LOW-DOSE KETAMINE AS A PERIOPERATIVE MULTIMODAL REGIMEN

by

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As members of the DNP Project Committee, we certify that we have read the DNP project prepared by Hyun Ju Oh, titled Low-Dose Ketamine as a Perioperative Multimodal Regimen and recommend that it be accepted as fulfilling the DNP project requirement for the Degree of Doctor of Nursing Practice.

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Final approval and acceptance of this DNP project is contingent upon the candidate’s submission of the final copies of the DNP project to the Graduate College.

I hereby certify that I have read this DNP project prepared under my direction and recommend that it be accepted as fulfilling the DNP project requirement.

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ABSTRACT

Background: Postoperative opioid consumption has caused surgical complications such as postoperative nausea and vomiting (PONV), respiratory failure, and prolonged hospital stay. The culprit of the epidemic opioid crisis in the United States (U.S.) is opioid exposure after surgery. The American Society of Anesthesiologists (ASA) recommends using multimodal pain management for all surgical patients to decrease opioid consumption and its complications. Ketamine, an N-Methyl-D-aspartate (NMDA) receptor antagonist, is an effective multimodal pain regimen that decreases postoperative pain and opioid consumption without increasing risk of severe side effects.

Objective: The purpose of this DNP project was to increase knowledge of ketamine as a multimodal pain regimen among the anesthesia providers and student nurse anesthetists at a regional medical center in southern California.

Design: This descriptive study includes a pre-questionnaire to assess the current knowledge of ketamine, an educational session, and a post-questionnaire after the educational session to assess increased knowledge of ketamine.

Measurements: The primary measurement includes the increase in knowledge of ketamine regarding time and frequency of administration, types of surgery that can be beneficial from ketamine, and financial advantages. The secondary measurement assesses barriers to adding ketamine to current practice.
INTRODUCTION

Pain control is one of the main concerns for anesthetic providers during the postoperative period, as greater than 75\% of surgical patients reported that their pain control was inadequate (Gan, Habib, Miller, White, & Apfelbaum, 2014). Pain produces not only anxiety for patients but also postoperative complications such as nausea, vomiting, delayed surgical recovery, and more extended hospital stays (Kehlet, Jensen, & Woolf, 2006).

Adequate pain control is a challenge for anesthetic providers, for it requires well-planned pain management strategies for optimal individualized pain control. Pain management should begin in the preoperative period before a patient experiences pain. A thorough pain assessment and individualized pain management plan should be established before the procedure begins. Inadequate pain control often leads to chronic pain development, lower patient satisfaction postoperatively, increased surgical complications, increased morbidity and mortality, and increased care cost (Khana et al., 2011).

Background

Inadequate surgical pain management creates significant adverse effects on health care. More than 85\% of patients who went under surgical procedures experienced acute surgical pain (Gan et al., 2014). More than 75\% of patients reported their pain was higher than moderate or severe (Apfelbaum, Chen, Metha, & Gan, 2003). Inadequate pain management is well known to increase the risk of surgical complications (Apfelbaum et al., 2003). Uncontrolled pain is associated with myocardial ischemia, pulmonary complications, thromboembolism, delayed wound healing, development of chronic pain, and extended hospital stays (American Society of Anesthesiologists [ASA], 2012). All these complications, in turn, lead to an increased financial
burden on the healthcare system. The annual cost of treating pain was approximately 600 billion U.S. dollars, which was higher than treating heart disease, cancer, and diabetes (Gaskin & Richard, 2011).

Poor pain management both consumes financial resources and raises risks of complications and causes elevated anxiety among patients (Vaughn, Wichowski, & Bosworth, 2007). More than 80% of the patients in the preoperative period stated that anticipated pain causes anxiety (Gan et al., 2014), a well-known factor that increases blood pressure and heart rate and causes cardiac arrhythmia and respiratory complications intraoperatively (Vaughn, Wichowski, & Bosworth, 2007). Anxiety also reduces a patient’s ability to cope with pain and increases the perception of pain (Vaughn et al., 2007).

Historically, opioids have been used as a mainstay of analgesics since ancient Greeks first derived them from opium (Ballantyne, 2003). Numerous agents have been given to treat acute pain, but no other drug has reached the same level of analgesia that opioids provide. Opioids are the first line of treatment for acute surgical pain and offer advantages such as fast onset and no ceiling effect (Coluzzi & Pappagallo, 2005). However, the side effects of opioids, complications caused by heavy opioid use, and increased care costs to treat its side effects raise concerns for opioid use during perioperative care.

**Problem Statement and Significance**

Current postoperative pain management with a high dose of opioids therapy has caused severe complications such as postoperative nausea and vomiting (PONV), hyperalgesia, muscle rigidity, sedation, and respiratory depression and failure. These complications led to prolonged post-surgical recovery and increased care cost. A nationwide retrospective analysis of patients
undergoing six major surgical procedures performed from 2002 to 2011 reported three times higher risk of developing respiratory complications in a group with opioid only pain regimen compared to one with multimodal pain management (Sayal, Bateman, Menendez, Eikermann, & Ladha, 2018).

An additional risk of opioid use is the increased risk of opioid physical dependence and addiction after exposure to opioids during perioperation (Klueh et al., 2018). There has been an epidemic of opioid abuse in the U.S. for the past few decades, and opioid exposure after surgery is one of the causes (Klueh et al., 2018). A retrospective cohort study showed that 3% of opioid-naïve patients continued to use opioids for more than three months after major surgery when expected pain level was normal (Clarke, Soneji, Ko, Yun, & Wijeysundera, 2014). The initial exposure to opioids during the postoperative period and excessive opioid prescription after surgery were reported as factors that increase addiction (Clarke et al., 2014). Another study reported that 44% of patients who received an opioid prescription were more likely to be long-term users (Alam et al., 2012). Anesthesia providers play a crucial role in preventing opioid addiction by providing adequate perioperative pain management. Sufficient pain control can be managed by using minimal opioids and adding other non-opioid analgesics (Goyal, Khurana, Jindal, & Sharma, 2013).

Of non-opioid analgesic strategies, multimodal pain management has vital importance in managing perioperative pain control. In 2012, American Society of Anesthesia (ASA) released its recommendation for multi-modal pain regimen for all surgical patients. Multimodal pain management refers to the analgesic modality that combines two or more analgesic drugs working on different pain receptors (ASA, 2012) to provide better pain relief while using less opioid dose
and decreasing the complications of opioid use (ASA, 2012). Increased number of modalities for pain management was associated with decreased rates of complications of opioids (Memtsoudis et al., 2018). A study of multimodal pain regimen in hip arthroplasty surgery in 2018 showed that patients with more than two modalities had 10% fewer respiratory complication and 26% fewer gastrointestinal (GI) complications (Memtsoudis et al., 2018). Also, increased modality use coincided with a reduced postoperative opioid prescription, showing the possibility of decreasing opioid addiction by switching to multimodal pain strategies from the current opioid only regimen (Memtsoudis et al., 2018).

The common multimodal pain regimen includes nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, alpha-2 antagonists, calcium channel antagonists, and N-Methyl-D-aspartate (NMDA) receptor antagonists (ASA, 2012). Ketamine is one of the NMDA antagonists commonly used as an induction agent and analgesic during perioperative care (Gorlin, Rosenfeld, & Ramakrishna, 2016). Ketamine decreases pain by blocking glutamate, a pain neurotransmitter that binds to NMDA receptors at the dorsal horn of the spinal cord, thereby preventing pain transmission (Gorlin, Rosenfeld, & Ramakrishna, 2016). NMDA receptors are involved in developing central sensitization, opioid-induced hyperalgesia, and opioid tolerance (Gorlin, Rosenfeld, & Ramakrishna, 2016). Sub-anesthetic doses of ketamine less than 0.3 milligram per kilogram (mg/kg) have analgesic and opioid-sparing effects and can prevent opioid-induced hyperalgesia (Gorlin et al., 2016). Sub-anesthetic doses of ketamine are not associated with significant side effects of high dose ketamine such as increased respiratory secretion, dissociative delirium, nystagmus, and double vision (Himmelseher & Durieux, 2005).
The American Pain Society recommends the use of intravenous (IV) ketamine as a component of multimodal analgesia in adults (ASA, 2012). Evidence supports the use of ketamine in acute surgical pain management. Ketamine has been administered preoperatively, intraoperatively, and postoperatively at widely varying doses from 0.1-2mg/kg before incision and at closure with or without infusions ranging from 0.12mg/kg/h to 2mg/kg/h (Chou et al., 2016). A study by Singh et al. (2013) reported reduction in pain scores and total opioid doses after giving IV ketamine less than 1 mg/kg without hallucinations. Other reports also support decreased pain scores and reduced opioid consumptions associated with ketamine use (Feld, Laurito, Beckerman, & Vincent, 2003; Gadre & Dhokte, 2017; Sollazzi et al., 2009). Another benefit of adding ketamine to the current pain regimen includes less anesthetic requirement and shorter extubation time (15 min versus 28 min, P<0.05) (Sollazzi et al., 2009).

**Local Problem and Needs Assessment**

During a clinical practice at a 450-bed acute care hospital, the author of this paper, a student nurse anesthetist, observed a high incidence of patients requiring opioids, such as fentanyl and hydromorphone, upon arrival to the post-anesthesia care unit (PACU). There was a need for adequate postoperative pain control while reducing opioid consumption at the facility, which is congruent with the ASA’s recommendation of multimodal pain regimen. However, the majority of anesthesia providers did not use multimodal pain modality. IV ketamine but not IV acetaminophen was available in the anesthesia medicine cart in the operating room (OR). Ketamine cost significantly less than IV acetaminophen; one vial of 500mg ketamine (50mg/ml) costs $8.9 versus $31 for one vial of 1,000 mg acetaminophen. Only two cases of multimodal pain management with low dose ketamine were observed during the first month of the clinical
rotation. In both cases, an IV bolus of ketamine at 0.1mg/kg was given at the beginning of the surgery. Both cases showed a smooth emergence and required no opioids upon PACU arrival as compared to the cases managed by opioid only.

**Clinical Question**

Among anesthesia providers (P), how does an educational session of low-dose ketamine (I) increase the knowledge of ketamine use as a multimodal pain regimen (O)?

**Purpose Statement**

The purpose of this doctor of nursing practice (DNP) project is to provide information on low dose ketamine as a multimodal pain regimen to increase knowledge and change the current practices of anesthesiologists, certified registered nurse anesthetists (CRNAs), and student nurse anesthetists (SRNAs) at the facility.

**Theoretical Framework**

**Conceptual and Theoretical Framework**

Lewin’s change theory (1997), which has been utilized in many healthcare organizations to produce organizational changes, helps explain human behaviors and patterns related to change. The theory identifies three stages of changes: unfreezing, moving, and re-freezing (Lewin, 1997). Lewin (1997) emphasized the importance of understanding and identifying factors that initiate the change such as restraining forces that discourage change and driving forces that promote the proposed change. A quality improvement project can be very successful when human behaviors and motives as well as the factors of change are fully understood.

Of Lewin's stages of change, the unfreezing stage has significant importance since the motivation for changes are weakened or strengthened in this stage (Cummings, Bridgman, &
Brown, 2016). The problems are identified, and the status quo of the organization is revealed so that the members of the organization are motivated for change (Cummings et al., 2016). Developing strategies to control driving and restraining forces are critical in this stage (Cummings et al., 2016). In the moving stage, a change takes place by strengthening the driving force and minimizing the restraining force (Cummings et al., 2016). The change is then evaluated and reinforced in the refreezing stage (Cummings et al., 2016). In this quality improvement project, Lewin’s change theory will be utilized as a conceptual tool to understand human behavior and motivation and the patterns of change. The pre-test was used to assess the current knowledge about multimodal pain management. An educational session about ketamine as a multimodal pain regimen was used to unfreeze the thoughts and elicit a change in practice in pain management. A post-test was conducted to assess the change in practice after an educational session.

The plan-do-study-act (PDSA) cycle of the Institute for Healthcare Improvement (IHI) (IHI, 2019) provided the theoretical framework that guided the development of strategies for change in pain management practice in this quality improvement project. The PDSA cycle is a useful quality improvement tool in implementing a healthcare change that uses four simple steps: setting up the strategies to test the change (plan), expediting the test (do), researching and learning from the results (study), and evaluating what modifications should occur (act) (Agency for Healthcare Research and Quality [AHRQ], 2015).

Plan cycle includes defining the project’s objectives, setting up a specific plan for change, and predicting project results (AHRQ, 2015). The project objects are to increase the knowledge of the multimodal pain regimen thereby change in knowledge thus pain management
practice among anesthesia providers. The project consists of a pre-test to assess the current pain regimen, an educational session about ketamine use as a multimodal pain regimen to motivate the change, and a post-test to evaluate the project’s effectiveness. Stakeholders include certified registered nurse anesthetists (CRNAs), anesthesiologists, and the chairman of the anesthesia department. A literature review, appraisal, and synthesis of the evidence was conducted to formulate the educational content for a sub-anesthetic dose of ketamine use as an additive to the current postoperative pain management. The audience of the educational session were anesthesiologists, CRNAs, and student anesthetists. The educational session provided information about the mechanism of action of ketamine using evidence-based studies that supporting the effectiveness of ketamine as a multimodal pain regimen to increase the in-depth knowledge of ketamine for postoperative pain management and decreased narcotic use. Also, the costs, time limitations, and overall feasibility of conducting this quality improvement (QI) project was considered in the planning. Finally, based on the project’s hypothesis that the increase in knowledge will promote changes in practice (Olson, Tooman, & Alvarado, 2010), the educational session is anticipated to increase the ketamine use as multimodal pain management and decrease opioid consumptions at the end of the project.

Do cycle includes activities such as carrying out the plan, documenting problems and unexpected observations, and beginning data analysis (AHRQ, 2015). An educational session and pre- and post-test would be executed as planned. Initial data analysis can take place while data are collected through the pre- and post-questionnaires obtained. Information about barriers to changing practice such as cost, resources, and time restraints will be collected through post-questionnaire.
The study cycle involves completing the data analysis, comparing data to predictions, and summarizing the lessons learned (AHRQ, 2015). Statistical analysis of the data from the pre- and post-test allows us to assess how an educational session improves the knowledge of low dose ketamine for pain management. Future studies can be carried out to compare opioid consumption before and after the education session. Potential barriers to practice change can be identified, and a solution would be determined during the cycle. Act cycle involves decision-making (AHRQ, 2015) regarding whether the practitioners would consider increasing ketamine use as a multimodal pain regimen at the facility. A plan for the next change may be suggested as well (AHRQ, 2015). The act cycle will be discussed in more detail in the recommendations for future study section.

**Synthesis of Evidence**

Many recent works support the notion that perioperative low-dose IV ketamine lowers postoperative pain and opioid consumption while producing no significant side effects (Jouguelet-Lacoste, La Colla, Schilling, & Chelly, 2015). A literature review was conducted using the Cumulative Index of Nursing and Allied Health Literature (CINAHL), PubMed, and ClinicalKey electronic search engines to appraise and synthesize the evidence of efficacy of perioperative low-dose IV ketamine use in postoperative pain control. The search terms used were ketamine, low-dose ketamine, sub-anesthetic dose ketamine, pain, analgesia, surgery, and perioperative. The initial search resulted in 141 articles in CINAHL, 92 articles in PubMed, and 14 articles in ClinicalKey. Inclusion and exclusion criteria were applied to the initial search by reviewing article titles and abstracts. Inclusion criteria were systematic review, meta-analysis, randomized clinical trials, and peer-reviewed. Exclusion criteria included intramuscular
injection, epidural or intrathecal injection, no postoperative opioid given, no peer-reviewed, non-human study, and not written in English. This further narrowed down to 28 CINAHL, 14 PubMed, and four ClinicalKey articles. Three duplicated articles were excluded. Based on the above inclusion and exclusion criteria, each article was reviewed for suitability to fit the proposed project. Eleven articles were appropriate for the DNP project.

**FIGURE 1.** Flow diagram for literature review.
<table>
<thead>
<tr>
<th>Author/Article</th>
<th>Qual: Concepts or Phenomena</th>
<th>Design</th>
<th>Sample (N)</th>
<th>Data Collection (Instrument/Tools)</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Deng, G., Zheng, J., Wang, S., Tian, B., &amp; Zhang, S. (2009).</td>
<td>Key Variables: administration of ketamine infusion 0.1mg/kg/hr (group A), 0.05mg/kg/hr (group B), 0.02mg/kg/hr (group C), and placebo normal saline (group D) started at anesthesia induction and last for 24 hours; all received remifentanil PCA in the PACU for 24 hours after surgery.</td>
<td>Double-blinded randomized controlled trials (RCTs)</td>
<td>200 patients underwent lower limb fracture repair; n=50 for all four groups.</td>
<td>Data recording and patient chart review by study nurses</td>
<td>Low dose ketamine infusion was effective in reducing postoperative pain (A=3.5, B=3.7, C=4.7, and D=4.7, p=0.006) and moderately decreased postoperative remifentanil requirement (1378mcg, 1531mcg, 1807mcg, and 1838mcg, respectively, P =0.003) without apparent adverse effects of ketamine.</td>
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<td>Dullenkopf, A., Muller, R., Dillmann, F., Wiedemeier, P., Hegi, T., &amp; Gautschi, S. (2009).</td>
<td>Key Variables: Pre-incisional administration of low dose ketamine 0.15mg/kg (Kl), moderate dose ketamine 0.5mg/kg (Km), and placebo</td>
<td>Double blinded randomized controlled trials (RCTs)</td>
<td>120 patients underwent general or orthopedic surgery; low dose ketamine 0.15mg/kg (Kl, n=36),</td>
<td>Data recording by study nurses</td>
<td>Pain score of Kl, Km, and P were 3, 4, and 4, respectively. Morphine consumption in postoperative 24 hours were 8.5, 9.0, and 10.3</td>
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<td>Author/Article</td>
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<td>Research Question</td>
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<td>ketamine does not affect postoperative analgesic requirements under clinical conditions. Anesthesia Intensive Care, 37(1), 753-757.</td>
<td>normal saline (P).</td>
<td>Hypothesis/Research Question: The perioperative ketamine administration will decrease postoperative pain and narcotic consumption.</td>
<td>moderate dose ketamine 0.5mg/kg (Km, n=41), and placebo normal saline (P, n=33).</td>
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<td>Hang, L., Shao, D., &amp; Gu, Y. (2011). The ED50 and ED95 of ketamine for prevention of postoperative hyperalgesia after remifentanil-based anesthesia in patients undergoing laparoscopic cholecystectomy. Swiss Medicine Weekly, 19, 141-149.</td>
<td>Key Variables: ED 50 (0.24 mg/kg) and ED 95 (0.33mg/kg) of ketamine bolus before skin incision in remifentanil-based anesthesia for laparoscopic cholecystectomy. Hypothesis/Research Question: The perioperative ED 50 and ED 95 of ketamine will prevent remifentanil-induced hyperalgesia.</td>
<td>Randomized controlled trials (RCTs)</td>
<td>54 patients undergoing laparoscopic cholecystectomy with remifentanil-based anesthesia; study group with pre-incisional administration of ketamine (n=27), control group with total IV anesthesia (n=27).</td>
<td></td>
<td>Chart review</td>
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<td>Author/Article</td>
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<td>Jouguelet-Lacoste, J., La Colla, L., Schilling, D., &amp; Chelly, J. (2015). The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: A review of the current literature. <em>Pain Medicine, 16</em>(2), 383-403.</td>
<td>Key variables: Adding infusion or single low-dose ketamine use in the perioperation to current narcotic pain regimen vs. narcotic only pain regimen</td>
<td>Hypothesis/Research Question: Low-dose IV ketamine in the perioperative use will decrease the postoperative pain score and narcotic consumption.</td>
<td>Systematic literature review</td>
<td>5 meta-analyses and 39 clinical trials representing 2482 patients</td>
<td>Literature review of clinical trials or meta-analysis using PubMed between 1966 and November 2013</td>
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<td>Laskowski, K., Stirling, A., McKay, W., &amp; Lim, H. (2011). A systematic review of intravenous ketamine for postoperative analgesia. Canada Journal of Anesthesia, 58(10), 911-923.</td>
<td>Key Variables: The types of clinical indications, surgery, and patients that can get benefit from perioperative ketamine administration</td>
<td>Systematic literature review</td>
<td>91 studies, which include 2,652 patients in ketamine groups and 2,049 patients in placebo groups</td>
<td>Literature search and review with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines</td>
<td>Perioperative intravenous (IV) ketamine is a useful adjunct in reducing postoperative pain. Ketamine use was especially useful in pain procedures such as upper abdominal, thoracic, and orthopedic surgeries. Ketamine effects were not related to the timing and dose of administration or the type of intraoperative opioids.</td>
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<td>Minoshima, R., Kosugi, S., Nishimura, D., Ihara, N., Seki, H., Yamada, T., ... Morisaki, H. (2015). Intra- and postoperative low-dose ketamine for adolescent idiopathic scoliosis surgery: A randomized controlled trial. Acta Anesthesiology Scandinavica, 59, 1260-1268.</td>
<td>Key variables: Low dose ketamine infusion intra- and postoperatively for 48 hours after surgery (Ketamine group) vs. placebo group of normal saline infusion (Placebo group) in idiopathic scoliosis surgery.</td>
<td>Controlled trials (RCTs)</td>
<td>36 patients undergoing idiopathic scoliosis surgery; ketamine group n= 17 and placebo group n=19</td>
<td>Data recording and chart review by study nurses</td>
<td>Morphine consumption through PCA for 48 hours after surgery was significantly lower in the ketamine group compared to the placebo group (0.89mg/kg vs.1.16mg/kg, p=0.019). Pain score, sedation scale, and postoperative nausea/vomiting (PONV) did not differ between the groups.</td>
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<td>Hypothesis/Research Question:</td>
<td>Intra- and post-operative Low dose ketamine infusion will decrease the morphine PCA consumption in 48 hours after surgery.</td>
<td>Randomized controlled trials (RCTs)</td>
<td>42 patients undergoing spine surgery: study K (n=14), group D (n=14), and group P (n=14)</td>
<td>Patient chart review</td>
<td>Both ketamine and dexmedetomidine were effective in reducing postoperative pain and narcotic consumption. However, there is not enough evidence to support one is superior to the other. 24-hour postoperative pain score on Visual analog scale (VAS) of the ketamine group and placebo group were 3.642 and 6.0 (p=0.01). Fentanyl consumed for postoperative 24 hours of group K, D, and P were 1164.9, 1035.4, and</td>
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<td>Hypothesis/Research Question:</td>
<td>The intraoperative ketamine and dexmedetomidine infusion</td>
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<td>Mitra, R., Prabhakar, H., Rath, G., Bithal, P., &amp; Khandelwal, A. (2017). A comparative study between intraoperative low-dose ketamine and dexmedetomidine, as an anesthetic adjuvant in lumbar spine instrumentation surgery for the postoperative analgesic requirement. <em>Journal of Neuroanesthesiology &amp; Critical Care</em>, 4(2), 91-98.</td>
<td>Key Variables: intraoperative administration of ketamine bolus 0.5mcg/kg followed by 0.25mcg/kg/h infusion (Group K), dexmedetomidine 0.5mcg/kg bolus followed by 0.5mcg/kg/hr infusion (Group D), and placebo normal saline (Group P) started after turning the patient prone.</td>
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<td>Nitta, R., Goyagi, T., &amp; Nishikawa, T. (2013). Combination of oral clonidine and intravenous low-dose ketamine reduces the consumption of postoperative patient-controlled analgesia morphine after spine surgery. <em>Acta Anesthesiologica Taiwanica, 51</em>(1), 14-17.</td>
<td>will decrease postoperative pain and fentanyl PCA use.</td>
<td>Key variables: IV-PCA morphine alone (Group M), IV-PCA morphine and intravenous post-operative ketamine (10mg IV bolus at induction and 2mg/kg/hr during operation) (Group MK), IV-PCA morphine and oral clonidine (4mcg/kg) (group MC), and IV-PCA morphine, ketamine, and oral clonidine administration (Group MKC).</td>
<td>RCTs</td>
<td>51 patients undergoing spine surgery: Group M n=13, group MK n=13, group MC n=13, and group MKC n=12</td>
<td>Data recording and chart review by study nurses</td>
</tr>
<tr>
<td>Author/Article</td>
<td>Qual: Concepts or Phenomena</td>
<td>Design</td>
<td>Sample (N)</td>
<td>Data Collection (Instrument/Tools)</td>
<td>Findings</td>
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<td>---------------</td>
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<tr>
<td>Pendi, A., Field, R., Farhan, S., Eichler, M., &amp; Bederman, S. (2018). Perioperative ketamine for analgesia in spine surgery: A meta-analysis of randomized controlled trials. <em>Spine</em>, 43(5), 299-307.</td>
<td>Key Variables: The use of perioperative supplemental ketamine as adjunct pain management</td>
<td>Meta-analysis of randomized controlled trials (RCTs)</td>
<td>649 patients of 14 RCTs went through the spine surgery and received adjunct ketamine perioperatively.</td>
<td>Literature search from PubMed, the Cochrane Central Register of Controlled Trials for prospective RCTs, Web of Science, and Scopus</td>
<td>The patient who received perioperative ketamine showed significantly reduced narcotic consumption and lower postoperative pain scores for the first 24 hours after spine surgery (p&lt;0.05) (level I evidence).</td>
</tr>
<tr>
<td>Sollazzi, L., Modesti, C., Vitale, F., Sacco, T., Ciocchetti, P., Idra, A., Tacchino, R., Perilli, V. (2009). Preinductive use of clonidine and ketamine improves recovery and reduces postoperative pain after bariatric surgery. <em>Surgery for Obesity and Related Diseases</em>, 5(1), 67-71.</td>
<td>Key Variables: Study group with the preoperative infusion of clonidine and low dose ketamine vs. a group with standard anesthesia induction</td>
<td>Randomized controlled trial (RCT)</td>
<td>50 morbidly obese patients undergoing open biliopancreatic diversion for weight loss surgery; study group with pre-induction clonidine and low dose ketamine (n=23), control group with standard anesthesia induction (n=27).</td>
<td>Patient chart review of hemodynamic profile, sevoflurane, and opioid consumption, tracheal extubation time, postoperative pain score</td>
<td>The study group with pre-induction clonidine and low dose ketamine required less sevoflurane requirement, lower fentanyl doses (3.8mcg/kg versus 5.0 mcg/kg) and shorter extubation time (15 min versus 28 min, P&lt;0.05). The study group showed a significantly better pain score (4 vs. 6 out of 10) during the first six hours after surgery.</td>
</tr>
</tbody>
</table>
Many studies have examined ketamine as a useful adjunct to the current pain regimen in reducing narcotic consumption in the postoperative period (Jouguelet-Lacoste et al., 2015). A literature review, including 39 clinical trials and five meta-analyses using PubMed between 1966 and November 2013, conducted by Jouguelet-Lacoste et al. (2015) reported that perioperative low-dose IV ketamine infusion or bolus decreased postoperative narcotic consumption by 40%. Also, postoperative pain scores were reduced on a dose-dependent manner (Jouguelet-Lacoste et al., 2015). No significant adverse effects of low dose ketamine, such as hallucination, bad dreams, or prolonged sedation, were reported up to 48 hours after surgery (Jouguelet-Lacoste et al., 2015). However, the appropriate ketamine doses or effects on the surgical site could not be determined due to the limited number of studies (Jouguelet-Lacoste et al., 2015).

A systematic review conducted by Laskowski, Stirling, McKay, and Lim (2011) reported the efficacy of low-dose ketamine as a multimodal pain management agent. In this review, Laskowski et al. (2011) included 91 randomized, placebo-controlled clinical trials between 1999 and 2010 with 2,652 patients in the ketamine group and 2,049 patients in the placebo group. A decrease in postoperative opioid consumption and delayed time to first opioid were reported across all studies (p < 0.001) (Laskowski et al., 2011). Ketamine was most useful in decreasing opioid and pain score in painful procedures such as thoracic, upper abdominal, and major orthopedic surgeries (Laskowski et al., 2011). In addition to reducing opioid consumption, lower pain score was reported by 78% of patients in ketamine treatment groups compared to the placebo group (Laskowski et al., 2011). In contrast to the study by Jouguelet-Lacoste et al. (2015), more hallucinations and nightmares were reported in ketamine groups (Laskowski et al.,
The most effective timing and dose of ketamine and its analgesic effect on the type of surgery could not be determined in this review (Laskowski et al., 2011).

Several randomized controlled trials (RCTs) emphasized the effectiveness of low-dose ketamine in reducing postoperative opioid consumptions and pain. The RCT conducted by Hang, Shao, and Gu (2011) reported pain scores, were evaluated by the visual analog scale (VAS) 10 minutes after extubation. The pain scores were significantly lower in the study group with low-dose ketamine than the control group (mean 3.6 vs. 5.5, respectively, p<0.01). Side effects of ketamine, such as hallucinations and excessive sedation, were not significantly different between bolus IV ketamine doses of effective dose (ED) 50 (0.24 mg/kg) and ED 95 (0.33mg/kg) given before skin incision. Ketamine was useful in preventing remifentanil-induced hyperalgesia (Hang et al., 2011). The RCT conducted by Dullenkopf et al. (2009) showed reduced postoperative VAS pain scores and morphine consumption within 24 hours postoperatively in the group that received low dose ketamine compared to the group treated with narcotics only. However, Dullenkopf et al. (2009) emphasized that the single dose ketamine does not significantly reduce pain or narcotic requirement, and moderate dose ketamine (0.5mg/kg) administration was associated with hallucinations, nightmares, and delayed awakening time. The five other RCTs were in agreement to support that the low-dose ketamine administration in the perioperative period reduced the postoperative pain scores and narcotic consumptions as compared to the groups treated with opioids only (Table 1) (Deng, Zheng, Wang, Tian, & Zhang, 2009; Minoshima et al., 2015; Mitra, Prabhakar, Rath, Bithal, & Khandelwal, 2017; Nitta, Goyagi, & Nishikawa, 2013; Sollazzi et al., 2009).
Other studies supported the effectiveness of ketamine in reducing postoperative narcotics consumption and pain but not chronic surgical pain (Klatt, Zumbrunn, Bandschapp, Girard, & Ruppen, 2015; Pendi, Field, Farhan, Eichler, & Bederman, 2018). A meta-analysis conducted by Pendi et al. (2018) reported the effectiveness of low-dose ketamine in patients who underwent spine surgery. Pendi et al. (2018) reported a level I evidence study of patients who received perioperative ketamine that showed a significantly reduced narcotic consumption and lowered postoperative pain scores in the first 24 hours after spine surgery (p<0.05). However, ketamine did not affect the narcotic consumption and pain score 36 hours after surgery. Recent literature also showed that the perioperative administration of low-dose ketamine does not reduce chronic surgical pain (Klatt et al., 2015). A systematic review and meta-analysis by Klatt et al. (2015) concluded that perioperative low-dose ketamine does not reduce chronic pain at one, three, six, and 12 months after surgery. A study by Klatt et al. (2015) showed that ketamine produced a marginally significant reduction in surgical pain one month after surgery.

There were common limitations in literature reviewed for this DNP project. First, the VAS pain score was not a reliable method to evaluate the effectiveness of ketamine since the pain score is very subjective, and it is difficult to compare pain levels between individuals. Therefore, narcotic consumption was also used as a reliable measurement of the efficacy of ketamine, which was a measurable strategy to assess the pain. Second, there was a lack of data on the most effective dose and timing of ketamine. The definition of low-dose ketamine was different between studies, ranging widely from 0.1mg/kg to 1mg/kg. Nevertheless, most studies agreed that there were no significant adverse events when the dose was equal to or less than 0.5mg/kg. More studies are warranted to investigate the relationship between the site of surgery
and low-dose ketamine administration. Other benefits of using ketamine to pain regimen were less anesthetic requirement and shorter extubation time (15 min versus 28 min, P<0.05) (Sollazzi et al., 2009). Finally, intraoperative use of ketamine bolus or infusion improved acute, but not chronic, surgical pain (Klatt et al., 2015).

METHODS

Design

A descriptive and comparative design was used in this project. The pre- and post-questionnaires were designed to gather practitioner demographic information and assess the current knowledge of the anesthesia providers regarding the multimodal pain regimen and ketamine use. The five pre-questionnaire questions requested information on age, gender, years of practice, type of anesthesia provider, current multimodal pain regimen of the provider, and frequency of current ketamine use. The six pre- and post-questionnaires were the same and assess time and dose of ketamine administration, surgery types that can benefit from ketamine, and financial advantages of ketamine. Other questions assessed the barriers of practice change for using ketamine as a multimodal pain regimen.

To increase participation, the educational session was scheduled at 7 AM during the department’s weekly educational meeting of the department. A month before the session, an informational flyer (Appendix B) about the educational session was posted in the anesthesia lounge to advertise the meeting in hopes of encouraging participation. At the beginning of the project, the DNP project and the right to refuse participation were explained to the anesthesia providers. An envelope containing a coded pre- and post-questionnaire was handed out to participants before the presentation (Appendix A). A PowerPoint presentation detailing the
information about the current opioid crisis, multimodal pain regimen, mechanism of action of ketamine, evidence-based research findings of the effectiveness of ketamine as a multimodal pain regimen, and recommended guidelines for ketamine dose and timing were provided (Appendix E). The time for completing the questionnaires and presentation was approximately 30 minutes. The post-questionnaires were collected at the end of the educational session.

**Setting**

The DNP project took place at a regional medical center, a trauma level II 453-bed acute care hospital in southern California. The educational session and survey with pre-questionnaire were conducted in the anesthesia lounge in the operating room during the weekly Wednesday meeting at the time designated. The post-education questionnaires were conducted immediately after the educational session.

**Participants**

The anesthesia providers at the facility included 10 anesthesia providers, 22 CRNAs, and 41 student anesthetists. All anesthesia providers were invited to participate in the DNP project through personal contact and informational flyers posted in the anesthesia lounge. The weekly Wednesday meeting usually includes four anesthesiologists, 11 CRNAs, and 11 student anesthetists, which was the minimum expected number of project participants.

**Data Collection**

The tools for data collection were pre- and post-education questionnaires. The questionnaires were developed by the primary researcher of the DNP project (Appendix A) and presented to subject matter experts, an experienced doctorally prepared acute care nurse practitioner and nurse scientist and a senior CRNA at the hospital to increase face validity. The
pre-education questionnaires include 10 questions about years of practice, type of anesthesia provider, current multimodal pain regimen of the provider, necessity of postoperative narcotic use, frequency of current ketamine use, and ketamine effectiveness to lower the postoperative narcotic consumption. The post-education questionnaires included the identical eight questions of the pre-questionnaire and an additional question about the effectiveness of the educational session in changing practice and barriers to preventing ketamine use. For confidentiality, the pre- and post-questionnaires were conducted anonymously, provided in an envelope, and sealed upon completion by each participant.

**Data Analysis**

Descriptive quantitative and qualitative analyses were used to analyze the data obtained from the pre- and post-questionnaires. The pre-education questionnaires included two demographic variables, six knowledge questions, and two follow-up questions regarding current practice and attitude toward ketamine usage. The post-questionnaire included the six identical knowledge questions, and two follow-up questions regarding the educational presentation and barriers to using ketamine. The questionnaires were used to compare the current practice status quo and the effectiveness of the intervention (an educational session about ketamine use) in changing the current practice. Wilcoxon signed rank test and McNemar’s test were used to compare the difference between the pre- and post-education questionnaire results. The qualitative data of the open-ended question was analyzed to determine for barriers to prevent the use of ketamine at the facility.
Ethical Considerations

Approval from the participating hospital (Appendix D) was obtained from the University of Arizona Institutional Review Board (IRB) (Appendix C) as this DNP project involves human participants, systematic collection and analysis of data, and dissemination of results. Voluntary participation in this project was explained before handing out the pre-questionnaires. It was explained that the completion of the questionnaires was regarded as consenting to the project and the withdrawal from the project would be permitted at any time. Confidentiality of provider information and answers was strictly maintained by anonymity.

RESULTS

A total of 21 anesthesia providers participated in the study. Two anesthesiologists, seven CRNAs, and 12 SRNAs were included. Figure 2 shows the percentage of the types of providers who participated in the study. The majority of providers were SRNAs (57%). All participants completed the pre- and post-survey and participated in the educational PowerPoint presentation. Table 2 summarizes the anesthesia providers’ years in practice. The average years in anesthesia practice is $5.12 \pm 9.1$ years with the SRNAs and $11.5 \pm 12.2$ years without the SRNAs.
FIGURE 2. Type of provider.

### TABLE 2. Years in practice.

<table>
<thead>
<tr>
<th>Type of Provider</th>
<th>Mean of Years in Practice</th>
<th>N (Number of Participants)</th>
<th>Standard Deviation (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesiologist</td>
<td>19.5</td>
<td>2</td>
<td>15.5</td>
</tr>
<tr>
<td>CRNA</td>
<td>7.6</td>
<td>7</td>
<td>9.3</td>
</tr>
<tr>
<td>SRNA</td>
<td>1.25</td>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean with the SRNAs</td>
<td>5.12</td>
<td>21</td>
<td>9.1</td>
</tr>
<tr>
<td>Mean without the SRNAs</td>
<td>11.5</td>
<td>9</td>
<td>12.2</td>
</tr>
</tbody>
</table>

The number of correct answers to questions regarding ketamine knowledge allowed deficit area knowledge to be assessed (Figure 3). Pre-survey questions 3, 4, 5, 6, 7 and 8 were identical to post-survey questions 1, 2, 3, 4, 5 and 6. Pre-survey question 3 (post-survey question 1) asked about ketamine’s mechanism of action (MOA), pre-survey question 4 (post-survey question 2) about the percentage of opioid consumption reduction by adding ketamine, pre-survey question 5 (post-survey question 3) about the price of a ketamine 50mg in syringe, pre-survey question 6 (post-survey question 4) about the effectiveness of repeated bolus dose, pre-
survey question 7 (post-survey question 5) about safe and effective dose range, and pre-survey question 8 (post-survey question 6) about the types of surgery that get the most benefits from ketamine. McNemar’s test was used to compare pre- and post-survey scores for each question.

MOA = mechanism of action

FIGURE 3. Numbers of correct answers in the pre- and post-survey.

In the pre-test, the participants had a high level of knowledge about the MOA of ketamine and the types of surgery that benefit most from ketamine. However, the participants exhibited knowledge deficit in ketamine’s effectiveness in opioid reduction as well as its price, effectiveness of repeated doses, and safe dose range.

For each survey question, more participants answered correctly on the post-survey as compared to the pre-survey, with all correctly responding to three of the six post-survey questions (Figure 3). For four questions, the increase in number of participants answering correctly was statistically significant (p < 0.05), with the greatest increase occurring for the question on bolus dose. The two questions for which the increases were not statistically
significant (MOA of ketamine and type of surgery) were both answered correctly by the majority of participants on the pre-test, leaving little room for improvement.

A score of ‘1’ was assigned to a correct answer and ‘0’ to an incorrect answer. Since there were six questions specifically related to ketamine knowledge, the maximum and minimum scores a person can obtain are ‘6’ and ‘0,’ respectively. Table 3 displays the average score between pre- and post-survey by provider types. A Wilcoxon signed-rank test was utilized to compare the total score of six ketamine questions in the pre- and post-survey. The total median score between pre- and post- survey had increased from ‘3’ (min =2, max = 4) to ‘6’ (min =4, max=6) ($p=0.0001$), which is a 50% increase, as a percentage of total score.

Post-survey question 7 asked if the educational session presentation helped them to consider using the ketamine as a multi-modal regimen. All participants responded with a “yes.”

**TABLE 3. Median scores of pre- and post-survey.**

<table>
<thead>
<tr>
<th>Type of Provider</th>
<th>Pre-survey Median (min, max)</th>
<th>Post-survey Median (min, max)</th>
<th>Number of Participants</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesiologist</td>
<td>3.5 (min=3, max=4)</td>
<td>6 (min=6, max=6)</td>
<td>2</td>
<td>$p=0.180$</td>
</tr>
<tr>
<td>CRNA</td>
<td>3 (min=2, max=4)</td>
<td>6 (min=4, max=6)</td>
<td>7</td>
<td>$P=0.028$</td>
</tr>
<tr>
<td>SRNA</td>
<td>4 (min=4, max=6)</td>
<td>6 (min=4, max=6)</td>
<td>12</td>
<td>$P=0.003$</td>
</tr>
<tr>
<td>Total</td>
<td>3 (min=2, max=4)</td>
<td>6 (min=4, max=6)</td>
<td>21</td>
<td>$P=0.0001$</td>
</tr>
</tbody>
</table>

Min=minimum, max=maximum

Figure 4 displays the current practice regarding using ketamine as a multimodal pain regimen. All participants used the low-dose ketamine at least once in their practice. The majority of (n=14; 66.7%) used ketamine one to six times within the last 14 days, while two did not use ketamine at all and another two used it often (more than 10 times) within the last 14 days. Pre-survey question 10 asked if participants were interested in using ketamine as their multimodal pain regimen, to which all responded, “Yes.” This showed that the anesthesia
providers are interested in using ketamine as a part of multimodal pain regimen more often than their existing practice pattern.

![Current Practice](image)

**FIGURE 4.** Status of providers’ current practice pattern of using ketamine as part of their multimodal pain regimen.

Six providers responded to post-survey question 8 on barriers to adding ketamine to their practice (Figure 5). Among them, four SRNAs stated that they would consider using ketamine if the anesthesiologist or CRNA agreed to it. Other barriers included the shortage of drug, no access to drug in the operating room (OR) Pyxis, cultural practice at a local institution, and/or uncertainty of safety in drug abuse population.
DISCUSSION

Results from the surveys suggest that there was a knowledge deficit of using low-dose ketamine as a multi-modal pain regimen, but the anesthesia providers are interested in using ketamine more often in their practice. The median score on knowledge related to ketamine in the pre-survey was ‘3’ out of ‘6’ (min=2, max=4), and the score increased to ‘6’ (min=4, max=6) in the post-survey. This showed that an educational session significantly increased the providers’ knowledge and the presentation helped them to consider using low-dose ketamine. The anesthesia providers expressed a high interest to use ketamine as an adjunct agent for pain management. The educational session’s success may be attributed to the participants’ high levels of motivation and the solid evidence from current research and literature that was presented to them during the training.

All participants had used ketamine as a multi-modal pain agent in the past. The majority (66.7%) used it one to six times within the last two weeks. However, they do not seem to have a
solid understanding of ketamine as a multi-modal agent. The greatest areas of knowledge deficit of low-dose ketamine were the effectiveness of ketamine in reducing opioid consumption, effectiveness of repeated bolus dose rather than a single bolus dose, and safe dose range. Post-survey scores on these questions were greatly improved. The results showed that a lack of understanding of the efficacy of ketamine and how to dose it might have contributed to the underuse of ketamine among anesthesia providers. On the other hand, these providers showed a high level of knowledge regarding ketamine MOA and the types of surgery that benefit most from ketamine.

The most common barrier to adding ketamine to current practice was identified by four SRNAs was the anesthesiologist or CRNA’s acceptance of ketamine in the case plan. Other barriers to using ketamine were unavailability of the drug due to drug shortages, lack of provision of the drug by the institute, cultural practice of the institute, and uncertainty of drug safety among drug-abused populations. The role of the leading provider for the patient was the most important factor that hinders or encourages the use of ketamine at an institution.

**Strengths and Limitations**

The strength of the study was that 21 anesthesia practitioners participated in the study. This sample size allowed assessment of pre-intervention knowledge levels, areas of the knowledge deficit, and effects of the educational event on knowledge improvement. Another strength of the study was that there was the minimum distraction of the educational event that can hinder the results of the survey response. The educational event was held during a Wednesday educational meeting. The anesthesia lounge was closed to non-anesthesia providers for the event, and disruptions and distractions were limited by staff. The TV screen and computer
provided were helpful to maintain the attention from the participants. All participants were able to complete the pre- and post-surveys and educational session.

Despite these positive aspects, there were several limitations in this project. Only two anesthesiologists participated in the study, and the information about the years of practice and type of anesthesia provider threatened their confidentiality. Reassurance was provided to participants that survey answers and scores are confidential, and responses are analyzed collectively.

Another weakness of this project was the validity of a pre-survey question in assessing knowledge on the efficacy of ketamine in reducing opioid use. This multiple-choice survey question offered responses as 0, 10, 20, 30, and 40%. However, in the existing literature, the efficacy of ketamine in reducing opioid use varies, which made it hard to measure the true knowledge of ketamine’s efficacy in reducing opioid use. Also, bias could interfere with the survey results about the barriers of adding ketamine. The barrier question was open-ended, and self-reported questions can be easily biased by the responders.

**Future Implications**

Although the project substantially increased the providers’ knowledge on low-dose ketamine, the effects of the increased knowledge on practice cannot be assessed through this project. Future quality improvement study is warranted to further investigate the effects of the knowledge gained on implementing low-dose ketamine to multimodal pain management in daily practice.
**Dissemination Plan**

The results of this project were presented as a poster at the Sun-N-Fun annual conference of Arizona Association of Nurse Anesthetists on March 12 to 15, 2020.

**Conclusion**

Adequate surgical pain management is a challenging but central component in anesthesia (ASA, 2012). Experiencing the serious complications of opioids, anesthesia providers expressed their interest in reducing opioid use by using an alternative multi-modal management method. This DNP project showed that there was a great interest among anesthesia providers in learning and adapting multimodal pain management as an alternative to opioids. The results of this project indicate knowledge deficit on the use of low-dose ketamine as an agent for multimodal pain management, especially regarding the drug’s efficacy and use. This DNP project showed the positive impact of a 30-minute educational session on increasing the knowledge of ketamine use. Simply providing the current evidence about its cost-effectiveness, efficacy in reducing opioids consumption, and evidence-based practice guidelines filled the knowledge gaps among the anesthesia providers.

This project does not assess the impact of the increased knowledge on practice change. Future studies should examine practice change such as increased frequency of ketamine use, decreased opioid consumption, decreased opioid-related complications, acceptance of ketamine by anesthesia leaders (anesthesiologist or CRNA), and the change of practice culture that is open to adding ketamine as a multimodal pain management agent.
APPENDIX A:

PRE- AND POST-QUESTIONNAIRE
Pre-Test

1. Years of practice in anesthesia: ___________ years

2. Type of provider:
   a. Anesthesiologist
   b. CRNA
   c. SRNA

3. For acute pain, Ketamine works by blocking?
   a. Central sensitization
   b. NMDA receptors
   c. GABA receptors
   d. Presynaptic Alpha receptors

4. One of goals of using multimodal pain regimen is to decrease opioid consumption. Ketamine is a NMDA antagonist, a part of American Society of Anesthesiologists’ recommended multimodal pain regimen. How much do you think that ketamine reduces postoperative opioid consumption by?
   a. 0%
   b. 10%
   c. 20%
   d. 30%
   e. 40%

5. IV acetaminophen, Ofirmev 1g costs about $ 31. Ketamine 500mg vial costs $9. What do you think a 50mg/5ml syringe of ketamine costs?
   a. $ 2.82
   b. $ 8.82
   c. $ 20.82
   d. $ 30.82

6. True or false: A single bolus dose and multiple bolus doses of IV ketamine can be equally effective in decreasing postoperative pain and opioid consumption.
   a. True
   b. False
7. What is the safe AND effective sub-anesthetic bolus dose of ketamine for postoperative pain reduction that does not cause significant side effects such as hallucination, bad dreams, or prolonged sedation?
   a. 0.1-0.3mg/kg
   b. 0.3-0.5mg/kg
   c. 0.5-0.8mg/kg
   d. 0.8-1.0mg/kg

8. What types of surgery do you think that ketamine is most beneficial in reducing pain and opioid consumption?
   a. OB/GYN
   b. ENT/plastics
   c. Thoracic/upper abdominal/orthopedics
   d. Cardiovascular/Neurovascular
   e. Pediatrics

9. How often did you use ketamine as a part of multimodal pain regimen within the last 14 days of practice?
   a. I have never used ketamine as part of a multimodal pain regimen.
   b. 0 times in the last 14 days, but I have used it in the past.
   c. 1-3 times
   d. 4-6 times
   e. 7-9 times
   f. 10 or more times

10. Are you interested in using ketamine as your multimodal pain regimen?
    a. Yes
    b. No
    If no, please comment on why? ________________________________

Participation in this project is voluntary. Completion of the questionnaire implies your consent to participate. You may choose to withdraw from this project at any time.
Post-Test

1. For acute pain, Ketamine works by blocking?
   a. Central sensitization
   b. NMDA receptors
   c. GABA receptors
   d. Presynaptic Alpha receptors

2. One of goals of using multimodal pain regimen is to decrease opioid consumption. Ketamine is a NMDA antagonist, a part of American Society of Anesthesiologists’ recommended multimodal pain regimen. How much do you think that ketamine reduces postoperative opioid consumption by?
   a. 0%
   b. 10%
   c. 20%
   d. 30%
   e. 40%

3. IV acetaminophen, Ofirmev 1g costs about $31. Ketamine 500mg vial costs $9. What do you think a 50mg/5ml syringe of ketamine costs?
   a. $2.82
   b. $10.82
   c. $20.82
   d. $30.82

4. True or false: A single bolus dose and multiple bolus doses of IV ketamine equally decreases postoperative pain and opioid consumption.
   a. True
   b. False

5. What is the safe AND effective sub-anesthetic bolus dose of ketamine for postoperative pain reduction that does not cause significant side effects such as hallucination, bad dreams, or prolonged sedation?
   a. 0.1-0.3mg/kg
   b. 0.3-0.5mg/kg
   c. 0.5-0.8mg/kg
   d. 0.8-1.0mg/kg
6. What types of surgery do you think that ketamine is most beneficial in reducing pain and opioid consumption?
   a. OB/GYN
   b. ENT/plastics
   c. Thoracic/upper abdominal/orthopedics
   d. Cardiovascular/Neurovascular
   e. Pediatrics

7. Did the Ketamine presentation help you consider using low-dose ketamine as a multimodal regimen for postoperative pain?
   a. Yes
   b. No

   If you answer no, please comment why?
   _________________________________________________________________
   _________________________________________________________________
   _________________________________________________________________

8. What would be barriers to adding Ketamine to your current pain regimen, if any exists?
   _________________________________________________________________
   _________________________________________________________________
   _________________________________________________________________

Participation in this project is voluntary. Completion of the questionnaire implies your consent to participate. You may choose to withdraw from this project at any time.
APPENDIX B:

INFORMATIONAL FLYER
LOW-DOSE KETAMINE MULTIMODAL PAIN MANAGEMENT

Educational Event: Presented by Hyun Ju Oh, SRNA, University of Arizona

WHEN
January 22, 2020
Wednesday
7am

WHERE
Anesthesia Lounge, Arrowhead Regional Medical Center

You are invited to attend an educational event that is part of a DNP project designed to assess the current practice of multimodal pain management and increase the knowledge of ketamine as a part of the postoperative pain management.

EVENT CONSIST OF:
1. Pre-survey
2. PowerPoint presentation
3. Post survey

Estimated time: 30 minutes

All survey responses will remain confidential.
APPENDIX C:
THE UNIVERSITY OF ARIZONA INSTITUTIONAL REVIEW BOARD APPROVAL LETTER
Date: August 12, 2019
Principal Investigator: Hyun Ju Oh
Protocol Number: 1908872374
Protocol Title: LOW DOSE KETAMINE AS A PERIOPERATIVE MULTIMODAL REGIMEN
Determination: Human Subjects Review not Required

Documents Reviewed Concurrently:
- Data Collection Tools: Questionnaires.docx
- HSPP Forms/Correspondence: determination of human research 728.pdf
- Other Approvals and Authorizations: site authorization.pdf

Regulatory Determinations/Comments:
- Not Research as defined by 45 CFR 46.102(l): As presented, the activities described above do not meet the definition of research cited in the regulations issued by U.S. Department of Health and Human Services which state that "Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research."

The project listed above does not require oversight by the University of Arizona.

If the nature of the project changes, submit a new determination form to the Human Subjects Protection Program (HSPP) for reassessment. Changes include addition of research with children, specimen collection, participant observation, prospective collection of data when the study was previously retrospective in nature, and broadening the scope or nature of the study activity. Please contact the HSPP to consult on whether the proposed changes need further review.

The University of Arizona maintains a Federalwide Assurance with the Office for Human Research Protections (FWA #00004218).
APPENDIX D:

SITE APPROVAL LETTER
Arrowhead Regional Medical Center
400 N. Pepper Ave.
Colton, CA 92324

Date June 25, 2019

University of Arizona Institutional Review Board
c/o Office of Human Subjects
1618 E Helen St.
Tucson, AZ 85721

Please note that Ms. Hyun Ju Oh, UA Graduate Student, has permission of Arrowhead Regional Medical Center to conduct research at our Arrowhead Regional Medical Center facility for her study, “Low-dose Ketamine as a Perioperative Multimodal Pain Regimen.”

Ms. Oh will recruit anesthesia providers by inviting them through a flyer to a live educational event to be held in the anesthesia break room. During the educational event, a pre-survey will be administered and then followed by a PowerPoint presentation and a post-survey. The pre- and post-survey will have de-identified participant information in her research. Ms. Oh’s on-site research activities will be completed by May 4th, 2020.

Ms. Oh has agreed not to interfere with the daily flow of operating room staff or schedules. Employees will not be allowed time from their work duties to complete the surveys or watch the PowerPoint presentation. Ms. Oh also has agreed to provide to my office a copy of the University of Arizona IRB-approved, stamped disclosure form before she recruits participants to the educational event.

If there are any questions, please contact my office.

Andre Cruz, CRNA, Clinical Coordinator
Department of Anesthesiology, Arrowhead Regional Medical Center

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APPENDIX E:

EDUCATIONAL POWERPOINT
LOW-DOSE KETAMINE AS A EFFECTIVE MULTIMODAL MANAGEMENT

Presented by Hyun Ju Oh, BSN, RN
University of Arizona

PURPOSE

• Purpose of the DNP project
  • increase knowledge of ketamine as a multimodal pain regimen among the anesthesia providers and student nurse anesthetists at Arrowhead Regional Medical Center (ARMC)
BACKGROUND/ISSUES

- **Inadequate Pain control**
  - 75% of surgical pts c/o moderate to severe pain.
  - The annual cost of treating pain was higher than treating heart disease, cancer, and diabetes (Seal & Richard, 2011).

- **Complications of postoperative opioid consumption:**
  - PONV
  - Respiratory failure
  - Excessive sedation

**epidemic opioid crisis**
- Initial opioid exposure after surgery
- 44% of patients who received the opioid prescription after surgery were most likely to be a long-term user (Kreek et al., 2018)

MULTIMODAL PAIN MANAGEMENT

- ASA recommends multi-modal pain regimen for **ALL surgical patients** whenever possible

- **What is multimodal pain management?**
  - Analgesic modality that combines two or more analgesic drugs that work at different pain receptors (ASA, 2012).

- **Does it really work?**
  - \# of modalities = \# of complications of opioids
  - Patients with >2 modalities:
    - 10% fewer respiratory complication
    - 26% fewer GI complications
    - 18.5% decrease in opioid prescription (Martín-Suárez et al., 2012).
HOW DOES KETAMINE WORK FOR ACUTE PAIN?

1. Ketamine: a NMDA antagonist

2. NMDA receptor: a receptor for excitatory neurotransmitter glutamate in the brain and spinal cord

3. Chronic pain: reverse central sensitization and enhance descending modulatory pathways

4. Acute pain: NMDA, mu opioid, monoamine, serotonin, sodium channel and muscarinic receptors.

INEXPENSIVE & POWERFUL ANALGESICS

Ketamine 50mg/5ml $2.82
Ketamine 500mg/10ml $9
OFIRMEV 1g $31
A Literature Review
Jouguelet-Lacoste et al, 2015
(1966-2013, 5 Meta-analyses & 30 RCTs, single dose/infusion/PCA)

- ↓ average narcotic consumption by 40%.
  - Either one time bolus or infusion
- Repeated bolus doses or continuous infusion are more effective in reducing pain and opioids use
  - A bolus dose only studies showed mixed results whereas studies with infusion following a bolus showed significantly reduced opioid and pain reduction.
- Sub-anesthetic dose Ketamine is safe to use
  - No significant adverse effects such as hallucinations, dreams, and diplopia or sedation

A Systematic Review
Laskowski, Stirling, McKay, and Lim (2011)
(1999-2010, 71 RCTs, single dose/infusion/PCA)

- ↓ pain score from 78% of patients
  - Most of patients experienced less pain when ketamine was added.
- most useful in ↓ opioid and pain score in painful procedures
  - Thoracic, upper abdominal and major orthopedic surgeries
- Significantly ↓ PONV in the ketamine group.
  - Another clinical benefit obtained from the improved quality of pain control
POTENTIAL BENEFITS
(Sollazzi et al., 2009)

- A RCT on 50 bariatric patients undergoing open biliopancreatic diversion for weight loss
  - Improves the recovery
- Significantly \( \downarrow \) extubation time
  - 15 min vs 28 min
- \( \downarrow \) anesthetic requirement
  - less end-tidal sevoflurane
  - lower total doses of fentanyl (3.8 vs 5.0 mcg/kg)

How to Use Ketamine
(Schwenk, et al., 2018)

1. Indications
   - Expected severe postop pain
     - Upper/lower abdominal
     - Thoracic
     - Orthopedic (limb and spine)
   - Opioid tolerant or dependent
   - Increased risk for opioid-related respiratory depression
     - OSA

2. Contraindications
   - poorly controlled cardiovascular disease
   - pregnancy
   - active psychosis
   - severe liver disease (e.g., cirrhosis)
   - elevated ICP or IOP

3. Administer repeated boluses or continuous infusion
4. Sub-anesthetic dose ketamine: 0.1–0.3 mg/kg for bolus, 0.1–1 mg/kg/hr for infusion
References

- Dullenkopf, Å., Muller, R., Dillmann, F., Wiedemeier, P., Hegi, T., & Gautschi, S. (2009). An intraoperative pre-incision single dose of intravenous ketamine does not have an effect on postoperative analgesic requirements under clinical conditions. *Anesthesia Intensive Care, 37*(1), 753-757.
REFERENCES


