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Ketamine for Acute-on-Chronic Pain

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Ketamine for Acute-on-Chronic Pain

by

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Abstract

Background: Ketamine is a N-methyl D-aspartate antagonist that blocks pain stimuli transmission and could prove useful for the complex treatment of acute-on-chronic pain.

Setting: A low-dose ketamine protocol as an adjunct to conventional treatment was implemented in a major urban center.

Aim: To explore the research question "what is the effect of low-dose ketamine continuous intravenous infusions on pain of highly opioid tolerant adults following spinal surgery?"

Participants: All patients had spine surgery and used a minimum of 100mg of oral morphine equivalent pre-operatively.

Methods: A retrospective chart review was conducted. Data from individuals treated with conventional therapy from the year prior to protocol implementation were compared to data from those who also received ketamine post-implementation. Outcome measures included pain scores and daily opioid consumption on post-operative day 0 through 5, time to ambulation, time to discharge and adverse effects.

Results: There were no statistically significant differences between conventional therapy and ketamine patients.

Preface

Individuals requiring surgery often suffer from chronic back pain and take opioid analgesics at home. Pain of highly opioid tolerant individuals can be difficult to manage post-operatively. A Low-Dose Ketamine Continuous Intravenous Infusion (LDKCII) protocol for post-operative pain management was implemented in the Calgary Zone of Alberta Health Services on April 20th, 2012. Exploration of the research question "what is the effect of low-dose ketamine continuous intravenous infusions on pain of highly opioid tolerant adults following spinal surgery?" was achieved by a retrospective before-and-after chart review. A year's worth of patient records were examined for the first year the protocol was used. This data was compared to the previous year's patient records of individuals who were solely treated with conventional therapy.

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Finally, I would like to acknowledge my family for their continued support during my studies, especially my parents who are the reason I value knowledge and education. And last but definitely not least, a very special thank you to my amazing husband, Navi, who helped me juggle life while I finished this degree. I could not have done this without all of you in my life.

Dedication

To my husband: the life partner that supported my passion for learning

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
AHS	Alberta Health Services
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APN	Advanced Practice Nurse
APS	Acute Pain Service
APSAD	Acute Pain Service Anesthesia Database
BP	Blood pressure
CHREB	Conjoint Health Research Ethics Board
CNS	Central Nervous System
CRPS	Complex Regional Pain Syndrome
FMC	Foothills Medical Centre
HR	Heart rate
IASP	International Association for the Study of Pain
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IV	Intravenous
LDKCII	Low-Dose Ketamine Continuous Intravenous Infusion
MAP	Mean arterial pressure
N_2O	Nitrous Oxide
NMDA	N-methyl D-aspartate
NOUGG	National Opioid Use Guideline Group
NRS	Numerical Rating Scale
NSAIDs	nonsteroidal anti-inflammatory drugs
OIH	opioid-induced hyperalgesia
PACU	Post-Anesthetic Care Unit
PCA	Patient Controlled Analgesia
POD	Post-operative day
prn	Pro re nata
SCM	Sunrise Clinical Manager
SNRIs	serotonin and norepinephrine reuptake inhibitors
SPSS	Statistical Package for the Social Sciences
SSRIs	selective serotonin reuptake inhibitors
TCAs	tricyclic antidepressants
THA	Total Hip Arthroplasty
THC	tetrahydrocannabinol

Epigraph

"Probably the most humbling and challenging aspect of caring for the patient with pain is to accept that the sensation of pain is completely subjective." (McCaffery & Pasero, 1999, p. 5)

CHAPTER 1: INTRODUCTION

Under-treatment of pain is a global problem (Boulanger et al., 2007; International Association for the Study of Pain [IASP], ND; Kohr & Sawhney, 2005). The prevalence of chronic pain in Canada is estimated to be 18.9% (Schopflocher, Taenzer & Jovey, 2011) with an estimated annual cost of $56-60 billion per year (Canadian Pain Society, n.d.). In examining the results of the National Population Health Survey, Perez (2000) reported that over one million Canadian workers aged sixteen or older developed chronic back problems within a two-year span. Opioids have become a common treatment for chronic pain (Angst & Clark, 2010; Ballantyne & Shin, 2008) and there is a subset of the Canadian population that takes large doses of opioids for relatively long periods to treat their chronic back pain. When these individuals are hospitalized as a result of an accident, trauma, or a planned surgery, they experience a phenomenon termed *acute-on-chronic pain*.

It is very difficult to manage acute-on-chronic pain (Angst & Clark, 2010; Fishman, Ballantyne, Rathmell, & Bonica, 2010; Gandhi, Heitz & Viscusi, 2011; Huxtable, Roberts, Somogyi & Macintyre, 2011; Subramaniam et al., 2011). There are multiple factors that influence the complexity of the treatment of patients with acute-on-chronic pain including opioid tolerance, opioid dependence, and opioid-induced hyperalgesia (OIH) (Angst & Clark, 2010). Tolerance is defined as a reduction of the analgesic efficacy of opioids by desensitization of opioid anti-nociceptive pathways when patients use opioids for prolonged periods of time; it can be addressed by escalating doses of opioids (Gandhi et al., 2011). Physical dependence is characterized by withdrawal occurring after a drug is discontinued (Fishman et al., 2010). OIH occurs when patients develop reduced pain thresholds and increased pain sensitivity as a result of using opioids (Gandhi et al., 2011). Opioid intake in patients with OIH ironically causes pain to

become worse (Angst & Clark, 2006; Compton, 2008). It is treated by decreasing opioid intake (Mitra, 2008), quite unlike the treatment for pain resulting from opioid tolerance (Compton, 2008; Gandhi et al., 2011).

A clinical challenge is presented when patients with acute-on-chronic pain come to the hospital; opioid doses are relatively high, and there is no obvious improvement in pain scores despite administration of these seemingly large doses. Care providers are thus left unarmed, as they have nothing in their 'toolbox' for these patients and often resort to administering more opioids (Angst & Clark, 2010). As a result of the opioid escalation during their acute stay, these patients are often discharged home on larger doses of opioids than they came in on, causing an increase to their physical opioid dependence. Frequently, primary care physicians do not know what to do for these individuals upon return to the community, resulting in failure to taper down opioid doses appropriately (Angst & Clark, 2010). The next time patients experience acute-on-chronic pain, they repeat this cycle of opioid escalation but with higher baseline doses.

While opioid therapy for chronic pain has been used increasingly over the past few decades (Ballantyne & Shin, 2008), chronic neuropathic and radicular pain are usually resistant to opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) (DeLeo, 2006). Future developments in non-opioid drug therapy may provide treatment options for those who suffer from chronic pain (DeLeo, 2006). One potential treatment option is ketamine.

Ketamine is an N-methyl D-aspartate (NMDA) antagonist that blocks transmission of painful stimuli. It can reduce opioid need and be used to treat hyperalgesia (Gandhi et al., 2011; Pasero & McCaffery, 2005). It is used as an adjunct to anesthesia, as well as an adjunct to or for the primary treatment of pain (Angst & Clark, 2010; Pasero & McCaffery, 2005). Post-operative ketamine infusions decrease opioid requirements and improve analgesia in opioid tolerant

patients with chronic pain (Gandhi et al., 2011). Ketamine may be a good adjunct for treating acute-on-chronic pain because of its analgesic and opioid-sparing properties (Angst & Clark, 2010), and could potentially reduce the amount of opioids these patients are taking on discharge.

Low-Dose Ketamine Continuous Intravenous Infusion Protocol

In April of 2012, the Calgary Zone of Alberta Health Services (AHS) Acute Pain Service (APS) successfully implemented the Low-Dose Ketamine Continuous Intravenous Infusion (LDKCII) protocol for analgesia (Vaid, 2013). Although the anesthesia department expressed a desire to use ketamine for many years, the administration of ketamine on AHS medical/surgical nursing units had been met with substantial resistance due to an institutional drug monograph that required exhaustive nursing care and physician presence whenever ketamine was administered (Vaid, 2013).

After the APS nurse conducted a literature and practice review, the restrictive drug monograph was found to be outdated and was amended for the LDKCII protocol (Vaid, 2013). A learning module, protocol draft, and physician order set were created based on the literature as well as practice recommendations and advice from pain specialists from other centers. Within the Calgary Zone of AHS, LDKCII was administered at low doses of 50-200mcg/kg/hour over a few post-operative days in opioid tolerant individuals in addition to standard post-operative analgesia regimes such as Patient Controlled Analgesia (PCA), opioids, and analgesic adjuvants (AHS, APS, 2012).

The evidence for using ketamine with the spinal surgery population and the feasibility of rolling out such an initiative were discussed among a multidisciplinary team of key stakeholders (Vaid, 2013). In addition to the self-study learning module, a large number of education sessions were offered to staff nurses that included pain theory, ketamine pharmacology review, a case

study scenario and low-fidelity simulated programming pump practice. April 20th, 2012 marked the first day that the LDKCII was administered to a patient post-spinal surgery.

Challenges of Treating Acute-on-Chronic Pain

Patients stabilized on an analgesic regime for chronic pain cannot have their analgesia needs met using a simple 'one size fits all' approach as doing so may lead to under-dosing and potential opioid withdrawal (Fishman et al., 2010). Analgesia needs to be tailored to individuals according to their pre-operative need of opioids (Huxtable et al., 2011; Mehta & Langford, 2006). Ideally, opioid tolerant patients should have their baseline opioid restarted post-operatively and given extra opioid for the acute event (Fishman et al., 2010; Mehta & Langford, 2006). There is no established way to determine opioid need of patients who are opioid tolerant and experiencing acute-on-chronic pain (Huxtable et al., 2011). Because there is no homogenous way to treat acute-on-chronic pain, it is quite difficult to study effectiveness of interventions such as the LDKCII.

Calgary Zone APS Practice Considerations for Acute-on-Chronic Pain

Although there are differences among the way that pain is treated for the spinal surgery patient population, there are some 'norms' that APS practitioners at Foothills Medical Centre (FMC) practice when caring for these patients. Pre-operatively, patients are encouraged to take their morning doses of analgesics. Intra-operative anesthesia varies depending on the anesthesiologist assigned to the case. Post-operatively, the general practice is that patients receive analgesia tailored to prior opioid consumption using a practice rule of total daily pre-operative opioid intake plus 30%-50% to account for the acute pain episode.

The Calgary Zone APS prescribes multimodal analgesia post-operatively to patients. Additional analgesics and adjuvants are commonly including acetaminophen (up to 4 g per day)

which is usually for prescribed for seven days. Any analgesics or adjuvants patients are stabilized on pre-operatively (such as antidepressants and anticonvulsants) are usually restarted as soon as possible post-operatively. Some spine surgeons do not allow NSAID use post-operatively as they believe that NSAIDs may impede bone healing. Thus, NSAIDs are generally not administered to this population at FMC.

Since the implementation of the protocol, patients with acute-on-chronic pain may receive ketamine IV infusion post-operatively in addition to 'standard' treatment (as described above) at a dose of 50mcg/kg/hr up to 200 mcg/kg/hr titrated to patient tolerance. Whether or not a patient receives ketamine is based on the practitioner's assessment. Generally speaking, if the practitioner does not feel the patient will do well on conventional therapy they are started on LDKCII. Known adverse effects of ketamine are nausea and psychotomimetic effects which can be treated by providing anti-emetics and benzodiazepines in addition to reducing the rate of ketamine infusion (AHS, APS, 2012). Anti-emetics are available to individuals receiving opioids, and benzodiazepines are available to all patients receiving LDKCII therapy when being followed by APS.

Study Purpose

The LDKCII treatment modality that was implemented for the post-operative spinal population in the Calgary Zone of AHS presented a unique opportunity to perform a retrospective study to examine the effectiveness of this protocol on patients' post-operative pain, opioid use, time to ambulation and time to discharge. The proposed research question was: "what is the effect of low-dose ketamine continuous intravenous infusions on pain of highly opioid tolerant adults following spinal surgery?"

CHAPTER 2: REVIEW OF THE LITERATURE

The purpose of this chapter is to review pain physiology and to present existing relevant literature on ketamine used for treating pain. The literature presented below provides significance and rationale for studying this topic. This review of current literature also shaped the research question and methods.

Review of Pain Concepts and Physiology

Pain is a complex phenomenon. The globally accepted definition of pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, Bogduk & IASP, 1994, p.210).

Types of Pain

Pain can be classified based on pathophysiological origin, there are two major types of pain: nociceptive and neuropathic (Pasero & McCaffrey, 2011). Nociceptive pain results from normal sensation processing resulting from tissue damage and is further divided into somatic and visceral pain (Pasero & McCaffrey, 2011). Neuropathic pain can be caused by disease or injury of nerves and results from abnormal sensory input processing by the nervous system. This type of pain is further divided into centrally and peripherally generated pain (Pasero & McCaffrey, 2011).

Pain can also be categorized into two subsets: acute pain and chronic pain. Acute pain results from injury that lasts a relatively limited time and resolves when the underlying cause and pathology resolve (Fishman et al., 2010). Chronic pain lasts for a longer period of time. The pathology does not explain the extent of the pain and likely results from a pathology other than the originating cause (Fishman et al., 2010). Chronic pain may be a result of nerve alteration and may be influenced by environmental and genetic factors (Fishman et al., 2010). Other important

pathophysiologic pain terms include *hyperalgesia*, (an increased sensitivity to noxious stimuli) and *allodynia*, (an increased sensitivity to non-noxious stimuli; DeLeo, 2006).

Acute and Chronic Pain Physiology

Pain processing occurs at three levels: peripheral, spinal and supraspinal (DeLeo, 2006) (see Figure 1). The pain pathway begins when tissue damage activates nociceptors (A delta and beta fibers, and C fibers) which release algesic mediators (Gandhi et al., 2011). Inflammatory mediators activate primary nociceptors and transmit their signals to the dorsal root ganglion of the spinal cord (Gandhi et al., 2011). Peripheral signals arrive at the dorsal horn of the spinal cord and activate receptors in spinal neurons that project to the brain (Dickenson, 2008). Peripheral sensory transmitters include substance P and glutamate; glutamate aids in transmitting nociception in acute and chronic pain (Dickenson, 2008).

The transmission of pain can be modulated at the dorsal horn or the brainstem and midbrain (Gandhi et al., 2011). Pain modulation occurs at the dorsal horn by ascending pathways that carry messages to higher centers or descending inhibitory pathways that inhibit release of algesic mediators (DeLeo, 2006). Within the central nervous system (CNS), nociceptive signals are modulated by numerous excitatory and inhibitory mechanisms when one experiences pain (Marchand, 2008). The modified transmission is sent to the somatosensory cortex which perceives and localizes the pain (Gandhi et al., 2011).

Figure 1: The Pain Pathway

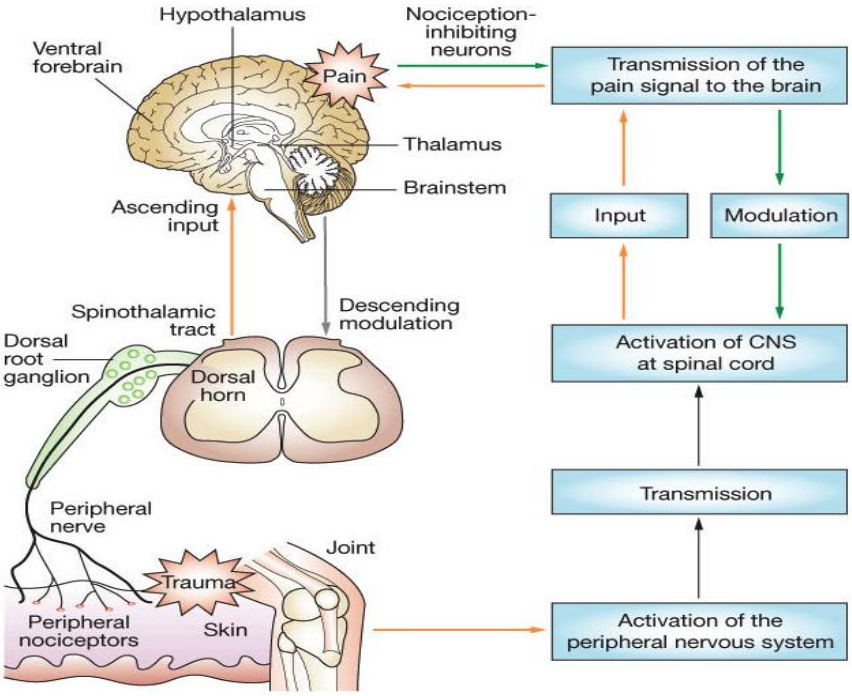

Figure 1 The nociceptive pain pathway. Activation of peripheral pain receptors (also called nociceptors) by noxious stimuli generates signals that travel to the dorsal horn of the spinal cord via the dorsal root ganglion. From the dorsal horn, the signals are carried along the ascending pain pathway or the spinothalamic tract to the thalamus and the cortex. Pain can be controlled by pain-inhibiting and pain-facilitating neurons. Descending signals originating in supraspinal centers can modulate activity in the dorsal horn by controlling spinal pain transmission. Abbreviation: CNS, central nervous system.

Figure 1. Reprinted by permission from Macmillan Publishers Ltd: Nature Clinical Practice Rheumatology (Bingham, Ajit, Blake & Samad, 2009. The molecular basis of pain and its clinical implications in rheumatology. *Nature Clinical Practice Rheumatology*, *5*(1), 28-37. doi:10.1038/ncprheum0972), copyright (2009). For copyright permission see Appendix A.

Pain is dynamic and nociceptive signals can be modulated throughout the CNS. Chronic pain can include changes at excitatory or inhibitory pain sites (Marchand, 2008). Plasticity alters nociceptive transmission and can lead to persistent pain states by way of sensitization of peripheral nerves, hyperexcitability of spinal cord neurons and changes in descending controls (Dickenson, 2008). Chronic pain can result due to changes within the CNS. One example of this is sensitization, where nociceptive neurons in the spine become hyperactive (Marchand, 2008).

NMDA receptor activation can be linked to wind up (an increased response to repeated stimuli), and to central sensitization (a decreased threshold for response or increased response to a stimulus) (Fishman et al., 2010). „Wind up' is a phenomenon characterized by repetitive firing of C fibers with increased dorsal horn response (see Figure 2). It is dependent on glutamate release which can act on receptors such as the NMDA receptors (DeLeo, 2006). NMDA receptors are activated by prolonged membrane depolarization and glutamate binding (Dickenson, 2008). Glutamate is a key part of central sensitization, which is a state of neuroaxis hyperexcitability (DeLeo, 2006). Magnesium can block NMDA receptor channels (Fishman et al., 2010). NMDA antagonists such as ketamine can block wind up and central sensitization and prevent these phenomena from occurring if given prior to NMDA receptor activation (Fishman et al., 2010). NMDA antagonists could be useful in reversing sensitization or if used prophylactically during surgery, and could prevent chronic pain (Marchand, 2008).

Figure 2: Wind-up Phenomenon

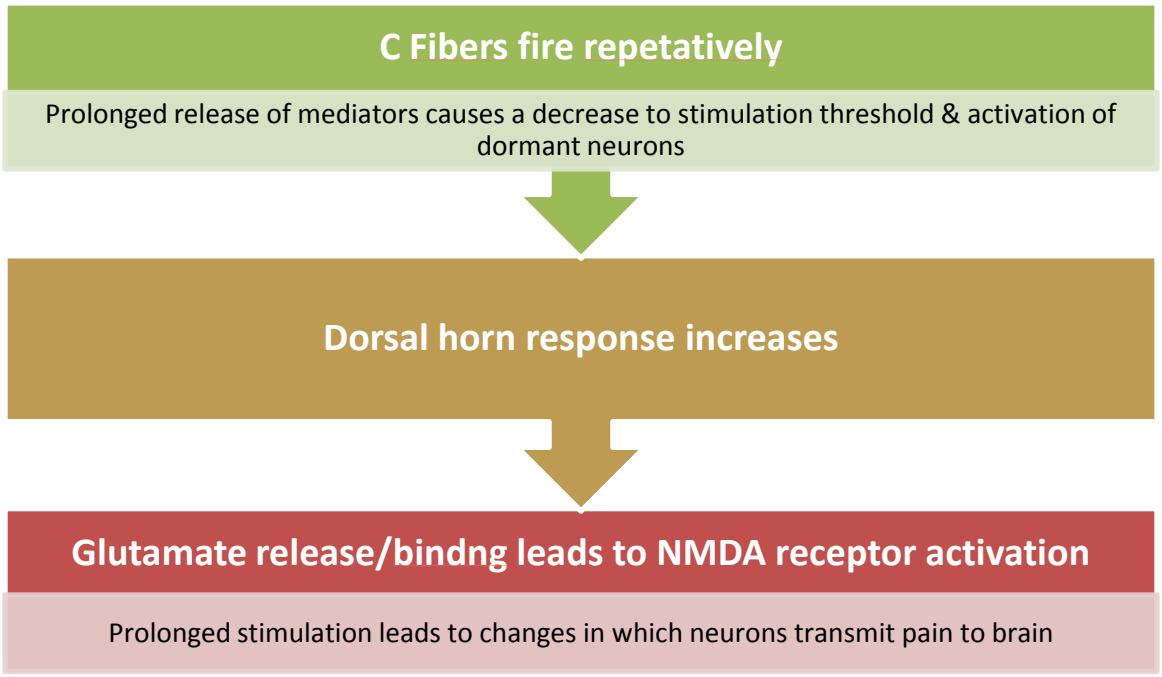

Figure 2. The wind up phenomenon process.

Literature Review of Ketamine Use for Pain

A literature search of journal articles using the title terms "ketamine", and key terms of "post-operative" and "chronic pain" was conducted using CINAHL and MEDLINE databases for the years 2007-2012. Search criteria included articles written in English with full text availability. Articles were eliminated if studies involved children. Attempting to obtain only recent sources resulted in a handful of relevant articles thus the search was expanded to the past ten years. Due to the scarcity of literature on this topic, some articles were also identified from reference lists of literature examined. The final fourteen articles found through this search were written from 2003 to 2011 predominantly from the disciplines of medicine and pharmacy; only one nursing article was returned.

Examining the Literature

The most common outcome measure was pain measured by using the numerical rating scale (NRS). This is a reliable measurement tool commonly used by healthcare professionals to assess patients' pain. Patients are asked to rate their pain on a scale from zero to ten, where zero is no pain and 10 is the worst pain imaginable (Pasero & McCaffery, 2011; Figure 3). Another outcome measure was opioid consumption, commonly measured in oral morphine equivalents based on the principle of opioid equianalgesia.

Figure 3: Numerical Rating Scale

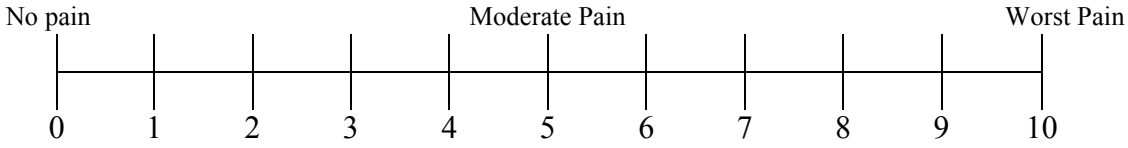

Figure 3: Numerical Rating Scale. Adapted from Pasero, C. , & McCaffery, M. (2011). *Pain assessment and pharmacologic management*, p. 58. St. Luis, Mosby. "The scale is in the public domain. May be duplicated for use in clinical practice" (Pasero & McCaffery, 2011, p. 58).

In all studies examined, ketamine was administered via intravenous (IV) route. Ketamine doses described in the articles were converted to mcg/kg/hr wherever possible to allow for easier comparison between studies. The literature was categorized into ketamine use for non-cancer chronic pain, post-operative analgesia, and post-operative analgesia in patients with pre-existing chronic pain (see Table 1).

Table 1: Literature Review Summary by Ketamine Indication

Ketamine For Chronic Non-Cancer Pain	Ketamine For Post-Operative Analgesia	Ketamine For Post-Operative Analgesia In Patients With Pre-Existing Chronic Pain
Hocking & Cousins (2003)	Laskowski et al., (2011)	Loftus et al. (2010)
Bell (2009)	Elia & Tramer (2005)	Subramaniam et al. (2011)
Schwartzman et al. (2009)	Chazan et al. (2010)	
Sigtermans et al. (2009)	Remerand et al. (2009)	
Kiefer et al. (2008)	Dualé et al. (2009)	
	Sen et al. (2009)	
	Nourozi et al. (2010)	

Note: Studies reviewed examining ketamine use as an analgesic summarized according to treatment indication.

Ketamine for Non-Cancer Chronic Pain

Hocking and Cousins (2003) conducted a systematic review of ketamine used for chronic pain and reported that ketamine was a used most frequently as a third line agent for treating acute-on-chronic pain (level IV). Overall, there was weak to moderate evidence to support the use of ketamine in treating chronic pain and the authors suggested that further study was needed (Hocking & Cousins, 2003). Since then, Bell (2009) conducted a topical review on the use of ketamine for chronic non-cancer pain, summarizing findings from twenty-nine controlled trials with a total of 579 patients. Different routes of ketamine administration were examined. Bell concluded that ketamine should not be used as long-term therapy for chronic pain. Suggestions for further research included finding an optimal route and dose for ketamine. There were no suggestions for use of ketamine in patients with acute-on-chronic pain. Since this review in 2009, three relevant studies have been conducted using varied range of doses and lengths of treatment using ketamine for complex non-cancerous chronic pain (see Table 2). Authors of all three studies examined complex regional pain syndrome (CRPS), a severe chronic pain condition, and found that ketamine reduced pain.

Table 2: Ketamine for Complex Regional Pain Syndrome

Author	Study Type	Sample Size	Ketamine Dose	Pain
Kiefer et al. (2008)	Open label phase 2 study	n=20	starting at 3000mcg/kg/hr up to 7000mcg/kg/hr by continuous infusion for 5 days	reduced
Schwartzman et al. (2009)	DBRCT	n=19	35mcg/kg/hr (or less than 25mg/hour) 4 hours per day for 10 days	reduced
Sigtermans et al. (2009)	DBRCT	n=60	infusion at a maximum dose of 432mcg/kg/hr for 4.2 days	reduced

Note: Studies examining ketamine use for CRPS. DBRCT= double blind randomized controlled trail.

Kiefer et al. (2008) conducted a study of twenty patients that were admitted for a five-day course of treatment with anesthetic doses of ketamine. All patients were admitted to ICU for monitoring; 85% of patients were intubated. All patients were given clonidine and midazolam in conjunction with the ketamine therapy. All were weaned off their infusions in ICU and then discharged home after a maximum of sixteen days in hospital. Overall mean NRS pain scores were 8.9 initially, and post-treatment were 0.5 at one week, 0.6 at one month, 0.9 at three months, and 2.0 at six months. Quality of life and ability to work improved in most patients. This particular study did not have a control group. Although there were drastic improvements in pain scores among the patients treated, there could be a large placebo effect due to the extent of intervention provided.

Schwartzman et al. (2009), concluded that ketamine reduced pain in patients with CRPS. Patients enrolled in this study had to have failed previous traditional pain treatments. The patients were placed randomly into two groups and received either normal saline infusion (control) or ketamine infusion (treatment). Clonidine and Midazolam were administered to both

groups. Patients in this study ranked their average overall pain pre-intervention on the NRS as 7.5 (control group) and 7.9 (treatment group). Schwartzman et al. were able to show that there was a 21.4% reduction in pain scores among the ketamine group vs. 3% reduction in pain scores of the control group, which was considered to be statistically significant despite the very small number of participants. Patients treated with ketamine showed an 85% reduction in waking throughout the night due to pain. Measured activity levels did not show a statistical change between the treatment and placebo groups. The trial was stopped half way through because the placebo group did not receive as much of a benefit as was initially expected. Unfortunately, Schwartzman et al. did not discuss prior opioid dosages or possible opioid dose reduction in either group. The only mention of previous medications stated that patients were able to continue their CRPS medications if they had been stabilized on them prior to enrollment.

Another RCT was conducted by Sigtermans et al. (2009), who also concluded that pain scores improved in patients with CRPS post ketamine treatment. Two groups of patients were admitted as inpatients and placed on 4.2 days of infusions; one received a placebo and the other received ketamine. Ketamine rates were titrated up to effect, and down when side effects were intolerable. Initially, ketamine was very effective as compared to placebo in improving pain scores; patients' mean initial NRS scores were 7.2 and 6.9 and changed to 2.7 and 5.4 in the first week after treatment for ketamine versus control groups respectively. Sigtermsans et al. reported pain improvement for up to 11 weeks, however there was no statistical difference between pain scores of both groups at twelve weeks post-intervention. This was a larger study with a more extensive intervention that required a four-day hospital admission with smaller doses of ketamine administered for a longer period. It would seem that the extent of the intervention does not seem justifiable if similar results can be attained by intermittent infusions to outpatients as

demonstrated by Schwartzman et al. (2009). The study by Sigtermans et al. (2009) excluded patients on large doses of strong opioids, which would exclude the proposed study population of this thesis.

Ketamine For Post-Surgical Analgesia

Elia and Tramèr (2005) conducted a systematic review of ketamine use for post-operative pain that found inconclusive evidence for the role of ketamine due to weak methodology, varying practice (ideal dose undetermined), limited sample sizes, and inconsistent outcome measure reporting. In a more recent systematic review examining ketamine use for post-operative analgesia, Laskowski, Stirling, McKay, and Lim (2011) concluded that ketamine was a useful adjunct to current therapies for large painful surgeries. Forty-seven studies from 1966 to 2010 were compared and analyzed. In 37.5% and 25% of the studies, there was significant improvement in early and late pain scores respectively in patients treated with ketamine compared to placebo. In these studies, patients in the placebo group consumed more opioids and reported higher pain scores over-all, particularly with very painful surgical procedures. There was no observed correlation of ketamine dose with pain score improvement, thus optimal dosage could not be determined. Laskowski et al. identified that prevention and treatment of chronic pain with ketamine has been inadequately studied and suggested further study should be targeted towards using ketamine for painful surgical procedures where high opioid use and chronic pain is more prevalent. The following studies (see Table 3) were conducted to examine ketamine use for post-operative pain following major surgeries.

Table 3: Double Blind Randomized Controlled Studies of Ketamine for Post-Operative Pain

Author	Sample Size	Study Population	Ketamine Dose	Pain	Opioid Use
Chazan et al. (2010)	n=46	Post-transthoracic surgery	ketamine 5mg per dose combined with narcotic in PCA x 72 hours	improved	reduced
Dualé et al. (2009)	n=86	Post thoracotomy	intra-operatively at a dose of 1000mcg induction dose followed by 1000 mcg/kg/hr intra-operatively, and then post-operatively with a dose of 42mcg/kg/hr for 24 hours	improved	no change
Nourozi et al. (2010)	n=100	Post major abdominal surgery	ketamine 250mcg/kg plus opioid given as bolus in recovery room	improved	reduced
Remerand et al. (2009)	n=154	Post total hip arthroplasty	intra-operatively (500mcg/kg) and then continually at a dose of 120mcg/kg/hr for 24 hours	no change	reduced
Sen et al. (2009)	n=60	Post elective hysterectomy	initial IV bolus of 300mcg/kg followed by infusion of 50mcg/kg/hr intra-operatively	no change	reduced

Note: Summary of double blind RCT studies examining ketamine use for pain.

Chazan, Buda, Nesher, Paz, and Weinbroum (2010) showed a 40% reduction in morphine use, increased patient and family satisfaction, and improved pain scores in patients treated with ketamine. Patients with chronic pain conditions or patients using chronic analgesia were

excluded. The main focus of outcomes surrounded patient and family satisfaction, which could have been skewed by noise on the unit, time to extubation, reactions to healthcare workers and successful tumor removal.

Dualé et al. (2009) found that ketamine use improved initial pain scores but failed to improve incidence of chronic neuropathic pain at six weeks and four months post-thoracotomy. The study excluded patients with chronic pain or patients on opioids pre-operatively.

Nourozi et al. (2010) conducted a study where patients were given either Demerol 10mg doses (control) or ketamine 250mcg/kg plus meperidine 5mg doses (treatment) in the recovery room post major abdominal surgery. Once all patients left the recovery room, their pain was treated with meperidine on an as needed basis. Nourozi et al. demonstrated a decreased need for opioid and lower pain scores in patients that received ketamine in the recovery room. The authors excluded patients with chronic pain or patients on chronic opioids pre-operatively. Notably, this study allowed the use of nitrous oxide (N_2O) intra-operatively and used meperidine as the opioid post-operatively where both have been found to have NMDA antagonistic properties similar to that of ketamine. Including both of these drugs in the treatment regime of all patients could have skewed the results.

Remérand et al. (2009) showed ketamine used in the acute phase post total hip arthroplasty (THA) reduced pain in both immediate and long term time periods. Patients received traditional analgesia consisting of acetaminophen, morphine, NSAIDs, plus either ketamine (treatment) or normal saline (placebo). Patients on ketamine infusions used 28% less morphine on the first post-operative day (POD), and less morphine overall as compared to the control group. Pain scores between the two groups were similar. The incidence of chronic pain at twelve to eighteen months after THA is 28% (Nikolajsen, Brandsborg, Lucht, Jensen, & Kehlet, 2006),

however Remérand et al. (2009) found that chronic pain at rest was reported in 21% of patients in the control group vs. 8% in the ketamine group at 6 month's time. Remérand et al. excluded participants who were on morphine doses exceeding 10mg oral equivalent, or neuropathic pain treatment agents such as clonazepam or gabapentin.

Sen et al. (2009) examined patients post elective hysterectomy who were randomized into three groups: one receiving IV and oral placebo, one receiving IV ketamine with initial IV bolus followed by infusion with oral placebo, and one receiving gabapentin 1.2g/day and IV placebo. Patients were treated post-operatively with IV morphine PCA and then oral codeine plus acetaminophen. Sen et al. reported that patients treated with ketamine and gabapentin had decreased opioid need in the initial post-operative phase. The authors excluded patients with chronic pain conditions, and patients on gabapentin or opioids pre-operatively.

Ketamine for Post-Surgical Analgesia in Patients with Pre-existing Chronic Pain

Laskowski et al. (2011) identified that prevention and treatment of chronic pain with ketamine has been inadequately studied and suggested further study should be targeted towards examining ketamine use for painful surgical procedures where high opioid use and chronic pain are more prevalent. There was very little literature available of ketamine use with this particular population subset; no systematic reviews were found. There were only two studies in which the use of ketamine in patients who were previously opioid tolerant were examined (see Table 4). The studies had contradicting findings.

Table 4: Studies Examining Ketamine Use in Opioid Tolerant Patients Post Spinal Surgery

Author	Sample Size	Ketamine Dose	Pain	Opioid Use	Other Findings
Loftus et al. (2010)	n=102	500mcg/kg on induction + 600mcg/kg/hr intraoperatively	improved	reduced	Trend lasted 6 weeks post-operatively
Subramaniam et al. (2011)	n=30	150mcg/kg bolus + 120mcg/kg/hr intraoperatively and 24hrs post-operatively	no effect	no effect	Side effects not increased with ketamine use

Note. Both studies were double blind randomized controlled trials where authors considered a $p < 0.05$ to be statistically significant.

Loftus et al. (2010) examined pain post spinal surgery with patients who had chronic back pain and took opioids pre-operatively. The study had two groups of participants, one that received saline as placebo, the other received ketamine. This study used a marker of 40% reduction in opioid for significance, which is much higher than the previous studies described thus far in this review. Loftus et al. found that using intra-operative ketamine reduced pain and total morphine consumption by 30% within the first 24 hours post-operatively (202 +/- 176 mg, placebo; 142 +/- 82 mg, treatment; $P = 0.032$). This trend continued to six weeks post-operatively where pain scores improved and opioid consumption was reduced (2.8 +/- 6.9 mg/h intravenously, placebo; 0.8 +/- 1.1 mg/h intravenously, treatment; $P = 0.041$). But Loftus et al. (2010) failed to control adjuvant analgesia, and the intervention group received less opioids but more NSAIDs intra-operatively than the control group (51mg mean morphine equivalent versus

67mg mean morphine equivalent, and 26% versus 6%, respectively). The authors described a consumption of 40mg oral morphine equivalent per day to be moderate. Furthermore, the pre-operative opioid use of patients enrolled in this study was not explicitly stated anywhere in the paper, yet the authors made large generalizations. According to what was reported, patients enrolled in this study used approximately 13mg of IV morphine equivalents pre-operatively (which is roughly 39mg oral using an acute pain conversion or 26mg using a chronic pain conversion). Patients used ten to twenty more times their prior morphine equivalent in the first twenty-four hours post-operatively. This was what was reported in table six of their study and would contradict their reported findings of reduced post-operative opioid consumption.

The study by Loftus et al. (2010) was critiqued by Seigne (2011) who pointed out the above deficits and an additional finding of larger extent of surgery in the treatment group versus placebo group which could have also changed statistical significance of the findings. Angst and Clark (2010) added a further criticism in that ketamine doses used were similar to those given to opioid naïve patients and that infusions should have been continued post-operatively.

Subramaniam et al. (2011) also examined pain of patients post major spine surgery. All patients received hydromorphone IV via PCA plus regional anesthesia, groups either received ketamine (treatment) or placebo of saline IV (control). The researchers found that ketamine did not improve analgesia ($P > 0.05$). The main factor that the authors failed to take into account what pre-operative opioid doses patients were taking. All patients were put on standard doses of hydromorphone PCA post-operatively (up to 1.25mg/hr, which is relatively low). This could have greatly under-dosed certain patients and caused an opioid debt resulting in higher pain scores in both groups. Patients may have gone through opioid withdrawal post-operatively if under-dosed.

Implications for Research Based on Literature Review

It is essential to address unique needs and explore novel treatment options for patients with acute-on-chronic pain. Most of the studies reviewed excluded individuals with pre-existing chronic pain on high doses of opioids. High-dose opioid therapy is defined as >200mg oral morphine equivalent per day (Chou et al, 2009). Patients with chronic back pain can be on pre-operative doses that well exceed this amount. According to the literature reviewed, ketamine use has been an effective treatment for complex chronic pain conditions and pain after major surgeries. However, the use of ketamine for acute-on-chronic pain has not been well examined.

Patients with acute-on-chronic pain may benefit from ketamine, both in the short and long term. The potential benefits of exploring this treatment modality could lead to improved patient outcomes in the opioid tolerant population, and provide an effective tool for healthcare professionals to use when faced with this complex patient situation. Therefore, the purpose of this study is to examine the question: "what is the effect of low-dose ketamine continuous intravenous infusions on pain of highly opioid tolerant adults following spinal surgery?" The methodology for this study is described in next chapter.

CHAPTER 3: METHODOLOGY

The intent of this chapter is to provide a description of methodology used in this study. Research design and sampling procedures will be depicted. A detailed explanation of the data collection and entry processes will be provided, followed by a list of operational definitions. Finally, ethical considerations will be discussed.

Research Design

A retrospective before-and-after (pre-post) between subjects design was used to address the research question: "what is the effect of low-dose ketamine continuous intravenous infusions on pain of highly opioid tolerant adults following spinal surgery?" The LDKCII treatment protocol implementation provided a unique study opportunity to examine this question.

The retrospective before-and-after design allows for an efficient way to study a patient population who has had a documented change in treatment due to a change in practice such as the introduction of the LDKCII. Retrospective studies in healthcare use medical records as pre-existing data sources (Hess, 2004). Before-and-after studies are performed by examining differences in dependent variables before and after an intervention and are often used to assess for wide-ranging interventions (National Institute for Health and Care Excellence, 2012).

Chart reviews are the most common method of healthcare quality assessments and are used widely for studying clinical and healthcare epidemiology (Wu & Ashton, 1997). Although retrospective before-and-after studies are not the gold standard of quantitative methods, this type of study allows researchers to assess interventions without the potential of harming patients by way of prospective interventions. The findings from these types of studies may be hypothesis generating and provide researchers with further direction to continue studying phenomena by way of prospective means (Hess, 2004), such as double blind randomized controlled trials.

Sampling

The Anesthesia Department approved the use of their database for the purpose of this study. A convenience sample of participants was identified using the Acute Pain Service Anesthesia Database (APSAD; see Figure 4). A list of all patients who were followed by the APS post spinal surgery in Calgary at FMC between April 20th, 2011 and April 19th, 2013 was pulled from the database. The control group consisted of patients who had surgery from April 20th, 2011 to April 19th 2012, while the treatment group consisted of patients who had surgery from April 20th, 2012 to April 19th, 2013. The patients in the control group were suitable to compare to the patients in the treatment group since APS is consulted for pain management of most patients who have acute-on-chronic pain post spinal surgery, and there were no additional known changes to treating this patient cohort.

Figure 4: Research Design

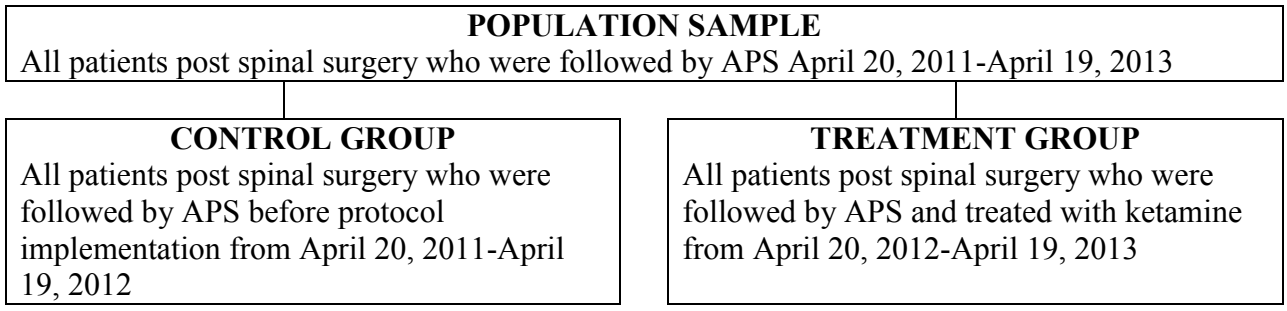

Figure 4. Research design for population sampling. Data collected from the pre-intervention group over a one year time span was compared to the next year's (post-intervention) group's data.

Outcome Measures

Primary outcome measures consisted of pain scores and daily opioid consumption on POD 0 through 5. Chronic pain can predispose patients to an increased amount and a slower resolution of post-operative pain (Chapman, Davis, Donaldson, Naylor & Winchester, 2011).

Examining pre-operative pain scores can aid with interpreting post-operative pain scores (Huxtable et al., 2011). Average daily pain scores may not be sufficient to analyze efficacy of an intervention for this population, therefore, worst and best pain scores were examined and compared to baseline data in hopes of detecting the most meaningful difference.

Secondary outcome measures were time to ambulation and time to discharge. Potentially confounding factors to the outcomes of this study included the use of intra-operative medications and post-operative analgesics and adjuvants. Use of intra-operative anesthesia, particularly the use of ketamine, opioid, lidocaine, magnesium and N_2O were examined. Timely re-starting of any pain medications patients were stabilized on pre-operatively was studied. Adverse effects (including CNS depression, vital sign changes, nausea and psychotomimetic effects) and treatment of these was examined in both groups.

Setting

This study was conducted at FMC, a level 1 trauma center and the only hospital in Calgary where spine surgery is performed. There are two patient care where post-spinal surgery patients are primarily admitted: unit 101 (a 19 bed unit) and unit 112 (a 27 bed unit).

Threats to Study Integrity

Several threats to this study should be acknowledged. First, the maturation threat: after surgery, patients are expected to have decreased pain levels and opioid use over time. Comparing the treatment group with a control group who received only standard therapy minimized this threat. Second, the historical threat: the LDKCII protocol was a fairly new modality for treating post-operative pain at the center where the study was conducted. The novelty of the protocol could have caused a variance in practice with length of infusion, provider response to adverse effects, and provider comfort to titrate therapy. Finally, the placebo effect of analgesia is up to

50% (Ballantyne & Shin, 2008; McCaffery & Pasero, 1999). This is a large limitation of the study as all individuals in the treatment group knew they were receiving ketamine. Both the historical and placebo threats could not be avoided using this method of study but could be addressed in a future prospective double blind RCT.

Inclusion and Exclusion Criteria

Eligibility criteria for both groups was limited to adults having spinal surgery with a documented chronic pre-operative opioid use of at least 100 mg daily oral morphine equivalent and who were followed by APS before POD 5. Exclusion criteria for both groups were:

- invasive anesthetic technique (such as single shot spinal opioid, nerve block or epidural placement),
- methadone use pre-operatively (as there is no calculation for conversion to morphine equivalent [Manfredi & Houde, 2003; Toombs2008]),
- cancer as primary diagnosis,
- lack of pre-operative data on pain or analgesic use, or
- unconventional opioid or IV drug use pre-operatively (as could not determine pre-operative morphine equivalent)

Patients who had surgery from April 20, 2011 to April 19, 2012 who were treated with ketamine post-operatively (either in ICU or oral use) were excluded from the control group.

Data Collection

Permission to access inpatient health records was obtained from AHS and the APS administration prior to undertaking chart reviews and data abstraction. All data were collected by a single reviewer between March and September of 2014 using a chart review template (Appendix B). Intra-rater agreement was based on the re-abstraction of many medical charts by

the abstractor at time 2 (on repeated occasions between April and September 2014) and comparing the re-abstracted data to data collected at time 1 (on repeated occasions between March and August 2014). While very few errors were found, those that occurred were corrected immediately. Unfortunately exact error rate was not recorded but intra-rater agreement was estimated to be well above an intraclass correlation 0.65.

After the initial query was done via query of the APSAD to generate a list of potential study participants, a manual chart review followed. Data were drawn from the inpatient health record (paper charts), the electronic health record called Sunrise Clinical Manager (SCM), as well as the APSAD.

Acute Pain Service Anesthesia Database

Data elements extracted from the APSAD included first name, last name, regional health record number, date of birth, age and procedure. Patient identifiers were used to obtain paper and electronic health records. They were kept confidential and were placed on a spreadsheet and cross-referenced with a unique study IDs (for template see Appendix C).

APSAD opioid use data were reviewed prior to electronic and paper records to apply the inclusion and exclusion criteria. The APSAD provided information on past medication use, course of analgesic treatment and response.

Sunrise Clinical Manager

Data obtained from SCM (the electronic health record) were accessed via desktop computer at FMC. The main data elements obtained from SCM included type of surgery, sex, weight, height, BMI, admission date, surgery date, discharge date, vital signs, analgesics used in hospital, adverse effects, medications used to treat adverse effects, ambulation date, pain scores, ketamine use, and pre-operative medication use.

Inpatient Health Record/Paper Chart

Medical records were obtained from the Health Information and Records Management Department. The data elements obtained from the paper records included any missing elements from the electronic review. These consisted of weight, height, BMI, vital signs, adverse effects, ambulation date, pain scores, ketamine use, and intra-operative and recovery room medication use.

Data Management

Data obtained from all of the sources were cross-referenced during the entire chart review process. Information collected was continually assessed for missing and illogical data. All errors found were corrected by referring to the electronic health record. All data were transcribed into electronic format using Microsoft Excel to prepare for analysis.

Data Analysis

Following transcription, all data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 19. A $p < .05$ was considered to be statistically significant. Percentages and ranges were used to describe the sample. Non-parametric data were explored using the Pearson Chi -square test for independence; the exact 2-sided significance was reported. If assumptions were not met for the Chi-square test, Fisher's Exact test was used.

All parametric data were first assessed for normality to determine on the route of appropriate analysis by way of the Kolmogorov-Smirnov statistic. When the value was less than 0.05 the assumption of normality was considered to be violated (Pallant, 2005). The independent-samples t-test was used as the parametric test whenever possible, and the Mann Whitney U was used as the non-parametric test when the t-test was not appropriate. For the t-test, Levene's test for equality of variances with a value of >0.05 was used to determine if equal

variances were assumed; the Sig. (2-tailed) value of < 0.05was used to determine any significant differences between groups (Pallant, 2005). The following chapter will further describe the statistical tests used for each data set in greater detail.

Operational Definitions

Below is an alphabetical list of operational definitions for terms used in this study.

Age

How old a participant was at the time of surgery; measured in years.

CNS Depression

Drowsiness or a sedation score of 2 "frequently drowsy, arousable, drifts off to sleep during conversation" (AHS, APS, 2015, p. 6; see Appendix D). CNS depression was measured using yes or no, depending on whether or not it was documented that patients were drowsy or had a documented sedation score of 2.

Hallucination

The experience of psychotomimetic effects such as auditory or visual disturbances. Measured as yes or no.

Morphine Equivalent

The amount of opioid converted to milligrams of oral morphine via the principle of equianalgesia Total opioid used in a 24 hour period was converted by using the table found in Appendix E, there was no amount taken off for cross tolerance. It was assumed that participants took maximum doses of as needed, or pro re nata (prn), opioid when calculating pre-operative 24-hour morphine equivalent.

Nausea

Uneasy feeling in the stomach; measured using yes or no, depending on whether or not it was documented that patients were nauseated, vomited, or received anti-emetics post-operatively.

Pain

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey et al., 1994, p.210). Pain at rest and with movement (wherever possible) was measured using the NRS. Any NRS scores greater than 10 were re-assigned a score of 10; any NRS scores less than zero were re-assigned a score of zero. If only one pain score was available pre-operatively, this was recorded as both 'at rest' and 'with movement' unless specified.

Pain Medication Reconciliation

The post-operative restarting of analgesics patients were stabilized on pre-operatively. This was measured as „yes' if all pre-operative analgesics were restarted or „no' if they were not. Medications reviewed included Tylenol, anticonvulsants, tricyclic antidepressants (TCAs), magnesium, NSAIDs and cox-2 inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, migraine specific modifications such as triptans, steroids, skeletal muscle relaxants, general anesthetics and cannabinoids.

Post-operative Day 0

Time frame from the end of the operation until 06:00 the next day.

Post-operative Day 1,2,3,4 and 5.

The 24 hour time period starting with how many days had passed since surgery (ie. POD 1 is the time from 06:01 on the day following surgery until 06:00 the next day).

Respiratory Depression

A decrease in breathing rate (breaths per minute); categorized as either yes or no. A score of yes was given if the patient received narcan for opioid induced respiratory depression, or action was taken to reduce opioid due to oxygen desaturation.

Sedation Score 3

Defined as "somnolent, minimal or no response to verbal and physical stimulation" (AHS, APS, 2015, p. 6; see Appendix D). Measured as yes or no.

Sex

A set of biological attributes, categorized as either male or female.

Spine Levels Operated On

How much surgery was performed on the spine; calculated by counting spinal levels operated on. „Ileum fusion' was counted as S1 unless otherwise specified.

Time to Ambulation

The duration between surgery date and moment patient first mobilized; recorded in days. The minimum amount of movement was marching at the bedside or taking a few steps.

Time to Discharge

The duration between surgery date and moment of patient left hospital; recorded in days. Calculated by subtracting admission date from the discharge date.

Ethical Considerations and Protection of Human Subjects

Ethics approval was granted by the Conjoint Health Research Ethics Board (CHREB). As this retrospective chart review did not involve any therapeutic interventions and presented minimal risk to participants, a waiver of consent was granted by the CHREB. Obtaining consent for access to this information would have been disruptive to patients and highly impractical.

Patients were not notified of this chart review, nor were they contacted at any time during the study. Their identity will not be revealed in the dissemination of the findings.

All data were kept secure. Personal identifiers, such as patient name and hospital number, were kept in a confidential file that cross-references participants to their assigned unique study number (for the format of this file see Appendix C). Personal identifiers were only used to obtain medical records from the Health Information and Records Management Department at FMC. Paper study records containing study data only had coded patient study numbers and were kept secure at all times. All electronic files that had any patient information were password protected. Confidentiality of identifying information was maintained at all times. Only aggregate data were presented in the study results, anonymity was protected as much as possible. Any published data will be presented in aggregate form so that participants cannot be identified.

CHAPTER 4: RESULTS

This chapter is intended to present the results of the study question "what is the effect of low-dose ketamine continuous intravenous infusions on pain of highly opioid tolerant adults following spinal surgery?" The purpose of this study was to examine the effectiveness of the LDKCII protocol on patients' post-operative pain, opioid use, time to ambulation and time to discharge. The chapter will begin with a summary of the sampling technique followed by a description of excluded subjects. Descriptive statistics will be used to characterize the sample and this will be followed by an analysis of potentially confounding factors. Finally an analysis of the primary and secondary outcomes data will be reported.

Sampling the Study Population

All patients who were followed by APS post spinal surgery in Calgary at FMC between April 20th, 2011 and April 19th, 2013 were identified by an initial database query. The APS followed 70 patients who had spinal surgery from April 20th, 2011 to April 19th 2012, and 97 patients who had spinal surgery from April 20th, 2012 to April 19th, 2013. Applying the exclusion criteria yielded a final **n= 28** for the control group and **n=17** for the treatment group (see Figure 5). Of note, during the treatment year, there were 11 patients that received LDKCII who used less than 100mg daily oral morphine equivalent and at least 17 patients that did not receive LDKCII but who used a pre-operative 100mg daily oral morphine equivalent.

Figure 5: Exclusion Criteria Application to Population Sample

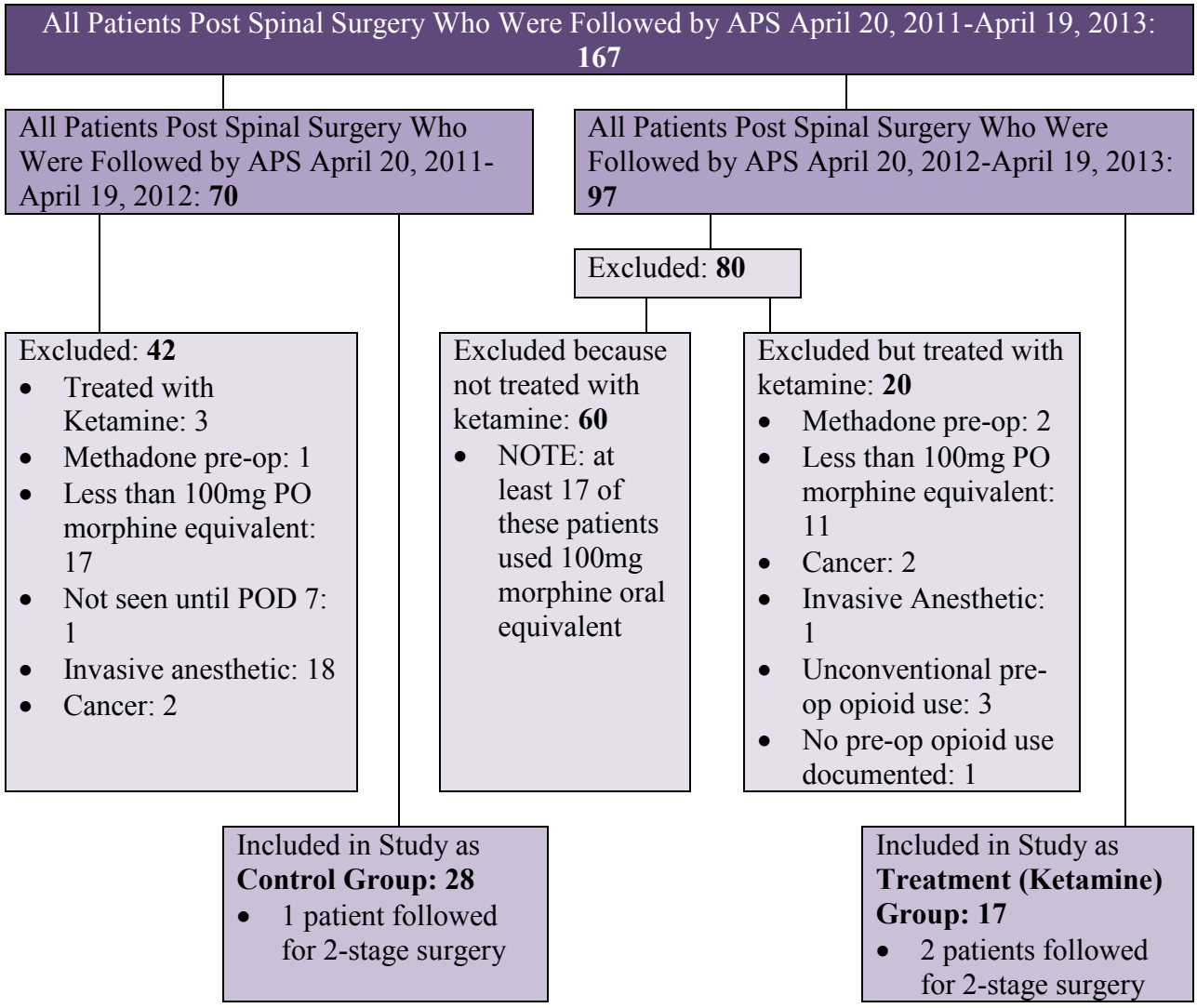

Figure 5. Application of exclusion criteria to the sample. Data collected from various sources, once exclusion criteria were applied to the initial samples of potential patients, two final groups of remained.

There was one subject in the control group who was followed by the APS for a two-stage surgery. The data from this subject were used as separate data sets where appropriate, therefore a total of n=29 participants were included in some of the following analyses. There were two subjects in the treatment group who were followed by the APS for a two-stage surgery. The data

from these two subjects were used as separate data sets where appropriate, therefore the n=19 for this group in some of the analyses. The rationale for treating the data from the 3 patients who had a two-stage procedure while being followed by APS as separate data sets is that APS followed all patients for whom they were consulted. Most of the health records reviewed for this study were of patients followed for a first stage surgery. There were only13.8% (n=4) in the control group and 10.5 % (n=2) in the ketamine group followed for a second stage procedure (p=1.0). Additionally, as the final n of the sample was quite small for both groups, including these patients as two separate encounters allowed for a more robust analysis.

Most of the patients included in this study were admitted on the day of procedure. There were six patients in the control group who were admitted prior to the spinal surgery date either because they had their first stage before the APS was involved (n=3), or because they were admitted for new symptoms that required them to have spinal surgery after investigations were completed (n=3). Only one patient in the control group was admitted prior to the date of their two-stage spinal surgery. Pre-operative data such as pain scores and opioid use were updated with the most recent 24-hours worth of hospital records for these patients.

Sample Characteristics

For the overall sample of n= 45 (control and intervention groups), age, weight and BMI were assessed for statistical significance using the independent samples t-test, while sex was assessed by using Chi Square. No statistically significant differences were found between groups (see Table 5). There were no missing demographic data in either group.

Table 5: Sample Characteristics

Characteristic	Control Group (n=28)	Ketamine Group (n= 17)	p-Value
Sex	9 male, 19 female	9 male, 8 female	.216
Age (years)	51.57 +/- 14.508 (24-81)	50.94 +/- 12.876 (29-78)	.884
Weight (kg)	83.93 +/- 25.435 (45-136)	83.59 +/-17.924 (57-127)	.962
BMI	31.32 +/- 7.414 (20-48)	30.41 +/- 5.397 (22-43)	.663

Note. All sample characteristics except sex are represented as Mean +/- Standard Deviation (Range). Total n=45.

The sample of n=48 (n=45 + 3) was further explored accounting for post-operative changes for the three patients who were followed for a two-stage surgery (see Table 6). Chi-Square analysis was used to examine whether or not home analgesic medications were reconciled while the Mann-Whitney U test was used to assess all other characteristics. None of the differences between groups were statistically significant.

Table 6: Sample Characteristics Where n=48

Characteristic	Control Group	Ketamine Group	p-Value
Pre-operative 24 hour Oral Morphine Equivalent	527.000 +/- 675.165 (105-3600)	570.105 +/- 579.577 (120-2288)	.487
Minimum Pre-operative Pain Score (R)	5.07 +/- 2.764 (1-10)	4.53 +/- 2.932 (0-10)	.726
Maximum Pre-operative Pain Score (R)	8.17 +/- 1.965 (4-10)	8.05 +/- 1.580 (5-10)	.610
Minimum Pre-operative Pain Score (M)	5.21 +/- 2.744 (1-10)	4.21 +/- 2.573 (0-8)	.402
Maximum Pre-operative Pain Score (M)	8.31 +/- 2.089 (3-10)	8.53 +/- 1.426 (5-10)	.883
Spine levels operated on	4.48 +/- 3.491 (1-17)	4.37 +/- 2.543 (2-10)	.597
Home Analgesia Reconciled[a]	72.4 % (n=21)	63.2 % (n=12)	.538

Note. All sample characteristics are represented as Mean +/- Standard Deviation (Range) except "home analgesia reconciled" which is represented as percentage of individuals who had their home analgesia reconciled post-operatively. Total n=48; control group n=29, ketamine group n=19. R=Rest, M=Movement.
[a] Measured using yes or no, depending if patients were re-started on their home analgesic regime post-operatively.

Medications not commonly reconciled included marijuana and NSAIDs. It was not this institution's practice to allow in-patients to smoke marijuana post-operatively. NSAIDs were typically avoided at this institution post spinal surgery due to fear of altered bone healing.

Intra-operative Analgesia

Intra-operative analgesia may affect post-operative pain outcomes in patients. As this was a retrospective chart review, there was no standardized approach to intra-operative anesthetics and analgesics. The intra-operative medications that were examined for the purpose of this study were those that can influence pain by way of NMDA receptors. There were no missing data for either group in any of the intra-operative analgesia analysis. There was no statistical difference detected via Chi-Square test in what patients from either group received intra-operatively for NMDA receptor affecting drugs as summarized in Table 7.

Table 7: Intra-operative NMDA Receptor Affecting Drugs

OR Medication	Control Group %(n)	Ketamine Group % (n)	p-Value
N_2O	6.9 (2)	10.5 (2)	1.000
Ketamine	65.5 (19)	63.2 (12)	1.000
Magnesium	17.2 (5)	31.6 (6)	.304
Lidocaine	34.5 (10)	47.4 (9)	.547

Note. All intra-operative medications are represented as percent of subjects that received the medication intra-operatively where n= number of patients in the group that received the medication. Total n=48; control group n=29, ketamine group n=19.

Intra-operative ketamine doses were also examined. There were two patients in the control group who received ketamine in the Post-Anesthetic Care Unit (PACU). The amount they received in PACU was counted towards their intra-operative dose. All other analgesics given in PACU were accounted for in the post-operative medication reconciliation list. The Mann-Whitney U test was used to show there was no statistical difference found between the two groups (see Table 8).

Table 8: Intra-operative Ketamine Doses

OR Ketamine	Control Group (n=19)	Ketamine Group (n= 12)	p-Value
Ketamine (mg)	77.900 +/- 37.539 (20-150)	95.817 +/- 51.714 (25-200)	.361

Note. Milligrams of intra-operative ketamine doses are represented as Mean +/- Standard Deviation (Range). Total n=31; control group n=19, ketamine group n=12.

The variation in anesthetic approach continued with type and amount of opioid used intra-operatively. All intra-operative opioids were converted to oral morphine equivalents for a more standard comparison between all patients (see Table 9). Data were not normally distributed so the Mann-Whitney U test was used.

Table 9: Intra-operative Opioid Use

OR Opioid Use	Control Group	Ketamine Group	p-Value
oral morphine equivalent (mg)	432.410 +/- 642.711 (60-3371)	452.160 +/- 220.127 (120-1000)	.018

Note. Intra-operative opioid doses were converted to oral morphine equivalents (in milligrams) and are represented as Mean +/- Standard Deviation (Range). Total sample n=48; control group n=29, ketamine group n=19.

There was a mean difference of 20 mg more of oral morphine equivalent opiod given intra-operatively to the ketamine group. This difference was considered to be statistically significant (p= .018) but would not necessarily be clinically significant given the large doses used. The total opioid used intra-operatively as well as in PACU was added to the POD 0 24-hour totals. Exploration of how much opioid both groups received post-operatively will be further elaborated on in the post-operative opioid use section.

Post-operative Ketamine Use

Patients in the treatment group received post-operative ketamine by continuous IV infusion ranging from 50-200mcg/kg/hr. The mean duration of infusion was 3.6 days with a standard deviation of 1.7 days, minimum 1.3 days and maximum 6.3 days.

Post-operative Pain

Pre-operative baseline pain scores were collected primarily from pre-operative records including the APSAD, the pre-operative nursing and physician assessments, SCM and consult notes. The best and worst recorded pain scores were documented and used for both pain and movement unless specified. For the three patients who underwent a two-stage surgery and were followed by the APS for both surgeries, the baseline pain scores were updated based on pain scores on the day prior to surgery, **only** if these differed from their previous baseline (this only applied to one minimum pain score with movement for one subject). POD 0 to POD 5 pain score data was collected primarily from SCM; very little was documented on pain scores in the paper record. Daily best and worst pain scores were collected wherever possible. If patients only had one score recorded for a full 24 hours, this was counted as the best and the worst pain scores for that day. Any pain score of greater than 10 was automatically re-assigned a score of 10 to prevent further skewing of data.

Pain scores of this study sample were expectedly higher than those without any pre-existing pain conditions. Unfortunately, data did not meet the normality assumptions to run a between groups repeated measures analysis of variance (ANOVA) to assess for any change over time between groups. The best and worst recorded pain scores in the post-operative period were analyzed using either the independent samples t-test or Mann-Whitney U test. There was no missing data in this modified analysis summarized in Table 10. No statistical difference on any type of pain score between the two groups was found.

Table 10: Post-Operative Pain Scores

Pain	Control Group	Ketamine Group	p-Value
Best Pain (R)	2.790 +/- 1.590 (0-6)	3.580 +/- 2.735 (0-10)	.267
Worst Pain (R)	9.100 +/- 1.235 (6-10)	9.260 +/- 8.060 (8-10)	.976
Best Pain (M)	4.030 +/- 2.383 (0-10)	4.580 +/- 2.610 (0-10)	.460
Worst Pain (M)	9.240 +/- 0.988 (7-10)	9.470 +/- 0.772 (8-10)	.508

Note. Pain scores are represented as Mean +/- Standard Deviation (Range). Total n=48, control group n=29, ketamine group n=19. R=Rest, M=Movement.

Missing data for pain scores resulted from lack of documentation, patients being discharged earlier than POD 5, or going to the operating room for the second stage of their surgery. For patients who were discharged early, the pain scores for that day were obtained from available data on the day of discharge, not the full 24 hours. The following are four line graphs of the mean pain scores of both groups preoperatively and on POD 0 to POD 5 (Figure 6-9). Missing data were excluded pair-wise. Overall there is a trend of an initial increase from baseline on POD 0 with a gradual decrease from this point (with some variation) over time.

Figure 6: Minimum Pain at Rest Over Time

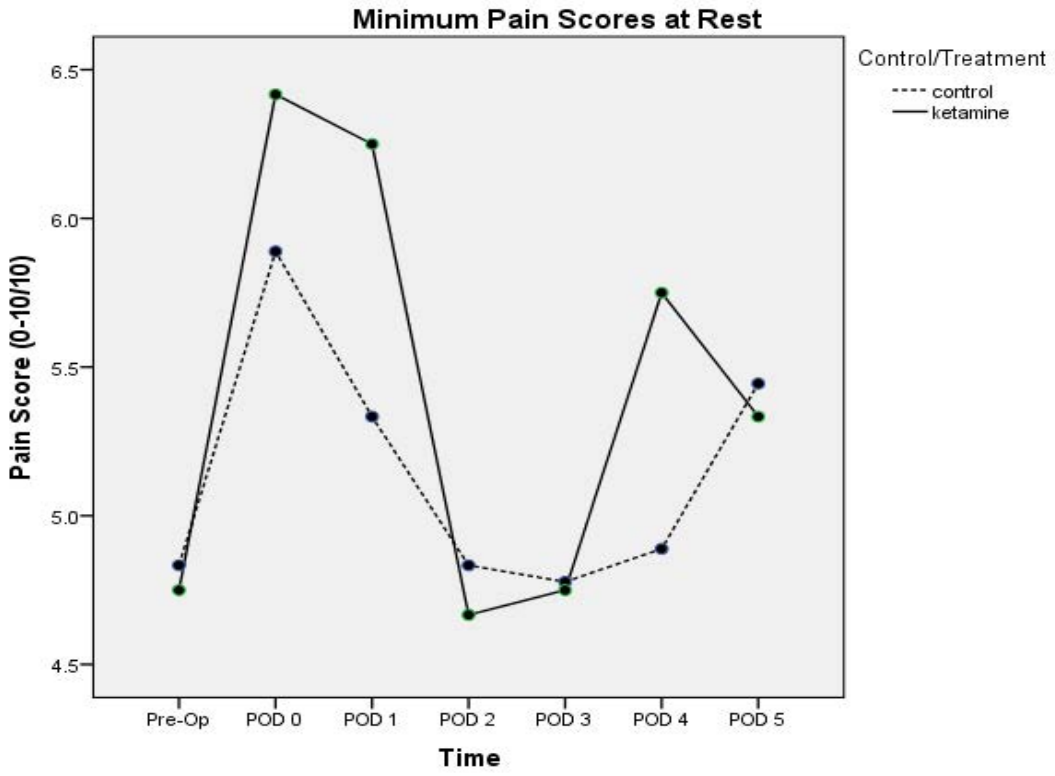

Figure 6. Mean minimum resting pain scores on the numeric rating scale pre-operatively, and post-operatively on days 0-5. Figure only represents patients with complete data; patients who were discharged early or went to the operating room were excluded from this graph. Total sample n=30; control group n=18, ketamine group n=12.

Figure 7: Maximum Pain At Rest Over Time

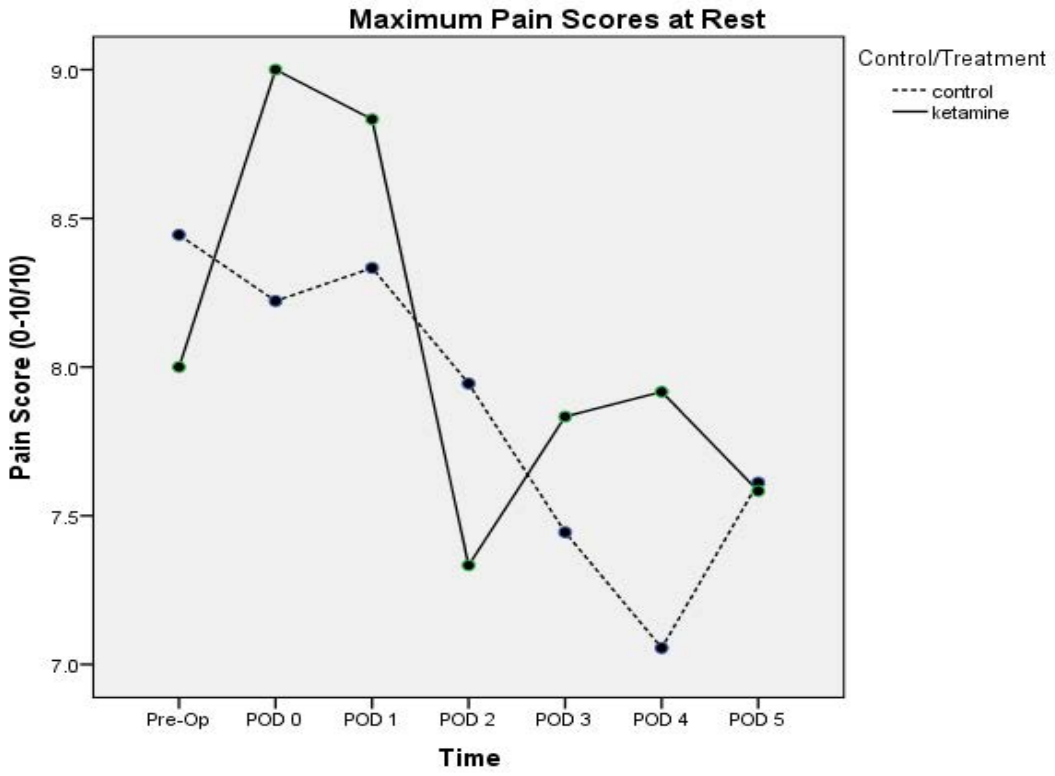

Figure 7. Mean maximum resting pain scores on the numeric rating scale pre-operatively, and post-operatively on days 0-5. Figure only represents patients with complete data; patients who were discharged early or went to the operating room were excluded from this graph. Total sample n=30; control group n=18, ketamine group n=12.

Figure 8: Minimum Pain With Movement Over Time

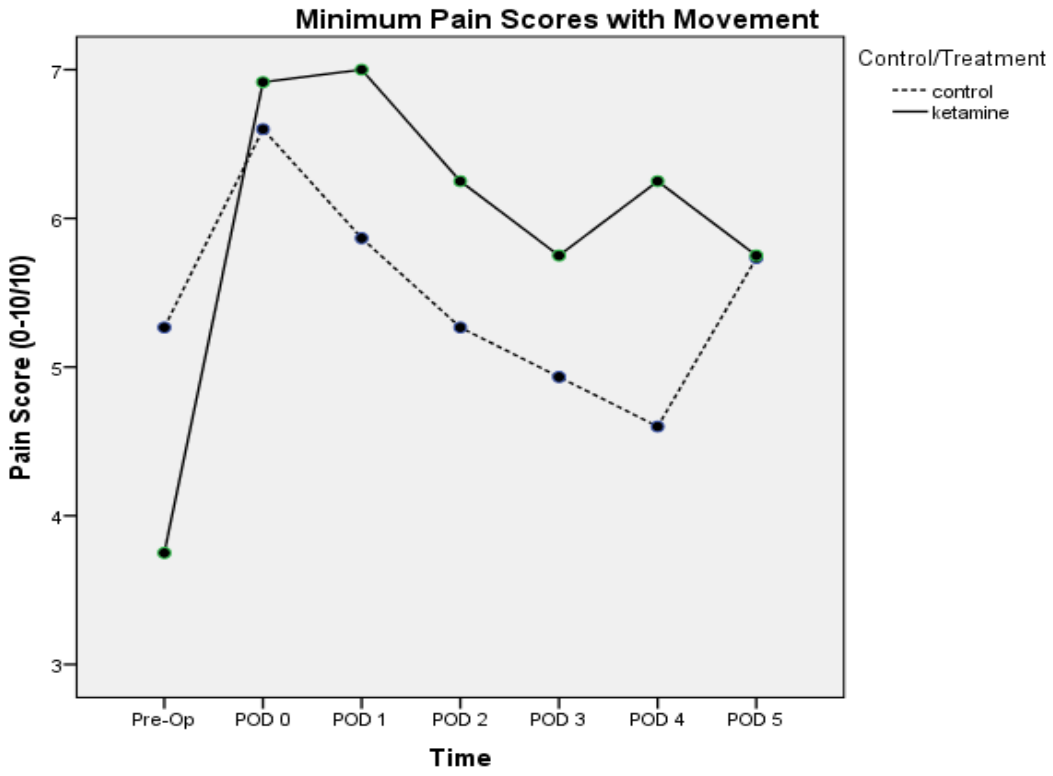

Figure 8. Mean minimum pain scores with movement on the numeric rating scale pre-operatively, and post-operatively on days 0-5. Figure only represents patients with complete data; patients who were discharged early or went to the operating room were excluded from this graph. Total sample n=27; control group n=15, ketamine group n=12.

Figure 9: Maximum Pain With Movement Over Time

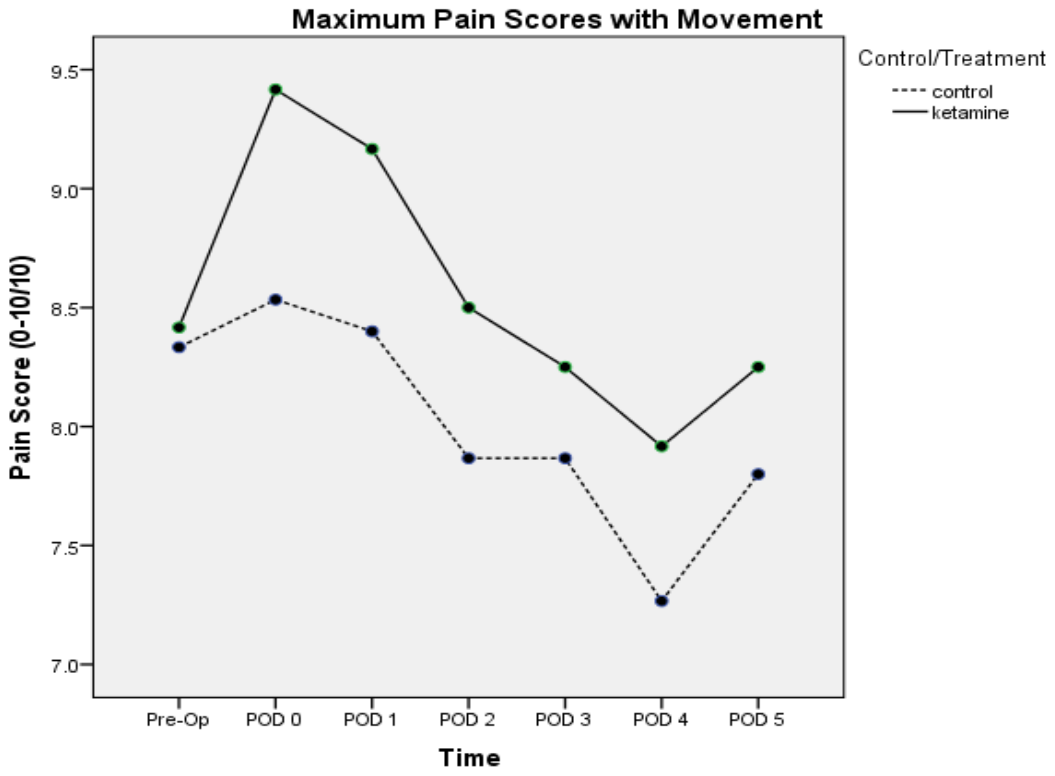

Figure 9. Mean maximum pain scores with movement on the numeric rating scale pre-operatively, and post-operatively on days 0-5. Figure only represents patients with complete data; patients who were discharged early or went to the operating room were excluded from this graph. Total sample n=27; control group n=15, ketamine group n=12.

Post-operative Pain Score Reduction

Post-operative pain was further analyzed by examining changes in pain scores from baseline. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus panel listed benchmarks of interpreting changes in chronic pain measures (Dworkin et al., 2008). For the NRS, they recommended a 10-20% decrease in pain be interpreted as minimally important, a 30% or greater decrease to be moderately important, and a 50% or greater decrease to be considered substantial (Dworkin et al., 2008). Pain scores were therefore examined for at least a 10, 30 and 50 % reduction and a Chi Square analysis was

performed (see Table 11). The comparison of baseline best pain scores pre-operatively and post-operatively revealed no significant difference between the two groups.

Table 11: Pain Score Improvement on the Numerical Rating Scale

Pain Reduction	Control Group % (n)	Ketamine Group % (n)	p-Value
10%=/< (R)	69.0 (20)	52.6 (10)	.362
30%=/< (R)	62.1 (18)	36.8 (7)	.140
50%=/< (R)	48.3 (14)	31.6 (6)	.370
10%=/< (M)	55.2 (16)	42.1 (9)	.556
30%=/< (M)	51.7 (15)	36.8 (7)	.382
50%=/< (M)	24.1 (7)	15.8 (3)	.719

Note. Pain score reductions are represented as percent of subjects that had a reduction from their baseline pain scores, where n= number of patients in the group that had a reduction in pain. Total n=48; control group n=29, ketamine group n=19. R=Rest, M=Movement.

Post-operative Opioid Consumption

Pre-operative opioid consumption data were collected primarily from pre-operative records including the APSAD, the pre-operative nursing and physician assessments, and consult notes. Unfortunately, only doses were available for analysis, not duration of outpatient opioid therapy. Opioids used on an as needed, or prn, basis were added to the pre-operative totals as though the participants took all of their daily allotted medication. The decision to estimate pre-operative opioid total in this manner was made because chronic pain patients have tendencies to underestimate their medication use (Kopf, Banzhaf & Stein, 2005). POD 0 to POD 5 opioid use data was collected from SCM. Daily opioid intake was collected and then converted to oral morphine equivalents in milligrams to allow for comparison between patient groups. Opioids given in the OR and PACU were added to the 24-hour POD 0 totals.

Missing data for these fields resulted from patients being discharged earlier than POD 5, or going to the operating room for the second stage of their surgery. For patients who were

discharged before POD 5, the opioid use was examined as a fraction of how many hours they were in hospital for that day and then converted to a 24-hour total.

For the six patients who were admitted prior to the date of their spinal surgery and the three patients who underwent a two-stage surgery and were followed by the APS for both surgeries, the pre-operative 24-hour morphine equivalent was used as a baseline to account for any acute pre-operative opioid escalation. Figure 10 displays mean opioid use in oral morphine equivalents over time for both groups. Cases were excluded pairwise if they had missing data; n=23 for control and n=14 for ketamine patients.

Figure 10: Opioid Use Over Time

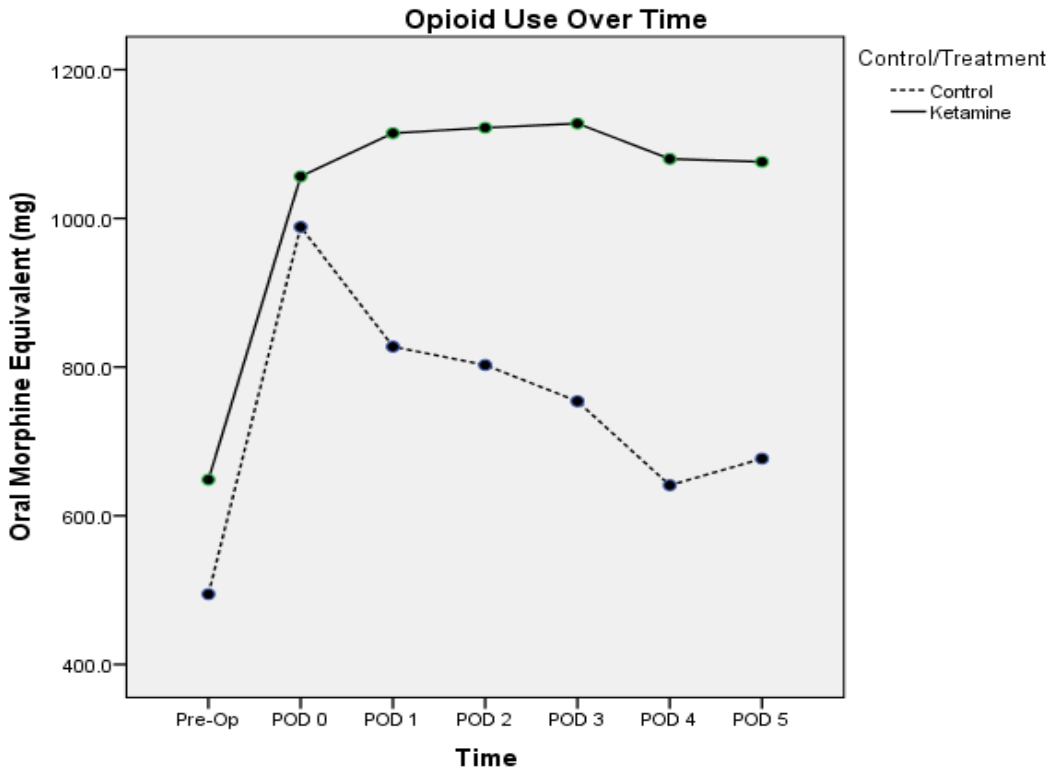

Figure 10. Mean daily oral morphine equivalent (in milligrams) pre-operatively and post-operatively on days 0-5. Figure only represents patients with complete data; patients who were discharged early or went to the operating room were excluded from this graph. Total n=37; control group n=23 and ketamine group n=14.

Unfortunately, data did not meet the normality assumptions to run a repeated measures ANOVA to assess for any statistical change over time between groups. To aid the assessment of post-operative opioid escalation, the minimum and maximum percent increase from baseline was calculated from POD 1 to POD 5 from all complete available data. The data from POD 0 data were not used in the minimum and maximum percent increase due to intra-operative analgesia variation and the acute need for increased opioid escalation intra-operatively. The data from estimated 24-hour totals for patients who were discharged early were also excluded from this analysis. The independent samples t-test was used for the maximum daily opioid analysis and Mann-Whitney U test was used for the pre-op and minimum daily opioid to analyze data; there was no missing data in this modified analysis. There was no statistical difference in opioid escalation between the two groups as summarized in Table 12.

Table 12: Post-operative Opioid Use

Opioid Use	Control Group	Ketamine Group	p-Value
Pre-op Oral Morphine Equivalent (mg)	527.000 +/- 675.165 (105-3600)	570.105 +/- 579.577 (120-2288)	.487
Minimum % Of Daily Pre-op Oral Morphine Equivalent	119.140 +/- 51.556 (10-200)	168.370 +/- 108.579 (50-561)	.148
Maximum % Of Daily Pre-op Oral Morphine Equivalent	228.860 +/- 118.017 (29-516)	299.110 +/- 179.885 (130-818)	.108

Note. Milligrams of oral morphine equivalent doses are represented as Mean +/- Standard Deviation (Range). Total n=48; control group n=29, ketamine group n=19.

Time to Ambulation & Time to Discharge

Time to ambulation and time to discharge were used as objective functional assessments of how patients did post-operatively. There was no missing data in this analysis. The data were not normally distributed; therefore the Mann-Whitney U test was used to compare the two groups. There was no statistical difference found as summarized in Table 13, although time to ambulation was noted to approach significance (p=0.07).

Table 13: Time to Ambulation and Time to Discharge (n=45)

Outcome	Control Group	Ketamine Group	p-Value
Time to Ambulation	1.25 +/- 0.75 (0-3)	2.53 +/- 2.98 (0-13)	.070
Time to Discharge	10.61 +/- 11.31 (2-53)	8.71 +/- 5.72 (3-22)	.731

Note. All outcomes are represented as Mean +/- Standard Deviation (Range). Total n=45, control group n=28, ketamine group n=17.

There were a few outliers that could have skewed the data, however the 5% trimmed means were not that different from the true means. The 5% trimmed means for time to ambulation were 1.22 and 2.09 while time to discharge 5% trimmed means were 9.03 and 8.28 for the control and ketamine groups respectively.

Adverse Effects

The adverse effects of ketamine include nausea/vomiting, sedation, hypotension/ hypertension, bradycardia/ tachycardia. Sedating drugs can potentiate other sedating drugs when given in conjunction; ketamine may potentiate the adverse effects of opioids. As all patients in this study were on high doses of opioids, adverse effects such as nausea, higher sedation scores, as well as CNS and respiratory depression were examined and compared between groups. Vital signs were examined and compared between groups to assess if patients treated with ketamine

were experiencing more hypotension/ hypertension, bradycardia/ tachycardia. Chi-square tests were used to assess for significance; overall, there was no statistical difference in adverse effects between groups (see Table 14).

Table 14: Adverse Effects

Adverse Effect	Control Group % (n)	Ketamine Group % (n)	p-Value
Nausea	51.7 (15)	57.9 (11)	.771
CNS Depression	65.5 (19)	47.4 (9)	.245
Sedation Score 3	10.3 (3)	5.3 (1)	1.000
Respiratory Depression	6.9 (2)	5.3 (1)	1.000
Hallucinations	6.9 (2)	10.5 (2)	1.000

Note. Adverse effect frequencies are represented as percent of subjects that had an adverse effect, where n= number of patients in the group that had an adverse effect. Total n=48, control group n=29, ketamine group n=19.

Vital signs values were collected from pre-operative data, and POD 0 through 5. Daily minimum and maximum values were collected to assess for possible respiratory depression, hypotension/hypertension by way of mean arterial pressure (MAP), and bradycardia/tachycardia (see Table 15). Physiologically impossible data were excluded as it was assumed these were errors in documentation. Missing data for these fields was a result of lack of documentation, patients being in ICU (assumed that patients would have homeostasis being maintained artificially), patients being discharged, or returning to the operating room for the second stage of their surgery. Factors that could influence vital signs such as intra-operative blood loss, fluid boluses, anti-hypertensive medications, medications that control heart rate (HR) were not explored as changes in vital signs was not the intent of this study.

Table 15: Vital Signs

Vital Sign	Control Group	Ketamine Group	p-Value
Pre-Op HR	77.17 +/- 10.393 (59-93)	86.84 +/- 19.213 (58-115)	.055
Post-Op Minimum HR	69.52 +/- 10.612 (54-93)	75.58 +/- 13.582 (53-98)	.110
Post-Op Maximum HR	106.41 +/- 12.935 (77-139)	112.32 +/- 12.374 (92-144)	.120
Pre-op MAP	87.79 +/- 12.827 (54-109)	98.68 +/- 12.968 (76-122)	.006
Post-op Minimum MAP	62.90 +/- 8.853 (45-89)	72.32 +/- 10.457 (52-98)	.003
Post-op Maximum MAP	103.03 +/- 10.445 (81-126)	112.00 +/- 10.919 (87-129)	.007
Pre-op RR	16.28 +/- 1.162 (14-20)	16.62 +/- 1.77 (14-22)	.465
Post-op Minimum RR	12.03 +/- 2.598 (6-16)	12.79 +/- 1.653 (10-16)	.348
Post-op Maximum RR	18.72 +/-4.061 (16-24)	19.37 +/- 2.316 (16-24)	.090

Note. All vital signs are represented as Mean +/- Standard Deviation (Range). Total n=48, control group n=29, ketamine group n=19. Pre-op = pre-operative. Post-op = post-operative.

There were no significant differences in respiration rates between groups. Blood pressure (BP) and HR were elevated in the ketamine group as compared to the control group pre-operatively. Minimum and maximum values for BP and HR were also elevated post-operatively. The mean MAP difference between groups was determined to be significant for minimum and maximum values, and was also significant pre-operatively while pre-operative HR approached significance. Post-operative BP and HR were further analyzed via a one-way between-groups

analysis of covariance (ANCOVA). The baseline BP and HR values were used as covariates in the analysis after preliminary checks for violations of assumptions were completed.

After adjusting for baseline BP values, the post-operative maximum BP differences between groups were statistically insignificant [F (1,45)=2.757, p= .104, partial eta squared .058]; however, the post-operative minimum BP differences between groups were statistically significant [F (1,45)=6.678, p= .013, partial eta squared .129]. The adjusted minimum post-operative MAP was 63.531 for the control group and 71.347 for the ketamine group, which were not that different from actual values (see Table 15). The adjusted maximum post-operative BP was 104.520 (control) and 109.733 (ketamine group). These four adjusted means were evaluated for a pre-operative BP of 92.1.

After adjusting for baseline values, the minimum and maximum post-operative HR values were statistically insignificant between groups [F (1,45)=.204, p= .654, partial eta squared .005] and [F (1,45)= .453, p=.504, partial eta squared 0.010] respectively. The adjusted means of minimum HR were 71.381 (control) and 72.734 (ketamine). The adjusted means of maximum HR were 107.776 (control) and 110.237 (ketamine). These four adjusted means were evaluated at a pre-op HR of 81.00.

Missing Data

This study was done by retrospective chart review. It was expected that there would be some missing data because of the nature of this study. Wherever the electronic data was missing information, the paper chart was reviewed and allowed for filling in of some missing electronic information. How missing data was handled has been described in each of the sections above as each analysis technique depended on the type of data that was collected. Although there was

missing data from lack of documentation, most resulted from patients being discharged before POD 5 or going back to the operating room for the second stage of their surgery.

CHAPTER 5: DISCUSSION

This final thesis chapter is intended for the discussion of the results of this study. The depiction of acute-on-chronic pain complexity will be followed by a summary of the findings. The strengths and limitations of this study will be discussed. Practice and research recommendations stemming from this study will be proposed.

Challenges of Studying and Treating Patients with Acute-on-Chronic Pain

Several difficulties exist when trying to study acute-on-chronic pain. Current treatments for chronic pain are usually not curative, chronic pain will persist despite treatment of chronic pain (Nilges, 1998; Turk, Wilson, & Cahana, 2011). It is not know if current pain treatments can even achieve substantial pain relief for patients with chronic pain (Dworkin et al., 2008). Treatment effectiveness is therefore difficult to examine. The focus of treatment needs to be on symptom relief and functioning (Turk et al., 2011). Functioning, patient satisfaction, adverse events, and pain should all be examined in studies (Turk et al., 2011).

Additionally obscuring the clinical picture, pain is complex and difficult to assess; simple pain measures do not always predict treatment success (Ballantyne & Shin, 2008). In a qualitative study, Hush, Refshauge, Sullivan, De Souza, and McAuley (2010) revealed that individuals with persistent back pain felt the NRS failed to capture their complex pain experience. Although NRS was designed to measure a sensory dimension of pain, participants in the study incorporated the impact of pain on their lives to the numerical score they reported (Hush et al., 2010). Participants also felt that the meaning of the scores and baseline could change over time. Some thought that the NRS could capture acute back pain stage progress. A majority of participants believed that their symptoms fluctuated and that a one time assessment on a NRS would fail to capture such changes and that perhaps an average measure over a week

or a month would be more acceptable. Patient views of other ways of assessing pain, such as the McGill Pain Questionnaire, have not been examined (Hush et al., 2010).

The confounding factor of acute pain on top of chronic pain may complicate pain assessment further. Patients who suffer from chronic pain may lack confidence in their post-operative trajectory and may be more anxious than those who do not suffer from chronic pain (Rapp, Ready & Nessly, 1995); because of anxiety, they may overestimate their pain intensity (Hill, Kornetsky, Flanary & Wilker, 1952). The complex pain experience of individuals who suffer from chronic pain is difficult to measure, which additionally complicates attempts of researching acute-on-chronic pain.

Summary of the Results

There were no statistically significant differences in primary or secondary outcomes found between patients in the control group and the patients treated with ketamine. Several reasons could have contributed to this; they will be elaborated following a brief summary of the findings.

Sample Characteristics and Potentially Confounding Factors

The demographic characteristics of the control group and the ketamine group patients were fairly homogenous. Their mean pre-operative opioid use was 527mg oral morphine equivalent (control) and 570.11mg (ketamine). Minimum and maximum pre-operative mean pain scores were approximately 4-5 and 8-9 out of 10 respectively for both groups. Both groups had an approximate mean of 4 spine levels operated on. The use of intra-operative medications that may affect the NMDA receptor including ketamine was not significantly different between groups. The ketamine group did receive a mean difference of approximately 20mg oral morphine

equivalent more intra-operative opioid than the control group (p= .018) but this would not necessarily be considered clinically significant.

Post-operatively, medications were reconciled 72.4% of the time as compared to 63.2% of the time in the control group and ketamine group respectively (p= .538). Treatment group patients received ketamine by continuous IV infusion ranging from 50-200mcg/kg/hr. The mean duration was 3.6 days with a standard deviation of 1.7, minimum 1.3 days and maximum 6.3 days.

Primary and Secondary Outcome Findings

Regrettably, no statistically significant differences were found in primary or secondary outcomes in relation to LDKCII. Post-operative mean opioid use escalated from baseline in both groups; the range was large, 10-818% of baseline use of opioid with a maximum mean increase of 229% in controls and 299% in ketamine patients (p= .108). Generally, pain scores peaked on POD 0 and decreased gradually with some fluctuation. As compared to best baseline pain ratings, best resting pain scores moderately decreased (reduced by at least 30%) in 62.1% of the control patients and 36.8% of the ketamine patients (p= .140), while best pain with movement decreased the same amount in 51.7% in controls and 36.8% of ketamine treated patients (p= .382). Minimal and considerable improvements in pain were also more prevalent in the control group as compared to the ketamine group but did not reach statistical significance.

Secondary outcomes of time to ambulation and time to discharge did not show statistical significance. Ambulation time means were 1.25 days for controls and 2.53 for ketamine patients (p= .07), while time to discharge means were 10.61 for controls and 8.71 for ketamine (p= .731). Nausea, CNS depression, respiratory depression, and hallucination frequencies were not

statistically different between the control and treatment groups. Patients in the ketamine group were less likely to be hypotensive.

Study Limitations

Several study limitations are inherent when using a retrospective chart review study design. Highlighted below are three limitations that should be acknowledged.

Sample Size

A major limitation is that this method yielded a small sample size. Participants for this thesis were chosen based on inclusion and exclusion criteria. Due to these criteria, the sample size of this study population was smaller than initially anticipated. Unfortunately, this could not have been predicted prior to the study commencing. The odds of finding significance may have been improved had there been a larger study sample size. For example, according to the sample size calculation (using the G*Power 3.1 Calculator) for best post-operative pain scores using the means and standard deviations from the 2 groups, an alpha of 0.05, and a power of 0.8; 326 participants would be needed in each arm to reveal statistically significan findings.

Data Sources

Another major limitation of this study design is that all data obtained came from records containing a limited amount of pre-recorded data. All outcomes that were examined in this study were incorporated into the design based on prior knowledge of what was commonly documented on patient health records in the Calgary Zone of AHS. One obvious missing element of this particular study is lack of in-depth assessment required to quantify chronic pain. The IMMPACT consensus panel recommends using two or more approaches to evaluate the clinical importance of changes in chronic pain (Dworkin et al., 2008). Elements such as sleep quality or patient satisfaction could not be measured using a retrospective design. Functional assessment of pain

was examined by analyzing time to discharge and time to ambulation, as this was the only method of examining function using data available for this chart review. The causes of delayed ambulation were not explored in this study. Staff availability, pain, ambulatory aids/splinting device availability, symptomatic hypotension, confusion, and patient refusal could all have been factors that may have delayed ambulation.

Original data examined were authored by a large number of individuals, which causes an unavoidable lack of standardization. While collecting data, it was noted that there was an insufficient amount of documentation. One example of this is that some patients only had one pain score listed per day, which was not in accordance with hospital documentation standards. It cannot be ruled out that there may have been times when patients had different pain scores that were not documented. Similarly, patients could have ambulated without a witness or documentation of such an event. A prospective design could allow for a more standardized and thorough examination of pain experienced by opioid tolerant individuals post-operatively.

Confounder Potential

There was an inherent lack of control over pain treatment intra-operatively and post-operatively due to the retrospective study design that needed to be examined and accounted for. Not having a homogenous way of treating pain intra-operatively and post-operatively led to additional statistical analysis. Potentially confounding factors were explored thoroughly in this study and showed no statistically significant differences between groups; however there is still a possibility that post-operative outcomes may be linked to a hidden confounder.

Study Strengths

This retrospective before-and-after chart review study had many strengths. The design itself made for a relatively quick and inexpensive method of examining this patient population

over a two-year time span. One researcher completed the chart review, which led to a consistent way of gathering data between subjects. Multiple sources of data were examined and cross-referenced by one researcher allowing for completeness of data.

The study was set up to examine a variety of factors that may influence the post-operative pain experience of opioid tolerant individuals with chronic pain. A thorough examination of analgesics used intra-operatively and post-operatively was done. The pain of individuals was examined by reviewing best and worst pain scores with and without movement in addition to functional assessments using time to ambulation and time to discharge. Known adverse effects of ketamine and opioids were also examined.

Recommendations for Future Research

Although no new information on the treatment of acute-on-chronic pain with LDKCII was gleaned, hypotheses can be generated to provide reason to further study this complex phenomenon.

Ketamine for Acute-on-Chronic Pain

Although the use of ketamine in acute-on-chronic pain is relatively not well examined in the literature today, ketamine has been shown to enhance analgesia in opioid tolerant individuals and can be a powerful tool to use post-operatively (Rakic & Golembiewski, 2009). It remains logical to hypothesize that patients with acute-on-chronic pain may benefit from this treatment, both in the short and long term.

Unfortunately, there were no statistically significant differences found between treatment groups. Despite a lack of findings, adding ketamine as an adjunct to current analgesia regimes may still be very valuable for patients with acute-on-chronic pain according to literature reviewed. Using a prospective method of study could decrease potential threats to study integrity

and allow for a more thorough examination and measurement of the experience of acute-on-chronic pain. Perhaps studying "what is the effect of low-dose ketamine continuous intravenous infusions on pain of highly opioid tolerant adults following spinal surgery?" via a prospective randomized, double-blind placebo controlled trial with a longitudinal design may help glean new strategies for helping this population subset.

Measuring Acute-on-Chronic Pain

The measurement of complex pain cannot be captured by the NRS; other methods of measure need to be utilized if a prospective study should go forward. A double blind, randomized placebo controlled crossover study by Lee et al. (2013) examining pain and hyperalgesia in relation to tetrahydrocannabinol (THC) administration revealed that participants who received THC had less perceived unpleasantness compared to those who received placebo. Pain and hyperalgesia intensity, however, were not statistically different between groups. Lee et al. concluded that the dissociative effects of THC were relevant to the pain experience. These findings highlight that the same pain experience can be interpreted in different ways by the same individuals. In this case, intensity and unpleasantness were specifically inquired about and measured by the researchers. Similarly, Schwartzman et al. (2009) found that patients with CRPS who were treated with ketamine had a 50% decrease in the affective component vs. 31% in the sensory component of the short form McGill pain questionnaire. Future studies examining effects of dissociative drugs like ketamine should examine the affective component of the pain experience more thoroughly, something that was not achievable using the retrospective chart review method.

Another method to examine post-operative outcomes of opioid tolerant patients with acute-on-chronic pain may be to record patient satisfaction with their post-operative pain control.

However, measuring satisfaction is very subjective and may be influenced by various factors; one of these being how much attention healthcare professionals provide to patients (Chazan et al., 2010; Peacock, Wright, Withers, Luntley, & Atkinson, 2000). If a future RCT examining efficacy of LDKCII is done, researchers should be aware of a potential confounding variable: caring attention given to patients with chronic pain may be just as helpful as any drug and create a bias in studies (Ballantyne & Shin, 2008). This may be unavoidable if patients are under the expert care of the APS and therapeutic relationships are established post-operatively.

Post-operative outcomes can also be measured by assessing care provider perceptions. Change is evaluated and interpreted differently between patients and healthcare providers; perspectives of benefits and clinical importance can vary (Dworkin et al., 2008). Health care providers evaluate how patients are doing based on benchmarks of others patients they have cared for in similar situations, where as patients use their own personal benchmarks to judge how they are doing (Dworkin et al., 2008). Anesthesiologists, APS Advanced Practice Nurses (APNs) and nurse clinicians, nurses and a spinal surgeon working with this particular patient cohort have anecdotally noted that they have noticed an improvement in the overall pain control and satisfaction of these patients. This could be due to fewer calls for pain crises, or some other factor that was not measurable via this study. A qualitative study could be performed to examine if the providers caring for opioid tolerant individuals in acute-on-chronic pain noticed any changes they could articulate since the LDKCII implementation, as well as their perceived significance of these changes.

Opioid Escalation in Opioid Tolerant Individuals

This thesis study allowed for a thorough examination of post-operative opioid use in opioid tolerant individuals. Patients in this study escalated their opioid use post-operatively on

average by 229% (control) or 299% (ketamine) from baseline. Although Carroll et al. (2004) state that there is no way to predict individual post-operative opioid need in opioid tolerant patients, Kopf et al. (2005) warn practitioners that post-operative opioid escalation can escalate up to 400%. However, the patients reviewed in this thesis had a maximum increase of 818% of baseline use, a figure much higher than that mentioned by Kopf et al. (2005).

There is a lack of evidence of how much opioids should be increased in patients with acute-on-chronic pain (Carroll, Angst & Clark, 2004; Dykstra, 2012; Kopf et al., 2005); practice is guided based on case reports, retrospective studies, and expert opinion (Mehta & Langford, 2006). Two studies were found where the post-operative use of opioids by opioid tolerant individuals was examined. First, Peacock et al. (2000) noted a 160-357% mean increase (with a wide range of 11-1000%) of oral morphine equivalent in opioid use among opioid tolerant individuals on POD 1 and 2. Second, Rapp et al. (1995) were able to analyze a small portion of their study population to examine increase in post-operative opioid use in tolerant individuals. They found that mean pre-operative opioid dose was 12.7mg of parenteral morphine (38.1mg oral morphine equivalents) and post-operative mean dose was 136.2mg parenteral morphine (408.6mg oral morphine equivalents), which would be a little more than a 10-fold increase in post-operative use. The group's post-operative mean dose was also more than two times higher than the opioid naïve matched control patients' post-operative mean of 66.9mg parenteral morphine equivalent.

In a recent literature review, Dykstra (2012) recommended that opioid tolerant patients with acute-on-chronic pain should continue with their pre-operative opioid doses and for practitioners to expect a higher opioid requirement. Dykstra (2012) did not quantify what a reasonable increase in opioid was. Although it was not the primary intent of this study to analyze

opioid escalation post-operatively, it is evident that there was a wide range of opioid escalation in opioid tolerant individuals regardless of whether or not they received ketamine post-operatively. This was done under the expert care of the APS team. Future research should be conducted to examine the efficacy of acute opioid escalation in opioid tolerant individuals.

Factors Influencing Treatment of Patients with Acute-on-Chronic Pain

APNs often manage complex patient situations and have the skills and resources to care for complex patients (Hamric, Spross & Hanson, 2009), such as those experiencing acute-on-chronic pain. A Canadian survey exploring APN pain management practices done in 2002 revealed that 66% of respondents felt they could influence treatment outcomes of patients in pain and 56% could influence analgesia prescribing (Kohr & Sawhney, 2005). The same survey revealed that APNs influence over analgesia prescribing was proportional to the number of patients seen by the APN who require pain management. Expert practitioners such as those who work for the APS can influence how patients in acute-on-chronic pain are treated both as individuals and as a patient cohort. Their perceptions of how patients are progressing post-operatively may influence care and treatment decisions. It is vital for these expert practitioners to introspectively examine what their own opinions of LDKCII are, and how these influence their recommendations for treatment.

It was noted in this study that there were at least 17 patients who used a minimum of 100mg morphine equivalent pre-operatively that were not treated with the LDKCII. It could be that the practitioners assessing these patients decided that those 17 patients did not need the LDKCII based on other factors such as nursing intuition or professional acumen. Perhaps there is more to the art of treating pain that has yet to be quantified by science; this could be explored further by a qualitative study.

Furthermore, it is plausible that the 17 excluded patients may have skewed the outcomes of the examined post-operative treatment markers. It is possible that the ketamine patient group appeared to have used more opioid post operatively, had higher pain scores and longer time to ambulation than the control group (although none of these measures reached statistical significance) because the patients who were expected to do better post-operatively during that year were not treated with ketamine and were excluded from data collection and analysis. Further investigation could also be done by adding these 17 patients' data to this study's data by way of another retrospective review.

Recommendations for Practice

The anesthesiologists, Clinical Nurse Specialists and Nurse Practitioners specializing in pain within the Calgary Zone of AHS are consulted for complex clinical situations and have a large amount of influence surrounding treatment provided for acute-on-chronic pain. They often provide expertise to other care providers, and collaborate to create evidence based care plans for patients. Understanding the complexities of treating acute-on-chronic pain as presented in this study is pivotal for helping improve outcomes for this marginalized population.

Documentation and Assessment of Acute-on-Chronic Pain

While looking through patient records, it was evident that desirable patient outcomes were not well articulated. The complexity of acute-on-chronic pain was not captured in the standard documentation that was available for review. Patient responses to LDKCII treatment were not clearly evident despite local expert opinion of this being beneficial to some patients. This not only affects the results of this study, but also could be interpreted as a deficiency in treatment by those who were not contextually involved in the care of this particular population. Relying on pain reports as an outcome measure is inadequate for patients with chronic pain

(Nilges, 1998). Although the NRS was designed to measure sensory components of pain, patients tend to combine other facets of their pain experience into their report of pain (Hush et al., 2010). Because patient reported outcomes such as the NRS pain scores are plagued with many confounding factors in patients with persistent pain (Nilges, 1998), it is crucial for health care practitioners to probe into what the pain score means for patients.

Leadership is a core competency of APN and can be exercised in clinical, nursing profession, systems and health policy settings (Hamric et al., 2009). APNs working in pain management can serve as leaders for other practitioners by modeling best pain management practice. They can implement local nursing policies to ensure quality pain assessment and management. The Calgary APS nurses were instrumental in establishing the LDKCII treatment protocol for acute-on-chronic pain management. These APNs provided leadership by reviewing relevant literature, collaborating with key stakeholders, writing the protocol and learning modules, writing the order-set, educating and certifying all staff nurses on the units, and providing practice guidance and follow up with the implementation of the protocol.

The lack of evidence of LDKCII benefit highlighted by this study contradicted local care provider opinion that it does. To help bridge this gap, the APS APNs could help institute the use of an expanded assessment tool for individuals suffering from acute-on-chronic pain within AHS. There are a variety of tools to measure pain that have been proven to be valid and reliable. Scales that measure function such as the Multidimensional Pain Inventory Interference Scale or the Brief Pain Inventory should be used in addition to the NRS. Additionally, the Short-Form McGill Questionnaire could be used to assess for sensory and affective pain components (Green, 2013).

Post-Operative Opioid Use in Patients with Acute-on-Chronic Pain

Although it is commonly stated that opioids do not have a ceiling effect, pain experts do acknowledge that there comes a point where patients stop displaying a benefit from opioid treatment. The watchful dose of opioids is 200mg oral morphine equivalent according to Canadian guidelines (National Opioid Use Guideline Group [NOUGG], 2010). Once patients use more than 200mg per day, escalations in opioid without a desirable response are considered to be futile and opioids should be switched or discontinued (NOUGG, 2010). Opioid efficacy should be measured by a reduction in pain by 30% and an improvement in function and patient response to opioid therapy should be clearly documented (NOUGG, 2010).

Patients in this study consumed anywhere from 105 to 3600mg of oral morphine equivalent per day pre-operatively, much higher doses than the recommended Canadian guidelines. They were allowed to use as much opioid as they needed post-operatively so long as they were not displaying signs of adverse effects such as opioid induced respiratory depression. Post-operatively, opioid use escalated to a maximum of 818% of baseline use.

Discussing realistic expectations with patients who suffer from chronic pain is crucial; treatment outcomes should have a focus on function improvement, not just pain scores (Turk et al., 2011). When examining how many patients had a moderate pain reduction (at least 30%), only 52% of patients experienced a decrease in pain at rest and 46% experienced decreased pain with movement. It could be hypothesized that some patients were not responding to opioids and should have had their opioids tapered down as tolerated. APS practitioners are in the position of exploring such possibilities and can make modifications to medications as needed, including tapering back on opioid therapy as tolerated if there isn't a marked improvement in pain scores or function. If opioid escalation effectiveness was thoroughly explored with patients who suffer

from acute-on-chronic pain, perhaps the LDKCII protocol could be used to its full potential and could decrease post-operative opioid need.

Conclusion

Managing acute-on-chronic pain in opioid tolerant individuals is complex and challenging. The pain experience of individuals who suffer from chronic pain is difficult to measure, further complicating attempts of researching acute-on-chronic pain. Because of the complexities of assessing this patient population's post-operative pain outcomes, efforts should be made to improve measurement and documentation acute-on-chronic pain. Local experts who work for the APS where this study was conducted were surprised to learn that there was no benefit of using LDKCII identified by way of this study. Ketamine has been show to enhance analgesia in opioid tolerant individuals and can be a powerful tool to use post-operatively (Rakic & Golembiewski, 2009) and it is still possible that patients with acute-on-chronic pain may benefit from this treatment.

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Appendix B: Chart Review Template Tool

Table B1 Chart Review Template

Study ID #:	**Date of review:**	**Surgery:**			
Sex: M=0 / F=1	**Date of Birth:** (yyyy/m/d)	**Age:** (years)		**Weight:** (kg)	**BMI:**
Admit Date: (yyyy/m/d)		**Discharge Date:** (yyyy/m/d)		**Surgical Date:** (yyyy/m/d)	
OR Analgesia/Anesthesia : N_2O Y=0 / N=1 **Ketamine** Y=0 / N=1 (dose: _____) **Opioid** Y=0 / N=1 (dose: _____) **Mg** Y=0 / N=1 **Lidocaine** Y=0 / N=1 (dose: _____) **Other:** _____					
Home Analgesic/Adjuvant: (Drug/Dose/Frequency)		**Hospital Analgesic/Adjuvant: (**Drug/Dose/Frequency)			
Pain Medications Reconciled : Y=0 / N=1		**First Documented Ambulation:** (date/time)			
Ketamine Start : (date/time)		**Ketamine End :** (date/time)		**Ketamine Duration:** (hours)	
Comments/ Missing Data:					

Hospital Stay Details							
	Home/Pre-op	**POD 0**	**POD 1**	**POD 2**	**POD 3**	**POD 4**	**POD 5**
Pulse	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max
Blood Pressure	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max
Respiration rate	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max
Pain Score Moving	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max
Pain Score Rest	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max	Min Max

Hospital Stay Details							
	Home/Pre-op	**POD 0**	**POD 1**	**POD 2**	**POD 3**	**POD 4**	**POD 5**
24hr opioid use Drug/dose/route							
		PACU:					
		OR:					
24hr PO morphine Equivalent							
Ketamine Use							
$\bar{x}$ Ketamine Dose							
Adverse Effects Treatment							
Adverse Effects							

Note: This table is a template for the actual chart review tool that was used to collect data.

Appendix C: Coding Tool

Table C1 Coded Identifier Tool

Name	Medical Record Number	Study ID

Note: This table is a template for the actual chart that was used to keep patient identifiers secure during data collection and coding.

Appendix D: Modified Sedation Score

Table D1 Modified Sedation Score

Assessing Sedation Score	
Score	Description
S	Sleep, easy to arouse
0	Awake and alert
1	Slightly drowsy, easy to arouse
2	Frequently drowsy, arousable, drifts off to sleep during conversation
3	Somnolent, minimal or no response to verbal and physical stimulation

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Appendix E: Opioid Equianalgesia Chart

Table E1 Opioid Equianalgesia Chart

Drug	Parenteral Dose (mg) Equivalent To 10 mg IV Morphine	Oral Dose (mg) Equivalent To 30 mg Oral Morphine
Morphine[a]	10	30
Meperidine [a]	75	300
Codeine [a]	120	200
Hydromorphone [a]	2	6
Fentanyl [a] (IV/SC/TD/PO)	0.1	0.1
Oxycodone [a]	-	20
Tramadol[b]	-	300
Butrans (TD)[c]	0.429	(5mcg/hr= 8.4mg PO, 10mcg/hr= 16.8mg PO, 20mcg/hr=33.6mg PO)
Sufentanil[d]	0.01	-
Remifentanil[e]	0.1	-

Note: Principle of equianalgesia used to calculate total daily morphine oral equivalent for study purposes only; patients were not converted to oral morphine equivalents. There was no amount of deduction for cross tolerance in the opioid conversions in this study.

[a]Adapted from Foothills Medical Centre Acute Pain Service Nurses, 2012. *FMC Acute Pain Service Orientation Manual*. Alberta Health Services. [b] Adapted from Fishman, S., Ballantyne, J., Rathmell, J. P., & Bonica, J. J. (2010). *Bonica's management of pain*. Baltimore, MD: Lippincott, Williams & Wilkins.[c] Adapted from Mercadante, S., Casuccio, A., Tirelli, W., & Giarratano, A. (2009). Equipotent doses to switch from high doses of opioids to transdermal buprenorphine. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer, 17*(6), 715-718. doi:10.1007/s00520-008-0546-6[d] Adapted from Gepts, E., Shafer, S. L., Camu, F., Stanski, D. R., Woestenborghs, R., Van Peer, A., & Heykants, J. J. (1995). Linearity of pharmacokinetics and model estimation of sufentanil. *Anesthesiology, 83*(6), 1194-1204. doi:10.1097/00000542-199512000-00010 . [e] Adapted from Egan, T. D., Minto, C. F., Hermann, D. J., Barr, J., Muir, K. T., & Shafer, S. L. (1996). Remifentanil versus alfentanil: Comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. *Anesthesiology, 84*(4), 821-833. doi:10.1097/00000542-199604000-00009 .