Adjuvant Low-dose Ketamine in Pediatric Sickle Cell Vaso-occlusive Crisis (AKTSS)

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Adjuvant low-dose ketamine in pediatric sickle cell vaso-occlusive crisis (AKTSS)

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Abstract

The adjuvant low-dose ketamine in pediatric sickle cell vaso-occlusive crisis (AKTSS) study is a historical cohort or time series study that will include a retrospective chart review, enrollment, and follow-up. The cohort is comprised of pediatric sickle cell patients between 10 and 25-years-old cared for at UCSF Benioff Children's Hospital Oakland (UCSFBCHO) presenting with vaso-occlusive crisis (VOC). The predictor variable will be exposure to IV bolus ketamine in the ED as an adjuvant to standard, opiate-based therapy. The main outcome will be mg/kg/hour of morphine equivalents used in the ED as an indicator of pain control. Secondary outcomes will be pain scores on discharge or admission to the hospital, time to 50% pain reduction, probability of discharge home from the ED, and risk of presentation to the ED in the subsequent 3 months. A survey will be given to determine subjective improvement in pain due to drug administration. Data will be collected after exposure to ketamine and compared with patients' prior presentations to the ED.

Research Question: In a group of sickle cell patients between 10- and 25-years-old with vaso-occlusive crises requiring frequent ED and inpatient hospital admissions at BCHO, does the addition of low-dose IV ketamine boluses as part of a standard, opiate-based pain control regimen decrease opiate use, time to pain control, increase probability of discharge from the ED, decrease pain scores on discharge or admission to the hospital, and decrease the risk of readmission?

Background and Significance

VOCs in sickle cell disease are due to microcirculation thrombotic events that lead to ischemia and pain, historically managed with opiates and nonsteroidal anti-inflammatory drugs (NSAIDs)(1). Opiate medications have a relatively narrow therapeutic window and over time, patients can develop tolerance and hyperalgesia (2). Hyperalgesia and tolerance is postulated to be a N-methyl-D-aspartate (NMDA)-receptor mediated process that leads to these effects via activation of the nociceptive system. Hyperalgesia manifests as a heightened sensitivity to pain, increasing symptom severity while tolerance manifests as increased opiate requirements and side effects for similar symptom control. As an NMDA receptor antagonist, ketamine has the potential to mitigate this activation (3). When administered as an IV infusion, it is efficacious in reducing post-operative, chronic, and cancer-related pain (4).Of note, IV boluses of ketamine as an adjuvant to opiates have been shown to reduce time to pain control and opiate use in adults in the ED setting (5, 6, 7, 8). In limited studies, ketamine infusions have also shown utility in pain-reduction in opiate-refractory sickle cell patients (1,4,9,10). Ketamine IV bolus as an adjuvant to opiates appears safe in adults presenting to the ED(11). The purpose of this study is to investigate whether a low-dose IV ketamine bolus is efficacious in improving pain control and reducing the need for hospitalized medical care in pediatric sickle cell patients.

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Study Design

In this historical control study, all consenting pediatric sickle-cell patients between 10 and 25 years old who are cared for at UCSF Benioff Children's Hospital Oakland (UCSFBCHO) presenting to the emergency department for VOC will be enrolled in the study. Patients will be compared to themselves in a time series, pre and post exposure to the study intervention (low-dose ketamine bolus at 0.2 mg/kg x 1 prior to second dose of IV opiate). The pediatric FACES pain scale will be used to measure pain scales at pre-designated time points in the ED per standard nursing protocol (FACES for younger kids, visual analog scale in adolescents/young adults). Opiate usage will be summed in the ED, converted to mg/kg/hour of morphine equivalents (since different opiate agents are given to different patients based on individual historical efficacy, and since length of stay in the emergency room could affect total morphine equivalents received), and compared between the pre and post-intervention groups. In addition, the proportion of discharged vs admitted patients, pain scores at admission, during the visit, and discharge, and proportion of patients re-presenting for care, will all be compared in the pre and post intervention groups. Data will be collected via chart review in the UCSFBCHO system by study investigators. Pre-intervention data from the past two patient encounters (e.g., the mean of the mg/kg/hour of morphine equivalents used in the last two patient encounters prior to receipt of ketamine) will be compared to the post intervention data. In addition, a survey, which is attached, will be given to patients/families at the time of the drug administration to attempt to discern if patients subjectively experienced improvement in their pain and if they experienced any negative side effects due to the drug administration.

Patients will be included for follow-up for three months after presentation to the emergency department to determine the likelihood of re-presentation before and after exposure to ketamine.

Informed consent will be obtained in two settings. First, patients who have standard follow-up with their hematologists prior to presentation to the emergency room for VOC will be consented for inclusion in the study as applicable. This will provide ample time for discussion between study providers and families/patients. Second, patients can be consented on presentation to the emergency room. Families will have time to consider their participation in the study while patients are beginning to receive IV access and associated opiate-based medications for their pain. Study investigators will use the read-back method to ensure that families understand what consenting to inclusion in the study entails. The form will be a combined one since some patients to be consented are minors and some are not.

Protocol

The study protocol will be almost completely that of the standard of care currently used in the UCSFBCHO. For the experimental portions, patients/families that have not otherwise been consented will be consented during triage and rooming. The current standard of care will then begin -- nurses will place patients on continuous monitoring and then give intranasal fentanyl (if desired by patient and family) for pain relief at standard dosing while obtaining IV access and drawing standard labs, including CBC, reticulocyte count, and if applicable for their care, other labs. Patients then typically receive IV toradol, IV fluids, and IV opiates (morphine or dilaudid). Prior to the second dose of IV opiates, the experiment will be to give patients a single

IV bolus of low-dose ketamine at the dose of 0.2 mg/kg pushed slowly over 1 minute (sub dissociative dosing; doses of either 0.15, 0.2, and 0.3 mg/kg were used in all currently available randomized control trials. The dose of 0.2 mg/kg was decided in conjunction with UCSFBCHO Department of Anesthesia). Since this is a historical control, we will not deviate from the standard practice currently in place regarding when nurses check patient pain levels and all other aspects of their care. Pain scores will be collected using the numerical FACES scale currently in place. Disposition from the emergency room will be determined by the attending physician and reports from the family/patient as to the ongoing need for IV opiate pain control or other considerations (such as the presence of fever, severe anemia, acute chest syndrome, and others) and will not be related to the receipt of IV low-dose ketamine. Pre-intervention data from at least one patient encounter in the past year will be used. If more are available, the data from these encounters will be averaged and compared to the ketamine exposure encounter. The following data will be collected: mg/kg/hour of morphine equivalents, pain scores on admission, during the encounter, and at discharge, the time to 50% pain reduction, whether or not the patient was discharged, and if re-presentation occurred in the subsequent 1 month. Demographic data including age, sex, race, current and prior medications and comorbidities, and as a quality control measure, adverse events, will all be collected to examine for confounding factors that may alter the findings of the study. All patient data will be de-identified post collection of the above.

In addition, a survey, which is attached, will be given to patients/families at the time of drug administration to determine if they experienced a subjective improvement in their pain and if they suffered any undue side effects due to drug administration. The survey uses a Likert scale to quantify their subjective response to ketamine and their desire to receive it for future pain crises. Please see the attached for further information.

Risk Assessment

Adverse events of administering low-dose ketamine 0.2 mg/kg (max dose) on top of standard opiates for all-cause pain in adult patients presenting to Highland Hospital in Oakland, California were experienced in 6% of 530 patients. 3.5% of patients experienced a dysphoric or emergene reaction, while 1.5% developed transient, mild hypoxia and 1% developed nausea/vomiting. No serious adverse events were reported. The study investigators noted that this complication rate was less than half of opiate-use in hospitalized patients (1). We therefore expect a very small proportion of patients to suffer undue side effects associated with the addition of ketamine to the standard opiate protocol and none to experience serious adverse events.

(1) Ahern, T. L. et al. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. Am J Emerg Med, v. 33, n. 2, p. 197-201, Feb 2015. ISSN 1532-8171. Disponível em: < http://www.ncbi.nlm.nih.gov/pubmed/25488336 >.

Safety Measures

Pediatric sickle cell patients who present to the emergency department for VOC are currently placed on a standard protocol which involves continuous pulse oximetry monitoring and frequent reassessment by trained nursing staff due to the use of opiates for pain control. Retrospective data provided above would not suggest that more monitoring/interventions will be

expected to be necessary. All providers in the pediatric emergency room are trained in cardiorespiratory resuscitation of pediatric patients. Therefore, in the unlikely circumstance of a serious adverse event, patients are in the proper setting for applicable care.

Risk-Benefit Assessment

Based on the favorable results of double-blinded, placebo controlled randomized clinical trial involving the addition of ketamine to opiates for all-cause pain in the adult emergency room setting, patients who receive ketamine in addition to opiates for their VOC-associated pain may have improved pain relief with lower opiate requirements (1) There is therefore the hypothetical benefit to both the individuals and to the greater society of people with sickle cell associated with lower opiate use (fewer side-effects such as constipation) and with mitigating tolerance and hyperalgesia (2). Compared with the risks, which the data presented in item 25 as above suggests are quite low, the ratio of benefit to risk seems appropriately high to conduct this research in this setting. The alternative to not perform this research does exist. However, given the risks of chronic opiate use in patients that require them for pain control, the potential ability to mitigate these risks due to ketamine's unique mechanism, and the efficacy with which it appears to work in adults with all-cause pain, this alternative seems less desirable.

(1) Beaudoin, F. L. et al. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: results of a randomized, double-blind, clinical trial. Acad Emerg Med, v. 21, n. 11, p. 1193-202, Nov 2014. ISSN 1553-2712. Disponível em: < http://www.ncbi.nlm.nih.gov/pubmed/25377395 >.

(2) Jennings, C. A. et al. Oral ketamine for sickle cell crisis pain refractory to opioids. J Pain Palliat Care Pharmacother, v. 27, n. 2, p. 150-4, Jun 2013. ISSN 1536-0539. Disponível em: < http://www.ncbi.nlm.nih.gov/pubmed/23692261 >.

Study Population

All English-speaking, sickle cell patients who receive their care at UCSFBCHO in the Department of Hematology who are 10-to-25-years-old presenting to the emergency department for VOC will be asked to enroll.

Inclusion criteria: all patients as described above are eligible.

Exclusion criteria: prior adverse reaction to ketamine. Patients will be asked during the consent process if they have ever received ketamine, and if so, if they had any serious adverse reaction, such as difficulty breathing, dysphoria, hallucinations, or allergic reaction. If they have, ketamine will not be given to these patients. Patients who have received ketamine and experienced nausea or vomiting will be asked if they wish to receive the medication. If they do not, they will not receive ketamine.

Statistics

Sample size:

Primary aim:

For the purposes of demonstrating tolerability and safety, a minimum of 30 patients will be enrolled in the study.

Secondary aim(s):

Beaudoin, F.L, et. Al. demonstrated a 30% reduction in opiate use in the ED setting when low-dose IV bolus ketamine was used as an adjuvant to IV opiates. Given the lack of funding for research personnel, the nature of emergency room care, the time constraints of a fellow-run project, the number of patient visits at UCSFBCHO for VOC in any given year, and the refusal rate of potential enrollees (which is unknown), the feasibility of this is questionable. Also, the design of the study creates more inherent confounding (this design was chosen for feasibility purposes), then for example a randomized clinical trial. However, patients with sickle cell who have repeated VOC crisis may more uniquely benefit from ketamine than patients who have just acute pain due to its action on NMDA receptors as in the “Background” section (i.e. the effect size in patients with sickle cell during a VOC may be higher). We therefore used the following calculation:

Sample size calculation using one-group paired t-test (one group, since this is a historical control study)

Effect size: 0.30

Standard deviation: no prior data to compare in the literature; this is the first such prospective study to look at the effect of low-dose ketamine on pain crisis in patients with sickle cell. Therefore, assume 1

Standardized effect size therefore = 0.30

Alpha 0.05; Beta 0.2

Sample size therefore = 90

We estimate that enrolling 90 patients will give us 80% power to detect a standardized effect size of 0.30 in the difference in total opiate received (measured in mg/kg/hour of morphine equivalents) comparing patients receiving opiates + ketamine vs. patients receiving opiates only in a historical control.

Based on EPIC chart review, approximately 210 patient encounters for patients aged 10 to 25 years old occur in our emergency room per year for sickle cell VOC. We therefore anticipate data collection to take a maximum of 18 months (given the difficulty in enrolling patients, lack of funding, and anticipated refusal rate (which is unknown) of potential enrollees).

We therefore plan to enroll a minimum of 30 patients to obtain our primary aim, and a maximum of 90 (if possible within the data collection period) to obtain our secondary aim(s).

Statistical Analysis:

As stated previously, at least one (more if available; data to be averaged from prior encounters within the last year) patient encounter in the last year will be compared to the visit in which ketamine was received. If a patient re-presents 4 weeks or more after involvement in the study, the patient will be re-enrolled in the study and again compared to historical data in their past. Our main outcome (predictor variable) is continuous – mg/kg/hour of morphine equivalents used pre and post exposure to ketamine in a time series study. Continuous outcome variables (opiate usage in mg/kg/hour of morphine equivalents, time to 50% pain reduction, and pain score on discharge or admission) will be compared using a matched t-test while dichotomous variables (proportion of patients discharged from the ED in the ketamine vs. no ketamine groups, proportion of patients exposed and not exposed to ketamine that re-presented for VOC within 1 months) will be compared using a chi-squared analysis. We will determine the mean of the pre-ketamine continuous variables using standard calculation.

The mean of the pre-ketamine continuous variables (as available, otherwise just pre and post comparison) will be used in the one group, paired t-test calculation (e.g. mean mg/kg/hour of morphine equivalents for a single patient pre-ketamine vs. mg/kg/hour of morphine equivalents used during the visit where the patient was exposed to ketamine).

Data analysis will be performed using STATA.

For the survey, percentages for each Likert scale response and the percent of who experienced the listed and “other” side effects will be calculated and reported in the study. General comments will be reported in the study as well.

Statistical Analysis:

As stated previously, we will perform a chart review of the two prior visits before ketamine exposure and the visit during which the patient received ketamine as part of our study. Our main outcome (predictor variable) is continuous – mg/kg/hour of morphine equivalents used pre and

post exposure to ketamine in a time series study. Continuous outcome variables (opiate usage in mg/kg/hour of morphine equivalents, time to 50% pain reduction, and pain score on discharge or admission) will be compared using a matched t-test while dichotomous variables (proportion of patients discharged from the ED in the ketamine vs. no ketamine groups, proportion of patients exposed and not exposed to ketamine that re-presented for VOC within 3 months) will be compared using a chi-squared analysis. We will determine the mean of the pre-ketamine continuous variables using standard calculation, e.g. below where n is the number of patient presentations (in this case two):

$$\bar{x} = \frac{x_1 + x_2 + x_3 + \ldots\ldots\ldots\ldots + x_n}{n}$$

The mean of the pre-ketamine continuous variables will be used in the matched t-test calculation (e.g. mean mg/kg/hour of morphine equivalents for a single patient pre-ketamine over two visits vs. mg/kg/hour of morphine equivalents used during the visit where the patient was exposed to ketamine).

Data analysis will be performed using STATA.

For the survey, percentages for each Likert scale response and the percent of who experienced the listed and “other” side effects will be calculated and reported in the study. General comments will be reported in the study as well.

Data Collection, Management, and Safety Monitoring

A data-safety monitoring form has been created that all attending physicians caring for patients who experienced any adverse events associated with ketamine administration must complete. For any complication that required support of the patient's airway or circulation (a severe adverse events), the co-investigator Dr. Cooper-Sood will be contacted directly within 24 hours of the event. He will convene a meeting with the nursing supervisor for the emergency department, the involved attending, and a co-investigator to discuss the adverse event and the associated clinical context. This group will perform a root-cause analysis of adverse events not directly associated with the drug itself. For effects deemed to be associated with the drug, the adverse event will be reported to the CHO IRB for further consideration as to the ongoing safety of continuing the prospective study as well as the FDA via MedWatch. Mild and moderate adverse events (such as nausea/vomiting, emergence phenomenon, etc.) will be recorded on the same form. These forms will be reviewed monthly by the co-investigator Dr. Cooper-Sood to ensure that levels of mild and moderate adverse events are in line with published rates. In addition, two UCSFBCHO physicians outside of the study will verify these results. Rates of adverse events above published values will be reported to the IRB. This sheet is included with this application.

Data will be checked for accuracy by data verification and protocol compliance checks will be performed by the data manager, Dr. Cooper-Sood. Data collected during the study will be de-identified and then entered into an Excel spreadsheet that will be stored on password-secured hospital servers.

Consent and Personnel

Pediatric patients less than 18 years-old will be consented via their parents. Patients 10-18 years old will also be asked for their assent to be involved in the study. Patients 18 years and older can consent themselves.

Informed consent will be obtained in two settings. First, patients who have standard follow-up with their hematologists prior to presentation to the emergency room for VOC will be consented for inclusion in the study as applicable. This will provide ample time for discussion between study providers and families/patients. Second, patients can be consented on presentation to the emergency room. Families will have time to consider their participation in the study while patients are beginning to receive IV access and associated opiate-based medications for their pain. Study investigators will use the read-back method to ensure that families understand what consenting to inclusion in the study entails. The form will be a combined one since some patients to be consented are minors and some are not.

The following individual's will be consenting and administering the experimental agent:

Attending pediatric emergency medicine physicians:
1). Kevin Whitelaw
2). Michael Bell
3). Kevan McCarten-Gibb
4). Augusta Saulys
5). Karim Mansour
6). Michelle Fleurat
7). Sara Leibovich
8). Charles Clemmons
9). Ellen Henderson
10). Christian Peter Baker
11). Lisa Hart
12). Sima Patel
13). James Naprawa
14). Nisa Atigapramoj
15). Cornelia Latronica
16). Alan Johnson

Fellow physicians, pediatric emergency medicine
1). Ashkon Shaahinfar
2). Tatyana Vayngortin
3). Primary investigator -- J. Bryan Cooper-Sood

Current Progress:

The study received IRB and RC approval and has been ongoing since 6/1/2016. Thus far, 40 patient encounters (since by study design, patients can be re-enrolled 4 weeks post receipt of ketamine) have been enrolled. At prior analysis (when 34 patient encounters had been enrolled), the following subjective experience and rates of adverse events were as follows:

Total patient encounters enrolled		34
Total individual patients enrolled		18
Percent of patient encounters reporting faster pain relief		69%
Percent of patient encounters reporting more complete rain relief		59%
Percent of patient encounters indicating their desire to receive ketamine again		80%
Serious adverse events (cardiorespiratory)		0%
Minor adverse events:		
Percent of patient encounters who experienced nausea/vomiting		2.90%
N of patient encounters who reported nausea/vomiting	1	
Percent of patient encounters reporting an emergence reaction		8.80%
N of patient encounters reporting an emergence reaction	3	
Percent of patients self-reporting a "dream-like" or "derealized sensation"		44%
N of patient encounters reporting a "dream-like" or "derealized sensation"	15	
Selected comments:	"I felt like I was on a high bridge and was going to fall off"	
	"I can't believe how well this worked!"	
	"Made my vision blurry"	
Published adverse reaction rates:		
Nausea and vomiting	1-3%	
Emergence reaction	approximately 3.5%	

An abstract was accepted by PAS for a poster presentation 5/2017 based on the above data. Patient enrollment and preliminary secondary outcome data analysis are ongoing. We are continuing to enroll patients thru 12/2017.