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Opioid-Sparing Analgesia in the Post-Anesthesia Care Unit: Subdissociative Ketamine Administration

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Abstract

Phase II Site: Fort Belvoir Community Hospital (FBCH), Fort Belvoir, Virginia

Project Title: Opioid-Sparing Analgesia in the Post-Anesthesia Care Unit: Subdissociative Ketamine Administration

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Background or Problem/Issue: Opioid-sparing practices are frequently utilized intraoperatively at FBCH as part of evidence-based ERAS protocols, but opioid-sparing practices have not been continued postoperatively in the post-anesthesia care unit (PACU).

Clinical Question or Purpose: In adult postoperative orthopedic patients, how does the use of an evidence-based opioid-sparing analgesia PACU order set that includes subdissociative ketamine (SDK), compared to current PACU orders, affect the of total dose of opioids administered, and PACU pain scores at time intervals at 15, 30, and 60 minutes after arrival in the PACU?

Project Design: This was a quality improvement project that incorporated the use of SDK in the PACU. The project utilized a pre and post implementation assessment between baseline data of 30 orthopedic cases to 30 cases post implementation of the total dose of opioids administered and PACU pain scores at time intervals of 15, 30 and 60 minutes. During the intervention period, SDK at a dose of 0.3 mg/kg was administered for a pain score of greater than or equal to 4/10 on a numeric pain scale.

Analysis of the Results: Assessment and comparison of the standard protocol with the SDK protocol revealed no effect on pain scores, a decrease in the number of patients who received fentanyl, and a decrease in the average dose of hydromorphone given to each patient.

Organizational Impact/Implications for Practice: By adding SDK to the order set, it would improve the ability of the PACU staff to administer alternative analgesics. This will increase FBCH's efforts to align with ERAS protocols and help optimize surgical outcomes for our patients.

Introduction

Opioids are powerful analgesics and have been used in balanced anesthesia techniques since at least the 1920s, but their side effects, including potentially lethal respiratory depression, hypotension, nausea, vomiting, and constipation warrant their cautious administration (Ng et al., 2017). The ongoing epidemic of opioid-related deaths further emphasizes the need to examine perioperative opioid administration to ensure the implementation of safe and effective postoperative pain management plans. National efforts to address the opioid crisis have increased support for evidence-based Enhanced Recovery After Surgery (ERAS) protocols. Surgical services at Fort Belvoir Community Hospital (FBCH) have implemented ERAS protocols, including practices to reduce the prevalence and extent of harm caused by opioid-related sequelae. ERAS practices traditionally focus on concerted efforts across preoperative, intraoperative, and postoperative environments to improve patient outcomes. While opioid-sparing and even opioid-free anesthesia may be administered to a patient undergoing surgery as part of evidence-based ERAS protocols, these opioid-sparing practices have not been fully employed in the post-anesthesia care unit (PACU). At FBCH, the PACU does not have defined protocols to deliver opioid-sparing practices during the immediate recovery period. Opioids are usually ordered as a first-line treatment for pain, and few feasible non-opioid analgesic medications are ordered or administered postoperatively. To expand ERAS practices into the postoperative environment, and to complement opioid-sparing techniques employed earlier in the patients' surgical experience, subdissociative ketamine was added to existing PACU protocols to treat postoperative pain. This empowered registered nurses (RNs) in the PACU to select this analgesic medication as a first-line alternative to opioids. Since the goal

is to optimize and not eliminate opioid use, opioids remained available for severe pain and patients for whom ketamine would not be appropriate.

Significance of the Problem

The side effects of prolonged or excessive opioid use can cause serious harm or death to patients, and certain practices and patient predispositions can make these harms more likely. Opioid-induced respiratory depression, the development of opioid use disorder, cognitive impairment, nausea and vomiting, delirium, lethargy, risk of falls, and urinary retention are all known side effects (Koepke et al., 2018). Furthermore, certain populations, including the elderly and those with comorbidities, are even more susceptible to harm from these known side effects. Lastly, chronic opioid use and its associated comorbidities can be problematic even for those who already take them on a routine basis. A study examining the Nationwide Inpatient Sample database found that preoperative opioid abusers were at increased risk of morbidity and mortality following orthopedic surgery (Menendez et al., 2015).

The wider medical community has recognized the adverse consequences of opioid administration for more than two decades. In 1999, Chia et al. found that patients who received high doses of fentanyl intraoperatively had both higher pain scores and higher opioid consumption postoperatively. According to Koepke et al. (2018), there is a known risk of opioid-naive patients becoming chronic users of opioids (defined as opioid use lasting longer than 90 days postoperatively) after surgery. In fact, the first time a patient may be exposed to opioids during their lifetime may be during surgery. Confounding concerns regarding opioid risks, pharmaceutical companies intentionally and selectively promoted misleading evidence regarding the safety of their opioid products (Zee, 2009). Anesthesia providers must therefore

be judicious with opioid administration and cognizant of factors that can contribute to a patient developing chronic opioid use, including diabetes, younger age, lower income, and the duration of the acute postoperative opioid use (Clarke et al., 2014).

The current opioid epidemic has become so severe that opioid overdose has passed motor vehicle crashes as the leading cause of accidental death in the United States (Koepke et al., 2018). Additionally, there have been improvements in the ability to treat pain using non-systemic opioid medications, making it possible to effectively treat pain without relying on large doses of systemic opioids. In response to the ongoing public health emergency and the development of the ability to avoid some of the negative consequences of opioid use by employing alternative techniques, anesthesia providers have initiated efforts to examine their services for ways to optimize pain control while mitigating risk. Supported by refined models of pain science and treatment, including ERAS protocols that focus on opioid-sparing techniques, the anesthesia community has critically examined and challenged traditional concepts that have prevented patients from achieving maximal outcomes from anesthetic management. As an example of one such former practice-shaping idea, in the 1990s, professional organizations described pain as the “fifth vital sign” and “an enemy that needed to be eradicated” (Baker, 2017). This resulted in the over-prescription of opioids by licensed medical providers, which was encouraged by large pharmaceutical companies who strongly advocated for their use (Koepke et al., 2018). Consequently, as a result of these and other mechanisms, opioid prescriptions in the United States grew from 76 million in 1990, to 116 million in 1999, and to 219 million by 2011 (Trasolini et al., 2018). In updating the schema around opioid

administration and pain science, there have been continued efforts to develop and implement opioid-sparing and opioid-optimizing techniques.

The current standard PACU order set at FBCH strongly favors opioid administration, which is contrary to evidence for long-term pain control in most surgical procedures. The opioids suggested for PACU use include a "use [this medication] first" qualifier in the orders, and there are recommendations to use opioids for a pain score as low as 1 (presumably on a 10-point scale, although this is not defined in the order set). Additionally, only two suggested analgesic options are not opioids. The first one, acetaminophen, may have already been given in the preoperative holding area or the operating room (OR) and may not be available for use in the PACU due to the required minimum times between doses. The second, ketorolac, includes an instruction to use "in conjunction with opiate (sic)." While a patient may need opioids for severe or intractable pain, the order set establishes a low threshold for their administration. Recognizing a potential opportunity to address this problem, we examined the evidence and searched for an additional non-opioid pharmacological adjunct that could be added to the standard PACU order set.

Relevance to Military Nursing

As described previously, the administration of SDK in the PACU achieved an opioid-sparing effect for beneficiaries at FBCH. Although the effect was small, care was positively affected within this military treatment facility. As of the Fall of 2021, FBCH paid $2.27 per single 500 mg vial of ketamine. Since each 500 mg vial can yield 10 syringes of 50 mg each, if the FBCH pharmacy provides the desired 50 mg/ 5 mL syringes, a dose of SDK could cost less than $0.25 for the medication itself. Such inexpensive solutions are rare.

Ketamine is a medication that has been successfully used on the battlefield for many years, so military RNs and other military medical assets should be familiar with its use within the combat environment. Most notably, ketamine is indicated as an analgesic in the prehospital care of combat wounded personnel as part of Tactical Combat Casualty Care (U.S. Army CALL, 2017). Incorporating this medication into practice at FBCH allows for the translation of efficacious combat medical practices into the hospital setting, and it also provides opportunities for military personnel to obtain meaningful experience using a drug they may likely use in combat and austere environments. As described in earlier sections, RNs should be familiar with different ways to care for patients in the setting of drug shortages, which are a continuous reality in combat settings where logistics are more difficult than in peacetime environments.

Clinical Question

In adult postoperative orthopedic patients, how does an evidence-based opioid-sparing multimodal analgesia PACU order set, compared to current PACU orders, affect the quantity of total dose of opioids given, and PACU pain scores at time intervals at 15, 30, and 60 minutes after arrival in the PACU?

Literature Review of Solution

The search terms focused on the use of ketamine and analgesic medications other than full opioid agonists for post-operative and acute pain. Search results were limited to randomized control trials on adult human subjects that have been published since 2015 in the English language. The search terms used for literature review were: “Postoperative pain control interventions”, “Methadone” and “Pain”, “Subdissociative Dose Ketamine”, “Ketamine Postoperative Period”, “Methadone decrease opioid adverse events”, “Multimodal analgesia

protocol opioid adverse events", and "Ketamine and "Acute Pain". The databases used for literature review were Web of Science, PubMed, and CINAHL. The initial search returned 387 results, which were imported into Covidence (Melbourne, Australia) for screening. After removing 142 duplicates, 245 studies remained. These were screened using titles and abstracts for appropriateness to the problem statement, and 224 studies were excluded. The remaining 20 studies were reviewed in their full-text forms for suitability, and 7 studies were excluded for an inapplicable study design or setting. A final total of 13 studies were suitable for possible solution synthesis, supporting the postoperative use of nonopioid pharmacologic adjuncts. Six randomized double-blind randomized control trials were found comparing the analgesic efficacy of subdissociative doses of ketamine versus morphine and placebos in perioperative and emergency room settings. One Cochrane review of perioperative ketamine use to treat postoperative pain was included. Four double-blind randomized control trials and one meta-analysis were found focusing on the efficacy of methadone versus morphine administration. A clinical guideline for management of postoperative pain made by the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia also guided solution synthesis.

Solutions to Revise Postoperative Opioid Administration Practices

General Pharmacological Interventions

Current literature supports the use of validated ERAS and multimodal anesthetic interventions. Many of these studies and professional clinical practice guidelines recommend the optimization of preoperative and intraoperative medications as well as the maximization of

neuraxial and local anesthetic techniques (Beverly et al., 2017; Chou et al., 2016). While relatively little of the available data and recommendations pertain specifically to the postanesthetic period, the evidence commonly supports the use of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) as analgesics (Beverly et al., 2017; Chou et al., 2016). These medications are already available for use in the FBCH PACU if there are no contraindications present in a specific patient's case. In order to bridge the gap in capability between acetaminophen and NSAID administration and the administration of powerful opioid agonists, we explored the additional use of ketamine and methadone for moderate pain. The literature supports ketamine and methadone as medications with the potential to manage postoperative pain with fewer serious side effects than commonly used opioid agonists (as detailed in the discussion below).

Postoperative Methadone Administration

Methadone has unique attributes that make it potentially advantageous in the intraoperative and postoperative settings. While methadone is a synthetic opioid agonist, it also acts as an NMDA receptor antagonist and a weak antagonist of serotonin and norepinephrine reuptake activity (Macres et al., 2017). Compared to intraoperative morphine, clinical trials show intraoperative methadone is superior for the prevention of pain in the immediate postoperative phase, and it may lead to less total opioid consumption without increases in side effects (Kendall et al., 2020; Moro et al., 2019). Methadone also has no active metabolites and does not require dose adjustments for renal impairment (Macres et al., 2017; Ferrari et al., 2004). However, there are few studies available to support methadone administration as a sole agent for postoperative pain, so it was removed from consideration for this project. However, if

future studies show its efficacy for acute pain, especially in the setting of chronic pain, preoperative opioid dependence, or pharmacogenomic indications, methadone may prove to be a valuable asset in treating pain and reducing overall opioid use. Additional research is needed.

Postoperative Ketamine Administration

Randomized control trials and professional recommendations also advocate for the consideration of ketamine to treat postoperative pain. While ketamine has been used to induce general anesthesia for decades, it has analgesic properties that may be advantageous when it is given in sub-anesthetic doses. Ketamine is a noncompetitive NMDA receptor antagonist that modulates nociception in the central nervous system (Peltoniemi et al., 2016). This action, and others that are less well understood, cause a dissociative state at anesthetic doses and reduce postoperative pain and opiate requirements at subdissociative doses. Ketamine has a hemodynamically stable action and does not cause respiratory depression, hypotension, or bradycardia (Abola et al., 2017; Peltoniemi et al., 2016). Side effects include hallucinations, nausea, light-headedness or dizziness, itching, nystagmus, and tinnitus, but these side effects usually resolve on their own within approximately 6 to 15 minutes when they occur (Beverly et al., 2017; Motov et al., 2015). These attributes are desirable in the PACU, and recent literature supports subdissociative (non-anesthetic) ketamine administration for postsurgical pain management.

An intravenous (IV) ketamine dose of 0.3 mg/kg has been found to be equivalent in its analgesic potency to 0.1 mg/kg of IV morphine (Motov et al., 2015). Other studies examining the role of subdissociative intravenous ketamine (SDK) in treating acute pain have found that SDK does not reduce pain scores to the extent that morphine does, but SDK administration still

causes a significant reduction in pain scores and an analgesic effect lasting approximately two hours (Miller et al., 2015). In terms of SDK's ability to reduce opioid consumption, a single dose of 0.3 mg/kg of IV ketamine administered over one minute can decrease the total amount of opioids the patient receives postoperatively in the PACU and medical-surgical wards (Sultana et al., 2017; Xu et al., 2019). A recent meta-analysis including the effects of ketamine on pain and morphine equivalents in patients undergoing total hip or knee arthroplasty found that IV ketamine significantly reduces pain during the first eight hours following surgery compared with placebos (Wang et al., 2019). This meta-analysis also reported significantly decreased morphine consumption during the first 48 hours following surgery. Furthermore, this meta-analysis showed that the incidence of nausea and vomiting was significantly lower in the IV ketamine groups than the placebo groups for these arthroplasty patients.

A Cochrane review of perioperative IV subdissociative doses ketamine to treat postoperative pain in adults indicated that IV ketamine is most likely beneficial when compared against placebos or other analgesics (Brinck et al, 2018). While it is difficult to control differences in design, dose selected, dose administered, surgical populations, practice settings, and other confounders, this meta-analysis was able to elucidate important findings regarding subdissociative ketamine administration for surgical patients. The review found reductions in the mean differences (MD) of postoperative morphine equivalents administered within the first 24 hours (MD: −7.6, 95% CI −8.9 to −6.4) and 48 hours (MD: −12.6, 95% CI −15.1 to −10.2). Using a 0-100 mm visual analogue scale, pain at 24 hours was reduced at rest (MD: −5, 95% CI −6.6 to −3.6) and with movement (MD: -6, 95% CI −11 to −0.5). Similar reductions in pain were observed at 48 hours. Notably, these effects were even greater for patients undergoing

major orthopedic surgery, with reductions in morphine equivalent units of −19.7 (95% CI −28.6 to −10.2) and pain reduction of −6 (95% CI −9.9 to −3.0). Across all included studies, there was a negligible difference between the ketamine and control groups in rates of adverse CNS effects, including the occurrence of hallucination, dizziness, confusion, drowsiness, sedation, nightmares, and visual disturbances, (risk ratio 1.17, 95% CI 0.95 to 1.43). Lastly, postoperative nausea and vomiting were found to be slightly improved with ketamine administration with a risk ratio of 0.88 (95% CI 0.81 to 0.96) compared with controls. Summarily, perioperative subdissociative ketamine administration is both effective and safe in treating postoperative pain.

Available evidence has reliably demonstrated ketamine's efficacy and safety, but variations in the specific timing, patient population, and dose of ketamine for acute and postoperative pain necessitates a conservative combination of these evidence-based approaches. Subdissociative doses of ketamine for postoperative or acute pain found in the literature include IV bolus doses of 0.2 mg/kg over 30 minutes for acute pain (Boenigk et al., 2018) and a 0.1 mg/kg bolus dose (Bowers et al., 2017). However, the studies found during the research phase for this project most commonly used an IV ketamine dose of 0.3 mg/kg over 1 minute (Miller et al., 2015; Motov et al., 2015; Wang et al., 2019). Since 0.3 mg/kg was the most prevalent dose, and these studies did not report an increase in severe adverse effects, it served as the preferred basis to treat pain in the PACU. This slow IV push dose also provides an advantage over longer administration times (e.g., 30-minute infusions) since rapidly efficacious interventions for pain are desirable in the PACU.

The Addition of IV Ketamine to the FBCH PACU Order Set

A framework to administer intravenous (IV) ketamine doses of up to 0.3 mg/kg to treat moderate pain in the PACU was developed. Using the conventional 0-10 numeric rating scale (NRS) already commonly used in the PACU, IV acetaminophen and ketorolac remained available (if appropriate) for mild pain (1-3/10 on NRS), ketamine was available for moderate pain (4-6/10 on NRS), and morphine, hydromorphone, and fentanyl remained available for severe pain (7-10/10 on NRS). Medications indicated for higher pain scores were available for lower pain scores if the specified medications were contraindicated. Opioids were therefore no no longer available as first-line considerations for low pain.

Focus Areas

We engaged multiple stakeholders and departments throughout FBCH to implement this project. This included anesthesia leadership, PACU leadership, PACU registered nurses (RNs), the pharmacy, orthopedic surgeons, and the Virginia Board of Nursing. While the Virginia Board of Nursing does not prohibit RNs from administering intravenous ketamine, FBCH policy only allows RNs to administer ketamine in anesthetic doses under the direct supervision of a physician to support rapid sequence induction (RSI) for intubation in the intensive care unit (ICU) and emergency department (ED). We decided to focus primarily on demonstrating the viability of SDK administration for pain in the PACU before potentially considering a change to policy following the completion of the project. This evidence-based quality improvement project obtained internal review board (IRB) exemption.

Organizing Framework

We chose the Johns Hopkins Nursing Evidence-based Practice (JHNEBP) Model to guide this EBP project because it provides a practical guide for implementing new nursing interventions from established evidence. The core idea of this model is the "PET" process. This acronym stands for Practice questions, Evidence, and Translation. The practice question stage focuses on refining the question for the project and establishing responsibilities for the team. The evidence stage comprises gathering and appraising evidence to provide strong recommendations for solutions to the problem. Lastly, the translation stage involves using the recommendations and creating a clear plan to create a new practice of care.

The JHNEBP model provides succinct steps for the goal of establishing the use of subdissociative doses of ketamine in the post anesthesia care unit. The team can evolve or change the recommendations based on the internal factors such as work culture or external factors such as accreditation, quality measures, and standards. It allows the team to reassess the "PET" process at any point when new factors or situations arise that may alter the recommendations for new practice (Dang & Dearholt, 2018). The JHNEBP model is not a linear process, but a dynamic one that is able to adapt to unforeseen circumstances and the publication of new research that may occur during this project.

Project Design

Setting and Population

This combined process improvement and educational intervention took place at Fort Belvoir Community Hospital, a military healthcare medical treatment facility in the eastern United States. It has an inpatient capacity of approximately 120 beds and provides care to over

20,000 beneficiaries, completing over 600,000 patient encounters per year. The hospital completes approximately 11,000 surgeries annually.

Interventional Process and Education

This project selected a population of adult orthopedic patients experiencing pain ≥4/10 on the NRS. Eligible patients were given 0.3 mg/kg of IV ketamine once each in the PACU. Anesthesia providers evaluated the appropriateness of the intervention for each individual patient. While the responsible anesthesia providers had the option to administer additional ketamine, this did not occur during the project. For each patient, the total doses of opioids given and PACU pain scores at time intervals of 15, 30, and 60 minutes after arrival in the PACU were recorded. To compare the effectiveness of the addition of SDK to standard PACU orders, data were collected on 30 adult orthopedic patients preceding the implementation of the SDK order.

PACU nurses received an educational brief consisting of an oral presentation supported by PowerPoint (Microsoft Corporation, Redmond, WA). This presentation focused on the practical aspects of administering SDK, including dosing, pharmacokinetic and pharmacodynamic implications, and potential adverse reactions. PACU nurses were given the opportunity to raise any questions or concerns they may have had during the presentation, and additional copies of the PowerPoint presentation were provided to the PACU. Continuing an established practice, an anesthesia provider provided medical coverage to the PACU and was readily available if there were any additional questions about ketamine administration or concerns about its effects when patients received SDK.

HIPAA Concerns and Considerations

This project had two independent groups of patients on whom data was collected from an electronic medical record. We did not directly collect protected health information (PHI). In recording opioid doses and pain scores for each patient, we utilized DoD ID numbers, which were then translated into participant numbers (1 through 60) to de-identify each patient. We stored the data electronically using encrypted files that could only be accessed using computers on-site at FBCH that required unique common access cards and personal identification numbers to access.

Project Results

Univariate and bivariate analyses were performed using STATA version 15 (StataCorp, College Station, TX). Two groups of patients in the post-anesthesia care unit (PACU) were compared on indicators of pain and opioid use. The first group consisted of patients under standard protocol and the second group consisted of patients under subdissociative ketamine (SDK) protocol. Differences in pain scores between 15 minutes and baseline, 30 minutes and baseline as well as 60 minutes and baseline were compared between the two groups using independent samples-tests and Wilcoxon's rank sum tests. Assuming $\alpha=0.05$, the difference in pain scores between follow-up and baseline times (15 minutes, 30 minutes, 60 minutes) did not differ significantly between the two groups based on either independent samples-tests and Wilcoxon's rank sum tests. Furthermore, we generated dichotomous variables for use of each type of opioid (fentanyl, oxycodone, hydromorphone, morphine) irrespective of dosage. Assuming $\alpha=0.05$, cross-tabulation of each of these indicators of opioid use against group status revealed no significant differences among the two groups in the proportion using oxycodone,

hydromorphone, or morphine based on Chi-square tests. By contrast, a significantly lower proportion of patients under the subdissociative ketamine protocol versus patients under the standard protocol used fentanyl (20 vs. 27 patients, p=0.03). Finally, when examining the dosage of distinct opioid medications by group using either independent samples t-test or Wilcoxon's rank sum test and assuming α=0.05, the two groups differed in terms of hydromorphone dosage (mean difference of 0.33 mg, p=0.02), but not in terms of fentanyl or oxycodone dosage.

Analysis of the Results

This quality improvement project achieved a slight decrease in opioid administration in the PACU without affecting pain scores. We had hoped to show some reduction in pain scores utilizing ketamine as a supplement to preexisting PACU practices, but we were unable to achieve that reduction using a one-time dose of 0.3mg/kg of ketamine. While pain scores did not improve with the addition of SDK, pain scores were not worsened, with an ultimate result of noninferiority (statistical insignificance) regarding analgesic benefit.

In terms of reducing opioid use, adding SDK did produce statistically significant reductions in the total number of patients requiring fentanyl and also a decrease in the average quantity of hydromorphone administered to each patient. Interestingly, though, there were no differences in the number of patients who received hydromorphone or the average dose of fentanyl administered to patients. There were no differences in measured use of oxycodone in either group, which is an expected finding since oxycodone is often used to transition patients to oral analgesic medications to control pain prior to PACU discharge. Therefore, while there were statistically significant decreases in measurements of opioid administration without any increases in these measurements, the inconsistency in these measurements comparing number of patients

receiving a medication and the averages received for that same medication suggests a small effect size.

There are limitations in the implementation and evaluation of SDK for postoperative pain as part of this quality improvement project. Differences in anesthesia practice, nursing practice, and the timing of ketamine administration likely influenced the measured outcomes of interest. Variance in anesthetic administration, including differences in the use of peripheral nerve blocks and other systemic analgesics, were not observed or recorded. PACU nurses may have similarly administered other analgesic medications differently, with variable preferences for drug selection, dosing, and timing. Variability in the timing of ketamine administration in relation to the timing of a patient's arrival in PACU presumably affected pain scores. Similarly, patients are commonly sedated on arrival to the PACU, with considerable inconsistency among patients in terms of how long it takes for mental status to recover enough after surgery to allow for the use of the 0-10 NRS to assess pain. Lastly, any patient's response to ketamine depends on surgical factors, comorbidities (such as chronic pain), and even possible pharmacogenomic factors, which were not addressed in the scope of this project.

Organizational Impact / Implications to Practice & Policy

This quality improvement project demonstrated that subdissociative ketamine should be considered as a possible option to treat postoperative pain in patients whom it is appropriate based on the clinical judgment of licensed personnel caring for the patients. SDK was utilized to achieve a small opioid-sparing effect without negatively impacting pain control, and considering its affordability, it can serve as a cost-effective adjunct in the future.

In the State of Virginia, RNs are permitted to administer ketamine with proper training and within the scope of practice described by their employers. Indeed, at the time of this writing, ketamine may be administered by PACU RNs in another military treatment facility in Virginia. Fort Belvoir Community Hospital may find that it would similarly benefit from expanding current medication administration policies to allow ketamine to be administered by RNs. Furthermore, since drug shortages seem to occasionally and unpredictably impact the medications that may be available to care for patients, nurses should have experience with alternative analgesic techniques in case a need to spare opioids due to a paucity of supply is identified in the future.

Future Directions for Research and Practice

Future practice should focus on empowering RNs to safely administer SDK within their scope of practice, as mentioned previously. To facilitate this, the pharmacy could support this effort by supplying the hospital with pre-filled syringes of ketamine, preferably 5 mL syringes with a concentration of 10mg/ mL (50 mg/ 5 mL syringes). This concentration, provided by the pharmacy, would allow PACU and anesthesia staff to safely administer ketamine without the need for bedside compounding and the handling of anesthetic-range concentrations of the medication. While this has not been examined or confirmed by the research, 5 mL of ketamine in 10 mg/ mL concentration may very well carry less risk of negative sequelae in the event of a medication error than the fentanyl currently available at FBCH in 50 mcg/ mL concentration. Stated differently, 50 mg of ketamine may carry less associated risk for patients in PACU than 100 mcg or 250 mcg of fentanyl.

Future utilization of ketamine in the PACU would benefit immensely from an expanded body of research related to its use. Ketamine was originally developed as an anesthetic medication and not as an analgesic. Consequently, the available evidence regarding its pharmacokinetics and pharmacodynamics relate to anesthesia and not analgesia. There is a need for additional research to determine the most efficacious way to administer ketamine for analgesic purposes and the patients for whom it would have the most benefit. While perioperative ketamine has been supported by the literature, the analgesic doses, duration (bolus vs. infusion), and implementation strategies should be delineated more clearly. Further delineation of ketamine's dose-response relationships for analgesia, side effects, and upper limits are warranted. In terms of achieving desirable postoperative outcomes, it is not known if intraoperative administration, postoperative administration, or some combination thereof provide the best results. While current research shows that perioperative ketamine has the most benefit for adult orthopedic patients, additional research is needed to determine its efficacy across a variety of patient populations. For orthopedic patients specifically, it is desirable to learn for which indications ketamine may be most useful as an analgesic. SDK may be more useful for certain procedures or when available peripheral nerve block techniques do not provide adequate regional pain control. Lastly, future research should look beyond ketamine's opioid-sparing effects and determine if its administration directly achieves the desirable outcomes associated with opioid-sparing techniques. The reduction in perioperative opioid use itself is a proxy for more important outcomes, including reductions in respiratory depression, decreased nausea and vomiting, decreased adverse events, and improved patient satisfaction.

Future research should more specifically evaluate ketamine's role in achieving these outcomes directly.

This project was initiated with ideas originating within the current trend of ERAS protocols. The original ERAS framework did not focus on specific outcomes or interventions but instead focused on communication among stakeholders. This communication was the key to improving outcomes– forming committees to formally evaluate and discuss how all care environments in the perioperative and intraoperative environments interact to impact surgical outcomes. Teams of doctors, nurses, and other allied health professions from the preoperative period through postoperative discharge phases of care meet to learn how they impact on another and how they can work together to maximize patient outcomes. While our SDK project did show an opioid-sparing benefit, SDK should not be seen as an independent and disconnected intervention; ERAS committees should be established for the various surgical specialties at FBCH.

Conclusion

This quality improvement project reviewed available scientific literature to search for interventions that could be implemented to improve opioid-sparing practices in the PACU at FBCH. We utilized the Johns Hopkins Nursing Evidence-based Practice Model to guide our literature search and implement our practice intervention. Intravenous administration of a single bolus of subdissociative ketamine, dosed as 0.3 mg/ kg, was selected to be administered in the PACU. Since the literature showed ketamine has the most benefit in adult orthopedic patients, we chose that population to analyze the efficacy of our intervention. Thirty patients received the intervention and were compared against 30 preceding patients meeting the same criteria who had

not received the intervention. Ultimately, a small opioid-sparing effect was achieved without sacrificing pain control.

We recommend modification of FBCH policy to allow trained PACU RNs to independently administer ketamine without the direct supervision of a licensed independent practitioner (LIP) when an LIP writes appropriate orders for a PACU patient. This would be facilitated by the pharmacy providing ketamine in 50 mg/ 5 mL syringes. Further research is needed to determine the most efficacious ways to utilize ketamine as an analgesic, adding to the body of evidence describing ketamine as an anesthetic. While we demonstrated ketamine's ability to achieve a small opioid-sparing effect at FBCH, future projects may use future research to optimize ketamine's effectiveness to achieve direct and easily measurable effects on postsurgical safety and patient outcomes. These future advances in safety and quality of care, using SDK as well as other evidence-based interventions, would best be achieved using ERAS committees within FBCH. Since improvement in medical practices, addressing the question in this project or others, requires ongoing analyses of available scientific literature, these ERAS committees are the optimal way to develop and utilize these strategies. Moving forward, ERAS committees at FBCH may find ways to improve upon our implementation of SDK or to find other ways to optimize the care delivered at FBCH.

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Appendices

Appendix A: CITI Certificates

Completion Date 24-Mar-2020
Expiration Date 24-Mar-2023
Record ID 36005761

This is to certify that:

Andre Brown

Has completed the following CITI Program course:

Not valid for renewal of certification through CME.

OUSD P&R Human Research
(Curriculum Group)
Biomedical Investigators and Research Study Team
(Course Learner Group)
1 - Basic Course
(Stage)

Under requirements set by:

Office of the Under Secretary of Defense (Personnel and Readiness)

Collaborative Institutional Training Initiative

Verify at www.citiprogram.org/verify/?w39a49792-fb30-4249-b64f-0ff588ec2f9d-36005761

Completion Date 02-Apr-2020
Expiration Date 02-Apr-2023
Record ID 36023097

This is to certify that:

Alex Jung

Has completed the following CITI Program course:

Not valid for renewal of certification through CME. Do not use for TransCelerate mutual recognition (see Completion Report).

OUSD P&R Human Research (Curriculum Group)
Biomedical Investigators and Research Study Team (Course Learner Group)
1 - Basic Course (Stage)

Under requirements set by:

Office of the Under Secretary of Defense (Personnel and Readiness)

Collaborative Institutional Training Initiative

Verify at www.citiprogram.org/verify/?w6d439454-70a2-4b63-836f-5b951de9c4ce-36023097

Completion Date 17-Mar-2020
Expiration Date 17-Mar-2023
Record ID 35965346

This is to certify that:

Eric Sanchez

Has completed the following CITI Program course:

OUSD P&R Human Research (Curriculum Group)
Biomedical Investigators and Research Study Team (Course Learner Group)
1 - Basic Course (Stage)

Under requirements set by:

Office of the Under Secretary of Defense (Personnel and Readiness)

Verify at www.citiprogram.org/verify/?w0f7de35c-252c-4284-abab-8ceb43325302-35965346

Appendix B: USU Form 3202N

USU
Uniformed Services University

OFFICE OF RESEARCH
4301 JONES BRIDGE ROAD
BETHESDA, MAYLAND 20814
PHONE: (301) 295-3303; FAX: (301) 295-6771

NOTICE OF PROJECT APPROVAL

Change Number: Original

VPR Site Number:	GSN-61-11774
Principal Investigator:	Brown, Andre
Department:	Graduate School of Nursing
Project Type:	Student
Project Title:	
Project Period:	3/1/2021 to 3/1/2022

Assurance and Progress Report Information:

Name	Sup	Approval Type	Status	Approved On	Forms Received
Progress Report	0			To be Submitted	N/A

Remarks:
This Notice Of Project Approval has been reviewed and approved. Please remember that you must submit a final Progress Report (Form 3210) upon completion of this project.

Questions regarding this approval should be directed to the following person in the Office of Research: Sharon McIver, (301) 295-9814.

RANDOLPH.TOYA.V.1242107698 Digitally signed by RANDOLPH.TOYA.V.1242107698 Date: 2021.03.01 16:19:20 -05'00'

Mark G. Kortepeter, MD, MPH Date
FACP, FIDSA, FASTMH
COL (R) MC US Army
Vice President for Research
Uniformed Services University of the Health Sciences

cc: File
Dr. Kennett Radford
Laura Taylor

Appendix C: PI Letter of Determination

DEFENSE HEALTH AGENCY
FORT BELVOIR COMMUNITY HOSPITAL
9300 DEWITT LOOP
FORT BELVOIR, VIRGINIA 22060-5901

DATE: 28 June 2021

FROM: Ms. Erica Reid, MS, CIP, Acting Human Protections Director and Exempt Determination Official, Fort Belvoir Community Hospital (FBCH), and Institutional Review Board (IRB) Chairperson, Walter Reed National Military Medical Center

TO: CPT Andre Brown, Fort Belvoir Community Hospital

SUBJECT: FBCH DRP Determination of Project #937289; Reference #937289

PROJECT TITLE: Opioid-Sparing Analgesia in the Post-Anesthesia Care Unit: Subdissociative Ketamine Administration

SUBMISSION TYPE: New Project

ACTION: Determination of "Not-Research" – Evidence Based Practice (EBP) Project

DECISION DATE: 28 June 2021

The FBCH DRP Determinations Official has determined the activity described in the above referenced submission does not meet the full definition of research as defined in 32 Code of Federal Regulations 219.102(l). Rather, the purpose of the project is to improve clinical practice through evidence-based practice activities. The outcome of this project is not intended to develop or contribute to "generalizable" knowledge as in the case of research, and does not involve randomization of individuals. The findings may directly affect local institutional practice, and may identify corrective action(s).

This project is an Evidence-Based Practice project aimed at instituting a new acute pain care option within FBCH's Post-Anesthesia Care Unit (PACU) standard order set. The project seeks to address the discrepancy where "the current PACU order set at FBCH strongly favors opioid administration, which is contrary to evidence for long-term pain control in most surgical procedures." The project team sees an "imperative to implement an evidence-based multimodal analgesic strategy in the PACU to improve patient safety without sacrificing analgesia and quality care."

Please register your project with the FBCH Department of Quality Management at https://fbchintranet.departments.med.ds.osd.mil/qualitymgt/SitePages/Home.aspx

If there are any changes in personnel or project procedures as outlined in the original submission, a Modification to the original project must be submitted in EIRB and a Determinations Official

will review the project again to ensure that the proposed changes do not affect the original determination of "Not-Research".

This is not an approval to receive extramural resources (i.e. personnel, drugs, supplies, equipment, money, and gifts from any source outside of FBCH). You must coordinate extramural resource approvals with the NCR Business Office at (301) 295-8248. If any extramural resources are received without DOD or MEDCOM approval, the individual who receives them may be found in ethics violation and prosecuted for criminal misconduct.

You may begin work pursuant to any additional required approvals and/or agreements.

Once project activities cease, within 30 days you are required to submit a Closure Form in EIRB, explaining any non-initiation, partial completion, full completion, or any other type of closure, stoppage, or termination of the project. Project data remains the property of FBCH and may not be removed without prior command authorization. Your department at FBCH must retain the project records for at least two years after Closure.

Any publications, posters, presentations, or manuscripts arising from this work presented outside our institution must be submitted and cleared through the publication clearance process. Many journals are interested in publishing Quality Management projects. If you do decide to disseminate your findings, please use paragraph headings such as "issue", "procedures for collecting and evaluating information", "information found", "lessons learned", etc. and avoid using headings such as "research questions", "methods", "results", "study limitations", etc.

Contact the FBCH Department of Research Programs staff if you have any questions or concerns. Please include your project number (937289) in all correspondence with this office.

REID.ERICA.MICHELLE.1388056149 Digitally signed by REID.ERICA.MICHELLE.1388056149 Date: 2021.06.29 15:22:41 -04'00'

Erica Reid, MS, CIP
FBCH Acting Human Protections Director
FBCH Determinations Official
WRNMMC IRB Chairperson

Appendix D: PAO Clearance

REQUEST FOR PUBLIC RELEASE

(This form is to be used at Fort Belvoir Community Hospital in requesting review and clearance of DoD information for public release in accordance with DoDD 5230.09)

1. DOCUMENT DESCRIPTION

a. TYPE	b. TITLE	
Evidence Based Practice Project	Opioid-Sparing Analgesia in the PACU: Subdissociative Ketamine	
c. DATE OF SUBMISSION	d. PAGE COUNT	e. RESEARCH OR PUBLIC CLEARANCE?
220418	3	Publication Clearance #937289
f. CLEARANCE REQUESTED BY *(YYYYMMDD) (All submissions require a minimum of 10 days for review)*		
20220430		

2. AUTHOR/SPEAKER *(If more than one author, include names of additional authors on separate sheet.)*

a. NAME *(Last, First, Middle Initial)*	b. AFFILIATION *(Armed service, civilian, contractor)*	c. RANK
Brown, Andre D	Army	MAJ
d. DEPARTMENT/CLINIC		
Anesthesia		

3. PRESENTATION/PUBLICATION DATA *(Date, Place, Event)*

20220519, USU Campus, Uniformed Services University Health Sciences University Research Symposium

4. POINT OF CONTACT

a. NAME *(Last, First, Middle Initial)*	b. EMAIL	c. TELEPHONE NO.
Brown, Andre D	andre.d.brown8.mil@mail.mil	2544664694

5. STAFF JUDGE ADVOCATE (SJA) COORDINATION

a. NAME *(Last, First, Middle Initial)*: NASH, Pamela M.

b. REMARKS

Photos on slides 4, 6, 15, and 16 need attribution. See attached guidance.

c. SUBMISSION IS: ○ APPROVED ◉ APPROVED WITH QUALIFICATIONS *(See REMARKS, block 5b)* ○ NOT APPROVED

d. SIGNATURE: NASH.PAMELA.M.1028659365 Digitally signed by NASH.PAMELA.M.1028659365 Date: 2022.04.27 14:57:00 -04'00'

e. DATE SIGNED *(YYYYMMDD)*: 20220427

6. PUBLIC AFFAIRS OFFICER (PAO) COORDINATION

a. NAME *(Last, First, Middle Initial)*: Brown, R. P.

b. REMARKS

Clearance granted for project with photo attributions as reflected above in SJA comments.

Use of project will include, but is not limited to the following:

(1) Final Report to be uploaded in the USU Archives, (2) Abstract/Impact Statement for USU Research Days, (3) Oral presentation during USU Research Days, and (4) Poster presentation during USU Research Days.

c. SUBMISSION IS: ○ APPROVED ◉ APPROVED WITH QUALIFICATIONS *(See REMARKS, block 6b)* ○ NOT APPROVED

d. SIGNATURE: BROWN.R.PARRISH.1047605780 Digitally signed by BROWN.R.PARRISH.1047605780 Date: 2022.05.04 07:41:35 -04'00'

e. DATE SIGNED *(YYYYMMDD)*: 20220503

Submitted documents require both Staff Judge Advocate (SJA) and Public Affairs Officer (PAO) approval in blocks 5c and 6c above before public release. Please note any qualifications for approval, which will be included in the REMARKS block (if applicable). If approved by both SJA and PAO, the material is approved for public release and clearance for open publication is recommended under the provisions of DoDD 5230.09

FBCH STRATCOM FORM 1910, OCT 2015

Appendix E: Forms Used in Data Collection

Figure 1: PRISMA Flow Diagram

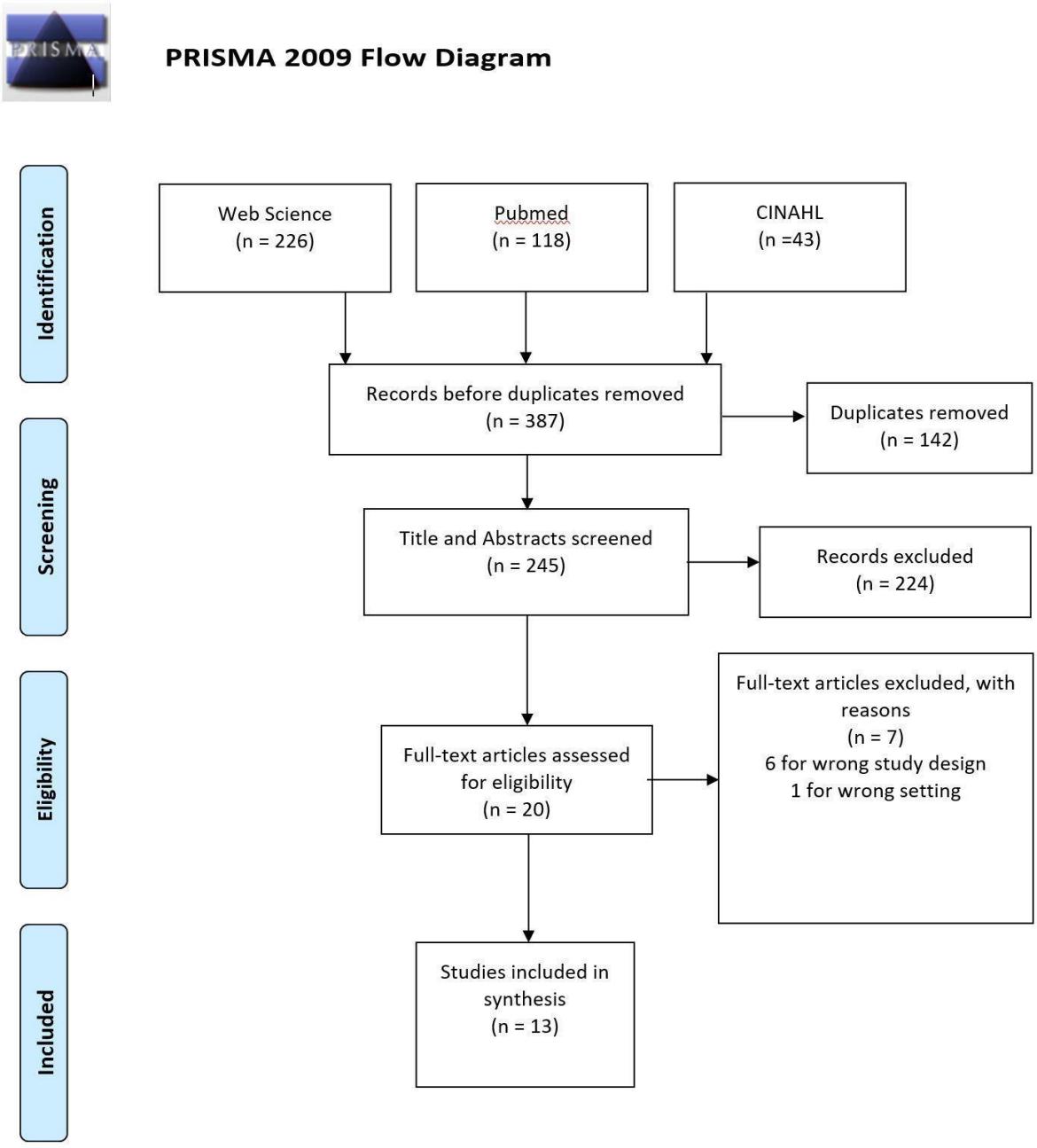


Figure 2: Table of Evidence

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Bowers et al., 2017	1) to measure and compare total opioid use and number of opioid doses in patients treated with opioids versus ketamine in conjunction with opioids; 2) to measure pain scores up to 2 hours after presentation in the ED patient with pain, comparing standard opioid pain control to ketamine in conjunction with opioids; 3) to compare patient satisfaction with pain control using opioids alone versus ketamine in conjunction with opioids; 4) to monitor and compare side effects in patients treated with opioids versus ketamine in conjunction with opioids; and 5) to identify effect variation between different subgroups of patients, with the purpose of focusing future research.	Hypothesized that low-dose ketamine, compared to placebo, as an adjunctive treatment to opioids would result in better pain control over 2 hours and greater patient satisfaction with pain control; further, this protocol will result in a lower opioid dosage over 2 hours.	Randomized, double-blinded, placebo-controlled trial conducted in the ED at Carilion Roanoke Memorial Hospital, a medical school affiliated Level I trauma center and tertiary care referral center with a yearly census of over 90,000 visits.	271 patients met initial inclusion criteria during the times in which a study member was present and enrolling in the ED. Of these 271 patients, 106 were excluded (10 due to provider concern for secondary gain, three due to provider's unwillingness to participate, 92 due to medical exclusion criteria) and 47 declined to participate in a research study. One potential subject was not enrolled due to inability to pass the Decision-making Capacity and Comprehension Assessment. A total of 116 patients were randomized to treatment groups, with 53 receiving ketamine and 63 receiving placebo. Two patients were enrolled in the study, but were never given study drug because their time to dosing exceeded the maximum.	SETTING: ED at Carilion Roanoke Memorial Hospital, a medical school affiliated Level I trauma center and tertiary care referral center with a yearly census of over 90,000 visits. INCLUSION: Real-time chart review; patients meeting age inclusion criteria, reporting pain equal to or greater than 6/10, and whose primary ED physician ordered intravenous (IV) opioid analgesia were eligible for inclusion in this study. EXCLUSION: Provider concern for secondary gain, provider's unwillingness to participate, medical exclusion criteria.	Ketamine or placebo prior to protocol-based dosing of additional opioid analgesia. NOMINAL
	Dependent Variables	**Statistical Analysis**	**Results**	**Strengths (how promoted internal/external validity)**	**Weaknesses (biases; poorly controlled threats to internal/external validity)**	**LEVEL OF EVIDENCE – using JHNEBP tool (Strength and Quality)**
	Pain level (0–10) (INTERVAL), satisfaction with pain control (0-4) (ORDINAL), side effects (NOMINAL), sedation level (INTERVAL), and need for additional pain medication (RATIO). Total opioid dose (RATIO), including the initial dose, was compared between groups.	The study was initially powered for analysis using two-sided independent sample t tests, requiring a randomized sample size of 110 to provide 80% power to detect, independently a difference of 1.5 on the NRS-11 scale and/or a difference of 0.5 on the 4-point Likert scale. However, the data collected were ultimately more suited to repeated measures analysis. The power analysis was repeated, and a randomized sample size of 88 (44 each arm) provided 80% power for a repeated measures analysis with a compound symmetry covariance structure. The comparison of treatment	Sixty-three subjects were randomized to the placebo group and 53 to the ketamine group. No significant differences were found in demographics between the groups. Patients receiving ketamine reported lower pain scores over 120 minutes than patients receiving placebo (p = 0.015). Total opioid dose was lower in the ketamine group (mean ± SD = 9.95 ± 4.83 mg) compared to placebo (mean ± SD = 12.81 ± 6.81 mg; p = 0.02). Satisfaction did not differ between groups. Fewer patients in the ketamine group required additional opioid doses.	Patients received initial provider-determined treatment for their painful condition (recorded as "initial dose") before the informed consent process to ensure that treatment was not delayed. Patients were reassessed after 15 minutes and if, after the initial dose of analgesia, the patient reported pain ≥ 6/10 informed consent was obtained, as well as an initial NRS-11 score (T0), and a study number was assigned. Each study number was correlated with a syringe containing study drug (ketamine or normal saline), the identity of which was known only to pharmacy staff not participating in ED bedside care.	This study was conducted in a busy ED in the general patient population, without special conditions, locations, or providers for study patients. The cohort includes subjects with chronic pain and long-term outpatient opioid use, as well as patients with new-onset acute pain; it is possible that the former patient population may react quite differently to the adjunctive ketamine usage than the latter. The environment of the ED allows for less precise control of certain other variables, such as timing of medication administration and specific opioids prescribed, which may have an effect on applicability of study results in	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Miller et al., 2015	To compare the maximum change in numeric rating scale (NRS) pain scores, in patients receiving low-dose ketamine (LDK) or morphine (MOR) for acute pain in the emergency department.	Hypothesized that ketamine would provide a greater maximum reduction in pain compared with morphine	Prospective, randomized, controlled, double-blinded superiority trial comparing the efficacy of IV low-dose ketamine to IV morphine for moderate to severe acute pain in the ED setting. The study was conducted in a military, level 1 trauma center ED [BAMC] where approximately 80,000 ED patients are treated annually. ED population is approximately 20% uniformed military and 80% civilians.	Initial N=45. Final N=45. Morphine N=21; Ketamine N=24.	Sample of convenience of ED patients utilized. Prospective participants were screened for enrollment from FEB12-MAR13. Inclusion: 18-59 yrs; complaint of abdominal, flank, low back, or extremity pain that the ED provider felt warrented IV opioid treatment. Excluded for hemodynamic instability, altered mental status, intoxication, specific chronic pain conditions, pregnant/breast-feeding, serious cardiac/pulm/CSN disease, extremes of weight, and acute ocular/head trauma	Ketamine 0.3mg/kg TBW (max 25mg) or morphine 0.1mg/kg TBW (maximum 8mg). A second dose (a repeat of the first) could be given as early as 20 minutes after completion of the initial dose. RATIO.
	Dependent Variables	**Statistical Analysis**	**Results**	**Strengths (how promoted internal/external validity)**	**Weaknesses (biases; poorly controlled threats to internal/external validity)**	**LEVEL OF EVIDENCE – using JHNEBP tool (Strength and Quality)**
	Primary: Maximum change on the verbal Numeric Rating System (NRS) pain scale compared with baseline immediately prior to the administration of the drug. Following administration, NRS documented at 5, 10, 20, and then every 20 minutes thereafter until 120 minutes. ORDINAL. Secondary: Richmond agitation-sedation scale. ORDINAL. Secondary: Vital signs. INTERVAL/RATIO. Secondary: Adverse events. Nominal. Secondary: Need for repeat dosing. NOMINAL. Secondary: Provider/ nurse satisfaction with study medication as scored by Lickert scale. ORDINAL.	Repeated-measures linear model. Primary DV analyzed as "two-sided test". Mean and SD also reported for the time intervals described [No statistical differences; test unknown]. RASS: Descriptive statistics. No significance reported. Blood Pressure: Presumably t-test. Adverse events reported nominally, incidence of adverse events reported as descriptive statistics. Repeat dosing: Chi-square and Fisher's exact. Provider/nurse satisfaction score: Descriptive.	Primary: Maximum NRS pain score change was 4.9 for ketamine (95%CI 5.8-4) and 5 for morphine (95%CI 6.6-3.5). No significant differences in rates of administration of second dose. RASS: no statistically significant differences. Ketamine BP significantly higher than morphine BP at 5 and 10 minutes following administration. Adverse events: Morphine-- 12 total adverse events. O2 dexaturation to 88% x1, nausea x2, vomiting x1. Pruritus x1. Ketamine-- 14 total adverse events. Nausea x3, vomiting x1, hallucinations x3. Neither midazolam or narcan were needed. Provider satisfaction (Lickert)-- Ketamine: mean 4 (IQR3-5). Morphine: mean 4 (IQR4-5). Nurse-- Ketamine: 4(IQR 3-5). Morphine: 5(IQR4-5). Low-dose ketamine not superior to	Prosopective, randomized, controlled, double-blinded superiority trial. Evaluated analgesic effects while also monitoring for adverse reactions that could be of clinical concern.	25% of ketamine group patients did not complete the entire 120 minutes of data collection (inadequate pain control or request for 3rd dose of study drug). Single-center study. Conducted in military facility, possibly limiting external validity. Small sample size. The analgesic dose of ketamine is not standardized. RASS has not been validated for use in the ED. No long-term follow-up data. Patients with chronic pain were excluded.	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Wang et al., 2019	A single low-dose administration of ketamine after bariatric surgery can improve pain and mood scores in the immediate postoperative period.	There were no significant differences in visual analogue pain scores between groups (group-by-time interaction) P=0.966; marginal group effect P=0.137. However, scores on the affective scale of SF-MPQ (secondary outcome) significantly decreased in the ketamine group as early as postoperative day (POD) 2 [mean difference=2.2 (95% bootstrap CI -2.9 to 1.6), Bonferroni adjusted P<0.001], compared with placebo group in which the scores decreased only by POD 7. Scores on the total scale of SF-MPQ for the ketamine group were smaller compared with the placebo group (P%0.034).	Randomised, double-blind, placebo-controlled study to compare a single subanaesthetic dose of ketamine (0.4mg/kg) with a normal saline placebo in the postanaesthesia care unit after laparoscopic gastric bypass and gastrectomy.	100 patients were randomised into the ketamine and saline groups. 8 patients withdrew consent before intravenous administration and 2 patients experienced surgical complications and were excluded. Final analysis includes 90 patients.	SETTING: Single-center, tertiary hospital. Post-anesthesia care unit. INCLUSION: English-speaking patients between the ages of 18 and 65 years who were undergoing laparoscopic gastric bypass or sleeve gastrectomy. EXCLUSION:Exclusion criteria included American Society of Anesthesiologists physical status greater than III, cognitive impairment, past ketamine misuse or abuse, schizophrenia, use of antipsychotic drugs, known sensitivity or allergy to ketamine, use of medication that interferes with the hepatic metabolism and renal clearance of ketamine, and a history of chest pain, cardiac arrhythmia, stroke, head trauma, or intracranial mass or haemorrhage.	Type of pain management strategy: 1.Intravenous Ketamine 0.4mg/kg --> NOMINAL/CATEGORICLAL. 2. Placebo of 0.9% Normal Saline --> NOMINAL/CATEGORICAL. DESCRIPTIVES: Age (CONTINUOUS/RATIO), Gender (NOMINAL/CATEGORICAL), Race (NOMINAL/CATEGORICAL), Height (RATIO), Weight (RATIO) ASA Score (NOMINAL/CATEGORICAL), Hx of Depression (NOMINAL/CATEGORICAL), Hx of Chronic Pain (NOMINAL)

Dependent Variables	Statistical Analysis	Results	Strengths (how promoted internal/external validity)	Weaknesses (biases; poorly controlled threats to internal/external validity)	LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)
Visual Analog Scale for Pain (ORDINAL), Short form McGill Questionnaire for pain (ORDINAL), Montgomery-Asberg Depression Scale (ORDINAL), Beck Depression Inventory (ORDINAL)	A SD (3) in all the repeated measurements and assuming a correlation between them of 0.8, 41 patients per arm were needed to detect a between-group difference of at least two points in the postoperative VAS score with a power of 0.8 and an a level of 0.05. Personal and intra-operative data between groups were analysed using Student's t test or Wilcoxon rank test, based on the results of the Shapiro–Wilk test. A x2 and Fisher's exact test for inferences on proportions.	There were no significant differences in visual analogue pain scores between groups (group-by-time interaction P=0.966; marginal group effect P=0.137). However, scores on the affective scale of SF-MPQ (secondary outcome) significantly decreased in the ketamine group as early as postoperative day (POD) 2 [mean difference=-2.2 (95% bootstrap CI -2.9 to 1.6), Bonferroni adjusted P<0.001], compared with placebo group in which the scores decreased only by POD 7. Scores on the total scale of SF-MPQ for the ketamine group were smaller compared with the placebo group (P=0.034).	Adhered to the inclusion protocol and excluded patients appropriately. Decreased confounding variables by selecting a a precision inclusion criteria. Used different scales to measures, pain, attitudes, and mood and use the appropriate statistical analyses for documenting the results.	Power analysis was based on the effect of continuous infusion of dexmedetomidine on VAS scores for bariatric surgery. Lack of impact of ketamine on the VAS scores may be due to the lower than expected baseline postoperative pain scores. Similar limitation is due to the MADRS and BDI scores due to lower than expected baseline levels. The strreamlined care of postoperative care at the institution (receiving a PCA post-op) may have contributed to the lack of difference in the hospital stay and the daily usage of opioids after surgery.	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Boenigk et al., 2019	The aims of our study were to examine whether postoperative ketamine infusion would reduce postoperative hydromorphone consumption in opioid-tolerant patients to a greater degree than it did in opioid-naı¨ve patients, and whether ketamine would improve pain control in opioidtolerant patients to a different degree than in opioid-naı¨ve patients.	We hypothesised that low-dose ketamine infusion after major spinal surgery reduces opioid requirements in opioid-tolerant patients, but not in opioid-naı¨ve patients.	Prospective randomised placebo-controlled trial	A total of 249 patients were assessed for eligibility from November 2012 to November 2014. Of these, 129 patients were prospectively allocated randomly to groups, but only 122 received the intended study intervention.	SETTING: Single-centre, tertiary care hospital, November 2012 until November 2014. INCUSION: Patients aged 16 to 75, ASA physical status 1 to 3, scheduled for elective lumbar fusion surgery at two or more levels under general anaesthesia. EXCLUSION: poorly controlled hypertension, severe cardiac or pulmonary disease, elevated intraocular pressure, severe hepatic or renal dysfunction, pregnancy, a history of psychiatric disorder, inability to speak English, inability to understand the numerical pain scale or to operate	Patients in the ketamine groups received a ketamine infusion (bolus 0.2mg/kg 1 over 30 min followed by 0.12mg/kg 1 h 1 for 24 h). Patients in the placebo groups received 0.9% saline.

Dependent Variables	Statistical Analysis	Results	Strengths (how promoted internal/external validity)	Weaknesses (biases; poorly controlled threats to internal/external validity)	LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)
Reduced opioid requirements in opioid-tolerant patients. INTERVAL/RATIO	We tested normality using the Shapiro–Wilk test and Q–Q plots. Continuous data were compared using one-way analysis of variance (ANOVA) or the Kruskal–Wallis H test, as appropriate. The x2 test and Fisher's exact test were used for inferences on proportions. A linear mixed model was used to analyse the effect of ketamine on cumulative hydromorphone consumption over time between groups, to accommodate an unbalanced design (unequal number of subject per group), and missing	Postoperative hydromorphone consumption was significantly reduced in the opioid-tolerant ketamine group, compared with the opioid-tolerant placebo group [0.007 (95% CI 0.006 to 0.008) versus 0.011 (95% CI 0.010 to 0.011)mg/kg, Bonferroni corrected P<0.001]. There was no difference in hydromorphone use between the opioid naı¨ve groups (0.004 and 0.005mg/kg in the opioid- naı¨ve ketamine and placebo group, respectively, P=0.118). Pain scores did not differ significantly between the opioid-tolerant ketamine group and the opioid-naı¨ve groups. There was no significant difference in side effects among groups.	Recruiting from a relatively homogeneous surgical population and using a standardised analgesic protocol. We chose not to use ketamine intraoperatively as we feared that it would lead to very different doses of intra-operative opioids used, and thus muddle the result.	Opioid-naı¨ve patients more frequently were younger and did not suffer from chronic pain because they presented for surgery for scoliosis correction, while the opioid-tolerant patients had often suffered from chronic back pain with concomitant psychological effects and expectations of pain medication. Another shortcoming of the study is we did not precisely quantify the amount of pre-operative opioid medication taken by the patients, so we are unable to confirm Loftus' and Nielsen's observations that the benefit of	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Motov et al., 2015	To assess and compare the analgesic efficacy and safety of subdissociative intravenous-dose ketamine with morphine in emergency department (ED) patients.	A subdissociative dose of ketamine administered as a single agent at 0.3 mg/kg will provide relief similar to that of a standard dose of morphine at 0.1 mg/kg for acute moderate to severe pain in the ED setting.	Prospective, randomized, double-blind trial comparing the safety and efficacy of subdissociative intravenous-dose ketamine with intravenous morphine for acute pain in the ED.	130 patients were screened initially. 40 patients were excluded based on requesting morphine only, refusing to participate in the study, undisclosed reasons, and requesting ketamine only. The final amount of patients enrolled in the study was 90 patients.	SETTING: 711-bed community teaching hospital. Convience Sampling INCLUSION:patients aged 18 to 55 years who presented to the ED with acute abdominal, flank, back, or musculoskeletal pain score of 5 or more on a standard 11-point (0 to 10) numeric rating scale and required opioid analgesia EXCLUSION: pregnancy, breast-feeding, altered mental status, allergy to morphine or ketamine, weight less than 46 kg or greater than 115 kg, unstable vital signs (systolic blood pressure <90 or >180 mm Hg, pulse rate <50 or >150 beats/min, and respiration rate <10 or >30 breaths/min), and medical history of acute head or eye injury, seizure, intracranial hypertension, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4 hours before) opioid	Patient received 0,3 mg/kg of Ketamine or 0.1 mg/kg of morphine in a 10ml normal saline solution to treat according to the predetermined randomization list with block randomization every 10 participants up to 90. NOMINAL

Dependent Variables	Statistical Analysis	Results	Strengths (how promoted internal/external validity)	Weaknesses (biases; poorly controlled threats to internal/external validity)	LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)
Numerical Rating Scale for Pain (ORDINAL), Complete Resolution of pain % (NOMINAL), Reduction of of pain according to NRS % (NOMINAL), Fentanyl rescue incidence % (NOMINAL), Adverse Effects (NOMINAL)	Data analyses included frequency distributions, paired t test to assess a difference in pain scores within each group, and independent-sample t test to assess differences in pain scores between the 2 groups at the various intervals. Mixed-model linear regression was used to compare changes in pain numeric rating scale across time points.	The primary change in mean pain scores was not significantly different in the ketamine and morphine groups: 8.6 versus 8.5 at baseline (mean difference 0.1; 95% confidence interval-0.46 to 0.77) and 4.1 versus 3.9 at 30 minutes (mean difference 0.2; 95% confidence interval-1.19 to 1.46; P=0.97). There was no difference in the incidence of rescue fentanyl analgesia at 30 or 60 minutes. No statistically significant or clinically concerning changes in vital signs were observed. No serious adverse events occurred in either group. Patients in the ketamine group reported increased minor adverse effects at 15 minutes post–drug administration.	Randomized control trial that ensured the reserachers and the subjects were blinded by proper protocols making it unable to determinethe interventions from each other. The preparing pharmacist, research manager, and statistician were the only people who knew the difference. The patients were put on a randomized list to exclude possible bias from researchers.	This was a single-center study in which patients were enrolled as a convenience sample according to predetermined inclusion and exclusion criteria. Sample size was near minimum for adequate power (80%). There was a potential for unblinding because some participants exhibited ketamine-specific reactions such as nystagmus. Patient enrollment was restricted to time frames in which both a member of the research team and pharmacy team were available.	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Chou et al., 2016	This guideline, developed based on a systematic review of the evidence, provides recommendations developed by a multidisciplinary expert panel on management of postoperative pain. Guideline developed as a CPG by the American Pain Society, the American Society of Regional Anesthesia and pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council	The panel recommends that clinicians offer multimodal analgesia, or the use of a variety of analgesic medications and techniques combined with nonpharmacological interventions, for the treatment of postoperative pain in children and adults (strong recommendation, high-quality evidence).	N/A Clinical Practice Guideline	N/A	N/A	N/A

Dependent Variables	Statistical Analysis	Results	Strengths (how promoted internal/external validity)	Weaknesses (biases; poorly controlled threats to internal/external validity)	LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)
N/A	N/A	32 recommendations made for the treatment of postoperative pain. Systemic pharmacological therapy recommendations that could be utilized in the PACU include the use of acetaminophen and NSAIDs and the consideration of IV ketamine as a component of multimodal analgesia in adults. Other recommendations discuss other medications, which may be administered pre-/perioperatively or via other routes (e.g., local anesthetics).	The APS, with input from the ASA, convened a panel of 23 members with expertise in anesthesia and/or pain medicine, surgery, obstetrics and gynecology, pediatrics, hospital medicine, nursing, primary care, physical therapy, and psychology to review the evidence and formulate recommendations on management of postoperative pain. The panel used methods adapted from the Grading of Recommendations Assessment, Development, and Evaluation Working Group to rate the recommendations included in this guideline.	This clinical practice guideline is a systematic review of previous studies does not test a theory or effectiveness of a medication. This is not a qualitative nor a quantitiatve study, but a synthesis of multiple studies by experts in the field for pain managment. Seeming lack of interprofessional/ multidisciplinary perspectives (e.g., nursing and APRNs), which are a core component of ERAS protocols.	IVA

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Kendall et al. 2020	Compare the analgesic efficacy of intraoperative methadone to intraoperative morphine for postoperative analgesia outcomes in patients undergoing surgical procedures. Also sought to examine potential side effects related to use of intraop methadone	Meta-analysis. Not different from declared objective of the study.	Comprehensive search of RCTs investigating intraoperative methadone to morphine on postoperative surgical analgesia using PubMed, Google Scholar, the Cochrane Database of Systematic Reviews, and Embase. Search conducted from inception to 2019.	Initial search identified 382 articles. Exclusion criteria applied to reach a final result of n=7.	Inclusion criteria: Adults (>18y), no language restrictions. Single- or double-blinded RCTs that compared intraoperative methadone with morphine for postoperative analgesia, reporting of either opioid consumption or pain scores. Exclusion criteria: unable to determine comparison between morphine and methadone, nonrandomized RCTs, animal studies, correspondence, or editorials. No minimum sample size was required for inclusion in the quantitative analysis.	Studies included administration of intraoperative methadone or intraoperative morphine
	Dependent Variables	**Statistical Analysis**	**Results**	**Strengths (how promoted internal/external validity)**	**Weaknesses (biases; poorly controlled threats to internal/external validity)**	**LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)**
	Primary: Studies evaluated postoperative opioid consumption reported up to 24 hours following surgery RATIO. Secondary: Postoperative pain scores (numeric or converted to numeric from VAS) in the PACU and at 24 hours following surgery ORDINAL, time to first analgesic request RATIO, and postoperative nausea and vomiting desplayed in terms of frequency NOMINAL.	Weighted Mean Differences (WMD) with 95% confidence interval (CI) were calculated and reported for continuous data for total opioid consumption up to 24hr and NRS pain scores at rest up to 24 hours.	Six studies analyzed found that intraoperative methadone had no statistically significant effect on opioid consuption following surgery. Four studies evaluating methadone on postsurgical pain compared to control in PACU following surgery demonstrated a significant effect, WMD (95%) CI of -1.11 (-1.88 to 0.33)(0-10 NRS), P=0.005. Postoperative pain at rest 24 hrs following surgery-- five studies-- methadone had a significant effect WMD (95% CI) of -1.35 (-2.03 to -0.67)(0-10NRS), P<0.001. No significant effect to first analgesic request in the postoperative period. No significant effect on nausea/ vomiting. Four studies reported no adverse events (respiratory depression and excessive sedation) or did not report events.	Meta-analysis performed exhaustive survey of available RCTs on the topic	Meta-analysis unable to control for limitations in individual studies	IA

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Mercadante et al., 2020	The aim of the study was to compare methadone and morphine for the mangement of post-operative pain for patients undergoing surgery for gynecological cancer.	Analgesic and adverse effects were compared between the two interventions.	Randomized Controlled Trial. Patients scheduled for the first operation were randomized by a computerized system to receive morphine or methadone. Patients were premedicated with midazolam 0.1mg/kg, plus morphine or methadone 0.15mg/kg intravenously. Foloowing the surgery, boluses of the study drugs in doses of 3 mg were given to keep the patient comfortable in the PACU if their pain intensity was >4/10.	72 patients assessed of eligibility. 3 patients did not meet inclusion criteria and 5 declined to participate. 64 patients for final analysis	SETTING: Postoperative recovering Area; ward. La Maddalena Cancer Center INCLUSION:Non-pregnant female patients were eligible for inclusion if they were at least 18 years old and had an American Society of Anesthesiologists physical status I to III. EXCLUSION:Patients were excluded if they were receiving opioids for chronic pain or for any other reason, had documented sleep apnea, alcohol or drug	Administration of Methadone vs Morphine during the prodecure with premedication and in post-op: 1. Methadone administration--> NOMINAL/CATEGORICAL. 2. Morphine administration:--> NOMINAL/CATEGORICAL. DESCRIPTIVES: Age (CONTINUOUS/RATIO), HYPERTENSION (NOMINAL/CATEGORICAL), DIABETES (NOMINAL/CATEGORICAL), CHRONIC RESPIRATORY DISEASE (NOMINAL/CATEGORICAL), Gender (NOMINAL/CATEGORICAL), ASA Score (NOMINAL/CATEGORICAL),, WEIGHT (CONTINUOUS/RATIO)
	Dependent Variables	**Statistical Analysis**	**Results**	**Strengths (how promoted internal/external validity)**	**Weaknesses (biases; poorly controlled threats to internal/external validity)**	**LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)**
	Pain intensity (ORDINAL), Nausea (NOMINAL). Vomiting (NOMINAL), Drowsiness (NOMINAL), Itching (NOMINAL), Morphine mg used (RATIO), Methadone mg used (RATIO)	Continuous data areexpressed as mean ± SD, unless otherwise specified. Frequency analysis was performed using the Pearson's chi-square test and Fisher exact test. The univariate analysis of variance (ANOVA) was performed to evaluate mean differences (age, weight, and opioid consumption) between patient groups. Whereas some variables were not normally distributed, we have used non-parametric tests and in particular the related-samples Friedman's two-way	Methadone infusion provided a better analgesia in comparison with morphine infusion on the second day. Pain intensity intervals and Summed Pain intensity difference over 48 hours were also lower with the methadone group, although the difference was not significant between the two groups.	Study controlled confounding variables by limiting the population to a very specific procedures and population (female only). Patients were excluded by not meeting the inclusion criteria and were removed accordingly. The procedure, hysterosalpingectomy, was chosed to represent a standard operation that could be used as an example for other general surgery operations.	Only women and a typical gynecologic surgery were chosen. In order to improve external validity, a broader population set may need to be included as well as more surgical procedures.	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Murphy et al., 2015	Patients administered intraoperative methadone would have both decreased morphine requirements in the first 24 hours after cardiac surgery and improved pain scores at 12 hours after extubation when compared to patients administered with standard doses of fentanyl.	Patients administered methadone would be more satisfied with their pain management in the first 24 hours after surgery than those administered fentanyl.	Randomized, Double-blinded Cinical Trial comparing patients who receive methadone vs fentanyl intraoperatively for cardiac surgical patients.	Initially, 164 patients were enrolled in the study. 8 patients dropped out due to failure to meet inclusion criteria. Final number at analysis: 156 patients.	SETTING: Single tertiary medical center INCLUSION: Patients presenting for elective cardiac surgery with cardiopulmonary bypass procedures and anticipated extubation within 12 hours of surgery. EXCLUSION: Preoperative renal failure requiring dialysis or serum creatinine greater than 2.0; significant hepatic dysfunction, ejection fraction less than 30%, pulmonary disease necessitating home oxygen therapy, preoperative requirement for inotropic agents or intraaortic balloon pump to maintain hemodynamic stability, emergency surgery, allergy to	Type of pain management strategy: 1.Intravenous Methadone --> NOMINAL/CATEGORICLAL. 2. Intravenous Fentanyl --> NOMINAL/CATEGORICAL. DESCRIPTIVES: Age (CONTINUOUS/RATIO), Gender (NOMINAL/CATEGORICAL), Race (NOMINAL/CATEGORICAL), Height (RATIO), Weight (RATIO) ASA Score (NOMINAL/CATEGORICAL), Baseline ejection fraction (RATIO), Type of surgical procedure (NOMINAL)
	Dependent Variables	**Statistical Analysis**	**Results**	**Strengths (how promoted internal/external validity)**	**Weaknesses (biases; poorly controlled threats to internal/external validity)**	**LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)**
	Morphine requirements in mg - RATIO. Level of pain without coughing- ORDINAL. Time to first morphine rescue - RATIO. Oral pain tablets used - RATIO	Morphine requirements an pain scores were compared between the randomized groups using the Mann–Whitney U test and median differences and their 99% CIs were calculated. The joint hypothesis was assessed using one-tailed tests, with the criterion for rejection of the null hypothesis $P < 0.025$ without adjustment for multiple testing . In estimating the sample size needed to test joint primary hypothesis, the criterion for rejection of the entire joint hypothesis was 0.025. A sample size of 52 patients per group gave 80% power at the 0.025 significance level to detect a clinically significant 30% reduction in morphine consumption in patients.	Postoperative morphine requirements during the first 24 h were reduced from a median of 10 mg in the fentanyl group to 6 mg in the methadone group (median difference [99% CI], −4 [−8 to −2] mg; $P < 0.001$). Reductions in pain scores with coughing were observed during the first 24 h after extubation; the level of pain with coughing at 12 h was reduced from a median of 6 in the fentanyl group to 4 in the methadone group (−2 [−3 to −1]; $P < 0.001$). Improvements in patient-perceived quality of pain management were described in the methadone group. The incidence of opioid-related adverse events was not increased in patients administered methadone.	External validity was promoted by the study's focus on implementing the interventions based on randomization. The double blind characteristics ensures the populations and the researchers are not prone to bias with the interventions. The interventions of methadone and Fentanyl were given in doses that were equivalent to each other.	Although the dose of methadone used in the current study was both safe and effective, the optimal intraoperative dose of methadone was not determined. Assessments for pain and opioid-related complications were only performed for 72 hours. High-risk cardiac surgical patients were excluded from enrollment. Finally, the effect of methadone on long-term chronic pain is being examined in an ongoing study.	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Moro et al., 2019	Assess the quality of recovery from anesthesia in patients undergoing laparoscopic cholecystectomy (LC) under total intravenous anesthesia, who received either methadone or morphine for post-surgical analgesia	Researchers investigated differences between morphine and methadone intraoperative and during PACU recovery on recovery from anesthesia as measured by the Quality of Recovery-40 (QoR-40) questionnaire.	Prospective, randomized, double-blind control trial comparing the effects of intraoperative and postoperative administration of either morphine or methadone on measures of postoperative recovery in adult patients undergoing laparoscopic cholecystectomy	Initial N=70, split between both groups (N=35 each). Four patients from each group were lost during the study due to changes in surgical approach, administration of medications outside protocol, and refusal to answer the QoR 40. The final sample sizes were N=31 for the morphine group and N=31 for the methadone group.	Sample of convenience of patients 18-65 years old, ASA category I or II, scheduled to undergo laparoscopic surgery at a single hospital. Exclusion criteria: patient refusal, unable to communicate due to alterations in LOC, neurological/ psychiatric disease, contraindications or allergies to any drugs used in the study, substance abuse disorders, routine use of opioids, and BMI >/=40.	Patients were randomly assigned to receive either morphine or methadone, which were administered immediately after induction of anesthesia as well as during recovery in the PACU. The patients received 0.1 mg/kg of either drug immediately after induction, and 10% to 20% of that dose in the PACU depending on pain scores. Morphine or methadone group-- NOMINAL.
	Dependent Variables	**Statistical Analysis**	**Results**	**Strengths (how promoted internal/external validity)**	**Weaknesses (biases; poorly controlled threats to internal/external validity)**	**LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)**
	Primary: Quality of recovery as measured by Quality of Recovery-40 (QoR-40) questionnaire [compilation of data ranking patient psychological support, physical comfort, emotional status, physical independence, and pain to provide a global score] in properative holding area and 24 hours after surgery; NOMINAL (although subcategories in the measure may be ordinal). Secondary: Time to eye opening; RATIO. Secondary: occurrence of nausea and vomiting; NOMINAL. Secondary: Pain score; ORDINAL. Secondary: Sedation (Ramsay score), ORDINAL. Secondary: Use of supplemental analgesics (tramadol); RATIO. Secondary: PACU length of stay.	Power analysis indicated the need for 30 participants in each group; study concluded with 31 in each group. Shapiro-Wilk used to test normal distribution. Primary outcome: QoR-40 scores, analyzed with Fisher's exact test. Secondary measures analyzed using Student's t-test for independent samples. Ordinal data and continuous but not normally distributed data measured with Mann-Whitney U test. Statistical significance assessed using two-tailed test for all outcomes.	Homogeneity of samples: No differences in surgical duration, gender, physical status, or BMI. However, methadone group had a higher mean age (48) compared to morphine (42.3). Primary outcome: no significant differences were observed between study groups [no difference between morphine and methadone r/t quality of recovery]. Side effects: 3 methadone patients and six morphine patients experienced PONV ($p=0.47$). One patient in the morphine group experienced hypoxemia, but $p=0.99$. Pain: No statistically significan pain scores. Opioid consumption in the PACU was higher in the morphine group ($p<0.02$). Sedation: methadone patients had lower sedation scores than the morphine group ($p<0.01$). Time to PACU discharge: No statistically significant difference. N/V on ward after PACU: no statistically significant differences. No statistically significant differences between postoperative pain at rest and with coughing, 2 hours after surgery, highest pain score on the ward, and tramadol consumption on the ward.	Prospective, randomized, double-blind control trial. Detail in the study, including specific intraoperative techniques and medications used, allow for increased understanding of internal and external validity.	Use of Fisher's exact test with groups of N>30 (31). Statistically significant difference in age between groups (see results). Specific patient population in terms of surgical procedure may not allow results to be externalized to other surgical populations (orthopedics, non-laparoscopic procedures, etc.). Specific intraoperative medications (including remifentanil) and procedures could influence study results. Parameters of the QoF-40 allows for multiple confounding variables, including the patient's emotional state, room cleanliness, ward noise levels, and opinions of medical providers, among others. Morphine and methadone compared using a 1:1 ratio, which may not reflect normal dosing of these medications. Interventions applied within the setting of multimodal analgesia plan, which could have obscured results of methadone or morphine as	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Robinson et al., 2020	To determine if there is an association of intraoperative methadone use and total perioperative opioid exposure in patients undergoing congenital heart surgeries	Determine if intraoperative methadone was associated with a difference in clinical outcomes, incidence of adverse events, and a dose-dependent reduction in opioid use.	Retrospective, case-match cohort study. Thirty seven patients undergoing congenital heart surgeries receiving intraoperative methadone were matched to another thirty seven patients based on age and procedure who did not receive intraoperative methadone.	66 patients were screened for eligbility assessment. 25 patients were excluded due to delayed sternal closure, opioids within 24 hours, receiving a postoperative nerve block, having a delayed sternal closure and opioids within 24 hours. 41 patients were then assesssed for matching. 4 patients were unmatched due to myectomy, Bi-direction Glenn, Bi-VAD placment, and Vascular Ring repair. 37 patients were then able to be matched to a control cohort consisting of 37 patients as well. Total patients of testing: 74 patients.	SETTING: Single center quaternary care hospital CONVIENCE SAMPLE. INCLUSION: Patients were categorized according to age and were identified using a pharamceutical database of all patients who received intraoperative methadone during a CHD surtical repair requiring a sternotomy between November 1, 2017 and July 30, 2018. EXCLUSION: If they received scheduled opioids 24 hours preoperatively, had delayed sternal closure postoperatively, require additional procedures within 24 hours postoperatively, recived postoperative regional nerve blocks, or were unable to be matched to a patient who did not recive intraoperatve methadone.	Administration of methadone vs not receiving methadone: 1. Methadone administration--> NOMINAL/CATEGORICAL. 2. No methadone administration:--> NOMINAL/CATEGORICAL. DESCRIPTIVES: Gender (NOMINAL/CATEGORICAL, WEIGHT (CONTINUOUS/RATIO), Age (CONTINUOUS/RATIO), Procedure length (RATIO), Cardiopulmonary bypass length (RATIO), Use of cardiopulmonary bypass(NOMINAL/CATEGORICAL)
	Dependent Variables	**Statistical Analysis**	**Results**	**Strengths (how promoted internal/external validity)**	**Weaknesses (biases; poorly controlled threats to internal/external validity)**	**LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)**
	Opioid medication usage in First 24 hours (RATIO), second 24 hours (RATIO), third 24 hours (RATIO). Medication usage of Benzodiazepine or Dexmedetomidine (RATIO)	All data were evaluated using descriptive statistics to determine central tendencies and normality. Continuous variables were reported either as mean +/- standard deviation or median with interquartile range (IQR). Categorical variables were reported as frequency and percentile. Depending upon the type and normality of data, either a two-tailed unpaired Student t test, two-tailed Mann-Whitney U test, x2 test, or Fisher exact test were used to determine difference. An alpha value of 0.05 was used to define significance. SPSS version 24 was used for all statistical calculations.	The methadone cohort required less opioids intraoperatively, in the first 12 hours postoperatively, and during the first 36 hours postoperatively (2.51 v 4.39 mg ME/kg, $p < 0.001$; 0.43 v 1.28 mg ME/kg, $p = 0.001$; and 0.83 v 1.91 mg ME/kg, $p < 0.001$) compared with the matched control cohort. There were no differences in clinical outcomes or adverse events. A dose-dependent reduction in opioid consumption in high- versus low-dose groups also was not observed.	Patients that received the intervention of perioperative methadone administration were matched with a patient that went through the same procedure with the same demographics to ensure the most accurate results. Pain medications were converted to morphine equilavent units to allow comparable data. Statistical analysis were performed to determine the statistical signficance of demographic values and morphine equivalent units for each opioid used postoperatively.	Intraoperative and postoperative opioids was not standardized in the facility. Exact conversions of opioids to morphine equivalents are not well established in literature. Potential for selection bias as to which patients received methadone, and specifically higher doses of methadone. Small sample size for study.	IIB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Ng et al., 2017	The purpose of this study is to determine if a multimodal analgesia protocol (MAP) reduces opioid-related adverse events (ORAE) and provides effective pain releif for patients after Laparoscopic sleeve gastrectomy (LSG).	Does the introduction of MAP reduce adverse opioid events and provide effective pain releif for patients undergoing LSG?	Retrospective cohort study. Collected information of patients who underwent LSG from May 2010 to November 2015. Compared patients before and after the implementation.	A total of 158 patients were included in our study. Ninety patients underwent LSG before implementation of the MAP (denoted as pre-MAP). Conversely, 68 patients underwent LSG after implementation of the MAP (denoted as post-MAP).	Setting: This study was conducted at University Hospital, Singapore. EXCLUSION: Patients who had severe post-operative complications such as gastric staple line leak were excluded from the study due to prolonged intensive care unit stay. Patients who were on long-term opioid analgesia for chronic pain or with hypersensitivity to acetaminophen. INCLUSION: Patients who had a stand-alone LSG performed.	MAP consists of mandatory pre-operative etoricoxib (NOMINAL), intra-operative acetaminophen (NOMINAL), and postoperative acetaminophen with optional post-operative tramadol (NOMINAL). MEASURMENT: NOMINAL
	Dependent Variables	**Statistical Analysis**	**Results**	**Strengths (how promoted internal/external validity)**	**Weaknesses (biases; poorly controlled threats to internal/external validity)**	**LEVEL OF EVIDENCE - using JHNEBP tool (Strength and Quality)**
	ORAE: (INTERVAL), Post-op pain scores (INTERVAL), Drug cost and lenth of stay (INTERVAL), opioid requirements (INTERVAL), and anti emetic requirements (INTERVAL)	Dichotomous variables were expressed in proportions and compared using the chi-square test, while continuous variables were expressed in mean and compared using the independent t test. Multivariate analysis was performed using logistic regression to account for confounding factors between the two groups.	One-third of patients in the pre-MAP group experienced postoperative ORAE, as compared to 8.8% in the post-MAP group ($p < 0.001$). Post-operative pain scores were comparable at 1, 6, and 48 h after LSG between the two groups. However, there was a significant reduction in pain scores 12 and 24 h after LSG in the post-MAP group. The cost of analgesia was significantly increased after the implementation of the MAP from 42.9 dollars to 50.5 dollars ($p = 0.049$). The average dose of opioids per patient administered intraoperatively was significantly reduced from 58.2 to 43.6 mg of oral morphine equivalent doses after implementation of the MAP ($p < 0.001$).There were no differences in the use of metoclopramide, ondansetron, or droperidol intra-operatively between both groups.	Performed multivariate analysis to account for the baseline differences in both groups.	Study was conducted in a retrospective fashion, which meant exposure to confounding factors and biases. The control and treatment groups were also derived from consecutive patients who underwent LSG from 2010 to 2014, with the control group defined as patients treated before the MAP was implemented, and the treatment group defined as patients treated after. As a result, improvement in surgical techniques across the years could have led to better patient outcomes in the treatment group.	IIIC

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
COCHRANE. Brinck 2018.	Meta-analysis of 130 studies to evaluate ketamine as a perioperative analgesic in adult patients	Efficacy and safety of perioperative intravenous ketamine in adult patients when used for the treatment or prevention of acute pain following general anesthesia compared to placebo or other analgesic	Meta-analysis	130 studies, 8341 participants	Patients receiving general anesthetics. Types of surgery included ear, nose or throat surgery, wisdom tooth extraction, thoracotomy, lumbar fusion surgery, microdiscectomy, hip joint replacement surgery, knee joint replacement surgery, anterior cruciate ligament repair, knee arthroscopy, mastectomy, haemorrhoidectomy, abdominal surgery, radical prostatectomy, thyroid surgery, elective caesarean section, and laparoscopic surgery.	The primary independent variable was the administration of intravenous ketamine intraoperatively or postoperatively. Doses were administered either intraoperatively or postoperatively. Subdissociative doses were used (equal to or less than 1mg/kg for a bolus or equal to or less than 1.2mg/kg/hr for an infusion). INTERVAL.

Dependent Variables	Statistical Analysis	Results	Strengths (how promoted internal/external validity)	Weaknesses (biases; poorly controlled threats to internal/external validity)	LEVEL OF EVIDENCE – using JHNEBP tool (Strength and Quality)
Primary outcomes were opioid consumption and pain intensity at rest and during movement at 24 and 48 hours postoperatively (INTERVAL). Secondary outcomes were time to first analgesic request, assessment of postoperative hyperalgesia, central nervous system (CNS) adverse effects, and postoperative nausea and vomiting. (RATIO, ORDINAL, NOMINAL)	Mean Differences (MDs).We calculated risk ratios (RR) We used random-effects models for both continuous and dichotomous outcomes.We used numbers needed to treat for an additional beneficial outcome (NNTB) and harmful outcome (NNTH), and pooled percentages as absolute measures of benefit or harm. We used 95% confidence intervals (CI) to express the uncertainty in each result.	ALL STUDIES, PRIMARY OUTCOMES: OPIOID CONSUMPTION: Morphine equivalents (mg) at 0-24 hours: −7.6 (95% CI −8.9 to −6.4). Morphine equivalents (mg) at 0-48 hours: −12.6 (95% CI −15.1 to −10.2). PAIN (VAS): At rest 24 hours: −5 (95% CI −6.6 to −3.6). Pain during movement 24 hours: −6 (95% CI −11 to −0.5). Pain at rest 48 hours: −5 (95% CI −6.7 to −3.4). Pain during movement 48 hours: −6 (95% CI −10 to −1.3). ALL STUDIES, SECONDARY OUTCOMES: TIME TO FIRST ANALGESIC REQUEST (ADMINISTERED PRE-/INTRA-OP): ketamine group 54 minutes later than control (95% CI 37 to 71). CNS ADVERSE EVENTS: CNS adverse events in 187 of 3614 (5%), participants receiving ketamine compared to 122 of 2924 (4%), participants receiving control treatment. RR 1.17 (95% CI 0.95 to 1.43). PONV: Ketamine treatment reduced the incidence of PONV (RR 0.88, 95% CI 0.81 to 0.96). AUTHORS' RECOMMENDATION FOR CLINICIANS: Perioperative intravenous ketamine is beneficial for individuals undergoing thoracic, major orthopaedic, or major abdominal surgery. It may be more	Meta-analysis performed exhaustive survey of available RCTs on the topic	Meta-analysis unable to control for limitations in individual studies; unable to account for a wide variety of confounding variables, including timing of administration, dose of administration, type of surgery, setting of administration, sample size, and other unseen/ unmeasured phenomena.	IB

1st Author Name (Publication Yr)	Study Purpose/Aims	Research Questions/Hypotheses	Study Design	Total Sample Size	Sampling Plan	Independent Variables
Xu et al., 2019	Meta-analysis of 10 studies to analyze the efficacy and safety of intravenous, intraarticular, and epidural routes of ketamine administration in adult knee and hip arthroscopy patients	The purpose of this meta-analysis was to evaluate the therapeutic benefits of ketamine in different administration routes for pain control after total knee or hip arthroplasty, as well as to elucidate its side effects. It was hypothesized that ketamine acted overall as an effective analgesic after total knee or hip arthroplasty without increasing the incidence of adverse effects.	Meta-analysis	10 studies, including a total of 587 patients	Studies incorporating: 1) patients undergoing total knee or hip arthroplasty surgery; 2) administration of ketamine for postoperative pain relief; 3) administration of saline in the control group and 4) randomized control trials.	The primary independent variable was the administration of ketamine through intravenous, intraarticular, or epidural routes. INTERVAL

Dependent Variables	Statistical Analysis	Results	Strengths (how promoted internal/external validity)	Weaknesses (biases; poorly controlled threats to internal/external validity)	LEVEL OF EVIDENCE – using JHNEBP tool (Strength and Quality)
Primary outcomes were pain intensity and morphine consumption. Pain was evaluated during the first 0-8 hours and 8-24 hours after surgery. Morphine consumption within the fisrt 0-24 and 0-48 hours postoperatively were compared between ketamine and placebo groups (INTERVAL). Secondary outcomes were nausea and vomiting and the occurrence of psychomimetic effects. (RATIO, ORDINAL, NOMINAL)	Weighted mean differences (WMDs) and Risk Ratios (RRs) were calculated to determine effects.	INTRAVENOUS KETAMINE: Compared with placebo, intravenous ketamine was effective during the first 8 hours after surgery in reducing pain scores (WMD -1.21, 95% CI -1.45 to -0.98). Cumulative morphine consumption in the IV ketamine group was significantly lower than that in the control group during both the 0-24 hour (WMD -17.76, 95% CI -31.25 to -4.27) and 0-48 hour (-21.79, 95% CI -25.46 to -18.11) postoperative periods.	Meta-analysis of available randomized control trials of the study question. Incorporated 587 participants across 10 studies, although seven were used to evaluate intravenous morphine and six were used to evaluate adverse effect	The authors identified significant heterogeneity in some of the results across different studies. The small number of available studies for this specific patient population and intervention limited the validity of some statistical methodology. Not all of the studies incorporated in the meta-analysis relate specifically to intravenous ketamine use, which is the intervention of interest for this project.	IIaB

Figure 3: John Hopkins Evidence-based Practice Model

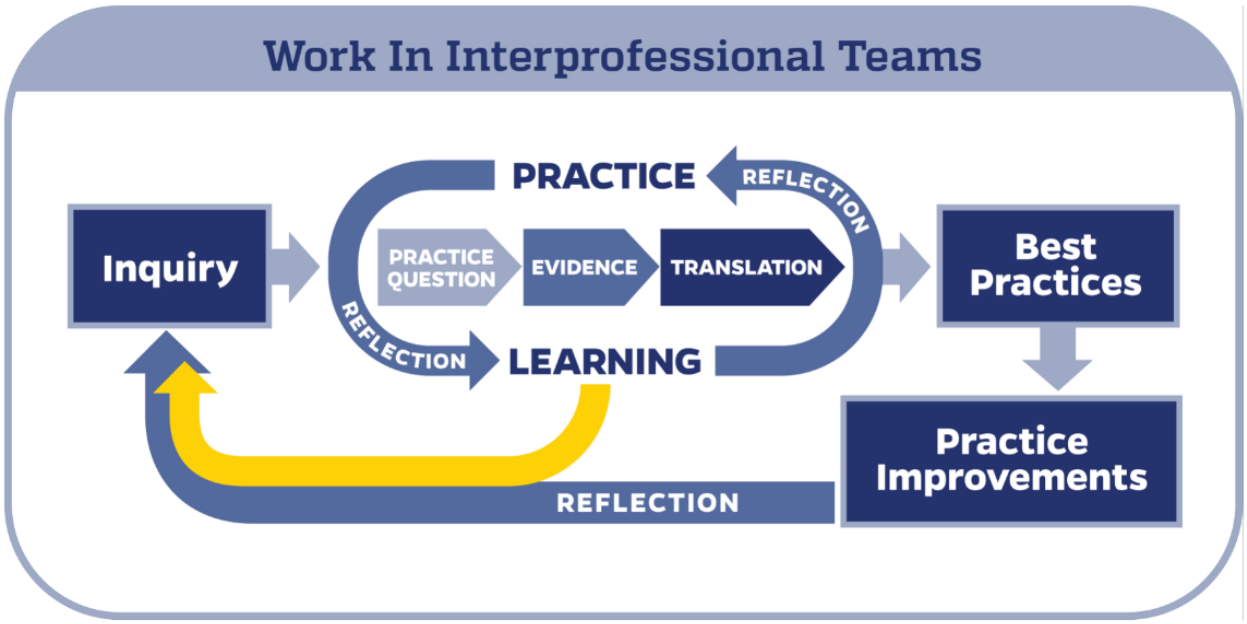


Figure 4: Project Timeline

Project Year 1 (2020)												
Activity/Month	**JAN**	**FEB**	**MAR**	**APR**	**MAY**	**JUN**	**JUL**	**AUG**	**SEP**	**OCT**	**NOV**	**DEC**
USUHS VPR Submission and Approval	X	X	X	X	X	X	X	X	X	X	X	
Site IRB Submission and Approval												X
Project Planning -Task 1: Stakeholder engagement meetings -Task 2: -Task 3:												
Project Implementation/Data Collection -Task 1: -Task 2: -Task 3:												
Data Analysis -Task 1: -Task 2: -Task 3:												
Dissemination -Task 1: -Task 2:												

Project Year 2 (2021)												
Activity/Month	**JAN**	**FEB**	**MAR**	**APR**	**MAY**	**JUN**	**JUL**	**AUG**	**SEP**	**OCT**	**NOV**	**DEC**
USUHS VPR Submission and Approval												
Site IRB Submission and Approval	X	X										
Project Planning -Task 1: Stakeholder engagement meetings -Task 2: -Task 3:			X									
Project Implementation/Data Collection				X	X	X						
-Task 1: -Task 2: -Task 3:												
Data Analysis -Task 1: -Task 2: -Task 3:							X	X	X			
Dissemination -Task 1: -Task 2:										X	X	X

Project Year 3 (2022)												
Activity/Month	**JAN**	**FEB**	**MAR**	**APR**	**MAY**	**JUN**	**JUL**	**AUG**	**SEP**	**OCT**	**NOV**	**DEC**
USUHS VPR Submission and Approval												
Site IRB Submission and Approval												
Project Planning												
Project Implementation/Data Collection												
Data Analysis												
Dissemination	X	X	X									

Figure 5: Data Analysis Plan Table

		Variable Name	Variable Description and type of measure	Data Source	Possible Range of Values	Level of Measurement	Time Frame for Collection	Statistical Test	Decision Rule
Population or **Event**	**IV** (in book referred to as descriptive variable)	Opioid sparing PACU order set	Description: Implementation of revised opioid-sparing PACU order set. PACU nurses are educated on the new order sets; PACU nurses utilizing the order set. Type: Process Measure	Essentris/ Electronic Health Record	0 = Prior to implementation of revised order set 1 = After implementation of revised order set	Nominal	April-June 2021	none	N/A
	DV 1 (in book referred to as outcome variable)	Quantity of total dose of opioids given	Description: Mean number the total dose of opioids given Type: Outcome Measure	Essentris/ Electronic Health Record	0+	Ratio	April-June 2021	Paired t-test, Wilcoxon signed-rank if not normal distribution	Decrease in total opioid PACU use by 20%.
	DV 2 (in book referred to as outcome variable)	PACU pain score at time intervals at 15, 30, and 60 minutes after arrival in the PACU	Description: Pain scores 0-10 recorded by PACU RN staff at select time intervals Type: Outcome measure	Essentris/ Electronic Health Record	1-10	Ordinal	April-June 2021	Wilcoxon signed-rank test	No change or decrease in PACU discharge pain scores

Figure 6: Business Case Analysis

BUSINESS CASE with VALUE BASED CARE ASSESSMENT
Proposed Title for Project/Initiative/Opportunity to Improve *Proposed Title*
Administration of low-dose ketamine by PACU nurses to improve postoperative pain control and opioid-associated risk
Opportunity Statement *(Description of proposed project/initiative/opportunity to improve)* *Opportunity statement*
FBCH's current PACU recovery protocols rely heavily on opioids for the control of postoperative pain with few practical alternatives. FBCH can utilize existing evidence to revise its opioid practices and to offer the same quality of postoperative care as other leading facilities. Opportunities to improve readiness, health, care, and financial stewardship using this opportunity are described below.
Business Opportunity/Objectives *(Prioritize listing – macro and micro objectives)* *Business Opportunity*
Macro: 1. Empower and enable PACU RNs to effectively employ opioid-sparing techniques that are consistent with Enhanced Recovery After Surgery protocols utilized across perioperative health care specialties at FBCH. 2. Enhance postoperative recovery, improve the patient's surgical experience, ensure patient safety, conserve financial resources, and promote the use of leading evidence-based surgical recovery practices. Micro: 1. Revise post anesthesia care unit order to include ketamine as an option for post-operative pain control. 2. Create an educational program for PACU nurses regarding the benefits of opioid-sparing techniques and the use, administration, and safety profile of Ketamine. This educational offering will include combined oral and visual presentations as well as printed handouts. 3. Support, follow-up with PACU nurses, and answer questions regarding low-dose ketamine administration.
Potential Impact of the Initiative/Project *(Identify outcome metrics & benchmarks/and how objectives align with Quadruple Aim, Value Based Care, and HRO goals)* *Potential Impact*
1. Readiness: Minimize opioid use for active duty military undergoing surgery. The proposed order set, which includes postoperative low-dose ketamine as an option, may reduce the negative effects of excessive opioid use, including predisposition to opioid dependence, prolonged recovery times, and increased cost. These sequelae negatively impact the health of the force, prolong a servicemember's return to duty, and cause increased costs for FBCH. 2. Better Health: By continuing the opioid-sparing protocols throughout the perioperative period, this project will promote better health by encouraging healthy behaviors of pain management that are not fully dependent on opioids to control pain. By adding ketamine as an analgesic adjunct, we will increase the ability to treat postsurgical pain while decreasing opioid use. Our patients will experience less pain and faster recovery times while minimizing the likelihood of opioid dependence. 3. Better Care: Adding ketamine to the PACU order set fills in a gap for a non-opioid intervention for moderate pain and improves multimodal management of postoperative pain in FBCH. Patients will experience pain control that is superior or equal to the current model and in-step with other leading facilities that have implemented this change in practice. This addition to the PACU order set expands the non-opioid options available, complementing existing non-opioid analgesics and reducing the occurrence of opioid-related sequelae. However, opioids may be used to safely supplement other analgesics for higher levels of pain that are not controlled by ketamine or other interventions. This revised model allows optimal pain control while reducing opioid administration to improve the patient's experience. Lastly, in the event of national opioid shortages, the addition of ketamine helps to diversify the availability of suitable analgesics that may be used, allowing opioids to be saved for patients who truly need them in those circumstances.

4. Lower cost: By reducing the use of opioids used in the postoperative period, patients are expected to have less sedation, respiratory depression, and postoperative nausea/ vomiting, which all require additional time, overhead, and medications to address. Avoiding these known consequences of opioid administration will translate to cost reduction. Furthermore, ketamine itself is inexpensive. FBCH currently buys single-use vials of ketamine for only $2.27 each. For less than the cost of a 16oz. drip coffee served from the Starbucks in FBCH ($2.45), patients can have an improvement in their postoperative experience. Furthermore, while rates are low, perioperative opioid use has been associated with initial opioid exposure and the development of opioid exposure (Trasolini et al., 2017). Mitigating the patient's exposure to opioids will also mitigate their risks for developing dependence, which is a costly and lengthy process to treat effectively.

5. Professional Agency: Ketamine availability and its associated training will empower PACU nurses by providing them with an additional tool to employ in their practice, improving their ability to affect their patients' care and improving their job satisfaction.

Alternatives (courses of action) chosen for Analysis *Alternatives*

1. Educate PACU nurses on opioid-sparing techniques without expanding access to non-opioid pain medications

2. Educate PACU nurses on opioid-sparing techniques and employ the use of methadone to treat pain

3. *"Status Quo"*: Retain the current PACU recovery order set without educating PACU nurses and without providing alternative non-opioid pain medications to treat postoperative pain

Analysis of Alternatives *Alternatives*

Alternative 1:	Educate PACU nurses on opioid-sparing techniques without expanding access to non-opioid pain medications

Pros	**Cons**
1. Provides education to PACU RNs on the importance of employing opioid-sparing techniques considering the current opioid crisis and the known risks of perioperative opioid administration. 2. PACU nurses may incorporate this education and limit their administration of opioids (without an alternative medication to administer).	1. Provides RNs with the training but not the support and resources they need to employ the opioid-sparing techniques. No new non-opioid medications will be available to them.

Alternative 2:	Educate PACU nurses on opioid-sparing techniques and employ the use of methadone to treat pain

Pros	**Cons**
1. Methadone is an old drug that has come into favor again recently related to its ability to control pain 2. Methadone is inexpensive. 3. Methadone acts on opioid and non-opioid receptors and helps treat pain through different pathways (multimodal analgesia). 4. Provides ERAS/ opioid-sparing education	1. Evidence in the literature supports the use of methadone in the perioperative period, but literature describing its use specifically for postoperative pain specifically is sparse. Most of the literature focuses on the use of intraoperative and not postoperative methadone. 2. While it does not have the potency of other opioids, methadone does act primarily on opioid receptors 3. A patient's response to methadone may depend heavily on their genetics; it may not be effective in all patients.

Alternative 3:	*"Status Quo"*: Retain the current PACU recovery order set without educating PACU nurses and without providing alternative non-opioid pain medications to treat postoperative pain

Pros	**Cons**
1. Existing protocols are simple and easy to maintain. 2. The opioids available in the current PACU order set are inexpensive.	1. The existing PACU orders promote the use of opioids, including in situations that may not be appropriate when other alternatives are supported by research and are already available in the hospital. 2. Keeping the PACU orders as they are may be seen as complacent in the setting of the opioid crisis and adverse to the characteristics of a High Reliability Organization (Reluctance to Simplify; Commitment to Resilience). 3. The United States has experienced opioid shortages in recent years, and heavy reliance on these medications during these shortages reduces capability.

Assumptions *Assumptions*

1. Providers will favorably view and utilize an order set with Ketamine.
2. PACU RNs will feel comfortable administering ketamine following a robust education program highlighting its effects within the body.
3. Pain scores will be equivalent or superior after the option of low-dose ketamine is added to treat post-operative pain.
4. Patient satisfaction is higher in institutions with evidence-based pain management strategies.
5. Pharmacy staff will make the concentration of Ketamine in appropriate doses for the PACU RN staff to give.

Recommendation and Rationale *Make a choice*

Recommendation *Make a choice*

Educate PACU nurses on the benefits for our patients of using opioid-sparing techniques, empower their practice, and add ketamine to the current PACU order set as an option for providers to order.

Rationale *Make a choice*

Low-dose ketamine gives an alternative to the current quick use of opioids, it is short acting, and proven to be effective against pain.

Value Based Care - Investment Required by the Organization and the Associated "VALUE" or $ GAINED. *Below represents two ways to present this information. Depending on the initiative, you may need to alter this outline. Please adjust as appropriate and if need be ... do not hesitate to create this portion on a separate document and then attach to this assignment. Outline the Value Based Care*

Value = Quality + Service
Cost

I. *Quality projected based on: Reduced opioid use in the post-operative period, the potential for reduced legal liability, PACU nurse satisfaction, and improved PACU recovery times.*

Patient Safety Related Benefit - *Opioid-Sparing Order Set decreases chance of adverse effects of opioid administration. Cost of Ketamine added to current PACU order set.*	
Financial Benefit- *FBCH already routinely stocks ketamine. The cost*	

of adding ketamine to the PACU order set will not cost the facility anything. *Operational Readiness Benefit-* *Active Duty Military healthcare providers will gain experience administering ketamine, increasing operational readiness. Ketamine is widely used in deployed settings and austere environments. Servicemembers undergoing surgery will experience improved postsurgical pain control.*	
Total	

II. Service projected based on: (suggestions-examples in blue font)

Patient Satisfaction/Benefit - *Patients will have improved pain control. They will have different options for pain control if they are unable to receive opioids due to clinical conditions.* *Provider Satisfaction/Benefit -* *Providers will be able to enact another option for patients that require decreased amounts of opioid administration.*	
Total	

III. Cost projected based on: (suggestions-examples in blue font)

Program Design and Development- *Designed and implemented by service members who are already on active duty and performing other roles in their full capacity.*	
Project Management	

Marketing- *No external marketing required. Project team will create pamphlets for PACU nurses and staff, which can be produced by the Public Affairs Office once approved.*	
Total	

PROJECTED VALUE :

Decreased risk of adverse opioid-related events, protecting the health of patients and reducing the likelihood FBCH would be implicated in torts or other legal proceedings related to opioid-related negative outcomes.	***Improved pain control and satisfaction for patients, including servicemembers undergoing surgery***
Ketamine is already available in FBCH for negligible cost	***Increased nursing capability; increased operational readiness for active duty RNs administering ketamine***
Implemented by student labor, with no additional cost to the hospital	***Other than ketamine itself, the cost to print educational materials are expected to be limited. The Public Affairs Office already has a budget for printing these materials.***

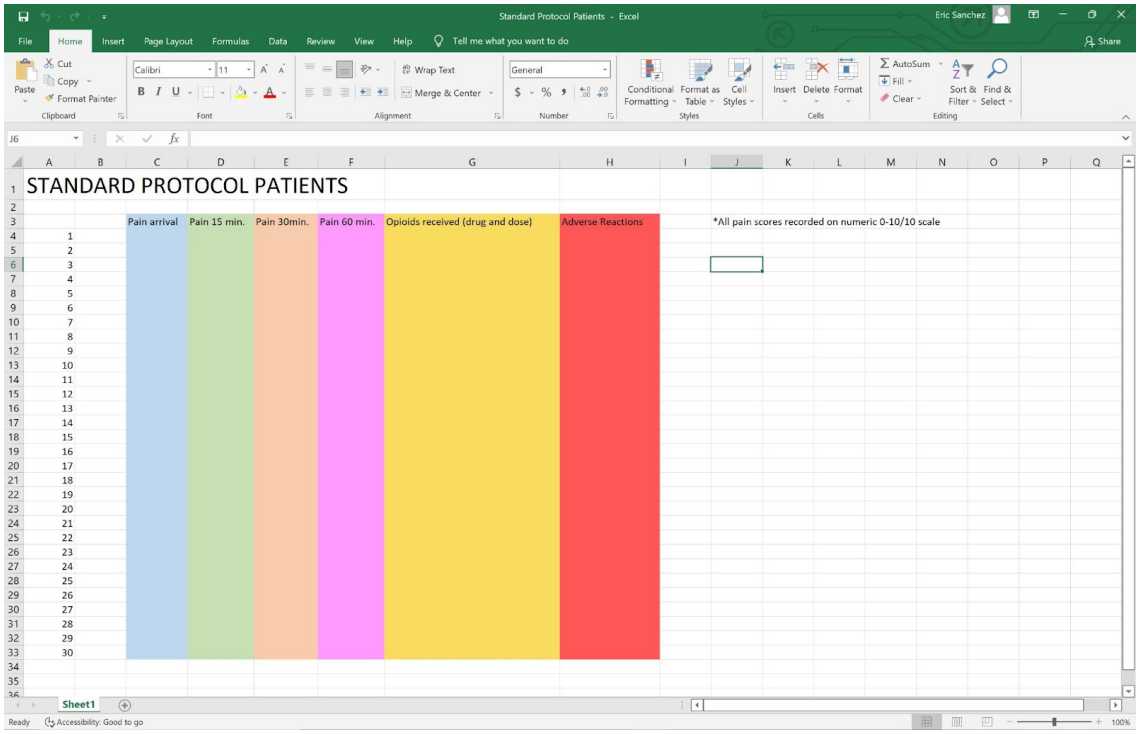
Risks and Mitigation Plan *Consider the risks:*	
Risks	**Plan**
1.Ketamine-induce adverse event	1. Training RNs to rapidly and reliably recognize, address, and report adverse events as they do with other medications.
2.Patient dissatisfaction	2. If ketamine is not tolerable to patients, investigate if it is related to pain or other factors.
3.PACU RN dissatisfaction	3. Hold open-forum sensing sessions to solicit RN feedback and evaluate ways to mitigate negative events.
4. Intervention results in unforeseen safety concerns or fails to improve outcomes	4. Revert to the original order set without ketamine.

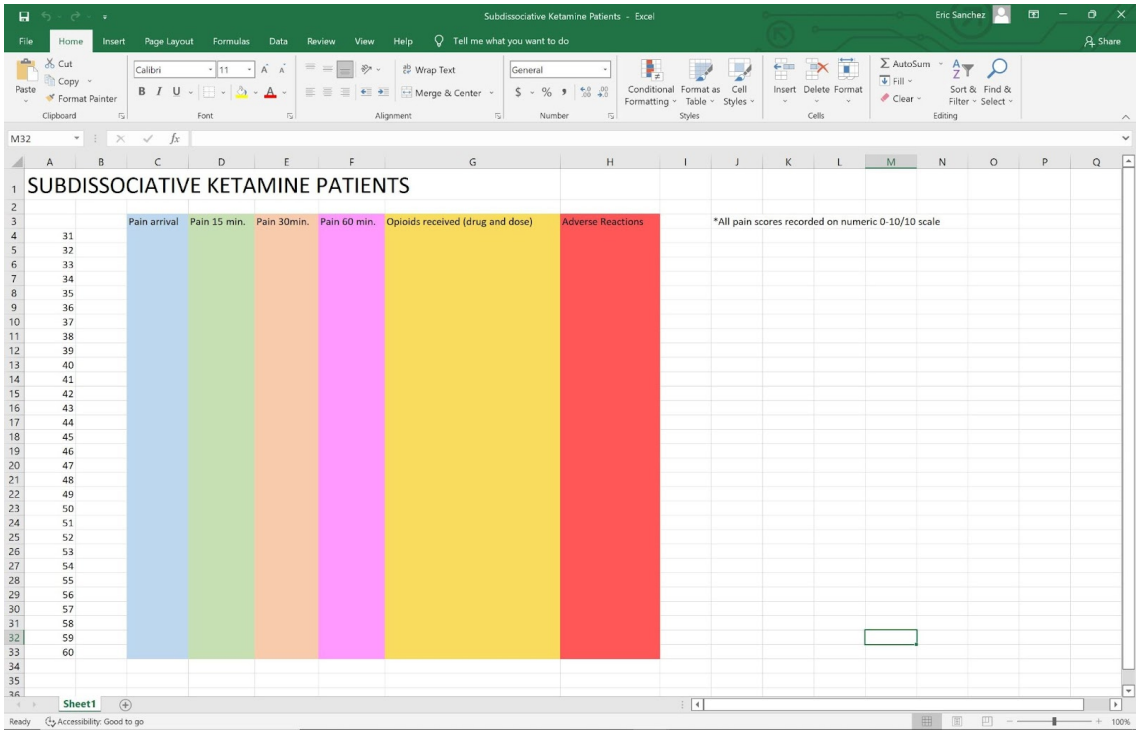
Implementation Plan *Implementation plan*			
Phase 1:	Gather Evidence and Research regarding safe use of non-dissociative low doses of Ketamine for acute pain.		
Milestone Description:	Search research databases to find relevant articles and evidence to support using alternatives that ketamine is a safe drug to use in the PACU with the correct dose and administration technique.		
Deliverables		Due Date	Accountable Person
Gather, sort, and critique high level evidence of at least 10 systematic reviews, meta-analyses, appropriate, well-designed studies, and expert opinions		[Completed, with ongoing revisions as new evidence becomes available until project completion]	Project Lead/ Delegate
Resources Needed			
Access to research databases such as Pubmed, Cinahl, and Web of Science. Utilize assistance from Learning Research Center staff to assist in making concise data searches.			
Expected Level of Benefit			
This will be the foundation for our evidence-based interventions in the PACU.			
Phase 2:	Verify that subanesthetic ketamine is appropriate to use in Virginia		
Milestone Description:	Ketamine has traditionally been used as a general anesthetic and as a sedative for procedural sedation. RNs may not give ketamine independently in these situations. PACU RNs may perceive that they may not administer ketamine in subanesthetic doses for pain control because they may not administer the drug in the significantly higher (approximately 3-10 times higher) doses associated with procedural sedation and general anesthesia.		
Deliverables		Due Dates	Accountable Person
Confirmation that subanesthetic doses of ketamine may be independently administered by RNs in Virginia		30OCT20	Principal POC
Resources Needed			
POC and time required to contact the Virginia Board of Nursing.			
Expected Level of Benefit			
PACU RNs will perceive subanesthetic ketamine administration as a safe and legal intervention in accordance with the scope of practice for RNs in Virginia.			
Phase 3:	Develop an appropriate training program for PACU RNs to use ketamine safely and confidently		
Milestone Description:	Develop set dates, times, and training environment for PACU staff to rotate through training without impacting patient care. New PACU order set must be written into the Standardized Operation Protocols (SOPs) with executive leadership's support for adoption of use.		
Deliverables		Due Dates	Accountable Person
Measurable goals: Produce written guidelines for the use of Ketamine and changes to PACU order set.		2 weeks after leadership approval to proceed.	Principal POC

30 min to 1 hour class for staff education. RNs will score satisfactory on post-test exhibiting understanding of Ketamine administration.		
Resources Needed		
Time for Principle POC/Investigator and RN PACU staff. Informative pamphlets and room to conduct staff education. Pre-test and Post to measure PACU staff understanding of Ketamine use and pharmacology.		
Expected Level of Benefit		
PACU staff will have a better understanding of ketamine as an adjunct to multimodal pain relief.		
Phase 4:	Conduct training to the PACU RN Staff	
Milestone Description:	To implement the new PACU opioid-sparing order set department wide, education must be provided to all staff that are expected to comply with change in policy.	
Deliverables	Due Dates	Accountable Person
Measurable Goal: 100% personnel exposure, including LPNs, Medics, Corpsmen, and CNAs who may interact with patients who have received ketamine	2 weeks after pilot training is complete	Principal POC Pilot Trainers/ Departmental Leadership
Resources Needed		
Time for all personnel to attend training (30 min - 1 hour). Handouts, posters, and contact information for questions and concerns. Utilization of the hospital's education and training department. Mitigate risks by engaging Anesthesia and PACU leadership to promote this addition as a positive change.		
Expected Level of Benefit		
Anesthesia and PACU adopts and complies with the new opioid-sparing PACU order set		
Phase 5:	Program evaluation	
Milestone Description:	Track results on the PACU length of stay and the amounts of opioids used in the PACU. Measurable goal: Decrease in the amount of opioids in the PACU at a 6 month evaluation. PACU pain scores. Surveys on PACU nurse satisfaction of new opioid-sparing protocol.	
Deliverables	Due Dates	Accountable Person
Status reports to leadership at 3 months and at 6 months on amounts of opioids, pain scores, and nurse satisfaction.	Ongoing, but report to leadership at 6 months.	Principal POC
Resources Needed		
Access to patient information and medical records; approval from institutional leadership to collect data. Mitigate risks by careful data collection, reassessing training to PACU staff, and monitoring staff for compliance		
Expected Level of Benefit		
The evaluation from the results gained will determine whether or not the new opioid-sparing PACU order set is an improvement to the status quo		

NOTE: Modified from Harvard Business Review Press. (2011). *Pocket mentor: Developing a business case.* Boston: Author (pp 82-85).

Figure 7: Data Collection Templates





Appendix G: Daniel K. Inouye Graduate School of Nursing
DNP Project Completion Verification Form

DOCTOR OF NURSING PRACTICE PROJECT
Completion Verification Form

The DNP Project titled: Opioid-Sparing Analgesia in the Post-Anesthesia Care Unit: Subdissociative Ketamine Administration

was completed at Fort Belvoir Community Hospital by the following student(s):

(Student Name)	*(Digital Signature)*
MAJ Andre Brown	BROWN.ANDRE.DUCHAIN.1168108920 Digitally signed by BROWN.ANDRE.DUCHAIN.1168108920 Date: 2022.04.29 14:23:01 -04'00'
CPT (P) Alex Jung	JUNG.ALEX.MATTHEW.1100421530 Digitally signed by JUNG.ALEX.MATTHEW.1100421530 Date: 2022.04.29 14:17:56 -04'00'
LCDR Eric Sanchez	SANCHEZ.ERIC.ALFORQUE.1165634680 Digitally signed by SANCHEZ.ERIC.ALFORQUE.1165634680 Date: 2022.04.29 10:56:03 -04'00'

The DNP Practice Project Team verifies that the following components of the DNP project, accomplished by the above students, is of sufficient rigor and demonstrates doctoral level scholarship to meet the requirements for USUHS GSN graduation:

- Presentation of DNP project to the leadership/stakeholders at the Phase II Site,
- Abstract/Impact Statement (*Appendix F*), and
- DNP Project written report (*Appendix E*).

Verified by:

(type name)		*(Digital Signature)*	
Sandra Bruner		BRUNER.SANDRA.SUE.1102080803 Digitally signed by BRUNER.SANDRA.SUE.1102080803 Date: 2022.05.06 11:00:53 -04'00'	Senior Mentor
			Team Mentor
			Team Mentor
MAJ Keith Lathrop	(for)	BRUNER.SANDRA.SUE.1102080803 Digitally signed by BRUNER.SANDRA.SUE.1102080803 Date: 2022.05.06 13:24:48 -04'00'	Team Mentor & Phase II Site Director

For RNA Students only *- add the following additional signature for final verification of project completion:*

LCDR Kenneth Barber	BARBER.KENNETH.DOUGLAS.1177263644 Digitally signed by BARBER.KENNETH.DOUGLAS.1177263644 Date: 2022.05.09 08:58:48 -04'00'
RNA Project Director *(type name)*	*(Digital Signature)*

Form Version: 4 December 2020

Appendix G: DNP Project Clinical Question and Team Mentor Agreement Form

Appendix G: Daniel K. Inouye Graduate School of Nursing
DNP Project Team Mentor (Committee Membership) Agreement Form

DOCTOR OF NURSING PRACTICE PROJECT
DNP Project Clinical Question and Team Mentor (Committee Membership) Agreement Form

Graduation Year: 2022 **Phase 2 Site(s) Name:** Fort Belvoir Community Hospital

Name(s) of DNP Project Student Team:

1.	Andre Brown	AGCNS ☐ FNP ☐ PMHNP ☐ RNA ■ WHNP ☐
2.	Alex M. Jung	AGCNS ☐ FNP ☐ PMHNP ☐ RNA ■ WHNP ☐
3.	Eric A. Sanchez	AGCNS ☐ FNP ☐ PMHNP ☐ RNA ■ WHNP ☐
4.		AGCNS ☐ FNP ☐ PMHNP ☐ RNA ☐ WHNP ☐
5.		AGCNS ☐ FNP ☐ PMHNP ☐ RNA ☐ WHNP ☐
6.		AGCNS ☐ FNP ☐ PMHNP ☐ RNA ☐ WHNP ☐

The tentative title of the DNP Project Proposal for this student group is:

Opioid-Sparing Analgesia in the Post-Anesthesia Care Unit:
Subdissociative Ketamine Administration

Committee Approved DNP Project Clinical Question:

In adult postoperative orthopedic patients, how does an evidence-based opioid-sparing multimodal analgesia PACU order set that includes subdissociative ketamine administration, compared to current PACU order sets, affect the quantity of total dose of opioids given, and

Names of DNP Project Team Mentors *(type the name and obtain digital signatures)*:

I agree to serve as a member of the DNP Project Team (Team Mentors) for the above DNP Student Project Team. As a Project Team Mentor, I agree to the duties and responsibilities outlined within the DNP Project Manual which include but are not limited to the provision of consultation and guidance supporting the entire DNP project journey and to ensure the DNP project is of sufficient rigor and demonstrates doctoral level scholarship to meet the requirements for USUHS GSN graduation.

NOTE: You may have 3-4 DNP Team Mentors [committee members including your DNP Senior Mentor (Chair)]. The Phase II Site Director may also be a member of the group, as well as other USUHS faculty or others who may serve as content experts. All non-USUHS faculty selected as a Team Mentor must be approved by the DNP Project Director.

Senior Mentor (Chair):	MAJ Keith Lathrop, CRNA	Signature:	LATHROP.KEITH.MICHAEL.1140909641 Digitally signed by LATHROP.KEITH.MICHAEL.1140909641 Date: 2021.01.22 09:38:04 -05'00'	Date:	1/22/21
Team Mentor (Member):	Dr. Sandra Bruner, CRNA	Signature:	BRUNER.SANDRA.SUE.1102080803 Digitally signed by BRUNER.SANDRA.SUE.1102080803 Date: 2021.01.22 11:27:31 -05'00'	Date:	1/22/21
Team Mentor (Member):		Signature:		Date:	
Team Mentor (Member):		Signature:		Date:	

Form Version: 4 December 2020

Opioid-Sparing Analgesia in the Post-Anesthesia Care Unit: Subdissociative Ketamine Administration

MAJ Andre Brown, LCDR Eric Sanchez, CPT(P) Alex Jung

MAJ Keith Lathrop: Senior Mentor, Phase II Site Director

Fort Belvoir Community Hospital (FBCH)

The Daniel K. Inouye Graduate School of Nursing

Doctor of Nursing Practice Project

Disclaimer

- The views expressed in the presentation are those of the authors and do not necessarily reflect the official policy or position of the Uniformed Services University, the Department of Defense, or the United States Government
- There are no financial relationships that exist between the speakers and a commercial entity

Introduction

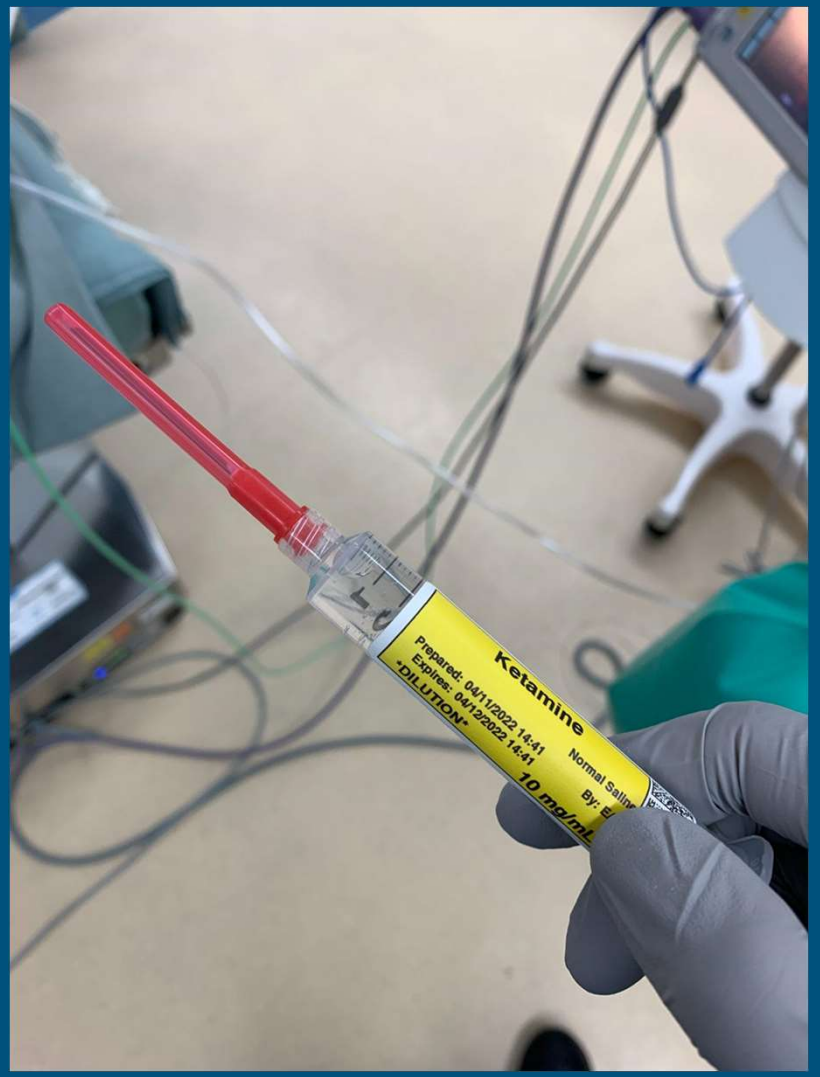
- Opioid-sparing/free anesthetic practices are frequently utilized intraoperatively at FBCH
- Part of evidence-based Enhanced Recovery After Surgery (ERAS) protocols.
    - Celebrex, Acetaminophen, Gabapentin
- These practices are not continued in the post-anesthesia care unit (PACU).
- Opioids, when given may cause adverse reactions: hypotension, nausea, vomiting, constipation, and respiratory depression
    - Leads to longer PACU stays
    - Delays in discharge

Significance

- Researched Non-opioid forms for Post-operative (post-op) analgesia

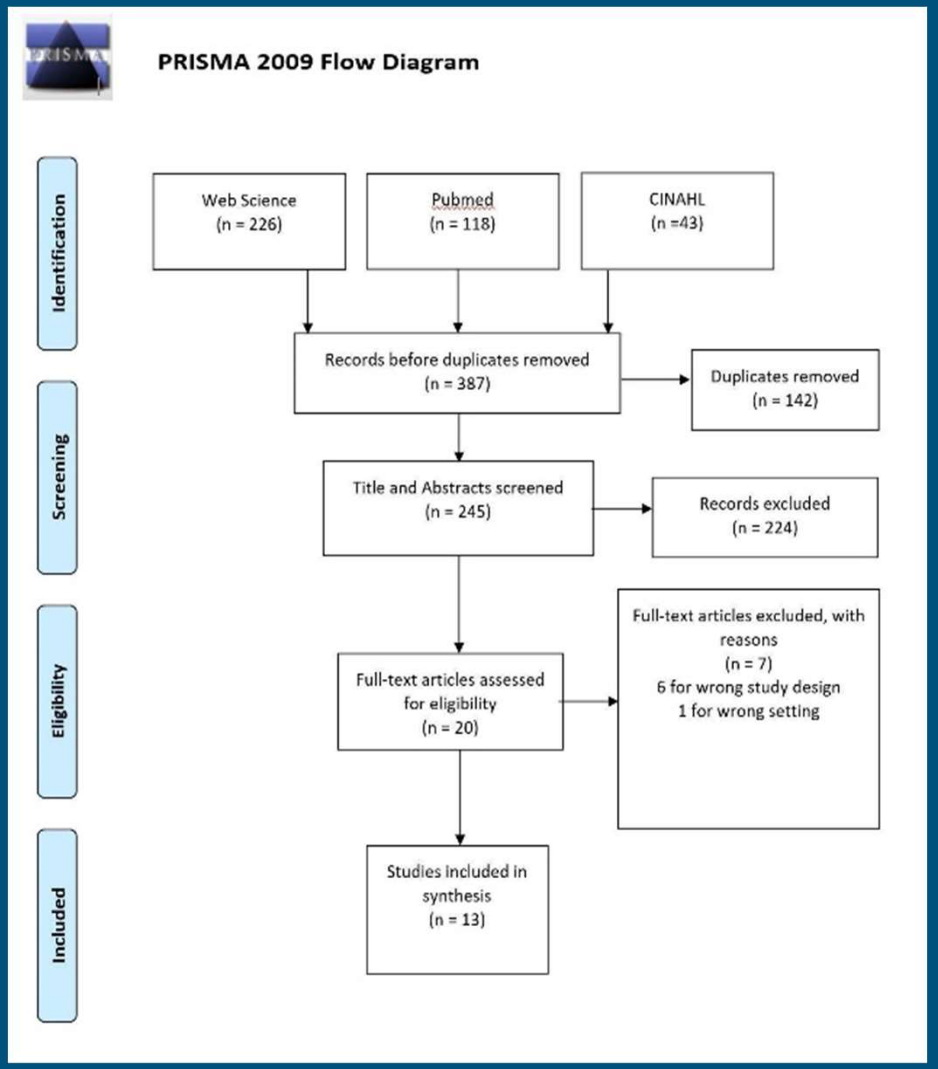
- Few options through evidenced-based practice were presented
  - Ketamine and methadone (opioid agonist)

- Focused on Ketamine for this project.0.3mg/kg = analgesic dose/ subdissociative dose.
  - This dosage was mainly used in the Emergency Department/ Perioperative setting.



Significance

- Databases:
  - Web of Science, PubMed, and CINAHL
- Search Terms
  - “Postoperative pain control interventions”
  - “Methadone” and “Pain”
  - “Subdissociative Dose Ketamine”
  - “Ketamine Postoperative Period”
  - “Methadone decrease opioid adverse events”
  - “Multimodal analgesia protocol opioid adverse events”
  - “Ketamine and “Acute Pain”
- 387 Results
  - 142 Duplicates
- 224 removed (not appropriate to problem statement)
- 7 removed (inapplicable study design of setting



System or Clinical Question

- In adult postoperative orthopedic patients, how does the use of an evidence-based opioid-sparing analgesia PACU order set that includes subdissociative ketamine (SDK), compared to current PACU orders sets, affect the of total dose of opioids administered, and PACU pain scores at time intervals at 15, 30, and 60 minutes after arrival in the PACU?

Focus Areas/Aims

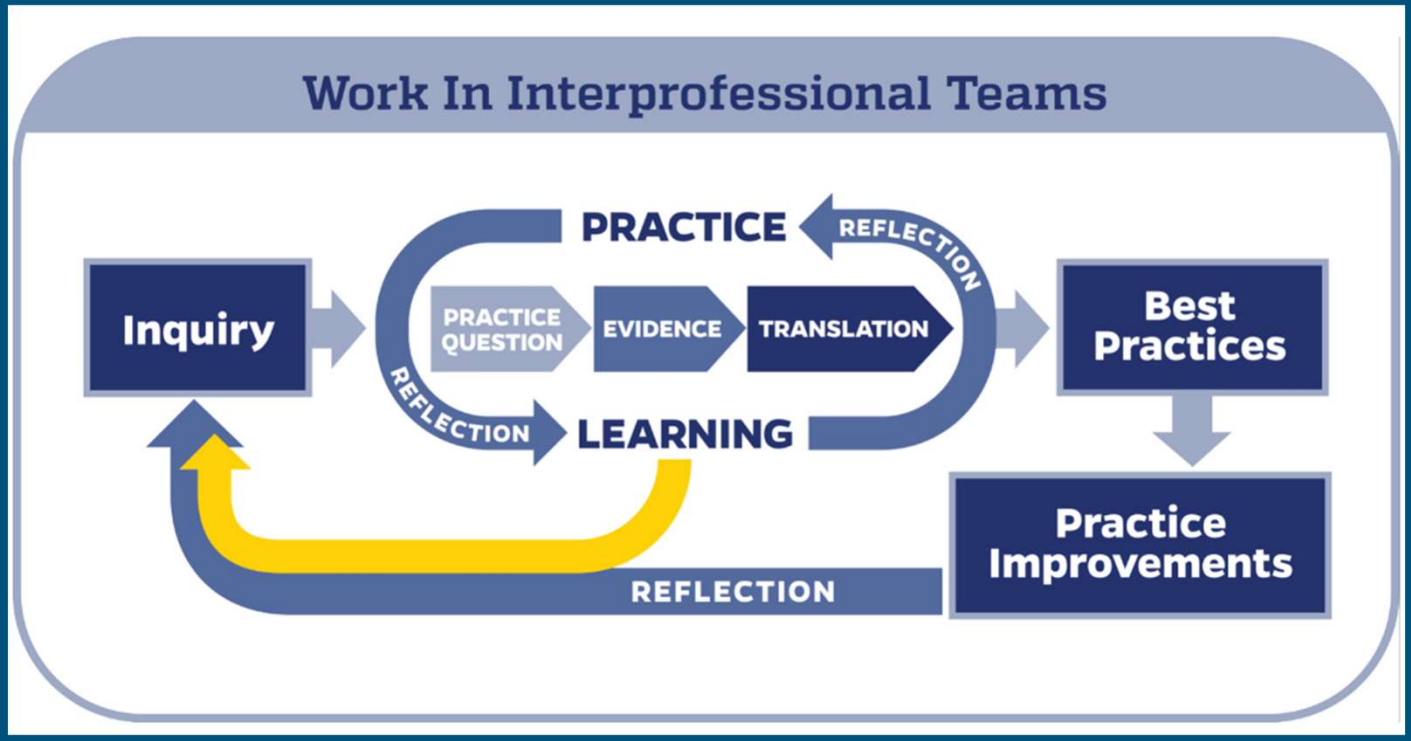
- Research
  - What other non-opioid adjuncts are available
- Who is going to give it? How?
  - PACU nurses were given the post-operative order for the SDK as well as the contact information of the SRNA responsible for administering the ketamine in the PACU. Once the SRNA was contacted, the SRNA administered the appropriate dose.
- Patient population
  - Orthopedic patients who stated of 4-6 out 10 on the Numeric Rating Scale in the post-anesthesia care unit (PACU) received SDK..
- IRB approval
  - This evidenced-based quality improvement project obtained internal review board (IRB) exemption.

Focus Areas/Arms

- Implementation
  - Eligible patient were given 0.3mg/kg of IV Ketamine x1 in the PACU after being notified by the PACU Nurse.
- Data collection
  - For each patient, the total doses of opioids given in the the PACU pain scores at time intervals of 15, 30, 60 min after arrival in the PACU were recorded. The total amount of patients for this intervention is 30 compared to 30 patients with the same surgical implications without the SDK the PACU
- Data analysis
  - Differences in the pain scores between the 15 minutes and baseline, 30 minutes and baseline, as well as 60 minutes and baseline were compared between the two groups using independent sample-tests and Wilcoxon's rank sum tests.
  - Dichotomous variables for use of each type of opioid (fentanyl, oxycodone, hydromorphone, morphine) irrespective of dosage were created.

Translation/Organizing Framework

- The John Hopkins Nursing Evidence-based Practice (JHNEBP) Model



Project Design

- Research non-opioid adjuncts
- Select adjunct/ setting for adjunct
- PACU nurse teaching/ Pharmacy support
- Collect baseline data
- Implement intervention
- Collect data from intervention for comparison
- Analyze data

Procedural Steps

- Analyzed existing PACU order sets
  - lack of non-opioid analgesic options.
- A review of the literature revealed SDK could be a viable non-opioid analgesic adjunct to treat acute pain.
- Doses most commonly found in the literature
  - ketamine 0.3 mg/kg IV
- Pain scores at 15, 30, and 60 minutes after arrival to PACU
  - Doses of opioids used were recorded (standard group, SG).
- SDK administered to 30 adult orthopedic patients by the SRNA once assessed by the PACU nurse
  - Pain scores >4/10.
  - Compared against SG.

Results

- Pain scores with SDK showed no difference when compared to the control group without.
- Regarding opioid, use, SDK produced statistically significant reductions in the total number of patients requiring fentanyl and hydromorphone.
- No differences were noted in the number of patients who received dilaudid or the average dose of fentanyl administered to patients.

Analysis

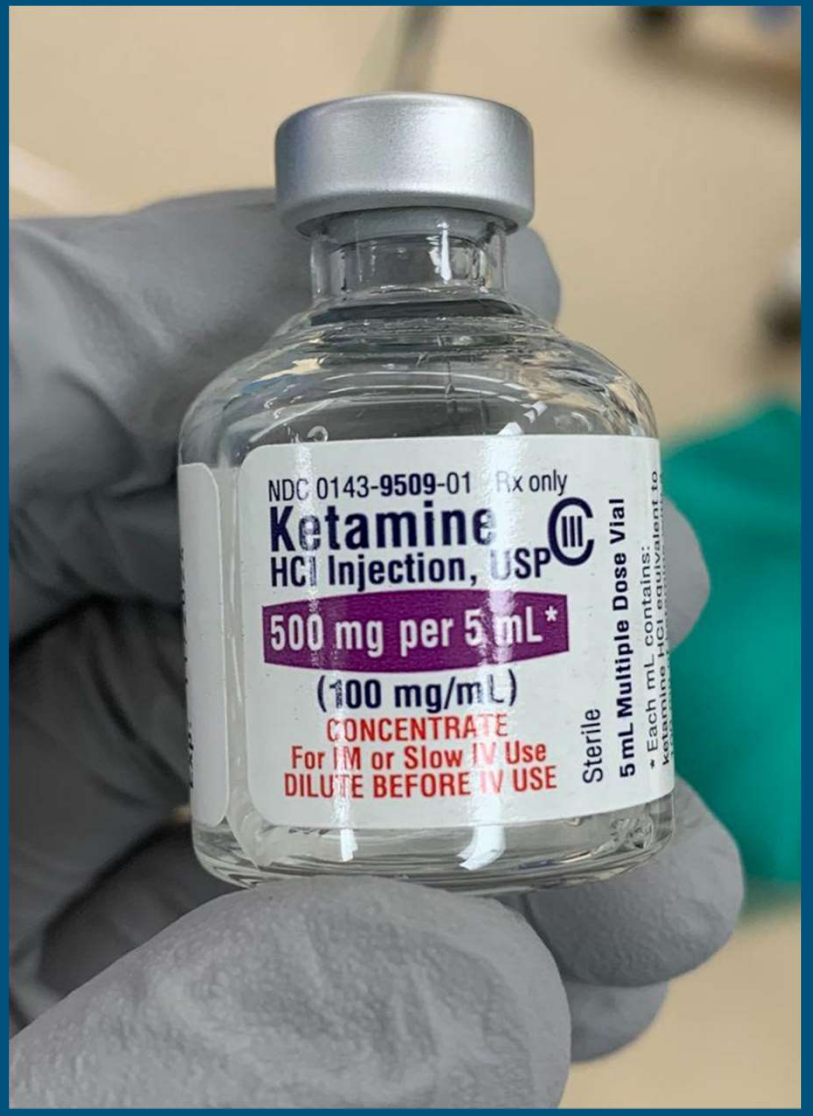
- A significantly lower portion of patients under the SDK protocol versus the patients under the SG used fentanyl.
- No significant difference in pain scores at 15, 30, and 60 minutes between the SG and SDK groups (independent samples and Wilcoxon's rank sum test).
- The number of patients using opioids did not differ between the two groups (Chi-square test).
- The total dose of opioid use in milligrams did not differ significantly between the two groups (Chi-square test).
- Addition of SDK was non-inferior compared with existing protocol.
- Not enough evidence to recommend a change in practice more research required.

Impact/Implications

- Findings support Fort Belvoir Community Hospital in expanding the use of multimodal analgesia in the PACU.
- Provides military service members with experience using medications available in operational environments.
- Provides a pathway for PACU RNs to expand their ability to administer opioid-sparing analgesic medications.
- May lead to policy changes in post-operative medication administration.

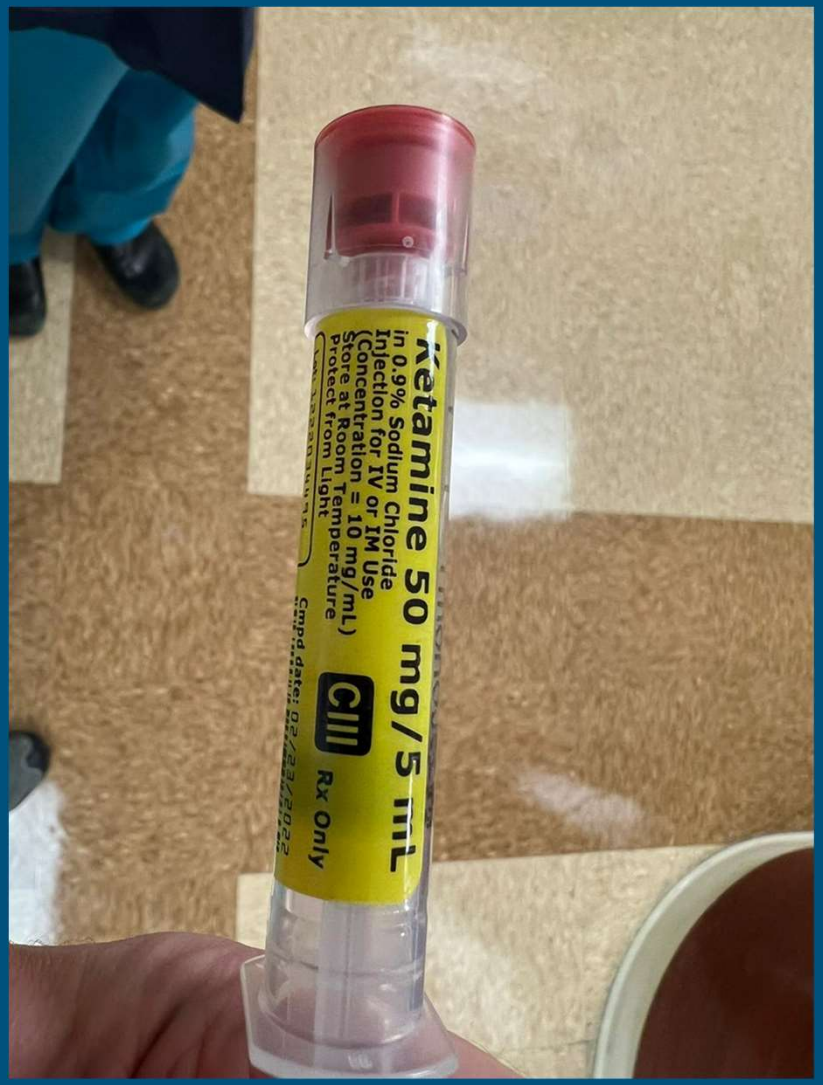
Barriers and Limitations

- Current policies
- 500mg vials of Ketamine
- PACU nurse interpretation of order sets
- Patient receiving nerve blocks before the procedure
- ERAS medications ordered differ per provider.



Future Directions

- Policy changes
  - Pharmacy can supply the hospital with pre-filled syringes of ketamine (50mg/5ml) to allow PACU and anesthesia staff to safety administer ketamine without the need for bedside compounding.
  - RNs ability and understanding to use ketamine in the PACU setting.
- Further research opportunities
  - Available research regarding the use of Ketamine regarding the pharmacokinetics and pharmacodynamics relate to anesthesia and not analgesia
  - Efficacy of pain control between intraoperative ketamine and postoperative use of ketamine.
  - The use of ketamine in opioid-sparing techniques.



Conclusion

- Military RNs would benefit from using ketamine to gain experience using a drug that used in combat. and austere environments
- Ketamine is a viable option in post-operative analgesia and has demonstrated non-inferiority when compared to the current PACU order set.
- SDK has shown to provide a small opioid-sparing effect at FBCH.
- Further research is needed to determine the most efficacious way to use ketamine as an analgesic.
- SDK can be incorporated into ERAS committees that can reduced the use of opioids in the PACU making it a mainstay in postoperative analgesia.

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Thank You!

Subdissociative Ketamine (SDK) Administration in the Post-Anesthesia Care Unit (PACU)

Andre Brown, BSN, RN, MAJ, AN; Eric Sanchez, BSN, RN, LCDR, NC; Alex Jung, BSN, RN, CPT(P), AN
Daniel K. Inouye Graduate School of Nursing, Uniformed Services University of the Health Sciences, Bethesda, MD
Fort Belvoir Community Hospital, Fort Belvoir, VA

Significance of the Problem

Opioids are powerful analgesics but may cause hypotension, nausea, vomiting, constipation, and respiratory depression, which may lead to complications in the PACU.
Opioid-sparing anesthesia is becoming more common with Enhanced Recovery After Surgery (ERAS) protocols, but these analgesic approaches are often not continued in the PACU.

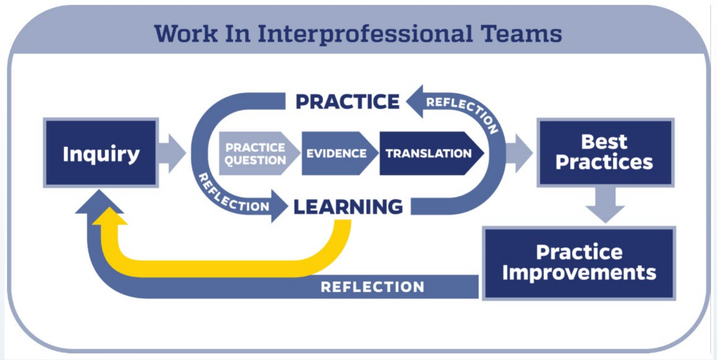
Purpose/ Clinical Question

In adult postoperative orthopedic patients, how does an evidence-based opioid-sparing multimodal analgesia PACU order set that includes subdissociative ketamine administration, compared to current PACU order sets, affect the quantity of total dose of opioids given, and PACU pain scores at time intervals at 15, 30, and 60 minutes after arrival in the PACU?

Project Design

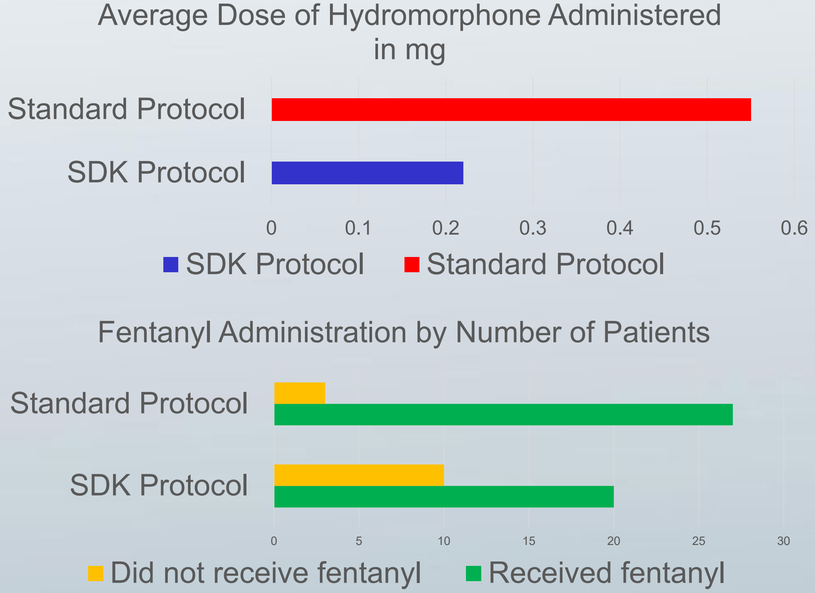
An analysis of existing PACU order sets revealed a lack of non-opioid analgesic options.
A review of the literature revealed SDK could be a viable non-opioid analgesic adjunct to treat acute pain.
Based on doses used in the literature, ketamine 0.3 mg/kg IV was selected.
SDK was administered to 30 adult orthopedic patients with pain scores ≥ 4/10.
Pain scores at 15, 30, and 60 minutes after arrival to PACU as well as doses of opioids used were recorded (standard group, SG).
To evaluate the effect of the intervention, these same pain scores and opioid dosing were compared against 30 adult orthopedic patients treated under standard PACU protocols with the addition of SDK.

Organizing Framework



Dang, D., Dearholt, S., Bissett, K., Ascenzi, J., & Whalen, M. (2022). *Johns Hopkins evidence-based practice for nurses and healthcare professionals: Model and guidelines.* 4th ed. Sigma Theta Tau International

Project Results



Analysis showed a statistically significant reduction in the number of patients requiring fentanyl in the PACU. (P=0.03)
There was a statistically significant decrease in the mean dosage of hydromorphone used by the SDK group (p=0.02)

Analysis of the Results

No significant difference in pain scores at 15, 30, and 60 minutes between the SG and SDK groups (independent samples and Wilcoxon's rank sum test).
There were no significant differences between groups for the proportions of patients using morphine, hydromorphone, or oxycodone.
No statistically significant differences in the mean doses of other opioids used.
No statistically significant difference in pain scores and a slight opioid-sparing effect.

Recommendations for Improvement

Consider addition of SDK to PACU order set.
Update current policies to allow PACU nurses the ability to administer SDK when appropriate.
Expand opioid-sparing education for PACU nurses.
Conduct additional investigations to evaluate the use of ketamine in different surgical populations.
Provide prefilled syringes of ketamine 10 mg/mL for PACU use.
Conduct additional research to fully elucidate the pharmacokinetic and pharmacodynamic properties of ketamine as an analgesic.

Organizational Impact

Support Fort Belvoir Community Hospital expanding use of multimodal analgesia in the PACU.
Provide military service members with experience using medications available in operational environments.
Provide a pathway for PACU RNs to expand their ability to administer opioid-sparing analgesic medications.

"The authors would like to acknowledge MAJ Keith Lathrop (Senior Mentor), LTC (Ret.) Sandra Bruner, CDR Kennett Radford, Capt. Heather King, LCDR Kenneth Barber, and Dr. Hind Baydoun, for their support, guidance, and assistance. Their time, effort, and dedication to this project is greatly appreciated.