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Increasing Practitioner Knowledge of Ketamine as an Adjunct Analgesic for Postoperative Pain

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INCREASING PRACTITIONER KNOWLEDGE OF KETAMINE AS AN ADJUNCT ANALGESIC FOR POSTOPERATIVE PAIN

by

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Dedication & Acknowledgements

This project is dedicated in honor and memory of my beloved father James Robert Coleman. My dad was a lifelong academic and always strove to encourage his daughters in the pursuit of their dreams. He was an avid reader of all things related to Florence Nightingale and had the utmost respect for the scientific method she embodied. He lived long enough to know this project was close to completion, and was a constant driving force in my doctoral pursuit. I know he would be exceptionally proud.

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Abstract

Postoperative pain is of serious concern to patients and anesthesia providers alike. Management of a patients' pain is a central component of anesthesia care. Ketamine as an anesthetic agent has been available for 50 years. It has been utilized as a general anesthetic and selectively as an anesthetic agent for high-risk patients. Due to dysphoric side effects associated with the dosage required to render general anesthesia, anesthesia providers may be reluctant to utilize this medication to its full potential. Recently there has been a resurgence of interest in ketamine as an analgesic agent. The researcher for this project performed a thorough literature review focusing on intravenous ketamine as an adjunct to standard opioid-based analgesia for postoperative pain. Four systematic reviews published in the last 10 years support the safety and efficacy of ketamine when administered intravenously in sub-anesthetic doses. The purpose of this project was to provide evidence-based education to anesthesia providers regarding the benefits of ketamine and follow-up to evaluate for evidence of changes in practice after the educational At a large community hospital data concerning ketamine utilization by anesthesia providers as a component of multimodal analgesia was collected for a six-month period, including three months pre- and three months post-educational intervention. Despite various methods utilized to present evidence regarding the safety and efficacy of ketamine, the results of this study demonstrated no significant change in practice. Based upon the extensive published literature the evidence is compelling that the addition of a sub-anesthetic (0.5 mg/kg) dose of ketamine to the surgical patient's operative pain management plan would improve comfort and decrease opioid-related side effects with minimal negative impact.

Keywords: ketamine, postoperative, acute postoperative, pain, anesthesia, multimodal analgesia, adjunct agents, opioid, side effect

Introduction

Management of a patient's pain is a central component of anesthesia care. Postoperative pain is a challenge for anesthesia providers with opioids being a commonly used intervention. Opioid-related side effects, such as nausea and vomiting, along with respiratory depression, are well documented in the literature (Koneti & Jones, 2013). Inadequate postoperative analgesia contributes to negative outcomes, such as hyperglycemia, immunosuppression, inadequate rehabilitation, and progression to chronic pain (Laskowski, Stirling, McKay & Lim, 2011). Adjunct therapies, including non-steroidal anti-inflammatory drugs (NSAID's), acetaminophen, and anticonvulsants, such as gabapentin, have been shown to reduce postoperative opioid consumption (Laskowski et al., 2011). Perioperative intravenous ketamine has been demonstrated to be a useful addition to multimodal analgesia for the surgical patient. Overall pain management can be improved by adding medications that act at different sites in the pain pathway. The anesthesia provider must balance the benefits of pain management medications with their potential side effects. Ketamine has a different mechanism of action than opioids, working at the level of the N-Methyl-D-aspartate (NMDA) receptor. There is considerable literature on the anesthetic and analgesic effects of ketamine, since it has been available for 50 years (Persson, 2013). However, anesthesia providers are still uncertain of its efficacy, concerned about its side effects, and may not have a full understanding of its safety profile when dosed accordingly for analgesia, as opposed to doses needed for anesthesia (Elia & Tramèr, 2005; Schmid, Sandler & Katz, 1999). The researcher for this project examined anesthesia providers' practices regarding utilization of ketamine as an adjunct analgesic for surgical pain in light of evidence of its effectiveness and safety profile when administered in this dose range.

Background

In 2010, over 51 million inpatient surgeries were performed in the United States. Excluding endoscopic, obstetric, and non-surgery-related diagnostic procedures, approximately 20 million general surgeries were performed (Centers for Disease Control and Prevention [CDC], 2010). The treatment of pain after surgery is a central component of postoperative care. It is unacceptable, both morally and ethically, to fail to relieve a patient's pain, which may be regarded as the fifth vital sign and should be addressed with as much importance as other vital signs (Koneti & Jones, 2013). Anesthesia providers are responsible for managing patients' pain during the perioperative (pre, per, and postoperative) period. A myriad of pain treatment options are available and it can be challenging for a clinician to formulate a rational treatment plan (Soto & Fu, 2003). Poorly controlled postoperative pain is distressing to the patient. In addition to distress, patients may develop hyperglycemia, immunosuppression, infection, skin ulcers, and venous thrombosis as a result of inadequately controlled postoperative pain (Laskowski et al., 2011; Rakic & Golembiewski, 2009). There is growing concern that poorly controlled acute pain affects the development of long-term chronic pain (Wilder-Smith & Arendt-Nielsen, 2006). It is important that anesthesia providers have the most up-to-date information on all available pain management therapies in their armamentarium to enable them to best care for their patients.

Opioids

The use of opium as a drug dates back thousands of years BC and archeology hints that the Neanderthals used the opium poppy over 30,000 years ago (Dickenson & Kieffer, 2006). Opioids are a mainstay of surgical pain management. They can be utilized alone or in combination with other medications to provide multimodal analgesia. Modern opioids such as

morphine, hydromorphone and fentanyl are routinely used for pain management in surgical patients. Opioids' produce analgesia, which is the absence or relief of pain, as well as euphoria and sedation (Stoelting & Hillier, 2006). Common opioid-related side effects include respiratory depression, nausea, vomiting, and constipation. Multimodal analgesia may reduce opioid consumption and, therefore, reduce some of these side effects. The goal of multimodal analgesia is to administer two or more classes of drugs concurrently to achieve the benefits of synergy with a reduction in side effects (Soto & Fu, 2003). With that aim in mind the anesthesia provider should consider all classes of drugs that provide analgesia in planning for the prevention and treatment of surgical pain.

Ketamine

Ketamine is a derivative of phencyclidine (PCP), which produces dissociative anesthesia. In dissociative anesthesia the patient is amnestic, has an absence of pain, and they may appear awake, with eyes open (Stoelting & Hillier, 2006). Ketamine first appeared in the literature in the early 1960's and was approved for use as a general anesthetic in 1965. It was the early 1970's before it was suggested to utilize sub-dissociative doses as an analgesic (Sadove, Shulman, Hatano & Fevold, 1971). Despite being used for this period of time, it was not until 1982 that Lodge and colleagues demonstrated ketamine's mechanism of action as an NMDA receptor antagonist (as cited in Persson, 2013). The NMDA receptor has been identified as processing nocioceptive input, which contributes to the response of pain. Acute postoperative pain is considered to be nocioceptive pain (Koneti & Jones 2013). Over time ketamine fell out of favor with practitioners due to its dysphoric side effects, postoperative delirium and potential for hallucinations (Rakic & Golembiewski, 2009). Ketamine also has abuse potential which is a concern for clinicians. There is now a large body of research regarding the analgesic use of

ketamine in sub-anesthetic doses to optimize postoperative pain management in the surgical patient.

Bell, Dahl, Moore and Kalso (2006) conducted a systematic review for the Cochrane collaboration. The results indicated that treatment with ketamine reduced morphine consumption and decreased postoperative nausea and vomiting (PONV) with mild or no side effects. Laskowski et al. (2011) conducted a systematic review, narrowing the inclusion criteria of studies to address the issues of heterogeneity. Laskowski and colleagues included only studies in which ketamine was administered intravenously. The results indicated that intravenous ketamine is an effective adjunct for postoperative pain particularly for painful surgeries.

Problem

Postoperative pain is a serious issue of concern to anesthesia providers and their patients. Ketamine is an analgesic agent, which can be utilized to assist in both the reduction of postoperative pain and the side effects of opioid medications. Because of the possibility of untoward side effects and abuse potential of ketamine, along with previous studies with conflicting results, anesthesia providers may not use this agent to its maximum therapeutic benefit. The PICO statement for this project is: (P) Do anesthesia providers caring for surgical patients at a 335-bed community hospital when (I) presented with high-level evidence of the effectiveness of low-dose ketamine (O) change their utilization of this drug? Low-dose ketamine may be defined as sub-anesthetic (Rakic & Golembiewski, 2009), sub-dissociative (Sadove et al. 1971), or for clinical purposes, a bolus dose of less than 1mg/kg administered intravenously (Schmid et al., 1999).

Project Purpose

The researcher for this project assisted in translating evidence into practice based on: (1) the high-quality nature of the evidence, (2) the desire of anesthesia providers to provide the best possible care to their patients and (3) utilization of adult learning strategies to facilitate change (Zaccagnini & Waud White, 2011). Research is available and the evidence is of high quality suitable for presentation. Numerous randomized controlled trials (RCTs) and several systematic reviews (SRs) have been published in the last 10 years. As an anesthesia provider at the project facility in which this study was conducted, the researcher had the opportunity to present new knowledge to both anesthesia students and professional colleagues in the anesthesia specialty. Dissemination of information in various formats did not involve cost to the facility or the anesthesia group practice. Change in practice patterns can be evaluated over time with additional reinforcement provided as necessary. The electronic medical record system in use allows for analysis of ketamine usage over time in relation to number of surgeries by type, and by provider. Evidence shows that "low dose" perioperative administration of ketamine can decrease opioid consumption and reduce negative side effects associated with opioids. This project had a goal to increase anesthesia providers' awareness of the benefits of ketamine as part of their multimodal pain management plan. Increased utilization of ketamine, based on evidence may have a positive impact on surgical patients pain management.

Definition of Terms

Analgesia: The absence of pain in response to noxious stimuli (Brown, 2009).

Clinical Heterogeneity: When differences in the patient population, outcome measures, definition of variables, and/or duration of follow-up of the studies included in the analysis create problems of non-compatibility (Petrie & Sabin, 2009).

Dissociative Anesthesia: "A state characterized by analgesia and changes in vigilance and perception, but not frank sedation or hypnosis"…. "They are unconscious, amnestic and deeply analgesic" (Berti, Baciarello, Troglio & Fanelli 2009, p. 708). A trance-like state (Berti et al., 2009).

Multimodal Therapy: Multiple drugs are utilized in order to leverage on their additive and especially, synergistic effects (Soto & Fu, 2003).

Nocioception: "Nocioceptors are free nerve ending receptors present in the skin, muscles, joints, viscera and vasculature. These nocioceptors are responsible for detecting the presence of noxious stimuli" and the communication of pain to the spinal cord (Stoelting & Hillier, 2006, p. 709).

NSAIDS: "NSAID is an all inclusive term denoting a varied group of drugs possessing analgesic, anti-inflammatory, and antipyretic effects" (Stoelting & Hillier, 2006, p. 276). These drugs inhibit the Cyclooxygenase (COX) enzyme. Examples include, ibuprofen, acetaminophen, ketorolac and aspirin.

Opioids: All exogenous substances, synthetic and natural, that bind to opioid receptors producing morphine-like effects. Morphine, fentanyl, and hydromorphone are examples (Stoelting & Hillier, 2006).

Receptor Antagonist: "Drugs that are antagonists inhibit or prevent receptor mediated agonists effects by competing for receptor occupancy" (Shafer & Schwinn, 2005, p. 86).

Summary

Management of postoperative pain is of critical importance to patients and their anesthesia providers. Side effects of opioid medications can impact the utilization of this class of medications. Multimodal analgesia aims to administer more than one class of medication, acting

on different sites in the pain pathway. This technique allows for better pain management with fewer side effects. Evidence exists which indicates that ketamine is a safe and effective addition to a pain management regimen. The researcher for this project will present evidence to anesthesia providers regarding the efficacy and safety of "low dose" ketamine in the treatment of postoperative surgical pain.

Review of Literature

Sources and Search Process

The aim of this researcher's literature search was to identify the most current, high-quality evidence regarding the utilization of ketamine for postoperative pain**.** For this review, the researcher searched the Cochrane, Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Pub Med and UNF One Search databases. The researcher used the following terms in various combinations: perioperative, ketamine, postoperative, acute postoperative, pain, analgesia, pre-emptive, randomized control trial, meta-analysis and systematic review. The researcher limited the searches to the years 2002 through 2013, the English language, and adults. Additionally, the researcher performed a manual search of citations from relevant articles. The search yielded four systematic reviews published between 2004 and 2011 addressing the role of ketamine in multimodal analgesia. As the last systematic review included studies only through 2010, the researcher conducted an additional search for RCT's from 2010 through 2013. See Figure 1 for a flow diagram of this researcher's article selection process for systematic reviews. (See Appendix A for Table 1) The assessment of multiple systematic reviews (AMSTAR) measurement tool created to assess the methodological quality of systematic reviews conducted by Bell et al. (2006), Elia and Tramèr (2005), Laskowski et al. (2011), and Subramaniam, Subramaniam, and Steinbrook (2004).

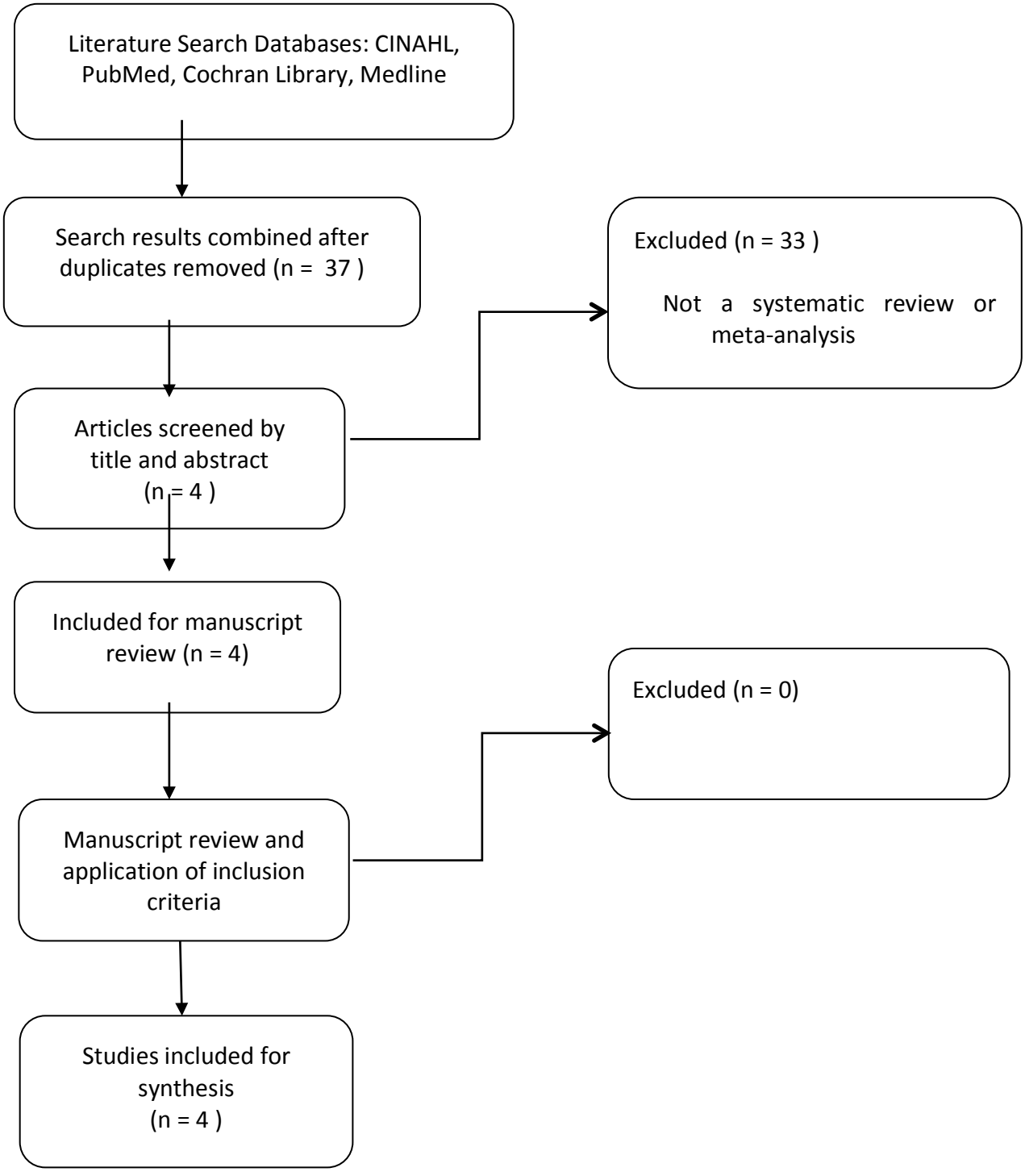

Figure 1. Flow diagram of article selection process for systematic reviews. Adapted from "Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement," by D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman DG, and The PRISMA Group, 2009, *PLoS Med 6*(7), e1000097.

Evaluation of Data-Extraction Tool

Table 1, (see Appendix A) provides information about the overall assessment of the four systematic reviews evaluating ketamine for acute postoperative pain. The researcher for this study used the assessment of multiple systematic reviews (AMSTAR) tool to perform the data extraction. The AMSTAR tool lists one of the eleven elements as "were the characteristics of the included studies provided?" (Shea et al., 2007, p. 5).

> In an aggregated form such as a table, data from the studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported (Shea et al., 2007, p. 5).

Utilizing this detailed definition none of the four systematic reviews met this one particular criteria item. Demographic information from the reviewed studies was generally not reported. Bell et al. (2006) included interventions, outcomes and types of surgeries. Elia and Tramèr (2005) included an online appendix which detailed dosages, methods of administration, types of operations, and outcomes. Laskowski et al. (2011) included age, dose, mode of delivery, timing, surgical site and outcome and Subramaniam et al. (2004) included dosage, mode of delivery, timing and type of surgery.

Meta-Analyses

Laskowski et al. (2011) performed a systematic review including meta-analysis of RCTs that specifically looked at intravenous ketamine for postoperative analgesia. Previous systematic reviews included a range of doses and routes of administration for ketamine with

some inconclusive results related to the wide heterogeneity of the studies. Utilizing the same search strategy as Bell et al. (2006), Laskowski et al. found 70 studies for review from 1996 to 2010 involving 4,701 patients specific for intravenous (iv) ketamine as an adjunct analgesic. Additionally, Laskowski et al. excluded studies in which regional anesthesia was involved. Forty-seven of these core studies could be quantifiably analyzed. The primary outcome of total opioid consumption using a random effects model demonstrated a standard difference in means (SDM) of -0.631 (95% CI = -0.802 to -0.459; $P < 0.001$), thus, providing evidence of the opioid sparing effect of adjunctive ketamine. Subgroup analysis showed no difference in opioid sparing in dosages ranging from 0.5 mg/kg to > 1 mg/kg. The most significant reduction in opioid consumption was in upper abdominal and thoracic surgery. Surgeries with higher postoperative pain scores demonstrated the greatest efficacy of ketamine. This was consistent with findings by Subramaniam et al. (2004). Evaluation of pain scores demonstrated that 78% of the placebo group experienced more pain despite higher opioid consumption. With increased opioid sparing, there was less PONV, but also an increase in neuropsychiatric side effects such as hallucinations and nightmares.

Bell et al. (2006) published a Cochrane review on the perioperative effects of ketamine for acute postoperative pain. The purpose of this review was to evaluate the evidence regarding ketamine in the perioperative period, its efficacy, and tolerability. Bell et al. (2006) concluded that a sub-anesthetic dose of ketamine reduced morphine requirements in the first 24 hours following surgery. The addition of ketamine reduced PONV and produced mild to no side effects. This review included 37 trials with 53 treatment arms including 2240 participants. Bell et al. (2006) reference both Subramaniam et al. (2004) and Elia and Tramèr (2005) systematic reviews that were published while preparing their review. Bell et al. (2006) note that due to

heterogeneity of data they chose to restrict quantitative analysis to 24-hour patient controlled analgesia (PCA) consumption and PONV, excluding visual analog pain scores (VAS), as utilized by Subramaniam et al. (2004). Elia and Tramèr (2005) produced similar findings regarding the efficacy of intravenous ketamine with both of these reviews including studies performed in children which were excluded from this review.

Elia and Tramèr (2005) performed a systematic review of ketamine including RCTs that reported on opioid sparing, pain outcomes, and adverse effects. The published abstract of this study concludes with the statement, "Despite many published randomized trials, the role of ketamine, as a component of perioperative analgesia, remains unclear" (p. 61). Due to the heterogeneity of studies, clinicians who delve no farther into the body of this systematic review could miss key findings that support the positive impact of ketamine when used intravenously. This review included 53 RCTs from 23 countries. Of these, in 16 studies, the route of administration was intravenous, with a median ketamine dose across all trials of 0.4mg/kg. Ten of these studies reported on pain intensity at rest with a consistent, statistically-significant decrease in VAS scores at 6, 12, 24, and 48 hours postoperatively. Four studies suitable for meta-analysis looking at morphine consumption demonstrated the weighted mean difference (WMD) in favor of ketamine of -16 mg. There were seven studies reporting on the amount of time to first analgesic request demonstrating an average improvement with ketamine of about 16 minutes. Although the overall conclusion of this systematic review was that the role of ketamine as a component of perioperative analgesia was unclear this was due to heterogeneity of the included studies. The findings regarding intravenous ketamine were favorable, demonstrating a decrease in pain intensity at rest, decrease in cumulative 24 hour morphine consumption and an average improvement in time to first analgesic request.

Due to the varied modes of ketamine administration in RCTs, Subramaniam et al. (2004) performed both a quantitative and a qualitative analysis including only intravenous and epidural administration. They excluded studies comparing pre-incision versus post-incision administration alone. This systematic review concluded that small-dose ketamine was useful and a safe adjunct to standard opioid-based analgesia. A single dose of IV ketamine improved analgesia postoperatively in combination with opioids with no increase in side effects.

The breadth of the studies, countries, and clinical settings, building on 50 years of reported outcomes, demonstrate the large worldwide interest in this drug. All four of these systematic reviews published in the last 10 years provide evidence of the efficacy and safety of ketamine when administered intravenously in sub-anesthetic doses. The compilation of this body of evidence supports its consideration by anesthesia providers as an adjunct analgesic in the perioperative period.

Summary

In summary, the evidence from these clinical trials and systematic reviews demonstrate the efficacy of intravenous low-dose ketamine. The evidence supports the use of low-dose intravenous ketamine to decrease postoperative pain and opioid consumption, as well as related opioid-induced side effects. Ketamine side effects were reported as minimal to none. This information will be disseminated to anesthesia providers in an effort to continuously improve management of a patients' postoperative pain through evidence-based practice.

Methodology

In this section, the researcher for this study includes a description of the study design, sample, and data collection tool that was utilized for this project. There will be a discussion of the interventions provided and the theoretical model behind them. The purpose of this project

was to provide evidence-based education to anesthesia providers regarding the adjunct utilization of intravenous ketamine and monitor for post educational changes in practice.

Design and Setting

The researcher for this study utilized a pre- and post-intervention single-center study review to assess for significant change in administration practices. Data were collected from October through December 2013 in a retrospective fashion, utilizing surgical information system (SIS) analytics software. The researcher conducted intervention in January 2014 via article dissemination and discussion, poster format and continuing education following the adult learning theory model. Continuing education consisted of a presentation on the history of ketamine, literature search process, findings and the benefits of low-dose ketamine in the surgical patient population. This was a self-study multi media format consisting of written literature, poster review, a Prezi ® software presentation followed by a ten item test. The researcher was available throughout the process to answer questions. For clarity, both the poster and the continuing education offering defined “low dose”, “sub-anasthetic” ketamine as 0.5mg/kg iv. Utilizing the same analytics software, the researcher retrospectively collected data for January through March 2014. Anesthesia providers were blinded to the fact that pre- and post- data collection was occurring.

The setting for this study was a large, 335-bed community hospital in the southeastern United States with a privately contracted anesthesia group. This anesthesia group consisted of certified registered nurse anesthetists (CRNA’s), anesthesiologists (full-time and as needed) and an anesthesiologist assistant who made independent decisions regarding anesthetic administration.

Sample

The researcher for this study conducted a pre- and post-intervention retrospective analysis of approximately 900 anesthetics per month administered by roughly 25 providers to determine the percentage of general anesthetics that included the drug ketamine. The researcher obtained permission to conduct this study from the investigator's project committee, the Institutional Review Board (IRB) at the University of North Florida, the facility IRB, and the president of the anesthesia group (see Appendix B, Appendix C, and Appendix D for this documentation).

Methods

The researcher for this study collected all data from October through December 2013 and January through March 2014. Evidence-based educational intervention occurred during January 2014. Utilizing analytics software, the researcher reviewed all charts with the exclusion of those identified as endoscopy procedures, (see Appendix E for this list) which are not reflective of patients undergoing general anesthesia with the potential for postoperative pain. Anesthetics administered by this investigator were also excluded to avoid potential bias.

Data Collection

The researcher for this study collected all data from October through December 2013 and January through March 2014. The researcher exported the raw data from analytic software to Microsoft Excel. The software reporting system to collect this data was only available to the principal investigator (PI). The researcher collected provider names to allow for further analysis if warranted. The researcher kept this information confidential.

Feasibility

This project was designed to evaluate the impact of the dissemination of high-level evidence regarding the benefits of intravenous ketamine to anesthesia providers in their practice. It is assumed that anesthesia providers have a desire to provide the highest level of care to their patients. The alleviation of pain is a primary component of anesthesia care. Over 90% of all CRNA's are members of the AANA that is routinely providing evidence-based practice related documents to the membership.

Income and Expenses

The primary expense for this project was the licensing of SIS analytics software. The anesthesia group incurred this cost of $1,500. The investigator incurred minimal printing and poster presentation costs.

Protection of Human Subjects

The researcher for this study evaluated data from existing patient charts. Ketamine is a formulary drug that is presently administered at the providers' discretion. Any increase in ketamine utilization post intervention has been show by the evidence to be of patient benefit, with minimal risk of side effects. Anesthesia providers are routinely provided with evidence-based education, therefore the intervention caused no harm to providers or patients.

Confidentiality

Data obtained from the SIS analytics program did not identify individual patients in any format. Anesthesia providers' drug utilization was collected individually. All results were reported in the aggregate, so no individual providers' practices were reported. The researcher for this study entered the Excel spreadsheet information into an encrypted external drive, which remained either with the principal investigator (on her person) or in a locked file cabinet in a secure location.

Data Analysis Plan

All data were transferred to an Excel spreadsheet and checked for errors. The researcher analyzed the data utilizing JMP® 10 software to perform a Pearson Chi square test between percentage of utilization between the pre- and post-intervention samples to determine whether there was a statistically significant difference in drug utilization. All data were reported in the aggregate. There was no discrepancy in the providers' practicing pre- and post-intervention, so no additional analysis was required.

Results

In this section, the researcher provides a description of the sample of records that met inclusion criteria. Records that were excluded based on procedure type are outlined in detail. The total number of anesthetics that met the inclusion criteria are identified along with those receiving ketamine as a component of their general anesthetic.

Sample Characteristics

The researcher included for the analysis the medical records of all patients receiving anesthesia during a six-month period. Thirty-eight of 726 coded procedures were excluded from analysis, as these were endoscopic procedures not reflective of general surgery post-operative pain management needs. See Appendix D for a complete list of excluded procedures. Of the anesthetics administered, 226 were excluded as they reflected anesthetics administered by the principal investigator. The researcher included the remaining 3,618 cases for review of ketamine utilization.

Quarterly Data

During the three months prior to the educational intervention, a total of 2,701 anesthetics were administered. Of these anesthetics, 1,796 met the inclusion criteria for this study. Of these

1,796 anesthetics, ketamine was administered in 106 cases. In the three-month period following the educational intervention, a total of 2,677 anesthetics were administered. Of these anesthetics 1,822 met the inclusion criteria for this study. Of these, ketamine was administered in 107 cases (See figure 2.)

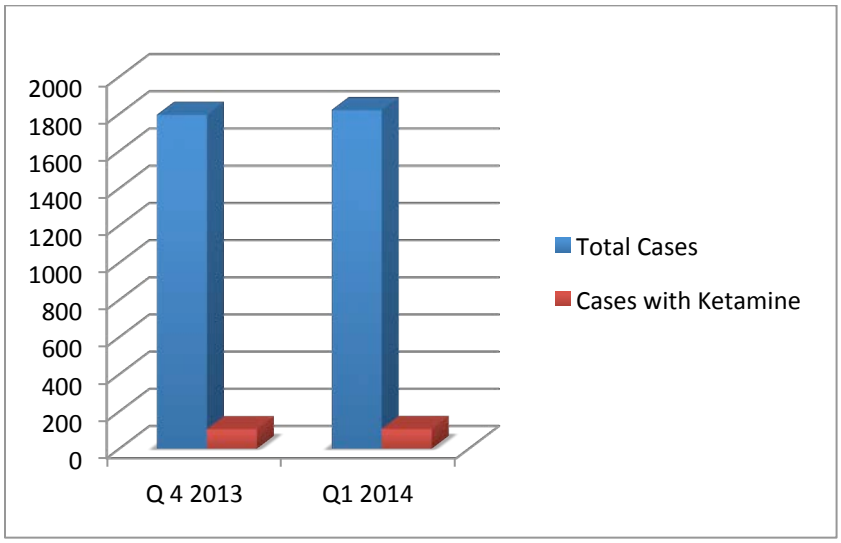

Figure 2. Total cases included for study and those including ketamine. This bar graph compares the anesthetics and administration of ketamine from the Q4, 2013 pre-intervention period to the Q 1, 2014 post-intervention period.

Discussion

In this section, the researcher for this study provides a discussion of the project outcomes as related to anesthesia providers' utilization of ketamine as an adjunct analgesic for postoperative pain following dissemination of evidence. The limitations of the study, implications for the dissemination of evidence, challenges to effecting change, and recommendations for future projects are also presented.

Management of a patient's pain is a central component of anesthesia care with opioids being a commonly used intervention. Opioid side effects, such as nausea and vomiting along

with respiratory depression, are well documented in the literature (Koneti & Jones, 2013). There is ample evidence from systematic reviews that ketamine, when utilized in sub-anesthetic doses, decreases post-operative pain, decreases opioid consumption and its associated side effects, with minimal to no adverse side effects (Bell et al., 2006; Elia & Tramèr, 2005; Laskowski et al., 2011; Subramaniam et al., 2004).

The purpose of this project was to examine anesthesia providers' practices regarding utilization of ketamine as an adjunct analgesic for surgical pain in light of evidence of its effectiveness and safety when administered intravenously in an analgesic (0.5mg/kg) range. Specifically, the researcher for this project evaluated if anesthesia providers at a large community hospital changed their utilization of ketamine following dissemination of evidence of its efficacy and safety when administered in sub-anesthetic doses. Dissemination methods included journal club, poster presentation, and continuing education. Although the dissemination of information appeared, subjectively, to be well received, and anesthesia providers have been shown to change practice based on evidence, there was no statistically significant change in practice noted during the period of this study (p=0.9701). Thus the results of this study do not provide evidence that the dissemination of high quality systematic reviews supporting the use of ketamine as an adjunct analgesic altered anesthesia providers' practices. It is possible that providers were already administering ketamine to the patient population they deemed maximally appropriate based on recent evidence. Another consideration would be the delivery method of information. Possibly it was not compelling or engaging enough to change practice patterns.

Limitations

This project had some limitations that should be noted. Although the sample size was robust, the number of providers that were subject to evidence dissemination and the wide range of anesthetics administered by them may have diluted the findings. An anesthesia provider who utilized ketamine in the control period, may not have worked, or worked rarely, during the post-dissemination period. The analytic software utilized to track ketamine administration was able to identify CRNA's, however all anesthesiologists and anesthesiology assistant data were aggregated together. Ketamine is a controlled substance and comes in a variety of strengths. At the study facility, the strength concentration to utilize sub-anesthetic dosing is not located in an area readily convenient to practitioners.

To avoid bias, all anesthetics administered by the principal investigator were excluded. During the time frame that post-intervention data was being collected the author increased her involvement in cases that routinely receive ketamine due to another unrelated research project. This separate project removed cases that receive ketamine per protocol from other providers whose data would have otherwise been included. The blinded nature of this study may have limited the impact on providers who would have otherwise been willing to attempt to change their practice. Providers were not aware that utilization of ketamine was being tracked.

Implications for Practice

The results of this project support some of the challenges met when trying to impact change. The passive diffusion model, as described by Lomas (1993), assumes that practitioners who read or hear about research proceed to adopt this information into their practice. However evidence from systematic reviews regarding this subject suggest that continuing medical education (CME) methods have little direct impact on improving professional practice (Dawes et al., 2005). Change champions are mentioned frequently in healthcare literature. When

disseminating evidence that would result in a change in practice, having an influential champion spearhead this effort may be beneficial.

Recommendations

Evidence supports the utilization of ketamine in sub-anesthetic doses to improve the surgical experience for the patient. Reduction in postoperative pain and reduction in opioid consumption with the related adverse side effects are important considerations. A more aggressive, interactive method for dissemination of this evidence is required, if changes to practice are to be made. Differences in the influence and power held by individuals may impact the success of interventions aimed at bringing the producers and users of research together (Rycroft-Malone, 2014). Dissemination of information via a champion who clearly recommends adopting a change in practice would help to overcome inertia (Shaw, Howard, West, Crabtree, Nease, Tutt & Nutting, 2012). Collaboration with the pharmacy to make ketamine, as packaged, for sub-anesthetic/analgesic dosing more conveniently accessible to anesthesia providers would reduce one of the barriers to utilization.

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Appendix A: Table 1
Evaluation of Systematic Reviews

Authors: Elia, N. & Tramèr, M.R.
Year: 2004

	Yes	No	Can't answer	Not Applicable
Was an 'a priori' design provided?	X			
Was there duplicate study selection and data extraction?	X			
Was a comprehensive literature search performed?	X			
Was the status of publication (i.e. grey literature) used as inclusion criteria?	X			
Was a list of studies (included and excluded) provided?		X		
Were the characteristics of the included studies provided?		X		
Was the scientific quality of the included studies assessed and documented?	X			
Was the scientific quality of the included studies used appropriately in formulation conclusions?	X			
Were the methods used to combine the findings of the studies appropriate?	X			
Was the likelihood of publication bias assessed?		X		
Was the conflict of interest stated?	X			

AMSTAR measurement tool created to assess the methodological quality of systematic reviews Shea, et al. (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology 7*, 10

Authors: Subramaniam, K., Subramaniam, B. and Steinbrook, R. A.
Year: 2004

	Yes	No	Can't answer	Not Applicable
Was an 'a priori' design provided?	X			
Was there duplicate study selection and data extraction?	X			
Was a comprehensive literature search performed?	X			
Was the status of publication (i.e. grey literature) used as inclusion criteria?	X			
Was a list of studies (included and excluded) provided?	X			
Were the characteristics of the included studies provided?		X		
Was the scientific quality of the included studies assessed and documented?	X			
Was the scientific quality of the included studies used appropriately in formulation conclusions?	X			
Were the methods used to combine the findings of the studies appropriate?	X			
Was the likelihood of publication bias assessed?		X		
Was the conflict of interest stated?		X		

AMSTAR measurement tool created to assess the methodological quality of systematic reviews Shea, et al. (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology 7*, 10

Authors: Laskowski, K., Stirling, A., McKay, W. P. and Lim, H. J.
Year: 2011

	Yes	No	Can't answer	Not Applicable
Was an 'a priori' design provided?	X			
Was there duplicate study selection and data extraction?	X			
Was a comprehensive literature search performed?	X			
Was the status of publication (i.e. grey literature) used as inclusion criteria?	X			
Was a list of studies (included and excluded) provided?		X		
Were the characteristics of the included studies provided?		X		
Was the scientific quality of the included studies assessed and documented?	X			
Was the scientific quality of the included studies used appropriately in formulation conclusions?	X			
Were the methods used to combine the findings of the studies appropriate?	X			
Was the likelihood of publication bias assessed?	X			
Was the conflict of interest stated?	X			

AMSTAR measurement tool created to assess the methodological quality of systematic reviews Shea, et al. (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology 7*, 10

Authors: Bell, R. F., Dahl, J. B. and Kalso, E. A.
Year: 2010

	Yes	No	Can't answer	Not Applicable
Was an 'a priori' design provided?	X			
Was there duplicate study selection and data extraction?	X			
Was a comprehensive literature search performed?	X			
Was the status of publication (i.e. grey literature) used as inclusion criteria?	X			
Was a list of studies (included and excluded) provided?	X			
Were the characteristics of the included studies provided?		X		
Was the scientific quality of the included studies assessed and documented?	X			
Was the scientific quality of the included studies used appropriately in formulation conclusions?	X			
Were the methods used to combine the findings of the studies appropriate?	X			
Was the likelihood of publication bias assessed?		X		
Was the conflict of interest stated?	X			

AMSTAR measurement tool created to assess the methodological quality of systematic reviews Shea, et al. (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology 7*, 10

Appendix B: University of North Florida IRB Authorization

UNF Institutional Review Board (IRB) Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution/Organization A):
Flagler Hospital

IRB Registration #: 00006886 IRBORG#: 0005712
Federalwide Assurance (FWA) #: 00003766

Name of Institution Relying on the Designated IRB (Institution B):
The University of North Florida

IRB Registration #: IRB00001451 IRBORG#: IORG0001057
Federalwide Assurance FWA #: FWA00000737

The Officials signing below agree that The University of North Florida may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (*check one*)

(___) This agreement applies to all human subjects research covered by Institution B's FWA.

(X) This agreement is limited to the following specific protocol(s):

Name of Research Project: Increasing Practitioner Knowledge of Ketamine as an Adjunct Analgesic for Postoperative Pain
Name of Principal Investigator: Alison Goldfarb (Dr. McDonough UNF Mentor)
Sponsor or Funding Agency: N/A Award Number, if any: ___

(___) Other (*describe*): ___

The review performed by the designated IRB will meet the human subject protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the Terms of its OHRP-approved FWA. This document must be kept on file by both parties and provided to OHRP upon request.

Signature of Signatory Official (Institution/Organization A):
Signature Deleted Date: 12/19/13

Print Full Name: John Kantner, Ph.D. Institutional Title: Assistant Vice President for Research

Signature of Signatory ~~Official~~ (Institution B):
Signature Deleted Date: 12/16/13

Print Full Name: *Joe Gordy, FACHE* Institutional Title: *President and CEO*

Appendix C: Facility IRB approval

FLAGLER HOSPITAL
ST. AUGUSTINE

400 Health Park Boulevard
St. Augustine, Florida 32086
(904) 819-5155
www.flaglerhospital.org

Flagler Hospital
Institutional Review Board (IRB)
IRB# 00006886
Initial Review

Date: December 4, 2013

To: Allison Goldfarb, CRNA (Principal Investigator)

From: Joseph Gordy, FACHE (Chairman, IRB)
Name

Signature Deleted

Protocol: Increasing Practitioner Knowledge of Ketamine as an Adjunct Analgesic for Postoperative Pain

Please be advised, your research protocol was reviewed by the IRB and approved on 12/4/2013. The IRB is recommending the following:

☒ Approved, please be advised of the following:

- You will need to submit a written report to the IRB, no later than 12/1/2014. The progress report should contain the following information:
  - Number of patients enrolled in trial
  - Statistics and information regarding outcomes
  - Synopsis of any significant event* (must be reported to the IRB at the time the adverse event occurs). A synopsis of the significant event also needs to be contained in your progress report.
  - Observations, recommendations, conclusions to date
  - A copy of the current approved informed consent
  - Your request for continuation, discontinuation, or modification of the trial/protocol, and reasons for substantiating your request
- It is your responsibility to immediately (at the time of the occurrence) notify the IRB of any significant adverse event.
- A copy of the approved informed consent must be given to each person enrolled in your trial.
- It is your responsibility to submit changes to the protocols and/or consents, to the IRB for approval, before they are implemented.
- The anticipated expiration date of your study is: 12/1/14

☐ Approved, contingent upon: ____

- Once the contingency is met, the IRB will issue a letter of approval, noting you have met the standards outlined above, under the approved section.

☐ Not Approved, based on the following: ____

If you have any questions or comments, please contact Kari Bates

Appendix D: Letter of Approval for Project

COASTAL
ANESTHESIOLOGY
CONSULTANTS, PL

October 29, 2013

To: Flagler Hospital Institutional Review Board

From: W. Sherman Turnage, MD

Regarding: IRB Application:

Increasing Practitioner Knowledge of Ketamine as an Adjunct Analgesic for Postoperative Pain

I approve the research study presented to the IRB to be performed by the principal investigator, Allison A. Goldfarb, CRNA.

Please feel free to contact my office if you have any questions or concerns.

Sincerely,

Signature Deleted

W. Sherman Turnage, MD
President / Chief of Anesthesiology Department

100 Whetstone Place, Suite 310
St. Augustine, FL 32086
Phone: 904-819-4478

www.coastalanesthesiology.com
Fax: 904-819-4993

Appendix E: Excluded Procedures

Bronchoscopy ** Bronchoscopy
Bronchoscopy, Laser
Bronchoscopy, Navigational
Bronchoscopy, Navigational ** Bronchoscopy, Ultrasound
Bronchoscopy, Ultrasound
Bronchoscopy, Ultrasound ** Bronchoscopy, Navigational
Colonoscopy ** Colonoscopy
Colonoscopy ** Endoscopic Ultrasound
Colonoscopy ** Esophagogastroduodenoscopy (EGD)
Colonoscopy ** Esophagogastroduodenoscopy (EGD) Esophagogastroduodenoscopy (EGD) US w/ FNA
Colonoscopy ** Esophagogastroduodenoscopy (EGD) w/ Peg Tube Insertion ** Laryngoscopy, Direct
Cysto Insertion Stent / Removal ** Cystoscopy With Ureteroscopy
Cystoscopy ** Colonoscopy
Cystoscopy ** Examination Under Anesthesia
Cystoscopy With Ureteroscopy
Endoscopic Retrograde Cholangiopancreatography (ERCP) ** Esophagogastroduodenoscopy (EGD)
Endoscopic Ultrasound ** Colonoscopy ** Esophagogastroduodenoscopy (EGD)
Esophagogastroduodenoscopy (EGD) ** Bronchoscopy
Esophagogastroduodenoscopy (EGD) ** Colonoscopy
Esophagogastroduodenoscopy (EGD) ** Enteroscopy
Esophagogastroduodenoscopy (EGD) ** Flexible Sigmoidoscopy
Esophagogastroduodenoscopy (EGD) ** Manometry
Esophagogastroduodenoscopy (EGD) ** Transesophageal Echocardiogram
Esophagogastroduodenoscopy (EGD) ** US Paracentesis
Esophagogastroduodenoscopy (EGD) w/ Peg Tube Insertion
Esophagogastroduodenoscopy (EGD) w/ Peg Tube Insertion ** Tracheostomy
Esophagogastroduodenoscopy (EGD), US w/ FNA
Esophagogastroduodenoscopy (EGD), US w/ FNA ** Endoscopic Retrograde Cholangiopancreatography (ERCP)
Esophagogastroduodenoscopy (EGD)/Colonoscopy
Esophagogastroduodenoscopy (EGD)/Colonoscopy ** Colonoscopy
Esophagogastroduodenoscopy (EGD)/Flex Sigmoid
Examination Under Anesthesia ** Examination Under Anesthesia ** Cystoscopy
Excision Of ** Esophagogastroduodenoscopy (EGD)
Gastrostomy Tube Placement, Laparoscopic ** Bronchoscopy ** Bronchoscopy

VITA

Allison A. Goldfarb is a Certified Registered Nurse Anesthetist (CRNA) employed by Coastal Anesthesiology Consultants and currently practicing at Flagler Hospital and the Saint Augustine Surgery Center in St. Augustine, Florida. Ms. Goldfarb is pursuing her Doctor of Nursing Practice degree at the University of North Florida (UNF) in Jacksonville, Florida. She began her career in nursing in 1979 and has spent many years in critical care, education and leadership positions. She completed her Master of Science in Nursing from UNF in 2008 and obtained her CRNA credential. Ms. Goldfarb currently serves as the clinical coordinator at Flagler Hospital for the nurse anesthesia students from both the UNF and the Uniformed Services University of the Health Sciences nurse anesthesia programs.

Publications:

Ziemann-Gimmel, P., Goldfarb, A. A., Koppman, J., Marema, R. T. (2014). Opioid-free total intravenous anesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. *British Journal of Anaesthesia* May; 112(5):906-11 doi: 10.1093/bja/aet551