalgesia. They proposed this phenomenon could be counteracted and prevented by administering ketamine in conjunction with remifentanil intraoperatively according to the researchers (Joly et al., 2005).

The authors selected 75 patients with similar demographics undergoing major abdominal surgery and separated them randomly into three groups of 25 (Appendix C.1, Data Collection Sheet #1). Group 1 (n=25) received low dose remifentanil (0.05µg/kg) intraoperatively plus a saline placebo infusion; group 2 (n=25) received high dose remifentanil (0.4µg/kg) intraoperatively plus a saline placebo infusion; group 3 (n=24) received high dose remifentanil (0.4µg/kg) in conjunction with 0.5 mcg/kg bolus of

ketamine on induction of anesthesia and a 5 mcg/kg/min infusion of ketamine intraoperatively until skin closure, and then 2 mcg/kg/min infusion of ketamine for 48 hours postoperatively (Joly et al., 2005).

Postoperative pain scores measured with a VAS were assessed and recorded by PACU nurses every 15 minutes for the first hour, hourly for the following 3 hours, and every 4 hours for the remaining 44 hours. Joly et al., (2015) found no significant differences in postoperative pain scores at 24 or 48 hours after surgery among groups 1, 2, or 3.

Joly et al., (2005) examined time to first morphine consumption (min) and total postoperative morphine consumption (mg) for the first 4 hours in PACU and up to 48 hours postoperatively. Researchers found no significant difference in the time to first postoperative opioid administration among groups 1, 2, or 3. Total morphine consumption (mg) in PACU did not significantly differ among any of the groups (Appendix D.1, Data Collection Sheet #2), however; total postoperative morphine consumption was significantly higher in group 2 who received intraoperative high-dose remifentanil compared to groups 1 or 3 (Joly et al., 2005).

Extent of hyperalgesia was measured using von Frey hair number 16 (pressure = 122 g/mm^2) adjacent to the surgical wound and an algometer was used to establish a pain pressure threshold (kPa). Preoperative tactile pain thresholds (g/mm^2) were similar among the 3 groups. Measurements at 24 hours and 48 hours postoperative were significantly higher in group 2 compared with groups 1 and 3 ($p < 0.01$). Extent of hyperalgesia to von Frey hair number 16 was significantly higher in group 2, compared to groups 1 and 3 ($p < 0.05$). Joly et al., (2005) concluded that large doses of intraoperative

remifentanil generated a hyperalgesic response postoperatively and that this response was prevented in the group that received ketamine in addition to large dose remifentanil (Joly et al., 2005).

When evaluating this study using CASP (Appendix E.1, CASP Checklist) Joly et al., (2005) adequately described the randomization process and accounted for variables such as sex, age, weight, and length of surgery. These variables were considered by researchers to be similar among their sample groups. The information allows the results of their experiments to be potentially generalizable among patients receiving major abdominal surgery. Postoperative pain was rated on a VAS and all participants were familiarized with this scale prior to initiation the study. The PACU nurses treating the patients in the postoperative phase were blinded to the group assignments and performed frequent pain assessments which added to the validity of the results. All patients were accounted for throughout the study and Joly et al., (2005) described how one patient was excluded from this study after its initiation due to respiratory depression requiring treatment with an opioid antagonist, naloxone.

Primary and secondary outcomes were clearly defined, assessed, and reported by Joly et al., (2005). Reported limitations to their study involved the increased desflurane requirement of the small-dose remifentanil group to maintain anesthesia throughout the case. Researchers admit that because the phenomenon of opioid-induced hyperalgesia and its implications are not well understood, more studies will have to be performed before recommendations can be made regarding attenuation of the hyperalgesic response with ketamine.

Yalcin et al., (2012) used the research performed by Joly et al., (2005) as a framework for their prospective, randomized control trial, comparing the effects of paracetamol and ketamine on prevention of remifentanil-induced hyperalgesia (Appendix C.2: Data Collection Sheet #1). Ninety patients undergoing a total abdominal hysterectomy were divided into 3 groups. Group I (n=27) received 0.4 mcg/kg/min infusion of remifentanil with a saline (placebo) infusion; group II (n=26) received 0.4 mcg/kg/min infusion of remifentanil with a ketamine infusion of 5 mcg/kg/min and a 0.5 mg/kg bolus of ketamine on induction of anesthesia; group III (n=26) received 0.4 mcg/kg/min infusion of remifentanil with an infusion of 1000 mg paracetamol over 15 minutes prior to induction of anesthesia (Yalcin et al., 2012). Researchers acknowledged previous studies have shown that high dose remifentanil (0.4 mcg/kg/min) is associated with inducing opioid-induced hyperalgesia and hypothesized that this effect could be reduced with paracetamol and ketamine.

Yalcin et al., (2012) found that overall postoperative VAS pain scores were significantly higher in group I compared to groups II and III (Appendix D.2: Data Collection Sheet #2). There were no significant differences in postoperative VAS pain scores between groups II and III. Researchers compared their findings of decreased postoperative pain scores on VAS in the ketamine group to the lack of significant findings regarding postoperative VAS pain scores in the research presented by Joly et al., (2005). Yalcin et al., (2012) deemed that appropriate timing of ketamine administration in their study contributed to their results. Analgesic demand and morphine consumption via PCA pump were evaluated and found to be significantly higher ($p < 0.05$) in group I compared to groups II and III. Analgesic demand and morphine consumption via PCA

pump were also found to be significantly higher ($p < 0.05$) in group III compared to group II at 24 and 48 hours postoperatively (Yalcin et al., 2012).

Hyperalgesia was measured and quantified using a mean pressure pain threshold (Lb) with a digital pressure algometer on the inner forearm and at the surgical incision preoperatively, 24 hours postoperatively, and 48 hours postoperatively (Yalcin et al., 2012). Baseline, preoperative values were similar among all three groups. Mean pain pressure thresholds (Lb) at the surgical incision (Appendix D.2, Data Collection Sheet #2) were found to be significantly lower ($p < 0.05$) in group I compared to groups II and III. Group I was found to have a significantly lower ($p < 0.05$) pressure and pain threshold compared to their baseline values at 24 and 48 hours postoperatively, indicating a hyperalgesic response. Groups II and III had a significantly higher ($p < 0.05$) pain pressure threshold at 24 and 48 hours postoperatively, indicating attenuation of the hyperalgesic response with ketamine and paracetamol.

When evaluating this study using CASP (Appendix E.2, CASP Checklist), it was found that the demographics of the three groups were comparable regarding sex, BMI, ASA status, and comorbidities which increase the validity of researcher's findings. All participants of this study were women undergoing total abdominal hysterectomy which may be a limitation for generalizability of these results for other types of surgeries or patients who are male. Yalcin et al., (2012) described the randomization process of patients and blinding of patients and health care providers. All participants of this study were accounted for, with 11 being excluded due to "postoperative fever, duration of surgery, and non-cooperation" (p. 329). Aside from the experimental interventions, all groups were treated equally in their anesthetic administration, adding to the validity of

the researcher's results. Yalcin et al., (2012) concluded that both paracetamol and ketamine, used in conjunction with high dose remifentanil were equally efficacious in preventing opioid-induced hyperalgesia.

Choi et al., (2015) conducted a study modeled after the study conducted by Joly et al., (2005) to compare the effects of high dose remifentanil, low dose remifentanil, and high dose remifentanil given in conjunction with ketamine on postoperative pain scores, postoperative opioid consumption, and postoperative incidence of hyperalgesia. Researchers hypothesized that the addition of ketamine to remifentanil based anesthesia would reduce the incidence of opioid-induced hyperalgesia. Choi et al., (2015) examined 75 patients undergoing laparoscopic gynecologic surgery and divided them into three groups (Appendix C.3, Data Collection Sheet #1). Group RL (n=25) received a low dose remifentanil infusion (0.05 mcg/kg/min); group RH (n=25) received a high dose remifentanil infusion (0.3 mcg/kg/min); group KRH (n=25) received a high dose remifentanil infusion (0.3 mcg/kg/min) with a 0.5 mcg/kg bolus of ketamine on induction of anesthesia and a 5 mcg/kg/min infusion of ketamine during the procedure (Choi et al., 2015).

Choi et al., (2015) found that postoperative pain scores reported on NRS were significantly higher ($p < 0.05$) in group RH compared to groups RL and KRH (Appendix D.3, Data Collection Sheet #2). There was no significant difference between time to first postoperative opioid administration between the three groups, but postoperative fentanyl (mcg) consumption was significantly higher ($p < 0.05$) in group RH compared to groups RL or KRH. Postoperative ketorolac (mg) consumption was also measured and found to

be significantly higher ($p < 0.05$) in group RH compared to groups RL or KRH (Choi et al., 2015).

Hyperalgesia was measured adjacent to the wound by Choi et al., (2015) preoperatively to obtain a baseline and at 24 hours postoperatively using a Touch-Test sensory evaluation. Differences between the baseline value and 24 hour postoperative value were evaluated, with a higher negative number being indicative of a hyperalgesic response. Preoperative baseline values were similar among the three groups and 24 hour postoperative Touch-Test sensory values were significantly lower ($p < 0.05$) in group RH compared to groups RL or KRH. The difference was found to be significantly more negative ($p < 0.05$) in group RH compared to groups RL and KRH, indicating a hyperalgesic response in group RH (Choi et al., 2015).

When evaluating the RCT by Choi et al., (2015) using the CASP checklist (Appendix F, CASP Checklist), it was determined that the aim of the study was clear. Though patients were said to be randomized, researchers did not describe the randomization process. Blinding was also not addressed by Choi et al., (2015) which may alter the validity of their results. Researchers evaluated patient demographics such as age, comorbidities, ASA status, BMI, baseline vital signs, and length of procedure and found no significant difference between these variables which could increase validity and generalizability of their results. They did not disclose the gender of their patients included in this study which is a limitation for generalizability of their results. They acknowledged a potential limitation of their research being that group RL received a higher end-tidal concentration of desflurane to maintain appropriate anesthetic depth compared to groups RH and KRH, but that there were no other differences in anesthetic

management of these patients (Choi et al., 2015). Choi et al., (2015) concluded that opioid-induced hyperalgesia was found to be reduced with the administration of ketamine when providing remifentanil based anesthesia.

Leal et al., (2015) performed a prospective, double-blind, RCT to evaluate the effect of intraoperative ketamine on reducing remifentanil-induced hyperalgesia (Appendix C.4, Data Collection Sheet #1). Researchers separated 56 patients, undergoing a laparoscopic cholecystectomy, into 2 groups. Group1 (n=28) received an intraoperative remifentanil infusion at 0.4 mcg/kg/min in addition to a 5 mcg/kg/min ketamine infusion, while group 2 received an intraoperative remifentanil infusion at 0.4 mcg/kg/min with a saline infusion (placebo) (Leal et al., 2015). Outcomes of their research (Appendix D.4, Data Collection Sheet #2) show that postoperative pain scores measured on NRS were significantly lower ($p < 0.05$) in group 1 compared to group 2 (Leal et al., 2015). No significant difference was appreciated in time to first postoperative opioid administration or total 24 hour postoperative morphine consumption (mg) between groups 1 and 2 (Leal et al., 2015).

Leal et al., (2015) measured hyperalgesia using Von Frey monofilaments and an algometer at the thenar eminence and periumbilical region preoperatively and 24 hours postoperatively to evaluate pain threshold. Significant differences ($p > 0.05$) in the hyperalgesic response were observed at the thenar eminence in group 1 compared to group 2, suggesting a potential reduction in secondary hyperalgesia. There were no other significant differences between groups 1 and 2 using the Von Frey monofilaments or algometer.

Hyperalgesia was also estimated by evaluating cytokine levels, specifically interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-10 (IL-10), preoperatively, 5 hours after incision, and 24 hours after surgery by comparing differences in blood levels (Leal et al., 2015). Researchers hypothesized that cytokine levels could be associated with the development of hyperalgesia. According to Leal et al., (2015), IL-6 is a pro-inflammatory marker associated with the extent of tissue damage incurred during surgery. Leal et al., (2015) also describes IL-8 as significant for recruiting neutrophils and is associated with inflammation, while IL-10 is an anti-inflammatory marker shown in previous studies to increase with administration of ketamine. Leal et al., (2015) found no significant differences in IL-6, IL-8, or IL-10 levels preoperatively, 5 hours after incision, or 24 hours postoperatively between groups 1 and 2.

When evaluating the RCT by Leal et al., (2015) using the CASP checklist (Appendix E.4, CASP Checklist), it was determined that the aim of the study was clear. The randomization and double-blinding process was thoroughly explained, adding to the validity of these results. Researchers evaluated patient demographics such as age, sex, comorbidities, ASA status, BMI, baseline vital signs, and length of procedure and found no significant difference between these variables which could increase validity and generalizability of their results. All participants in this study were accounted for and both groups were given the same anesthetic, with the exception of the experimental group receiving ketamine, which adds to the validity of the results. A limitation of this RCT is that there is not enough evidence that certain inflammatory markers examined in this study are undoubtedly indicative of a hyperalgesic response. More research needs to be conducted before definitive conclusions can be drawn regarding the correlation between

hyperalgesia and IL-6, IL-8, and IL-10. A strength of this RCT is that in addition to inflammatory markers, Leal et al., (2015) also measured and evaluated primary and secondary hyperalgesia using a Von Frey monofilament and algometer which have been used to measure hyperalgesia in many other studies, increasing validity of these results. Leal et al., (2015) concluded that there was no significant attenuation of the hyperalgesic response induced by remifentanil with the addition of ketamine.

A prospective, randomized, double-blinded RCT was performed by Kido et al., (2019) to examine if low dose intraoperative ketamine prevents acute remifentanil-induced tolerance (Appendix C.5, Data Collection Sheet #1). Researchers included 40 patients, undergoing orthognathic surgery, and separated them into three groups. Group RH (n=12) was given a high dose, remifentanil infusion at 0.6 mcg/kg/min; group RL (n=12) was given a low dose, remifentanil infusion at 0.2 mcg/kg/min; group KRH was given a high dose, remifentanil infusion at 0.6 mcg/kg/min in addition to a 0.5 mcg/kg bolus of ketamine on induction of anesthesia with a 5 mcg/kg/min infusion of ketamine throughout the case (Kido et al., 2019). Outcomes of their research (Appendix D.5, Data Collection Sheet #2) show that no significant differences in postoperative VAS pain scores were appreciated between any of the groups. Postoperative analgesic demand and fentanyl (mcg/kg) consumption via a PCA pump were significantly higher in group RH compared to groups RL ($p < 0.05$) and KRH ($p < 0.01$) (Kido et al., 2019).

Kido et al., (2019) tested the inflammatory markers C-reactive protein (CRP), neutrophils, lymphocytes, and neutrophil to lymphocyte ration (NRL) which they hypothesized to be associated with a hyperalgesic response. Researchers obtained baseline blood samples preoperatively and again on postoperative day 1 (POD 1) and

postoperative day 7 (POD 7). There were no significant differences in CRP levels or neutrophil levels among any of the groups preoperatively, POD 1, or POD 7 (Kido et al., 2019). Lymphocyte levels were significantly lower ($p < 0.05$) in group KRH on POD 1 compared to group RH while NLR levels were found to be significantly higher ($p < 0.001$) in group KRH on POD 1 compared to group RH and group RL (Kido et al., 2019). Kido et al., (2019) concluded that high dose remifentanil was associated with increased postoperative opioid requirements, a higher postoperative analgesic demand, and hyperalgesia whereas administration of ketamine in conjunction with high dose remifentanil anesthesia can decrease the incidence of opioid-induced hyperalgesia and also decrease postoperative opioid requirements.

When utilizing the CASP checklist (Appendix E.5, CASP Checklist) to evaluate this RCT, it was found that the trial addressed a clearly focused issue. The process of randomization of participants and blinding of health care providers was described by Kido et al., (2019), adding to the validity of their results. Patients included in this study were similar regarding demographics, ASA status, and comorbidities, increasing generalizability of these results to patients undergoing orthognathic surgery. All patients were accounted for throughout this RCT, with one being excluded because of a psychiatric illness and three being withdrawn due to the need for a second surgical procedure (Kido et al., 2019). Several limitations were identified in this RCT including the fact that the high dose of remifentanil is higher than what is typically used for remifentanil based anesthesia, which is acknowledged by Kido et al., (2019). Another limitation of this RCT is that there is not enough evidence that certain inflammatory markers examined in this study are undoubtedly indicative of a hyperalgesic response.

More research needs to be conducted to determine the correlation between inflammatory markers and hyperalgesia as only one study, for example, has found that higher NLR levels to be associated with decreased postoperative pain scores (Kido et al., 2019). The relationship between these inflammatory markers and opioid-induced hyperalgesia needs to be determined before definitive conclusions can be inferred (Kido et al., 2019). The validity of the researcher's speculations about hyperalgesia should be questioned because they did not perform an assessment of hyperalgesia using Von Frey monofilaments and algometers which have been accepted and used to assess primary and secondary hyperalgesia in multiple other research studies.

Next, the summary and conclusions will be discussed.

Summary and Conclusions

The phenomenon of hyperalgesia has been defined as an abnormal and intensified response to a painful stimulus (Mauermann et al., 2015). As described throughout this systematic review, hyperalgesia can be induced by chronic opioid administration, but can also be induced by acute opioid administration, such as intraoperatively, in healthy, opioid naïve individuals. Although the exact mechanism of opioid induced hyperalgesia (OIH) is not fully understood, it is believed that both peripheral and central nociceptive pathways are involved, and an imbalance of excitatory and inhibitory neurotransmitters may be culpable in the occurrence of OIH. Agonism of the NMDA receptor by opioids due to upregulation of pronociceptive, excitatory neurotransmitters such as substance P and glutamate is believed to contribute to this phenomenon (Bottemiller, 2012). Antagonism of the NMDA receptor with ketamine has been shown in multiple randomized control trials included in this systematic review as an efficacious treatment for reducing the incidence OIH, reducing postoperative pain scores, and reducing postoperative opioid consumption.

The purpose of this systematic review was to examine the effect of ketamine, on reducing the phenomenon of opioid-induced hyperalgesia. A literature review discussing the physiology of pain, individual differences in pain perception, abnormal pain responses, and pharmacological treatment of pain was completed. The theoretical framework that guided this systematic review is the Gate Control Theory of pain which later evolved into the Neuromatrix Theory of Pain, which encompasses both the physical and emotional response to pain and how perception of pain may differ among individuals. These theories describe the concepts of wind up and central sensitization which directly correlate with hyperalgesia.

In order to find randomized control trials suitable for use within this systematic review, a comprehensive literature search was conducted using databases and websites including MEDLINE, PubMed, CINHAL, Up-to Date, and Google Scholar. Current research regarding the effect of ketamine on opioid induced hyperalgesia was found and quality of the research was assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement. The PRISMA Statement incorporates a 27-item checklist (Appendix A, Prisma Checklist) and flow diagram (Appendix B, Prisma Flow Diagram) aimed at improving the quality of the systematic review by providing the reader with transparency and clarity of the studies examined for purposes of this review (Hutton et al., 2015; Moher et al., 2017). By ensuring meticulousness of the findings of this systematic review, validity of the results were elevated.

The randomized control trials that were chosen for this systematic review were appraised using the Critical Appraisal Skills Programme (CASP) and relevant data was collected and analyzed. The CASP appraisal tool involves the use of multiple checklists that examined the usefulness and validity of the studies chosen for this systematic review. Utilizing CASP checklists to evaluate the relevance and reliability of randomized control trials used for this systematic review promotes trustworthiness of the findings (CASP, 2017).

In order to examine the effects of ketamine on reducing opioid-induced hyperalgesia in adult surgical patients in the perioperative period, tables were created (Appendix C, Data Collection Sheet #1 & Appendix D, Data Collection Sheet #2) for ease of comparison and analysis of different variables in each study. Finally, a cross study analysis (Appendix F, Cross Study Analysis) was performed which evaluated the

relationship between the doses of intraoperative opioids, whether or not ketamine was administered and at what dose, postoperative pain scores, evidence of hyperalgesia, time to first postoperative opioid administration, and total dose of postoperative opioid consumption.

This systematic review yielded mixed results regarding the benefits to utilization of intraoperative ketamine to attenuate the incidence of OIH in the perioperative phase. In three out of five of the randomized control trials examined for this systematic review, groups that received ketamine in conjunction with high dose opioids had significantly lower postoperative pain scores when compared with groups receiving high or low dose opioids alone or with a placebo. Total postoperative opioid consumption was lower in the group that received ketamine in four out of five studies, while time to first opioid consumption produced statistically insignificant results in all five studies. Ketamine was shown to attenuate the incidence of OIH in four out of five randomized control trials assessed for purposes of this systematic review.

Mixed results in this systematic review regarding the ability of ketamine to mitigate OIH in the perioperative phase may be due to several limitations encountered while formulating this systematic review. There were limited randomized control trials available that assessed all relevant aspects of the potential effects of using ketamine to prevent OIH. Many prospective articles did not measure hyperalgesia, but only measured the effect of ketamine on postoperative pain scores and total postoperative opioid consumption, yielding them unusable for this systematic review. The articles selected for this systematic review included a low number of participants, ranging from 40 total participants to 90 total participants. Further studies with larger patient populations would

add to the validity of these results. The types of surgeries evaluated in the randomized control trials used for this systematic review varied immensely and therefore level of pain elicited from these surgeries was inconsistent. This makes generalizability of the results of these studies difficult. Lastly, the methods of evaluating hyperalgesia differed among the selected randomized control trials. Some trials used an algometer to establish a pain pressure threshold to evaluate primary and secondary hyperalgesia while other studies evaluated hyperalgesia by measuring inflammatory markers. Inconsistencies in measurement of hyperalgesia may invalidate the results. These limitations may skew the veracity of the results and further, more comprehensive research is needed on this topic before definitive conclusions can be made regarding attenuation of OIH with the use of ketamine.

Recommendations and implications for advanced nursing practice will be discussed next.

Recommendations and Implications for Advanced Nursing Practice

Pain in the postoperative period is a serious issue that can have a negative impact on patient outcomes. Poorly managed pain in the perioperative phase can result in pathologic conditions such as deep vein thrombosis, pulmonary embolism, pneumonia, and impaired wound healing (Apefelbaum, Chen, Mehta, & Gan, 2003). Pain can result in emotional and psychological complications such as demoralization, insomnia, and patient dissatisfaction (Apefelbaum et al., 2003). These postoperative complications can result in extended length of stay in the hospital, hospital readmissions, as well as the economic burden of continued treatment (Apefelbaum et al., 2003). Better management of pain by the advanced practice nurse in the perioperative phase can result in better patient outcomes, fewer postoperative complications, and increased patient satisfaction. Bottemiller (2012) estimated that medical expenses related directly to medical or surgical pain management along with indirect costs of lost workdays and decreased productivity cost Americans approximately $635 billion per year. These staggering statistics reveal the importance for advanced practice nurses to understand the complexity of pain so that they may be better equipped to treat it.

The aim of this systematic review was to examine the effect of ketamine on reducing the phenomenon of opioid-induced hyperalgesia (OIH). Recognition of OIH is paramount because OIH may be easily mistaken for acute opioid tolerance. Since acute tolerance and OIH have a similar clinical presentation, it is imperative for the advanced practice nurse to differentiate between them. With acute opioid tolerance, an increase in opioid dosage will alleviate painful symptoms whereas with OIH, an increased dose of opioids will intensify painful symptoms. Treatment options for tolerance include

increasing the dose of opioids and using a multimodal approach to pain management to produce analgesia (Flood et al., 2015). Although overall results of the randomized control trials included in this systematic review are mixed, there is a suggestion that the use of ketamine may attenuate the incidence of OIH, reduce postoperative pain scores, and reduce postoperative opioid consumption.

Further research is required before recommendation of the use ketamine for treatment and prevention of OIH can be definitively made; however, results from this systematic review suggest that pharmacological antagonism of the NMDA receptor with ketamine is a viable option to manage this phenomenon, especially with remifentanil based anesthesia. Although more extensive research on this topic is needed, utilization of information from this systematic review may lead to a reduction in OIH and may result in improved patient outcomes and patient satisfaction.

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Appendix A

PRISMA 2009 Checklist

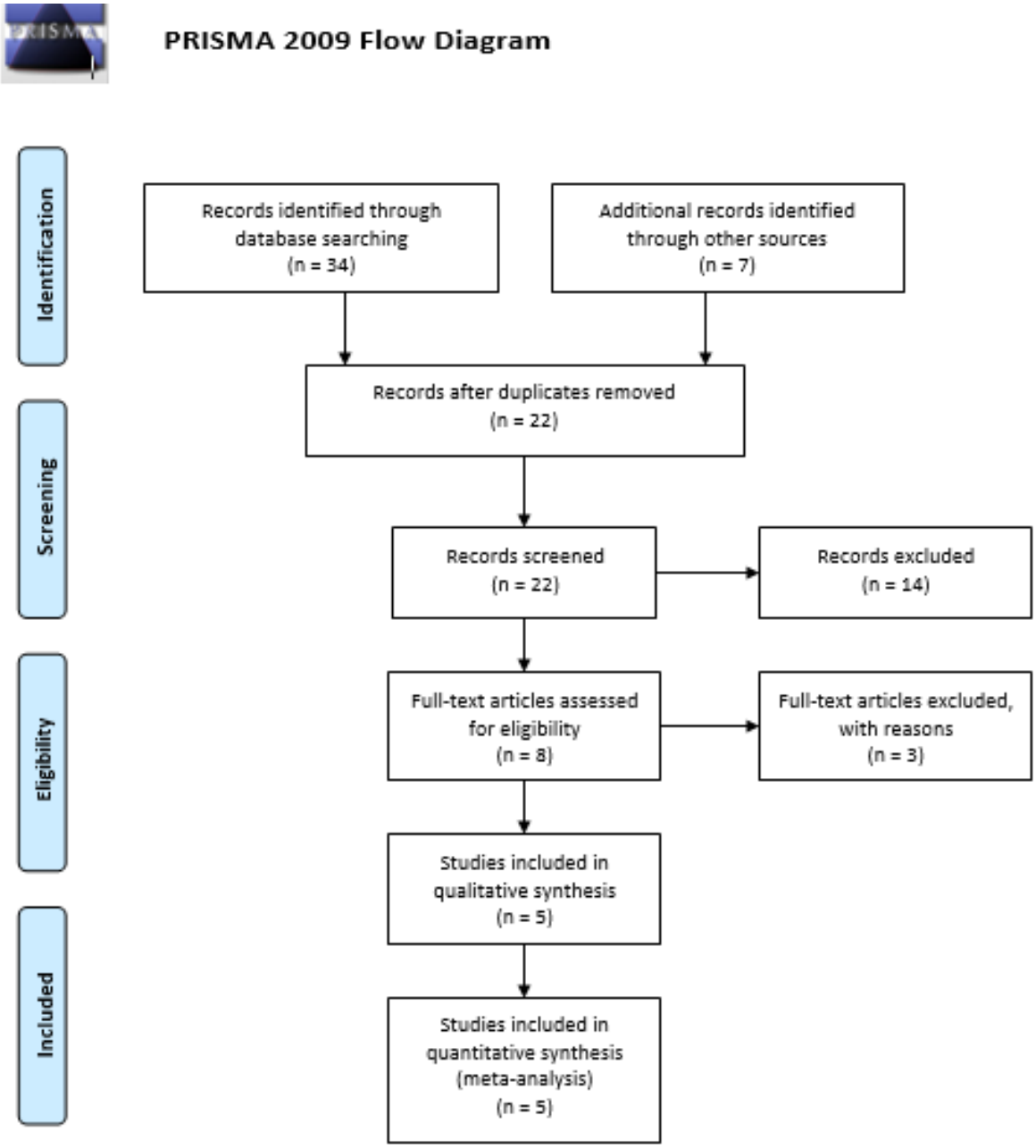
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Appendix A: PRISMA 2009 Checklist (Moher et al., 2017)

Appendix B

PRISMA 2009 Flow Diagram



(Moher et al., 2017)

Appendix C
Data Collection Sheet #1

Appendix C.1

Joly, V., Richebe, P., Guignard, B., Fletcher, D., Maurette, P., Sessler, D. I., & Chauvin, M. (2005). Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology, 103*(1), 147-155. doi:10.1097/00000542-200507000-00022

Aim	To examine if high-dose remifentanil can induce hyperalgesia and to assess if hyperalgesia can be prevented with low-dose ketamine
Design	Double-blind randomized control trial
Sample	75 patients undergoing major abdominal surgery Preoperative pain scores on VAS*, tactile pain threshold, and baseline vital signs were comparable among all patients. Surgical characteristics such as duration of surgery/anesthesia were similar among all patients. Patients included had similar demographics and comorbidities and were 44-71 years old. Patients were excluded if the surgical plan included keeping the patient intubated after surgery, they suffered from a chronic inflammatory disease, they had a history of substance abuse, were chronic opioid users, they had a history of psychiatric disease or cardiac disease that was a contraindication to ketamine administration, they did not understand how to self-administer opioids via a PCA pump, or if they were obese.
ASA Score	I – III
Methods	75 patients were divided into 3 groups: <u>Group 1</u>: Small-dose remifentanil (n=25): 0.05 mcg/kg/min remifentanil infusion plus a saline placebo infusion <u>Group 2</u>: Large-dose remifentanil (n=25): 0.4 mcg/kg/min remifentanil infusion plus a saline placebo infusion <u>Group 3</u>: Large-dose remifentanil + Ketamine (n=24): 0.4 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine until skin closure, then 2 mcg/kg/min x 48 hours postoperatively. Morphine PCA* pump with no continuous dose, demand dose of 1 mg, with a 5 minute lockout was given to all patients 4 hours after extubation. Student *t* test, Fisher exact test, Kruskal-Wallis test, and Statview for Windows were used to measure and compare statistical significance of the data.

Outcomes Measured	Morphine dose (mg) administered in PACU* 48 hour cumulative postoperative morphine (mg) requirement Tactile pain threshold (g/mm^2) preoperatively, 24 hours postoperatively & 48 hours postoperatively, 2-3 cm adjacent to the incision measured with von Frey hair Extent of hyperalgesia to von Frey hair number 16 (pressure = 122 g/mm^2) 24 hours postoperatively and 48 hours postoperatively VAS 24 hours postoperatively and 48 hours postoperatively Algometer (kPa) measurement preoperatively, 24 hours postoperatively, and 48 hours postoperatively

**Note:* VAS: Visual Analog Scale; PCA: Patient-controlled analgesia; PACU: Post-anesthesia care unit
(Joly et al., 2005)

Appendix C.2

Yalcin, N., Uzun, S. T., Reisli, R., Borazan, H., & Otelcioglu, S. (2012). A comparison of ketamine and paracetamol for preventing remifentanil induced hyperalgesia in patients undergoing total abdominal hysterectomy. *International Journal of Medical Sciences,9*(5), 327-333. doi:10.7150/ijms.4222

Aim	"To compare the effects of ketamine and *paracetamol on preventing remifentanil induced hyperalgesia" (p. 327)
Design	Prospective randomized control trial
Sample	90* patients undergoing total abdominal hysterectomy Preoperative pain scores on VAS* (0-10) were comparable among all patients. Preoperative QST* pain pressure threshold with digital pressure algometer was comparable among all patients. Surgical characteristics such as duration of surgery/anesthesia were similar among all patients. Patients included were 35-70 years old. Patients were excluded if they had a psychiatric history, inability to use a PCA* device, chronic pain disorders, cardiac disorders, renal insufficiency, hematologic disorders, or if on chronic analgesics or opioid treatment. Patients were also excluded the duration of surgery was greater than 120 minutes.
ASA Score	I – II
Methods	Patients were divided into 3 groups; group I, group II, group III <u>Group I</u> (n=27): 0.4 mcg/kg/min remifentanil with saline infusion <u>Group II</u> (n=26): 0.4 mcg/kg/min remifentanil infusion with ketamine infusion 5 mcg/kg/min and 0.5 mg/kg ketamine bolus <u>Group III</u> (n=26): 0.4 mcg/kg/min remifentanil infusion with 1000 mg paracetamol infusion over 15 min pre-induction of anesthesia ANOVA and SPSS software were used to compare results from each group.
Outcomes Measured	Pain scores reported on VAS 0, 2, 4, 6, 12, and 24 hours postoperatively Analgesic delivery (morphine mg) via PCA at 2, 4, 6, 12, 24, and 48 hours postoperatively Analgesic demand (PCA button pressed) at 2, 4, 6, 12, 24, and 48 hours postoperatively Mean pressure pain threshold (Lb) preoperative, 24 hour hours postoperative, and 48 hours postoperative

**Note:* Paracetamol = Acetaminophen; 11/90 patients excluded; QST: Quantitative Sensory Tests; VAS: Visual Analog Scale; PCA: Patient-controlled analgesic (Yalcin et al., 2012)

Appendix C.3

Choi, E., Lee, H., Park, H. S., Lee, G. Y., Kim, Y. J., & Baik, H. (2015). Effect of intraoperative infusion of ketamine on remifentanil-induced hyperalgesia. *Korean Journal of Anesthesiology, 68*(5), 476-480.

Aim	To examine the effect of intraoperative ketamine on the incidence of remifentanil induced hyperalgesia
Design	Randomized control trial
Sample	75 patients undergoing laparoscopic gynecologic surgery Preoperative pain scores on NRS* were comparable among all patients. Preoperative Touch-Test Sensory Evaluation threshold was comparable among all patients. Surgical characteristics such as duration of surgery/anesthesia were similar among all patients. Patients included were 23-60 years old. Patients were excluded if they had a psychiatric history or substance abuse history.
ASA Score	I – II
Methods	75 patients were divided into 3 groups; RL, RH, and KRH <u>Group RL</u> (n=25): 0.05 mcg/kg/min remifentanil infusion <u>Group RH</u> (n=25): 0.3 mcg/kg/min remifentanil infusion <u>Group KRH</u> (n=25): 0.3 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine ANOVA and Bonferoni post-hoc analysis using GraphPad Prism were used to compare results from each group.
Outcomes Measured	Pain scores reported on NRS* 0, 1, 6, and 24 hours postoperatively 24 hour postoperative analgesic (ketorolac) requirement (mg) 48 hour postoperative fentanyl (mcg) requirement Touch-Test Sensory Evaluation to examine hyperalgesia (preoperative, postoperative, and difference)

**Note:* NRS: Numerical Rating Scale
(Choi et al., 2015)

Appendix C.4

Leal, P. C., Salomão, R., Brunialti, M. K., & Sakata, R. K. (2015). Evaluation of the effect of ketamine on remifentanil-induced hyperalgesia: A double-blind, randomized study. *Journal of Clinical Anesthesia,27*(4), 331-337. doi:10.1016/j.jclinane.2015.02.002

Aim	To evaluate the effect of intraoperative ketamine on reducing remifentanil-induced hyperalgesia
Design	Prospective, double-blind, randomized control trial
Sample	56 patients undergoing laparoscopic cholecystectomy. Preoperative evaluation of hyperalgesia using von Frey monofilaments was comparable among all patients. Surgical characteristics such as duration of surgery/anesthesia were similar among all patients. Patients included were ≥18 years of age, male or female, with similar demographics and comorbidities. Patients were excluded if they had a psychiatric history, substance abuse history, if they had contraindications to self-administering opioids via a *PCA pump, or if they were on chronic opioids or had taken opioids within 12 hours before surgery.
ASA Score	I – II
Methods	56 patients were divided into 2 groups: Group 1 (n=28): 0.4 mcg/kg/min remifentanil infusion with 5 mcg/kg/min ketamine infusion Group 2 (n=28): 0.4 mcg/kg/min remifentanil infusion with saline infusion SPSS 17 was used for sample size calculation and statistical analysis. Kolmogorov-Smirnov and Shapiro, Fisher exact test, Mann-Whitney test, and Student *t* test were used to evaluate the data. CONSORT was used to outline the data collected and used for this randomized control trial.
Outcomes Measured	Pain scores reported on NRS* 1, 6, 12, and 24 hours postoperatively Time to first postoperative supplemental morphine (min) 24 hour postoperative consumption of morphine (mg) Evidence of hyperalgesia using 6 von Frey monofilaments and an algometer in the thenar eminence and periumbilical regions (preoperative and 24 hours postoperative). Serum levels of *IL-6, IL-8, & IL-10, preoperative, 5 hours after incision, and 24 hours postoperatively.

**Note:* PCA: Patient-controlled analgesia; NRS: Numerical Rating Scale; IL: Interleukin

(Leal et al., 2015)

Appendix C.5

Kido, K., Toda, S., Shindo, Y., Miyashita, H., Sugino, S., & Masaki, E. (2019). Effects of low-dose ketamine infusion on remifentanil-induced acute opioid tolerance and the inflammatory response in patients undergoing orthognathic surgery. *Journal of Pain Research,12*, 377-385. doi:10.2147/jpr.s177098

Aim	To examine if low dose intraoperative ketamine prevents acute remifentanil-induced tolerance
Design	Prospective, randomized, double-blind study
Sample	40* patients undergoing orthognathic surgery Preoperative pain scores on VAS* were comparable among all patients. Surgical characteristics such as duration of surgery/anesthesia were similar among all patients. Patients included were 18-41 years old. Patients were excluded if they had a psychiatric disorder, chronic opioid use, obesity, a chronic inflammatory disease, or acute cardiac disease.
ASA Score	I – II
Methods	40 patients were divided into 3 groups; RH, RL, and KRH Group RH (n=12): 0.6 mcg/kg/min remifentanil infusion Group RL (n=12): 0.2 mcg/kg/min remifentanil infusion Group KRH (n=12): 0.6 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine G* power software, Kolmogorov-Smirnov test, Kruskal-Wallis test, Chi-squared test, and GraphPad Prism were used to analyzed statistically significant results.
Outcomes Measured	Pain scores reported on VAS 1, 3, 6, 12, and 24 hours postoperatively 24 hour postoperative analgesic delivery (fentanyl, mcg/kg) via PCA* pump 24 hour analgesic demand (PCA button pressed) Inflammatory markers: CRP* (mg/dL), Neutrophils (x1000/µL), Lymphocytes (x1000/µL), NLR* (preoperative, POD1*, and POD7*)

**Note:* 40 patients enrolled, 1 excluded due to psychiatric disorder, 3 excluded due to need for an additional surgical procedure
VAS: Visual Analog Scale; PCA: Patient-controlled analgesia; CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio;
POD1: Postoperative day 1; POD7: Postoperative day 7
(Kido et al., 2019)

Appendix D
Data Collection Sheet #2

Appendix D.1

Joly, V., Richebe, P., Guignard, B., Fletcher, D., Maurette, P., Sessler, D. I., & Chauvin, M. (2005). Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology, 103*(1), 147-155. doi:10.1097/00000542200507000-00022/

<table>
<tr><td>Intraoperative Opioid & Ketamine Doses</td><td>Group 1: Small-dose remifentanil (n=25): 0.05 mcg/kg/min remifentanil infusion plus a saline placebo infusion
Group 2: Large-dose remifentanil (n=25): 0.4 mcg/kg/min remifentanil infusion plus a saline placebo infusion
Group 3: Large-dose remifentanil + Ketamine (n=24): 0.4 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine until skin closure, then 2 mcg/kg/min x 48 hours postoperatively.</td></tr>
<tr><td>Postoperative Pain Score</td><td>
<table>
<tr><td></td><td>Group 1 (n=25)</td><td>Group 2 (n=25)</td><td>Group 3 (n=24)</td></tr>
<tr><td>VAS score at 24 hours</td><td>42 ± 26</td><td>44 ± 21</td><td>36 ± 20</td></tr>
<tr><td>VAS score at 48 hours</td><td>43 ± 20</td><td>37 ± 23</td><td>33 ± 18</td></tr>
</table>
</td></tr>
<tr><td>Evidence of Hyperalgesia</td><td>Tactile Pain Threshold: Von Frey Hair (g/mm^2)
<table>
<tr><td></td><td>Group 1(n=25)</td><td>Group 2 (n=25)</td><td>Group 3 (n=24)</td></tr>
<tr><td>Preoperative</td><td>177 ± 0.5</td><td>178 ± 0.5</td><td>176 ± 1</td></tr>
<tr><td>24 Hours Postoperative</td><td>132 ± 7</td><td>106 ± 14†</td><td>136 ± 8</td></tr>
<tr><td>48 Hours Postoperative</td><td>138 ± 6</td><td>102 ± 14†</td><td>140 ± 7</td></tr>
</table>
Extent of hyperalgesia (cm) to von Frey hair number 16 (pressure = 122 g/mm^2)
<table>
<tr><td></td><td>Group 1 (n=25)</td><td>Group 2 (n=25)</td><td>Group 3 (n=24)</td></tr>
<tr><td>24 Hours Postoperative</td><td>7 ± 6</td><td>12 ± 7†</td><td>8.5 ± 6</td></tr>
<tr><td>48 Hours Postoperative</td><td>5.5 ± 3</td><td>12 ± 7.5†</td><td>6.5 ± 6.5</td></tr>
</table>
</td></tr>
</table>

Time to First Postoperative Opioid Administration (min)	Group 1 (n=25)	Group 2 (n=25)	Group 3 (n=24)
	35 (28-46)	24 (20-33)	41 (32-52)

Postoperative Analgesic Consumption	Group 1 (n=25)	Group 2 (n=25)	Group 3 (n=24)
Morphine (mg) PACU	16 (10-24)	20 (17-27)	20 (14-23)
Morphine (mg) 48 Hours Postoperative	68 (50-91)	86 (59-109)‡	62 (48-87)

**Note:* VAS: Visual Analog Scale; PCA: Patient-controlled analgesia; PACU: Post-anesthesia care unit
Data is shown as mean ± standard deviation or median (interquartile range).
† Indicates statistically significant results ($p < 0.05$) between group 1 & group 3
‡ Indicates statistically significant results ($p < 0.01$) in group 2 compared with group 1 & 3
(Joly et al., 2005)

Appendix D.2

Yalcin, N., Uzun, S. T., Reisli, R., Borazan, H., & Otelcioglu, S. (2012). A comparison of ketamine and paracetamol for preventing remifentanil induced hyperalgesia in patients undergoing total abdominal hysterectomy. *International Journal of Medical Sciences,9*(5), 327-333. doi:10.7150/ijms.4222

Intraoperative Opioid & Ketamine Doses	Group I (n=27): 0.4 mcg/kg/min remifentanil with saline infusion Group II (n=26): 0.4 mcg/kg/min remifentanil infusion with ketamine infusion 5 mcg/kg/min and 0.5 mg/kg ketamine bolus Group III (n=26): 0.4 mcg/kg/min remifentanil infusion with 1000 mg paracetamol infusion over 15 min pre-induction of anesthesia

Postoperative Pain Score

	Group I (n=27)	Group II (n=26)	Group III (n=26)
*VAS 0	7.8	6.7✡	7.2
VAS 2	5.1	4.0✡	4.2
VAS 4	3.4	2.4✡	2.4†
VAS 6	2.5	1.9✡	1.7†
VAS 12	1.6	0.8✡	0.8
VAS 24	0.5	0✡	0.2

Evidence of Hyperalgesia*

Mean Pressure Pain Thresholds (Lb*)

	Group I (n=27)	Group II (n=26)	Group III (n=26)
Baseline Inner Arm	4.2 ± 0.2	4.0 ± 1.3	4.3 ± 1.0
Baseline Incision	3.8 ± 0.2	3.6 ± 1.1	4.0 ± 1.0
24 hours Inner Arm	4.2 ± 0.2	4.0 ± 1.3	4.3 ± 1.0
24 hours Incision	2.6 ± 0.1†	4.9 ± 1.1✡†	4.9 ± 1.1† ‡
48 hours Inner Arm	4.0 ± 0.2	4.0 ± 1.3	4.3 ± 1.0
48 hours Incision	2.6 ± 0.1†	4.9 ± 1.1✡ †	4.9 ± 1.1† ‡

Analgesic Demand via PCA (Number of times button was pressed)	Hours	Group I (n=27)	Group II (n=26)	Group III (n=26)
	2	32.85 ± 8.19✡	23.0 ± 7.08	28.69 ± 7.01
	4	53.03 ± 12.19✡ ┼	32.84 ± 11.83	39.34 ± 9.02
	6	70.81 ± 15.03✡ ┼	40.61 ± 15.56	49.11 ± 11.70
	12	102.44 ± 27.49✡ ┼	52.19 ± 20.40	66.73 ± 16.14
	24	134.5 ± 41.07✡ ┼	60.11 ± 23.74 ‡	92.69 ± 20.44
	48	146.19 ± 21.20✡ ┼	73.20 ± 15.63 ‡	104.81 ± 14.57
Postoperative Analgesic Consumption (Actual morphine (mg) infused via PCA)	Hours	Group I (n=27)	Group II (n=26)	Group III (n=26)
	2	15.66 ± 2.63✡	12.15 ± 3.0	14.03 ± 3.56
	4	26.11 ± 4.57✡ ┼	18.46 ± 6.54	21.8 ± 6.13
	6	36.70 ± 7.16✡ ┼	23.53 ± 8.96	28.15 ± 8.36
	12	57.07 ± 15.49✡ ┼	30.92 ± 12.19	39.34 ± 11.50
	24	73.03 ± 22.41✡ ┼	35.34 ± 13.71 ‡	48.53 ± 12.40
	48	86.05 ± 29.46✡ ┼	45.52 ± 15.08 ‡	57.11 ± 16.71

Note: *VAS 0, VAS 2, VAS 4, VAS 6, VAS 12, VAS 24: Visual Analog Scores 0, 2, 4, 6, 12, and 24 hours postoperatively;
Evidence of hyperalgesia "mean pressure pain thresholds (Lb) determined with digital pressure algometer on inner forearm and the surgical incision area at the preoperative period and then postoperative 24th and 48th hour" (p. 331); (Lb): Level of blunt pressure
Data is shown as mean or mean ± standard deviation.
✡ Indicates statistically significant results between Group I and Group II ($p < 0.05$); ┼ Indicates statistically significant results between Group I & Group III ($p < 0.05$); ‡ Indicates statically significant results between Group II and Group III ($p < 0.05$)
(Yalcin et al., 2012)

Appendix D.3

Choi, E., Lee, H., Park, H. S., Lee, G. Y., Kim, Y. J., & Baik, H. (2015). Effect of intraoperative infusion of ketamine on remifentanil-induced hyperalgesia. *Korean Journal of Anesthesiology, 68*(5), 476-480.

Intraoperative Opioid & Ketamine Doses	Group RL (n=25): 0.05 mcg/kg/min remifentanil infusion Group RH (n=25): 0.3 mcg/kg/min remifentanil infusion Group KRH (n=25): 0.3 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine
Postoperative Pain Score	

	RL (n=25)	RH (n=25)	KRH (n=25)
NRS 0	4.0 ± 1.2	4.5 ± 1.6	4.2 ± 1.1
NRS 6	2.2 ± 1.1	2.9 ± 1.3†	2.0 ± 0.8
NRS 24	1.2 ± 0.5	2.0 ± 1.5†	1.0 ± 0.5

Evidence of Hyperalgesia

Touch-Test Sensory Evaluation

	RL (n=25)	RH (n=25)	KRH (n=25)
Preoperative	4.05 ± 0.16	4.01 ± 0.46	4.02 ± 0.16
Postoperative	3.92 ± 0.43	3.30 ± 0.78†	3.76 ± 0.64
Difference	-0.37 ± 0.37	-0.72 ± 0.72†	-0.27 ± 0.67

Time to First Postoperative Opioid Administration (min)

RL (n=25)	RH (n=25)	KRH (n=25)
52.1 ± 27.0	39.6 ± 18.4	51.6 ± 26.7

Postoperative Analgesic Consumption

	RL (n=25)	RH (n=25)	KRH (n=25)
Ketorlac (mg)	9.6 ± 14.3	25.2 ± 18.7†	16.8 ± 21.4
Fentanyl (mcg)	243.3 ± 77.9	310 ± 53.9†	225.1 ± 38.1

Note: *NRS0, NRS6, NRS24: Numerical Rating Scale scores 0, 6, and 24 hours postoperatively

Data is shown as mean ± standard deviation.

† Indicates statistically significant results ($p < 0.05$)

(Choi et al., 2015)

Appendix D.4

Leal, P. C., Salomão, R., Brunialti, M. K., & Sakata, R. K. (2015). Evaluation of the effect of ketamine on remifentanil-induced hyperalgesia: A double-blind, randomized study. *Journal of Clinical Anesthesia,27*(4), 331-337. doi:10.1016/j.jclinane.2015.02.002

<table>
<tr><td>Intraoperative Opioid & Ketamine Doses</td><td>Group 1 (n=28): 0.4 mcg/kg/min remifentanil infusion with 5 mcg/kg/min ketamine infusion
Group 2 (n=28): 0.4 mcg/kg/min remifentanil infusion with saline infusion</td></tr>
<tr><td>Postoperative Pain Score</td><td>
<table>
<tr><td></td><td>Group 1 (n=28)</td><td>Group 2 (n=28)</td></tr>
<tr><td>*NRS 1</td><td>4.6 (3.0)</td><td>5.1 (2.5)</td></tr>
<tr><td>NRS 6</td><td>0.9 (1.2)</td><td>0.7 (1.0)</td></tr>
<tr><td>NRS 18</td><td>1.57 (1.8)</td><td>1.3 (1.6)</td></tr>
<tr><td>NRS 24</td><td>1.4 (1.5)</td><td>0.8 (1.0)</td></tr>
</table>
</td></tr>
<tr><td>Evidence of Hyperalgesia</td><td>
<table>
<tr><td>Von Frey Monofilament</td><td>Group 1 (n=28)</td><td>Group 2 (n=28)</td></tr>
<tr><td>Thenar Eminence:
- Preoperative
- 24 hours postoperative</td><td>
300 (0)
290 (54.8)†</td><td>
300 (0)
247 (115)†</td></tr>
<tr><td>Periumbilical:
- Preoperative
- 24 hours postoperative</td><td>
279 (77.1)
248 (114)</td><td>
269 (92)
205 (140)</td></tr>
<tr><td>Algometer</td><td>Group 1 (n=28)</td><td>Group 2 (n=28)</td></tr>
<tr><td>Thenar Eminence:
- Preoperative
- 24 hours postoperative</td><td>
2.51 (1.43)
0.56 (0.44)</td><td>
2.19 (0.92)
0.51 (0.44)</td></tr>
<tr><td>Periumbilical:
- Preoperative
- 24 hours postoperative</td><td>
3.6 (1.5)
3.5 (1.6)</td><td>
3.9 (1.4)
3.7 (1.7)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Evidence of Hyperalgesia</td><td>
<table>
<tr><td>Interleukin Levels (pg/mL)</td><td>Group 1 (n=28)</td><td>Group 2 (n=28)</td></tr>
<tr><td>*IL-6:
- Preoperative
- 5 hours after incision
- 24 hours postoperative</td><td>
3.3 (9.5)
29.3 (23.6)
24.1 (21.3)</td><td>
2.1 (3.4)
34.8 (48.7)
24.8 (31.5)</td></tr>
<tr><td>IL-8:
- Preoperative
- 5 hours after incision
- 24 hours postoperative</td><td>
3.3 (4.1)
8.0 (6.8)
6.0 (7.2)</td><td>
2.2 (3.2)
11.3 (15.1)
4.5 (6.1)</td></tr>
<tr><td>IL-10:
- Preoperative
- 5 hours after incision
- 24 hours postoperative</td><td>
7.8 (20)
9.1 (19.1)
8.6 (18.5)</td><td>
1.9 (3.3)
5.5 (7.9)
5.0 (5.5)</td></tr>
</table>
</td></tr>
<tr><td>Time to First Postoperative Opioid Administration (min)</td><td>
<table>
<tr><td>Group 1 (n=28)</td><td>Group 2 (n=28)</td></tr>
<tr><td>18 (0-600)</td><td>15 (2-130)</td></tr>
</table>
</td></tr>
<tr><td>Postoperative Analgesic Consumption</td><td>Morphine (mg)
<table>
<tr><td>Group 1 (n=28)</td><td>Group 2 (n=28)</td></tr>
<tr><td>27.4 (18.3)</td><td>27.7 (12.9)</td></tr>
</table>
</td></tr>
</table>

Note: *NRS1, NRS6, NRS 18, NRS24: Numerical Rating Scale scores 1, 6, 18, and 24 hours postoperatively; IL: Interleukin
Data is shown as mean (standard deviation) or (minimum value – maximal value)
$^{+}$ Indicates statistically significant results ($p < 0.05$)
(Leal et al., 2015)

Appendix D.5

Kido, K., Toda, S., Shindo, Y., Miyashita, H., Sugino, S., & Masaki, E. (2019). Effects of low-dose ketamine infusion on remifentanil-induced acute opioid tolerance and the inflammatory response in patients undergoing orthognathic surgery. *Journal of Pain Research,12*, 377-385. doi:10.2147/jpr.s177098

<table>
<tr><td>Intraoperative Opioid & Ketamine Doses</td><td>Group RH (n=12): 0.6 mcg/kg/min remifentanil infusion
Group RL (n=12): 0.2 mcg/kg/min remifentanil infusion
Group KRH (n=12): 0.6 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine</td></tr>
<tr><td>Postoperative Pain Score</td><td>
<table>
<tr><td></td><td>Group RH (n=12)</td><td>Group RL (n=12)</td><td>Group KRH (n=12)</td></tr>
<tr><td>VAS score at 1 hour</td><td>35 ± 14</td><td>22 ± 15</td><td>31 ± 24</td></tr>
<tr><td>VAS score at 3 hours</td><td>34 ± 14</td><td>20 ± 15</td><td>22 ± 15</td></tr>
<tr><td>VAS score at 6 hours</td><td>21 ± 15</td><td>18 ± 14</td><td>20 ± 15</td></tr>
<tr><td>VAS score at 12 hours</td><td>23 ± 19</td><td>22 ± 15</td><td>15 ± 11</td></tr>
<tr><td>VAS score at 24 hours</td><td>18 ± 14</td><td>19 ± 11</td><td>12 ± 7</td></tr>
</table>
</td></tr>
<tr><td>Evidence of Hyperalgesia</td><td>
<table>
<tr><td>Inflammatory Markers</td><td>Group RH (n=12)</td><td>Group RL (n=12)</td><td>Group KRH (n=12)</td></tr>
<tr><td>*CRP (mg/dL):
- Preoperative
- POD 1
- POD 7</td><td>
0.0
4.1 ± 1.8
0.5 ± 0.6</td><td>
0.0
3.4 ± 1.8
04 ± 0.8</td><td>
0.0
3.9 ± 1.3
0.6 ± 0.9</td></tr>
<tr><td>Neutrophils (x1000µL):
- Preoperative
- POD 1
- POD 7</td><td>
3.4 ± 0.9
15.6 ± 2.4
6.0 ± 2.2</td><td>
3.2 ± 1.4
14.9 ± 3.0
4.5 ± 2.1</td><td>
3.0 ± 0.8
14.9 ± 3.3
4.5 ± 2.1</td></tr>
<tr><td>Lymphocytes (x1000µL):
- Preoperative
- POD 1
- POD 7</td><td>
2.0 ± 0.4
1.2 ± 0.3
1.9 ± 0.5</td><td>
2.1 ± 0.6
1.0 ± 0.3
2.1 ± 0.5</td><td>
1.8 ± 0.3
0.8 ± 0.3☼
</td></tr>
</table>
</td></tr>
</table>

Evidence of Hyperalgesia	Inflammatory Markers	Group RH (n=12)	Group RL (n=12)	1.8 ± 1.3 Group KRH (n=12)
	*NLR: - Preoperative - POD 1 - POD 7	1.8 ± 0.5 14.0 ± 3.8 3.7 ± 2.6	1.6 ± 0.7 15.8 ± 4.4 2.2 ± 0.9	1.7 ± 0.6 19.0 ± 6.6┼‡ 2.6 ± 1.3
Analgesic Demand via PCA (Number of times button was pressed in 24 hours postoperatively)	Group RH (n=12)	Group RL (n=12)	Group KRH (n=12)	
	12.8 ± 9.3 ϕΞ	5.9 ± 2.3	4.8 ± 5.0	
Postoperative Analgesic Consumption		Group RH (n=12)	Group RL (n=12)	Group KRH (n=12)
	24 hour Postoperative fentanyl dose (mcg/kg)	4.65 ± 3.34 ϕΞ	2.41 ± 1.06	1.65 ± 1.62

**Note:* VAS: Visual Analog Scale; PCA: Patient-controlled analgesia
Data is shown as mean ± standard deviation
* Indicates statistically significant results between Group KRH and Group RH ($p < 0.05$)
┼ Indicates statistically significant results between Group KRH and Group RL ($p < 0.05$)
‡ Indicates statically significant results between Group KRH and Group RH ($p < 0.001$)
ϕ Indicates statistically significant results between Group RH and Group RL ($p< 0.05$)
Ξ Indicates statistically significant results between Group RH and Group KRH ($p < 0.01$)
(Kido et al., 2019)

Appendix E

Critical Appraisal Skills Programme (CASP) Checklist: Randomized Control Trials

Appendix E.1: CASP Checklist

Joly, V., Richebe, P., Guignard, B., Fletcher, D., Maurette, P., Sessler, D. I., & Chauvin, M. (2005). Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology, 103*(1), 147-155. doi:10.1097/00000542-200507000-00022

A. Are the results of the RCT valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, healthcare workers, and personnel 'blind' to treatment?	X		
5. Were groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?			X
B. What are the results?			
7. How large was the treatment effect?	75 patients undergoing major abdominal surgery		
8. How precise was the estimate of the treatment effect?	Ketamine was shown to reduce the incidence of OIH*		
C. Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harm and cost?	X		

**Note*: OIH: Opioid-induced hyperalgesia
Patients in the small dose remifentanil group were anesthetized with larger doses of Desflurane

Appendix E.2: CASP Checklist

Yalcin, N., Uzun, S. T., Reisli, R., Borazan, H., & Otelcioglu, S. (2012). A comparison of ketamine and paracetamol for preventing remifentanil induced hyperalgesia in patients undergoing total abdominal hysterectomy. *International Journal of Medical Sciences,9*(5), 327-333. doi:10.7150/ijms.4222

A. Are the results of the RCT valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, healthcare workers, and personnel 'blind' to treatment?	X		
5. Were groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?			
7. How large was the treatment effect?	90 patients undergoing total abdominal hysterectomy		
8. How precise was the estimate of the treatment effect?	Ketamine and paracetamol were both equally effective in preventing OIH*		
C. Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?		X	
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harm and cost?	X		

Note: OIH: Opioid-induced hyperalgesia

Appendix E.3: CASP Checklist

Choi, E., Lee, H., Park, H. S., Lee, G. Y., Kim, Y. J., & Baik, H. (2015). Effect of intraoperative infusion of ketamine on remifentanil-induced hyperalgesia. *Korean Journal of Anesthesiology, 68*(5), 476-480.

A. Are the results of the RCT valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, healthcare workers, and personnel 'blind' to treatment?		X	
5. Were groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?			X
B. What are the results?			
7. How large was the treatment effect?	75 patients undergoing laparoscopic gynecologic surgery		
8. How precise was the estimate of the treatment effect?	Ketamine was shown to attenuate OIH*		
C. Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?	X		
10. Were all clinically important outcomes considered?	X		
11. Are the benefits worth the harm and cost?	X		

Note: OIH: Opioid-induced hyperalgesia
Patients in the low dose remifentanil group were anesthetized with larger doses of Desflurane

Appendix E.4: CASP Checklist

Leal, P. C., Salomão, R., Brunialti, M. K., & Sakata, R. K. (2015). Evaluation of the effect of ketamine on remifentanil-induced hyperalgesia: A double-blind, randomized study. *Journal of Clinical Anesthesia,27*(4), 331-337. doi:10.1016/j.jclinane.2015.02.002

A. Are the results of the RCT valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, healthcare workers, and personnel 'blind' to treatment?	X		
5. Were groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?			
7. How large was the treatment effect?	56 patients undergoing a laparoscopic cholecystectomy		
8. How precise was the estimate of the treatment effect?	Ketamine was not determined to prevent or reduce OIH* when providing remifentanil based anesthesia		
C. Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?	X		
10. Were all clinically important outcomes considered?		X	
11. Are the benefits worth the harm and cost?	X		

Note: OIH: Opioid-induced hyperalgesia

Appendix E.5: CASP Checklist

Kido, K., Toda, S., Shindo, Y., Miyashita, H., Sugino, S., & Masaki, E. (2019). Effects of low-dose ketamine infusion on remifentanil-induced acute opioid tolerance and the inflammatory response in patients undergoing orthognathic surgery. *Journal of Pain Research,12*, 377-385. doi:10.2147/jpr.s177098

A. Are the results of the RCT valid?	**YES**	**CAN'T TELL**	**NO**
1. Did the trial address a clearly focused issue?	X		
2. Was the assignment of patients to treatments randomized?	X		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
4. Were patients, healthcare workers, and personnel 'blind' to treatment?	X		
5. Were groups similar at the start of the trial?	X		
6. Aside from the experimental intervention, were the groups treated equally?	X		
B. What are the results?			
7. How large was the treatment effect?	40 patients undergoing orthognathic surgery		
8. How precise was the estimate of the treatment effect?	Ketamine was determined to prevent acute opioid tolerance		
C. Will the results help locally?	**YES**	**CAN'T TELL**	**NO**
9. Can the results be applied in your context?		X	
10. Were all clinically important outcomes considered?		X	
11. Are the benefits worth the harm and cost?	X		

Appendix F

Cross Study Analysis

Study	Intraoperative Opioid & Ketamine Doses	Evidence of Hyperalgesia	Results
Joly et al., (2005)	75 patients undergoing major abdominal surgery were divided into 3 groups: Group 1: Small-dose remifentanil (n=25): 0.05 mcg/kg/min remifentanil infusion plus a saline placebo infusion Group 2: Large-dose remifentanil (n=25): 0.4 mcg/kg/min remifentanil infusion plus a saline placebo infusion Group 3: Large-dose remifentanil + Ketamine (n=24): 0.4 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine until skin closure, then 2 mcg/kg/min x 48 hours postoperatively.	Extent of hyperalgesia was measured using von Frey hair number 16 (pressure = 122 g/mm^2) adjacent to the surgical wound. An algometer was used to establish a pain pressure threshold (kPa). Preoperative tactile pain thresholds were similar among the 3 groups. Measurements at 24 hours and 48 hours postoperative were significantly ($p < 0.01$) higher in group 2 compared with groups 1 & 3. Extent of hyperalgesia to von Frey hair number 16 was significantly higher ($p < 0.05$) in group 2, compared to groups 1 & 3.	No significant differences in postoperative pain scores at 24 hours and 48 hours postoperatively. No significant difference in time (min) to first postoperative morphine dose or amount of morphine (mg) administered. Group 2 received a significantly ($p < 0.01$) higher total dose of morphine (mg) compared with groups 1 & 3, 48 hours postoperatively Large-dose intraoperative remifentanil was shown to induce hyperalgesia. This phenomenon was prevented by administration of ketamine.

Study	Intraoperative Opioid & Ketamine Doses	Evidence of Hyperalgesia	Results
Yalcin et al., (2012)	90 patients undergoing total abdominal hysterectomy divided into 3 groups: <u>Group I</u> (n=27): 0.4 mcg/kg/min remifentanil with saline infusion <u>Group II</u> (n=26): 0.4 mcg/kg/min remifentanil infusion with ketamine infusion 5 mcg/kg/min and 0.5 mg/kg ketamine bolus <u>Group III</u> (n=26): 0.4 mcg/kg/min remifentanil infusion with 1000 mg paracetamol infusion over 15 min pre-induction of anesthesia	Hyperalgesia was quantified using mean pressure pain threshold (Lb) with a digital pressure algometer on inner forearm & at surgical incision 24 & 48 hours postop Baseline values comparable among three groups Mean pressure pain thresholds (Lb) at 24 & 48 hours postop at surgical incision significantly lower in group I compared to groups II & III Group I: lower pressure pain thresholds at 24 & 48 hours postop than their baseline values, indicating hyperalgesia. Groups II & III: significantly ($p < 0.05$) higher pressure pain thresholds at 24 & 48 hours postop compared with baseline values, indicating attenuation of the hyperalgesic response with paracetamol and ketamine.	Postop VAS scores: - Significantly higher ($p < 0.05$) in group I compared to group II at 0, 2, 4, 6, 12, & 24 hours postop - Significantly higher ($p < 0.05$) in groups I compared to group III at 4 & 6 hours postop - Not statistically significant between groups II & III Analgesic demand via PCA pump: - Significantly higher ($p < 0.05$) between group I compared to group II at 2, 4, 6, 12, 24, & 48 hours postop - Significantly higher ($p < 0.05$) in group I compared to group III at 4, 6, 12, 24, & 48 hours postop - Significantly ($p < 0.05$) higher in group III compared to group II at 24 & 48 hours postop Morphine consumption (mg) via PCA pump: - Significantly ($p < 0.05$) higher in group I compared to group II at 2, 4, 6, 12, 24, & 48 hours postop - Significantly ($p < 0.05$) higher in group I compared to group III at 4, 6, 12, 24, & 48 hours postop - Significantly ($p < 0.05$) higher in group III compared to group II at 24 & 48 hours postop Paracetamol & ketamine were both shown to be equally efficacious in preventing opioid-induced hyperalgesia

Study	Intraoperative Opioid & Ketamine Doses	Evidence of Hyperalgesia	Results
Choi et al., (2015)	75 patients undergoing laparoscopic gynecologic surgery divided into 3 groups: Group RL (n=25): 0.05 mcg/kg/min remifentanil infusion Group RH (n=25): 0.3 mcg/kg/min remifentanil infusion Group KRH (n=25): 0.3 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine	Hyperalgesia measured adjacent to the wound preop & 24 hours postop to conduct Touch-Test sensory evaluation. Difference between the two values was measured; higher negative number indicates a hyperalgesic response. Preop baseline values of Touch-Test sensory evaluation was similar among 3 groups 24 hour postop Touch-Test sensory evaluation values significantly lower in group RH compared to groups RL & KRH. Difference was more negative in group RH compared to groups RL & KRH indicating hyperalgesic response in group RH.	NRS pain scores significantly ($p < 0.05$) higher in group RH compared to groups RL & KRH at 6 & 24 hours postop No significant difference between time (min) to first postop opioid administration among the 3 groups Postop ketorolac (mg) consumption significantly ($p < 0.05$) higher in group RH compared to groups RL & KRH Postop fentanyl (mcg) consumption significantly higher ($p < 0.05$) in group RH compared to groups RL & KRH Opioid-induced hyperalgesia was shown to be reduced by ketamine administration

Study	Intraoperative Opioid & Ketamine Doses	Evidence of Hyperalgesia	Results
Leal et al., (2015)	56 patients undergoing laparoscopic cholecystectomy: Group 1 (n=28): 0.4 mcg/kg/min remifentanil infusion with 5 mcg/kg/min ketamine infusion Group 2 (n=28): 0.4 mcg/kg/min remifentanil infusion with saline infusion	Hyperalgesia measured using Von Frey monofilaments & an algometer at the thenar eminence & periumbilical region preop & 24 hours postop to measure pain threshold. Blood samples taken preop, 5 hours after incision, & 24 hours postop to measure IL-6, IL-8, & IL-10 levels which were hypothesized to be a component of the inflammatory response associated with hyperalgesia. Significant ($p < 0.05$) difference in the hyperalgesic response at the thenar eminence in group 1 compared to group 2 No other significant hyperalgesic responses between groups 1 & 2 at the thenar eminence or periumbilical region No significant difference in IL-6, IL-8, or IL-10 levels preop, 5 hours after incision, or 24 hours postop in group 1 & 2.	Pain scores at 1 hour postop were significantly ($p < 0.05$) lower in group 1 compared to group 2 No significant difference in time to first postoperative opioid administration (min) between group 1 and group 2 No significant difference in total, 24 hour, postop morphine consumption (mg) between group 1 and group 2 Ketamine was not shown to attenuate the response to opioid-induced hyperalgesia

Study	Intraoperative Opioid & Ketamine Doses	Evidence of Hyperalgesia	Results
Kido et al., (2019)	40 patients undergoing orthognathic surgery divided into 3 groups: Group RH (n=12): 0.6 mcg/kg/min remifentanil infusion Group RL (n=12): 0.2 mcg/kg/min remifentanil infusion Group KRH (n=12): 0.6 mcg/kg/min remifentanil infusion with 0.5 mcg/kg bolus of ketamine and 5 mcg/kg/min infusion of ketamine	Inflammatory markers: CRP, neutrophils, lymphocytes, and NLR measured preop to obtain baseline & measured POD 1 & POD 7 No significant differences in CRP levels among any groups preop, POD 1, or POD 7 No significant differences in neutrophil levels among any groups preop, POD 1, or POD 7. POD 1: - Lymphocyte levels significantly ($p < 0.05$) lower in group KRH compared to group RH - NLR levels significantly higher ($p < 0.001$) in group KRH compared to group RH - NLR levels significantly higher ($p < 0.05$) in group KRH compared to group RL	No significant differences in postop VAS scores between groups RH, RL, or KRH. Analgesic demand via PCA pump: - Group RH had significantly ($p < 0.05$) higher analgesic demand compared to group RL. - Group RH had significantly ($p < 0.01$) higher analgesic demand compared to group KRH 24 hour postop fentanyl (mcg/kg) requirement: - Group RH had significantly ($p < 0.05$) higher requirement compared to group RL - Group RH had a significantly ($p < 0.01$) higher requirement compared to group KRH. High dose remifentanil (group RH) was associated with higher postop analgesic demand, opioid requirements & hyperalgesia Administration of ketamine with remifentanil anesthesia decreased opioid-induced hyperalgesia & postop opioid requirements