Perioperative Low-Dose Ketamine Infusion and its Impact on Postoperative Pain: An Evidence Based Practice Analysis

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Introduction

Acute pain after surgery is a common problem with multiple consequences. Patients, anesthesia professionals, and surgeons want adequate pain control with minimal side effects. Opioid analgesics are commonly relied upon in the perioperative and postoperative periods to provide analgesia. Large doses of opioids are associated with sedation, respiratory depression, pruritus, nausea, vomiting, and potentially opioid induced hyperalgesia (OIH).[1] The use of multimodal analgesia targeted at different pain mechanisms both peripherally and centrally has been reported to decrease pain and reduce opioid consumption.[1]

Ketamine non-competitively inhibits N-methyl-D-aspartate (NMDA) receptors and has been widely used in anesthesia practice due to its analgesic effect and cardiovascular stability. Ketamine has gained popularity in recent years as an adjunct to multimodal perioperative pain control. There is a lot of variability in the literature in both dose and timing of ketamine administration, and an optimal dosing regimen could potentially lead to more consistent and effective results. For the purpose of this project and as previously described, low-dose ketamine is defined as giving no more than a 1mg/kg bolus followed by an infusion of no more than 20 mcg/kg/min.[2]

Purpose Statement

The primary purpose of this evidence based practice analysis project is to identify if low-dose perioperative ketamine bolus and infusion decreases postoperative pain and opioid consumption in adult surgical patients.

Methodology

PICO question. Evidence based practice aims to analyze and apply the most current knowledge to improve and guide clinical practice. A well-designed Population, Intervention,

Outcome, and Comparison (PICO) question helps provide framework and assists in locating pertinent evidence.[3] The PICO question used to provide framework and guide inquiry was "Does the administration of low-dose ketamine bolus and infusion during surgery (I) in adult patients (P) decrease postoperative pain and opioid consumption (O) compared to patients who did not receive low-dose ketamine infusion (C)?

Evidence acquisition. Compilation of relevant evidence was accomplished by searching CINAHL, PUBMED, and Cochrane Collection during June 26th – June 30th 2017. Keyword search was performed using *Ketamine, Infusion*, *Low-dose*, *Intraoperative, Perioperative, Postoperative Pain,* and *Postoperative Opioids* alone and in varying combinations. Evidence considered for inclusion were randomized controlled trials (RCTs), meta-analysis, and systemic reviews published in the English language in peer-reviewed journals from 2009-2017. Nineteen RCT sources were selected for further review based on title. Upon further review 12 sources were excluded based on the method or timing of ketamine administration and only evidence sources with perioperative low-dose intravenous (IV) ketamine bolus and perioperative low-dose ketamine IV infusion intervention was included. The remaining 7 studies met all inclusion criteria and critical appraisal and extraction into a table of evidence was performed.

Literature Review

A total of 7 RCTs were critically appraised and extracted into a table of evidence (table 1). Total population size of all evidence sources was 466 adult patients, 315 (68%) females, and 150 (32%) males. The largest study sample size was 102 subjects [4] while the smallest sample size was 52 [5] (median sample size, 60). All sources used adequate sample sizes as calculated by power analysis with five sources assuming power 80% and alpha level 0.05[5-9] and 2 sources assuming power 90%.[4,10] Six out of 7 sources were from authors practicing outside the United

States.[5-7,9,10] A large portion of the overall sample population was female (68%) which can be explained because 2 of the sources investigated populations undergoing abdominal hysterectomy[9] and cesarean section.[5] One subject was not included in analysis due to deviation from the treatment plan in one investigation[8] (sample size still adequate), and one study reported that less than 10% of subject data regarding its primary outcome was missing due to early patient discharge and these subjects were equally found in control and treatment groups. No other evidence sources reported any missing data or withdrawn or excluded subjects.

Six studies focused on adult American Society of Anesthesiologists Physical Status (ASA-PS) classification 1-2 elective surgical patients who were opioid naïve, had no history of substance abuse, and did not suffer from chronic pain.[5-10] One study focused on adult ASA-PS 1-4 elective surgical patients with a history of daily opioid use and chronic pain.[4] All surgical procedures were elective and included cesarean section,[5] open cholecystectomy,[7] laparoscopic cholecystectomy,[6] robotic or endoscopic thyroidectomy,[8] abdominal hysterectomy with salpingo-oophrectomy,[9] renal (52 nephrectomies, 2 pyelolithotomies, 1 pyeloplasty),[10] and instrumented lumbar spine surgery.[4] Average mean age of subjects ranged from 29[5] to 51[4] with no significant difference in age between treatment groups reported.

Perioperative anesthesia care was standardized within each study. Three studies pretreated subjects with glycopyrrolate 0.2mg IV,[7] 0.2mg IM,[6] or .004mg/kg IV.[10] Four studies pretreated subjects IV with midazolam 2mg,[4,6] 0.03mg/kg,[8] or 0.07mg/kg.[9] General anesthesia was induced with IV thiopental[5,10] or IV propofol[4,6-9] along with IV fentanyl, remifentanil, or tramadol. Tracheal intubation was facilitated in 3 studies with atracurium,[9] rocuronium,[6] or succinylcholine[10] while the remaining 4 studies did not report the use of a paralytic medication. Anesthesia was maintained with inhaled agent,[4] inhaled agent and remifentanil infusion,[6] inhaled

agent and nitrous oxide,[5,7,9,10] or total intravenous anesthesia (TIVA) using propofol and remifentanil.[8]

The only treatment group compared against placebo in 5 of 7 sources was low-dose ketamine IV bolus after induction of anesthesia and subsequent low-dose infusion until skin closure. Two studies also tested a 3rd treatment group which received gabapentin[9] and nefopam[6] respectively. The initial bolus dosing of ketamine ranged from 0.15mg/kg[10] to 1mg/kg[8] (mean, 0.42mg/kg, median 0.3mg/kg). Perioperative ketamine infusion dosing ranged from 0.83mcg/kg/min[9] to 10mcg/kg/min[4,5] (mean 4.7mcg/kg/min, median 2mcg/kg/min).

Outcomes. All evidence sources reported on postoperative pain while 6 sources reported on postoperative opioid consumption. All evidence sources used postoperative pain scores as their primary or secondary outcome. Postoperative pain was assessed using the visual analog scale[4,7,9,10] (VAS) or numerical rating scale[5,6,8] (NRS) at specific time intervals. Postoperative pain scores were reported in the first 24 hours after surgery in 6 of 7 sources[4,5,7-10], with 2 sources reporting up to 48 hours,[4,8] and one source reporting up to 6 weeks.[4] One source only reported pain scores during the first hour after surgery[6]. Postoperative opioid consumption was [10]measured in milligrams of morphine consumed with 5 of 7 sources reporting 24 hour cumulative morphine consumption.[4,5,7,9,10] One source reported 24-hour, 48 hours, and 6-week cumulative morphine consumption.[4]

Postoperative Pain. All evidence sources reported significantly decreased postoperative pain with ketamine treatment compared to placebo, however the time at which intraoperative ketamine produced significantly lower pain scores varied. Six[4-7,9,10] out of 7 evidence sources reported significantly ($p < 0.05$) lower 1st hour pain scores in ketamine treatment groups versus placebo. Kim et al.[8] found no significant difference between groups pain scores during the first

hour and theorized this was because both groups may have had lingering sedation related to anesthesia. The duration of decreased pain scores between treatment and placebo groups included 15 minutes,[5] 30 minutes,[6] 6 hours,[7] 12 hours,[10] 24 hours,[8,9] and 48 hours[8] respectively. . Loftus et al.[4] found ketamine treatment caused a significant reduction (26.7%, p=0.033) in pain intensity in the post anesthesia care unit (PACU). This significance was not shown at 24 or 48 hours however a significant reduction (26.2%, p =0.026) in pain scores was noted at 6 weeks postoperatively. Two[8,9] out of 6 sources found a significant reduction in late pain scores at 24 hours and 1[9] of 6 sources found a significant reduction at 48hrs. Four[4,5,7,10] out of 6 studies did not find a significant difference in pain between groups at 24 hours. All sources that included morphine consumption as an outcome found ketamine treatment significantly decreased opioid consumption versus placebo at 24 hours which suggests an increased quality of pain control.

Postoperative Opioid Consumption. Intraoperative ketamine administration was shown to decrease opioid consumption in 5 of the studies included in this project. Ketamine significantly decreased 24 hour morphine consumption in 5 studies by 31%[5], 71%[7], 35%[9], 32%[10], 30%[4] Loftus et al. also reported ketamine significantly decreased cumulative morphine consumption at 48 hours (37%) and 6 weeks (71%) as compared to control in chronic pain patients who take opioids. It should be noted that at 48hrs the authors found no significant difference between groups in regards to pain. Kim et al.[8] did not include morphine consumption as an outcome but instead looked at the need for postoperative rescue analgesia. No significant difference was found between ketamine and control group need for rescue analgesics.

Adverse Events. Decreasing postoperative opioid consumption would lead one to believe that opioid related side effects such as PONV would also decrease. This is not the case as evidence sources included in this review did not find any significant difference in incidence of

side effects experienced by participants. Many anesthesia professionals are wary of administering ketamine due to the psychotomimetic side effects that accompany anesthetic dosages. No significant adverse reactions or events associated with ketamine administration were reported between ketamine and placebo groups.[4-10] Four of 7 studies pretreated subjects with IV midazolam to prevent ketamine related adverse events.[4,6,8,9]

Conclusion

Intraoperative low-dose ketamine bolus after induction of general anesthesia and infusion until skin closure has been shown by the 7 evidence sources analyzed in this project to significantly decrease pain postoperatively. The duration of significant decreases in either VAS or NRS pain scores varied according to evidence sources and ranged from 15 minutes (first assessment in PACU) to 48 hours. For ASA I-II opioid naïve subjects undergoing elective procedures requiring general anesthesia, intraoperative ketamine administration appears to decrease acute postoperative pain during the first hour after surgery and may last 24-48hrs. According to Loftus et al[4], ASA I-IV adult chronic pain patients who take chronic opioids who receive intraoperative ketamine have significantly decreased acute postoperative pain in PACU and have significantly decreased chronic pain scores at 6 weeks.

Five of 7 evidence sources reported significantly decreased 24-hour morphine consumption in subjects receiving intraoperative ketamine as compared to control. Intraoperative ketamine administration decreased postoperative 24-hour cumulative morphine consumption in 5 studies by 31%[5], 73%[7], 35%[9], 32%[10], 30%[4] (mean 40%, median 32%). Loftus et al. also found that ketamine significantly decreased cumulative morphine consumption at 48 hours (37%) and 6 weeks (71%) as compared to control in chronic pain patients who take opioids undergoing elective lumbar back surgery. In contrast, Kim et al. found no significant difference in need for

postoperative rescue analgesics between ketamine treatment and placebo control in ASA I-II adults undergoing BABA thyroidectomy.[8]

Postoperative pain remains a significant obstacle for patients, surgeons, and anesthesia professionals. Multimodal therapy is recommended to combat acute postoperative pain using therapies and modalities that work on different pain mechanisms.[1] The results of this evidence based practice analysis supports intraoperative low-dose ketamine bolus and infusion as an adjunct to opioids in intraoperative pain management as a means of decreasing postoperative pain in the first hour after surgery which may last up to 24 hours. Reduction in opioid requirements may also be a realized benefit with the majority of evidence analyzed signifying a 31-35% decrease in 24-hour opioid consumption. Patients with chronic pain may experience decreased pain levels and decreased opioid consumption for up to 6 weeks.

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Evidence Matrix (Table 1)

Table 1

Evidence Source	Treatment & Dose	Sample size	Surgical procedure	Results / Notes
Haliloglu et al.[5] (2016) RCT	Ketamine 0.5mg/kg + 10mcg/kg/min Control – equal volume of saline + infusion	n=50 control n=26 ketamine n= 26 ASA I-II adult parturient nulliparous females 18-35 years old	Cesarean section under general anesthesia	Postop pain: NRS lower at 15min postop Opioid Consumption: Treatment group used less cumulative morphine in 24hrs (31%). No difference in PONV, pruritic, or rescue analgesics between treatment and control. No nystagmus, hallucinations, or diplopia were reported.
Kuar et al.[7] (2015) RCT	Ketamine 0.2mg/kg + 1.67mcg/kg/min Control – equal volume saline bolus and infusion	n=80 control n=40 ketamine n=40 ASA I-II adults 21-50 years old. Opioid Naive	Open cholecystectomy	Postop pain: Group K had lower VAS scores up to 6 hours postop. Opioid consumption: Ketamine had less 24-hour cumulative morphine consumption (73%) compared to control. 5/40 subjects in ketamine group required rescue analgesics as compared to 40/40 subjects in control. No difference in PONV and no reported ketamine side effects.
Kim et al.[8]	Ketamine 1mg/kg + 1mcg/kg/min	n=58 control n= 28 ketamine n= 29	Bilateral axillo-breast approach: (BABA) robotic	Postop pain: ketamine group lower NRS scores at 6, 24, and 48 hours postop. No difference at 1 hour.

Evidence Source	Treatment & Dose	Sample size	Surgical procedure	Results / Notes
(2016) RCT	Control – equal volume saline bolus and infusion	ASA I-II adult 19-69 years old. Opioid naive	or endoscopic thyroidectomy	Opioid consumption: Opioid dose totals not recorded. no difference in need for rescue analgesics between groups. No difference in incidence of PONV, HA, dizziness, or shivering. No reported adverse effects of ketamine.
Sen et al.[9] (2009) RCT	Ketamine 0.3mg/kg + 0.83mcg/kg/min Control – PO placebo + equal volume saline bolus and infusion Gabapentin 1.2g PO + equal volume saline bolus and infusion	n=60 control n=20 ketamine n=20 gabapentin n=20 ASA I-II adult females	Abdominal hysterectomy with salpingo-oophrectomy	Postop pain: VRS scores lower in all intervals for 24hrs in gabapentin group, lower in all intervals for first 16 hours in ketamine group. No difference between ketamine and control at 24hrs. Gabapentin group demonstrated lower VRS at 1, 3 and 6 months follow up compared with ketamine and control Postop opioids: No difference between control and treatment groups in morphine pca requirements at 1 and 4 hours postop. Both treatment groups required less morphine than control at all intervals from 8-24hrs postop. Total 24-hour morphine PCA requirements for ketamine (35%) and gabapentin (42%) less than control. No difference in Side effects between treatment and control groups. No reported adverse effects of ketamine.
Parikh et al.[10]	Ketamine 0.15mg/kg + 2mcg/kg/min	n=60 control n=30	Renal (52 nephrectomy, 2	Postop pain: Ketamine group lower mean VAS for first 12hrs postop. Mean VAS same for both groups at 24hrs.

Evidence Source	Treatment & Dose	Sample size	Surgical procedure	Results / Notes
(2011) RCT	Control – equal volume saline bolus and infusion	ketamine n=30 ASA I-II adult 18-70 years old. Opioid naïve	pyelolithotomy, pyeloplasty	Postop Opioids: Ketamine group used less 24 cumulative morphine than control (32%) Ketamine group had longer time to first analgesic dose as compared to control (mean hours k= 21.6, c=3.8) No reported adverse effects of ketamine, No significant difference in side effects however clinically significantly more PONV in control compared to ketamine (4/30, 0/30).
Loftus et al.[4] (2010) RCT	Ketamine 0.5mg/kg+ 10mcg/kg/min Control – equal volume saline bolus and infusion	n=102 control n=50 ketamine n=52 ASA I-IV adults, daily opiate use for at least 6 weeks and chronic back pain for at least 3 months	Lumbar back surgery	Postop pain: Ketamine group VAS 26.7% lower than control in PACU and 26.2% lower at 6 months. No difference observed at 24 or 48 hours. Postop opioids: Ketamine group used on average 30% less cumulative morphine at 24 hours and 37% less at 48 hours. Ketamine group reduced opiate consumption by 71% at 6 months compared to control. No significant difference of side effects or adverse events between ketamine or control group at 48 hours and 6 months.
Choi et al.[6] (2016) RCT	Ketamine 0.3mg/kg + 3mcg/kg/min Control – equal volume of saline + infusion	n=54 control n=18 ketamine n=18 nefopam n=18 ASA 1-2 adults age 19-69, opioid naïve.	Laparoscopic cholecystectomy	Postop pain: ketamine and nefopam groups lower VAS scores at all intervals up to 30 min in PACU compared with control. No significant difference between nefopam and ketamine in VAS. Postop opioids: ketamine and nefopam had significantly less subjects requiring morphine analgesia (k 8, n 4, c 14), less cumulative milligrams of morphine per person (k 14.4, n 6.6, c 30.5), and longer time in minutes until requiring first rescue morphine (k 25, n 31, c 15 as compared to control

Evidence Source	Treatment & Dose	Sample size	Surgical procedure	Results / Notes
				Ketamine group longer time required to extubate than nefopam or control (time from last suture to extubation in minutes k 12, n 10, c 9.)
Total		466		

Note: Treatment groups named after the medication they received. Results reported significant at $p \leq 0.05$.