ORIGINAL ARTICLE

Ketamine Infusions Improve Trauma and Surgical Pain

Caitlin F. Mullins[1], PharmD, BCCCP, Nathan Kugler[2], MD, Meghann Luc[3], PharmD, BCCCP, William J.Peppard[4], PharmD, BCPS, FCCM, Jasmeet S. Paul[5], MD, FACS

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OBJECTIVE: Acute pain management is intimately tied to patient satisfaction following trauma or surgery. Despite extensive adverse effects, opiate-based therapy remains the mainstay of acute pain management due to a lack of safe, viable alternative therapies. Ketamine infusions have historically been utilized following failure of traditional opiate therapy. Previous work demonstrates its safety and utility in the setting of opiate tolerant patients undergoing elective operations. This study aims to demonstrate the utility of adjunct continuous intravenous (IV) ketamine in the setting of critically ill trauma and surgical patients.

METHODS: A single center, retrospective review of adult patients who received adjunct IV ketamine infusions while in the surgical intensive care unit (SICU) between January 2009 and May 2015 was conducted. The primary outcome was improved pain management following institution of ketamine therapy. Pain management was assessed utilizing numeric pain scores (NPS) 0-12 hours prior to and 12-24 hours post-initiation of ketamine infusions. Cumulative opioid consumption, standardized to oral morphine equivalents, was assessed for the same intervals.

RESULTS: Sixty-two patients received IV ketamine infusions with twenty-eight excluded (paucity of documented pain scores; palliative care, etc). Thirty-four patients were analyzed: mean age was 53 years, 56% were male, 32.4% were opiate tolerant (≥ 30 mg PO morphine daily for > 3 weeks), and 47% were admitted to the trauma service. Analysis of the mean NPS pre- and post-ketamine demonstrated a significant improvement (6.54 vs. 5.37; p = 0.005). Additionally, there appears to be a significant decrease in median oral morphine equivalent requirements (102 mg vs. 42.5 mg; p=0.001) following initiation of the ketamine infusion.

CONCLUSION: Adjunct continuous ketamine infusions significantly improved pain management and decreased opiate consumption among patients experiencing acute traumatic or post-operative pain. A prospective study in this population is warranted to better demonstrate its efficacy.

Key Words: *Trauma; Anesthesia; Ketamine infusions; Opioid therapy; Delirium; Hallucinations*

INTRODUCTION

Inadequate acute pain management results in increased complications following trauma and surgery, with prolonged issues including chronic pain development and a diminished quality of life (1,2). Surveys demonstrate acute pain as the symptom of greatest concern, and ranks among the top three least desired outcomes (3,4). Opioid-based pharmacotherapy has long been the core of acute pain management regimens for the majority of trauma and surgical patients despite known adverse effects, due to a lack of viable alternative therapies (5). In recent years there has been an emphasis on the utilization of non-opioid adjunctive medications including non-steroidal anti-inflammatory drugs and acetaminophen, along with regional anesthesia for management of acute post-operative and traumatic pain. Within our institution, adjunctive ketamine infusions have been utilized following failure of traditional opioid therapy for the management of acute pain. Its alternative mechanism of action through pain prevention and treatment via N-Methyl D-Aspartate (NMDA) receptor blockade provides analgesia following trauma or surgery. Previous work demonstrates the safety and utility of ketamine among opioid tolerant patients undergoing elective operations (6,7). This study aims to demonstrate the utility of adjunctive continuous intravenous (IV) ketamine in the setting of critically ill trauma and surgical patients.

METHODS

Froedtert Memorial Lutheran Hospital (FMLH) is a tertiary care 550-bed Level I adult trauma center in Milwaukee, Wisconsin and the primary affiliate of the Medical College of Wisconsin. We conducted an Institutional Review Board approved retrospective review of adult patients who received continuous IV ketamine infusions while in the surgical intensive care unit (SICU) between January 2011 and May 2015. Patients were identified utilizing an administrative billing database. Patients were excluded if there was insufficient numeric pain score (NPS) data (less than three documented NPS in a 12-hour period), those in whom the prior to admission (PTA) or discharge medication list was unable to be reconciled, or those patients receiving ketamine infusions for palliative care. All patient charts were reviewed for complete demographic and hospital admission details including admitting service, length of SICU admission, and any surgical procedures. Patients were evaluated for opioid tolerance (defined as ≥30 mg PO morphine equivalent daily for > 3 weeks) utilizing reconciled mean opioid use PTA standardized to oral morphine equivalents (OME). A review of all inpatient opioid and ketamine infusion data was completed along with analysis of acute pain adjunctive therapies. Ketamine infusion initiation date and time, absolute (mg/hr) and weight adjusted (mcg/kg/min) starting, maximum, and dose at time of discontinuation were noted. Additionally, patients who transitioned to oral ketamine upon discontinuation of IV infusion were documented.

The primary outcome was improved self-reported pain control following institution of ketamine therapy. This was assessed using documentation of a zero to ten NPS 0-12 hours prior to and 12-24 hours post-initiation of ketamine infusions. There was a 12-hour time period beginning from the initiation of ketamine (hour zero) where data was not collected to allow for dose adjustments and the steady state concentration of ketamine to be reached. Secondary outcomes included reduction in opioid utilization in the aforementioned pre- and post-ketamine initiation intervals utilizing cumulative opioid consumption standardized to OME. Pre-initiation and post-initiation NPS data and cumulative opioid consumption were compared utilizing a Wilcoxon Signed-Rank test. All normally distributed variables were reported utilizing mean with standard deviation, while skewed data is reported utilizing median and interquartile range.

RESULTS

Sixty-two patients who received IV ketamine infusions were identified, with

[1]*Department of Pharmacy, Tufts Medical Center, Boston, MA, USA;* [2]*Department of Surgery, Division of Trauma and Acute Care Surgery, Froedtert & Medical College of Wisconsin, USA;* [3]*Department of Pharmacy, Froedtert & Medical College of Wisconsin, USA;* [4]*Department of Pharmacy, Froedtert Hospital, Assistant Professor – Department of Surgery, Froedtert & Medical College of Wisconsin, USA;* [5]*Department of Surgery, Division of General Surgery, University of New Mexico, USA.*

Correspondence: Dr Caitlin F. Mullins, Pharm D, BCCCP, 800 Washington Street, Department of Pharmacy, Tufts Medical Center, Boston, MA 02111, USA, Telephone (617) 636-1431, fax (617) 636-4633, e-mail cmullins@tuftsmedicalcenter.org

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28 patients excluded (insufficient NPS = 20, palliative care = 6, unable to perform PTA medication reconciliation = 2), resulting in a total of 34 patients for evaluation. The cohort was majority male at a median age of 53.5 years (IQR 42.8, 59.8) with approximately one-third demonstrating opioid tolerance on admission. Table 1 outlines additional general and surgical characteristics of the study cohort. Ketamine infusions were managed by the regional anesthesia and acute pain service (RAAPS) per FMLH hospital policy to ensure appropriate initiation, adequate dosing, and monitoring of potential adverse reactions.

TABLE 1

General and surgical characteristics of the population

Characteristics	Participants (n=34)
Male, n (%)	19 (56)
Age, years	53.5 (42.8-59.8)
Residence PTA, n (%):	
Home	32 (94)
Facility	2
Survivor Discharge Location, n (%):	
Home	21 (61.7)
Facility	11 (32.4)
Inpatient Rehab	2 (5.8)
Surgical Admitting Service, n (%):	
Trauma	16 (47)
Surgical oncology	7 (21)
Urology	3 (9)
Vascular	2 (6)
General	2 (6)
Orthopedic	2 (6)
Colorectal	1 (3)
Internal medicine	1 (3)
Opioid tolerant[a], n (%)	12 (35.2)
Surgical procedure, n (%)	23 (67.6)
SICU LOS, days	2 (1.1-6.1)
Hospital LOS, days	13.3 (7.6-17.1)
RAAPS consult n (%)	32 (94.1)
Time to initiation of ketamine, hours	31.5 (18.6-70.0)
Starting dosage, mg/hr	10 (10,10)
Starting dosage, mcg/kg/min	1.96 (1.51-2.68)
Duration of ketamine therapy, hours	47.0 (24.3-111.1)
Transition to oral ketamine, n (%)	5 (14.7)

The median time to initiation of ketamine from admission was 31.5 hours (IQR 18.6, 70.0) with greater delay noted among those individuals who were not initially identified as opioid tolerant. The median absolute starting and maximal ketamine doses were 10 mg/hr and 15.1 mg/hr, respectively. When adjusted for patient weight, the starting and maximal ketamine doses were 1.96 mcg/kg/min and 2.64 mcg/kg/min, respectively. Nearly half of patients (47.1%) required a dosage adjustment with a median absolute dose change of 10 mg/hr. Patients remained on continuous ketamine infusion for a median of 47.0 hours (IQR 24.3, 111.1).

Complete analysis of NPS data is outlined in Table 2 and demonstrates a statistically significant improvement in NPS following ketamine initiation (6.54 vs. 5.37; p=0.005). Additionally, there appears to be a significant decrease in median OME requirements (102 mg vs. 42.5 mg; p=0.001) following initiation of the ketamine infusion (Table 3). A single (2.9%) patient experienced hallucinations and anxiety-like symptoms shortly after ketamine initiation resulting in discontinuation with resolution shortly thereafter. A total of nine trauma patients required epidural placement for the management of rib fracture pain, six prior to initiation of ketamine and three after ketamine initiation.

Subgroup analyses are provided in Table 2 and Table 3. Within the trauma population there was a statistically significant improvement in NPS following initiation of a ketamine infusion (6.36 vs. 4.84; p=0.015), and an insignificant median reduction in cumulative opioid utilization (60mg vs. 48mg; p=0.112). The surgical population subgroup demonstrates a statistically significant reduction in both NPS (7.04 vs. 5.64; p=0.008) and median reduction in OME (82.5mg vs. 25 mg; p=0.016) following ketamine initiation. In the elderly population, the effects of ketamine on self-reported NPS (4.28 vs. 4.12; p=NS) and cumulative opioid utilization (77mg vs. 30mg; p=NS) were insignificant. In the chronic pain population, there was a non-significant reduction in NPS post-ketamine initiation (6.71 vs. 5.98; p=NS) and opioid utilization (148.8mg vs. 101.1mg; p=0.384).

TABLE 2

Effects of ketamine on numeric pain scoring

Characteristic	0-12 hours pre-ketamine initiation	12-24 hours post-ketamine initiation	Change in mean NPS	NPS Percent Reduction (%)	*p*-Value
Total population (n=34):	6.54 (2.23)	5.37 (2.56)	1.17 (2.2)	17.9	0.005
Trauma (n=16):	6.36 (2.01)	4.84 (3.05)	1.52 (2.14)	23.9	0.015
Surgical (n=23):	7.04	5.64	1.40 (2.16)	19.9	0.008
Elderly† (n=7):	4.68	4.12	0.55 (1.97)	11.9	NS
Opioid tolerant (n=12)	6.71	5.98	1.28 (2.37)	10.9	NS

NPS: Numeric Pain Scores; SD: Standard Deviation; OME: Oral Morphine Equivalents (mg); NS: Not Significant;

†Elderly defined as ≥ 65 years of age

TABLE 3

Effects of ketamine on cumulative opioid utilization standardized to OME (mg)

Characteristic	0-12 hours pre-ketamine initiation	12-24 hours post-ketamine initiation	Reduction in median opioid requirements (mg)	*p*-Value
Total population (n=34)	102 (48.5-173.9)	42.5 (15- 95.8)	36.5 (8.5-88.8)	0.001
Trauma (n=16)	118.1 (45.4-258.3)	60 (15-131.0)	48 (4.5-77.5)	NS
Surgical (n=23)	82.5 (43.5-148.8)	25 (6-89.7)	35 (3-87.5)	0.016
Elderly† (n=7)	77 (40-86.25)	30 (15-50)	37 (0-63.8)	NS
Opioid tolerant (n=12)	148.8 (82.5-225.8)	101.1 (45.3-167.7)	33.3 (85.5-108.5)	NS

OME: Oral Morphine Equivalents (mg); NS: Not Significant; All values are presented as medians with interquartile ranges; †Elderly defined as ≥ 65 years of age

DISCUSSION

The mainstay of acute pain management in critically ill trauma or surgery patients continues to be opioid based therapy despite their known adverse effects. This study demonstrates a significant reduction in mean NPS (17.9%) in adult patients receiving adjunctive ketamine infusions. Despite statistical significance, the clinical significance of this reduction is arguable. Literature has demonstrated that NPS performs as well as the visual analogue scale (VAS) in assessing changes in pain (8). However, a reduction of 13 mm on a VAS or a 2-point (18.2%) reduction on an 11-point NPS indicates a clinically significant improvement (9-11). Thus, a 1.17 point reduction in NPS suggests conventional clinical significance was not obtained. However, within a patient population in which conventional opioid and adjunctive measures have failed to provide adequate control this reduction may have been clinically significant.

Interpretation of clinical significance is difficult given the retrospective nature of this study.

While the improvement in NPS following ketamine initiation may not have provided a clinically significant reduction in pain, the reduction in opioid consumption standardized to OME was both statistically and clinically significant. A total of four patients did not demonstrate a reduction in opioid utilization, all of whom demonstrated opioid tolerance. The significant reduction in opioid consumption combined with the reduction in NPS demonstrates adjunctive continuous ketamine infusions significantly improved pain management among patients experiencing acute traumatic and/or post-surgical pain.

This study included a diverse patient population, including trauma, post-operative, chronic pain, and elderly patients. In the trauma patient population, immediate information regarding opioid tolerance is often unavailable. Although opioids plus ketamine for out-of-hospital adult trauma patients has demonstrated superior analgesia to opioids alone, no literature has previously defined the optimal dose of ketamine in adult patients with moderate to severe acute pain resulting from trauma (12,13). Within the trauma cohort, acute pain management challenges were often the result of

rib fractures as nine (56.3%) of the 16 trauma patients required epidural placement, the majority (66.7%) of which were placed prior to the initiation of ketamine. Thus it appears in these cases ketamine was essentially utilized for "failure" of epidural analgesia.

In post-operative patients, sub-anesthetic doses of ketamine have been found to improve post-operative analgesia and decrease morphine consumption with minimal adverse effects (6,7,14). While all patients in this cohort were admitted to a surgical in nature, the majority (67.6%) underwent a surgical procedure. Nearly a quarter of patients included in this study were surgical oncology patients, a population often excluded from pain studies due to the high amounts of opioids that are often required to treat cancer-related pain. With both the primary and secondary outcomes demonstrating statistical significance in this retrospective study, the role of ketamine in surgical oncology patients warrants further investigation.

The elderly population was also represented in this study, including seven patients that were greater than 65-years of age. Previous literature demonstrates conflicting results regarding the use of ketamine among elderly individuals. A single study found no improvement in analgesia among elderly patients with ketamine initiation, while another demonstrated low-dose ketamine markedly reduced opioid requirements(15,16). Due to the small sample size (n = 7), it is possible there exists a benefit in reduction of both NPS and opioid requirements, but the difference was unable to be detected. The reduction in cumulative opioid utilization suggests the use of adjunctive ketamine in the elderly population may prove beneficial for acute pain management while minimizing potential adverse effects.

Finally, chronic pain patients who undergo prolonged exposure to opioids often develop opioid-induced hyperalgesia and require individualized pain management plans (17). A single study demonstrated benefit to post-operative ketamine infusion at 0.2 mg/kg/hour with a significant reduction in pain scores; however the authors found no significant reduction in the use of opioids (18). Our study population encompassed 12 patients (35.2%) who were considered opioid tolerant and demonstrated non-significant improvements in both self-reported pain control and cumulative opioid consumption. However, the patient subset is a small again suggesting a potential benefit may exist but was unable to be detected.

Delirium and hallucinations are feared side effects with utilization of ketamine therapy. Delirium is common in older patients admitted to an ICU, with previous work suggesting a 10% increase in the incidence for every year over the age of 50-years (19). Significant risk factors for the development of delirium are influenced by clinical treatment decisions including opioid utilization, restraint use, sedation, and an altered sleep cycle (3). Within this cohort, ketamine infusions were found to significantly decrease opioid consumption, potentially reducing risk for delirium. Ketamine itself poses a risk for the development of hallucinations and delirium; however, this study demonstrates a favorable adverse effect profile in a diverse patient population. It should be noted that the single patient who experienced an adverse event had a remarkably high starting dose of 20 mg/hr (3.45 mcg/kg/min). Following cessation of therapy this patient's hallucinations ceased without further adverse effects. No additional episodes or delirium were noted within the study population: including among the seven patients greater than 65-years, and the 21 patients greater than 50-years.

This study is limited by the retrospective design and small sample size. Unfortunately, the majority of patients were excluded due to lack of sufficient documented pain scores. Utilization of patient controlled analgesia (PCA) administration led to some difficulty in the assessment of demand, as only total opioid received was documented. Epidural catheter placement could confound results, however; only one patient received an epidural three hours post ketamine initiation, with the remainder placed at least ten hours pre- or post-initiation of ketamine. Moreover, cross resistance between ketamine and opioids may have occurred, and the dose of ketamine utilized in the opioid tolerant population may have been too low. However, the aforementioned limitations prohibit any specific conclusions to be drawn.

CONCLUSION

In conclusion, the addition of continuous ketamine infusion therapy to the acute pain management regimen within a diverse population of patients demonstrates a significant benefit manifested through improved patient reported NPS and an overall reduction in opioid consumption. The results of this retrospective study support the findings of previous work on specific populations, while demonstrating a potential benefit within new groups. The type of patients, types of pain, doses, routes of administration, or duration of use for which ketamine is truly effective and optimal has yet to be fully elucidated. The findings of this study should encourage the study of ketamine infusions in a broad range of subjects via prospective clinical trials.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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