Title

Ketamine and/or lidocaine analgesia for abdominal surgery

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INTRODUCTION

Opioid overdoses cause 115 deaths per day in the United States, and cost more than $500 billion in 2015, i.e. 2.8% of the nation's GDP (1). Concerningly, mortality due to the opioid epidemic has steadily increased with the number of deaths in 2016 being five times greater than in 1999 (2), and opioid prescribing having quadrupled in the same time frame (3).

The misuse of prescription opioids is reportedly the strongest risk factor for heroin abuse (3, 4), and in surgical patients, may have its roots in the perioperative period where over 80% are routinely exposed to opioids (5). Alam *et al.* reported a 44% increase in the risk of long-term opioid use in patients who were prescribed opioids after short-stay surgeries; even in opioid-naïve patients, an opioid prescription at hospital discharge was associated with 4.9 times the risk of chronic opioid use one year later (5). Thus, perioperative providers may be able to mitigate this threat by minimizing perioperative opioid use.

Background

Systemic lidocaine and ketamine are both analgesic agents, but by different mechanisms. The analgesic effects of intravenous lidocaine remain poorly characterized, but are thought to be related to its anti-inflammatory effect and possibly blunted excitatory neuronal response (6). Ketamine is a NMDA antagonist, which has been implicated in nociception and the development of chronic pain (7).

Gilbert *et al.* first presented a case series in 1951 showing that an infusion of intravenous lidocaine markedly reduced pain in a wide spectrum of settings including cancer pain, postoperative pain, and labor pain (8). Following that, Ito and Ichiyanagi in 1974 showed that an infusion of a subanesthetic dose of ketamine also decreased postoperative pain after upper abdominal surgery (9). Many subsequent studies evaluated perioperative infusions of both agents; however, the doses and timings used across different types of surgery have been inconsistent, and the results have accordingly been variable (see Tables 1 and 2).

Dose	Lidocaine (n = 23)		Ketamine (n = 21)	
	Positive (n = 17)	Negative (n = 6)	Positive (n = 16)	Negative (n = 5)
Bolus	NO BOLUS (10) 100 mg (11-13) 1.5 mg/kg (14-23) 2 mg/kg (24-26)	NO BOLUS (27) 1.5 mg/kg (28-32)	NO BOLUS (33) 0.1 mg/kg (34) 0.15 mg/kg (35-38) 0.3 mg/kg (39-41) 0.5 mg/kg (42-47) 1 mg/kg (48)	0.15 mg/kg (49) 0.2 mg/kg(50) 0.3 mg/kg (51) 0.35 mg/kg (31) 0.4 m/kg (52)
Infusion	2 mg/min for < 70 kg or 3 mg/min for ≥ 70 kg (19) 2 mg/min (11, 12) 3 mg/min (13) 1.5 mg/kg/hr (21, 22, 26) 2 mg/kg/hr (14-18, 20, 23, 25) 3 mg/kg/hr (10, 24)	1 mg/min for < 70 kg or 2 mg/min for ≥ 70 kg (27) 2 mg/min (28) 2 mg/kg/hr (29, 31, 32) 3 mg/kg/hr (30)	NO INFUSION (36-38, 44, 48) 0.015 mg/kg/hr (33) 0.05 mg/kg/hr (41) 2 mcg/kg/min = 0.12 mg/kg/hr (34, 35, 47) 3 mcg/kg/min = 0.18 mg/kg/hr (39, 40) 0.25 mg/kg/hr (42, 43) 5 mcg/kg/min = 0.3 mg/kg/hr (45) 0.5 mg/kg/hr (46)	NO INFUSION (49, 51, 52) 2.5 mcg/kg/min = 0.15 mg/kg/hr (50) 0.2 mg/kg/hr (31)

Table 1.   Comparison of doses used in studies showing a positive versus negative effect on postoperative opioid consumption.

Timing	Lidocaine (n = 23)		Ketamine (n = 21)	
	Positive (n = 17)	Negative (n = 6)	Positive (n = 16)	Negative (n = 5)
Bolus	Before induction (13-17, 19, 25) At induction (18, 20, 23) After induction and before incision (10-12, 21, 22, 24, 26)	Before induction (28-30) At induction (32) After induction and before incision (27, 31)	Before induction (34, 37, 45) At induction (39, 40, 43, 46) After induction and before incision (33, 35, 36, 38, 41, 42, 44, 47, 48)	Before induction (51) After induction and before incision (31, 49, 50, 52)
Infusion	Until end of surgery (10, 16-18, 20, 23-26) 1 hr postop (19, 21, 22) 24 hr postop (11-15)	Until end of surgery (30) 4 hr postop (28) 24 hr postop (31, 32) 48 hr postop (29) 5 days postop or the day after return of flatus (27)	Until end of surgery (34, 35, 39-42, 45, 46) 48 hr postop (33, 43, 47)	2.5 hr after incision (50) 24 hr postop (31)

Table 2.   Comparison of timings used in studies showing a positive versus negative effect on postoperative opioid consumption.

Disappointingly, Grady *et al.* did not show reduced 48-hour postoperative pain scores or opioid consumption with infusions of lidocaine with ketamine in patients recovering from open abdominal hysterectomy (31). Single preoperative doses of lidocaine and ketamine also did not reduce postoperative pain or opioid consumption after gynecological laparotomies (53). Conversely, ketamine has been found to reduce postoperative analgesic requirements as well as pain scores when used as an adjunct to lidocaine for intravenous regional anesthesia (54).

Objective

We therefore propose to test the hypothesis that perioperative infusions of lidocaine and/or ketamine reduce opioid consumption and pain scores in adults recovering from elective inpatient abdominal surgery.

METHODS

Trial Design

We propose a prospective, randomized, double-blind, placebo-controlled clinical trial (RCT) with a factorial design

Participants

We will include adults 18 to 80 years old having elective inpatient open or laparoscopic abdominal surgery with general anesthesia lasting 2 hours or longer.

Exclusion criteria:
1. Planned postoperative mechanical ventilation
2. Planned regional anesthesia/analgesia
3. Perioperative gabapentin, magnesium, or nitrous oxide use
4. Pregnancy or breastfeeding
5. Morbid obesity (BMI $\geq$ 35 kg/m^2)
6. ASA physical status IV-V
7. Allergy to study medications
8. Contraindication to lidocaine (severe cardiac arrhythmia)
9. Contraindication to ketamine (psychiatric disorder, substance abuse, uncontrolled hypertension, pulmonary hypertension, increased intracranial or intraocular pressure, use of MAO inhibitors)
10. Chronic preoperative opioid use ($\geq$ 90 morphine mg equivalents per day for > 3 months (55))
11. Significant preoperative hepatic dysfunction (ALT or AST > 5 times normal (56)) or planned liver transplantation
12. Preoperative cardiac failure (left ventricular ejection fraction $\leq$ 40% (57))
13. Unable to communicate or comprehend study instructions

Interventions

- Patients will be given 1 g oral acetaminophen with a sip of water shortly before anesthetic induction.
- Patients will be factorially randomized to receive either lidocaine or placebo and either ketamine or placebo, resulting in the following four equal-sized groups:
  - i. Lidocaine + ketamine
  - ii. Lidocaine + placebo
  - iii. Ketamine + placebo

iv.   Placebo + placebo

Blocked randomization (random sized) 1:1:1:1 will be based on computer-generated codes developed by Department of Outcomes Research statisticians. Allocation will be concealed until shortly before anesthetic induction with a web-based system that will record access and assignments.

- Lidocaine will be given as a 1.5 mg/kg bolus followed by an infusion of 2 mg/kg/hr based on actual body weight.
- Ketamine will be given as a 0.5 mg/kg/ bolus followed by an infusion of 0.3 mg/kg/hr based on actual body weight.
- Both the bolus and infusion will be started after induction and before incision.
- The infusion will be stopped one hour after transfer to PACU
- The boluses and infusions will be prepared by the pharmacy department, with normal saline as the placebo. Patients, anesthesiologists, and research fellows assessing the patients' postoperative outcomes will therefore all be blinded to the treatment group assignments.
- General anesthesia will be induced with propofol or etomidate and maintained with isoflurane. Intraoperative opioids will be restricted to only fentanyl.

Measurements

Data to be collected includes:
i.   Baseline demographics: MRN, date of birth, gender (male/female), ethnicity, weight (kg)
ii.   Surgery details: date of surgery, diagnosis, surgery, start case time (hr:min), end case time (hr:min), intraoperative opioid (mg)
iii.   Postoperative details: PACU discharge time (hr:min), hospital discharge time (date)
iv.   Total amount of perioperative lidocaine use (mg)
v.   Total amount of perioperative ketamine use (mg)

The following will be measured at the end of the PACU stay as well as on the 1st and 2nd postoperative mornings:
vi.   Opioid consumption: preoperative (yes/no, type of opioid, average daily dose), postoperative (yes/no, type of opioid, cumulative dose from surgery to morning of POD2)
vii.   Pain scores: preoperative (0-10), postoperative (0-10)
viii.   Incidence of postoperative nausea or vomiting (yes/no)

Data that will be calculated from the aforementioned variables will include the following:
i.   Age (years)
ii.   Surgery duration (hr:min)
iii.   PACU length of stay (hr:min)
iv.   Hospital length of stay (days)
v.   Total amount of opioid consumption in PACU, POD1, and POD2 (oral morphine equivalent in mg)

Patient who are discharged before the 2nd POD will be contacted by phone for outcomes, and outpatient opioid consumption will be assessed by pill counts.

Data will be securely stored on the following: CCF's REDCap, CCF's shared network drives, CCF-issued computers, and CCF-issued encrypted USB drives. It may also be sent confidentially through the CCF email network. Results will be reported in an aggregate form and in a de-identified manner. The Cleveland Clinic Department of Outcomes Research will conduct the data analysis.

Outcomes

Joint primary outcome of:
1. Pain scores on a scale of 0-10/10, and
2. Total opioid consumption in oral morphine equivalents (mg) from the time of transfer to PACU through to the morning of POD2.
- The intervention will be deemed effective if both outcomes are non-inferior, and at least one is superior, to the control group.

Secondary outcomes:
1. Overall benefit of analgesia score (OBAS)
2. Quality of recovery (QoR-15) score

All outcomes will be measured at the end of the PACU stay as well as on the 1st and 2nd postoperative mornings. On the 1st postoperative morning, patients will be asked to consider the period starting after discharge from the PACU. On the 2nd postoperative morning, patients will be asked to consider the period starting after the first postoperative morning.

Tertiary or exploratory outcomes
1. Time to first opioid administration (minutes)
2. Postoperative hospital length of stay (days)
3. Nausea or vomiting (yes/no)

The following adverse events will be monitored at the end of the PACU stay, on the morning of POD1 and the morning of POD2:
i. Patient questionnaire: drowsiness, hallucination, peripheral neuropathy (numbness/paresthesiae), tinnitus, nausea/vomiting
ii. Nurse questionnaire: hypersensitivity reactions (rash, dyspnea, anaphylaxis), cardiac arrhythmia, confusion, seizure
iii. Chart review: bradycardia/tachycardia (HR < 60 bpm or > 100 bpm), hypotension (SBP < 90 mmHg)

The trial will be managed by an Executive Committee consisting of Daniel I. Sessler, M. Alparslan Turan, and Edward J. Mascha.

Statistical Methods

Randomized groups for each of the 2 factors (Lidocaine and Ketamine) will be compared on baseline variables using standardized difference. All analysis will be intent-to-treat.

Primary Outcomes

Following the study aims, we define effectiveness of the analgesic agent (lidocaine or ketamine) for pain management as being noninferior to placebo on both pain control and opioid use, and at the same time being superior on either or both of pain control and opioid use. Therefore, we will first assess whether the agent (lidocaine or ketamine) is noninferior to placebo on each of pain score and opioid consumption. If the analgesic agent is found to be noninferior on both pain control and opioid use, we will then test whether the analgesic agent is superior over placebo on either pain control or opioid consumption, or both. We will first assess the treatment effects on each outcome, and then use those treatment effect estimates to test for noninferiority and superiority.

Pain score. The effects of lidocaine and ketamine, as well as their interaction, on the first primary outcome of pain score in the first 2 postoperative days will be assessed using a linear mixed effects model to adjust for the within-subject correlation on the pain scores over time. If there is a statistically significant (e.g., $P<0.15$) and clinically important (particularly, if effects are in opposite directions) interaction between the intervention factors on pain score, the interaction and confidence interval will be reported, and the main effects of each factor will be assessed within levels of the other factor. Otherwise, the main effects will be assessed collapsing over the other factor.

Opioid consumption. The effects of lidocaine and ketamine, as well as their interaction, on the second primary outcome of total opioid consumption through POD2 will be assessed using linear regression on the log-transformed values of the outcome, if appropriate. Otherwise, cumulative logit model or other appropriate method will be used to assess the main effects and their interaction. In the presence of a significant interaction, the main effects of each factor will be assessed within levels of the other factor. Otherwise, the main effects will be assessed collapsing over the other factor.

Noninferiority. For each analgesic agent (lidocaine and ketamine), we will test for noninferiority on pain score through a one-sided test using the treatment effect estimates and standard errors from the above linear mixed effects model and using a noninferiority delta of 1 point. We will test for noninferiority on opioid consumption using 1-tailed t-test on log-transformed opioid consumption (if appropriate – see above methods), using a noninferiority delta of 0.18 (log-scale equivalent of a ratio of 1.2 in geometric means). Noninferiority will be assessed at the overall 0.025 significance level for each agent, and using the same 0.025 as the significance criterion for each outcome within each agent. No adjustment for multiple testing will be needed since noninferiority is required on both outcomes for an agent (intersection-union test).

Superiority. Superiority test on pain control and opioid use will be performed only when the analgesic agent is noninferior to placebo on both pain score and opioid consumption. One-sided tests using the estimated treatment effects and standard errors and a significance criterion of $0.025/2=0.0125$ will be used, adjusting for the fact that significance on either outcome would be sufficient to claim "superiority".

Secondary Outcome

We will assess the effect of lidocaine and ketamine, as well as their interaction on OBAS and total QoR-9/QoR-15 scores through linear regression model.

Tertiary Outcome

For time to first opioid administration and hospital length of stay, the two variables will be transformed to meet model assumptions of normality. We will then assess the effect of lidocaine and ketamine, as well as their interaction through linear regression model.

For nausea or vomiting at the end of PACU stay, POD1 and POD2, we will then assess the effect of lidocaine and ketamine, as well as their interaction through a generalized mixed effect model to account for within-subject correlation (random effect for subject) and the binary outcome type.

Interim Analyses.

Interim analyses will be done at each 25% of the planned maximum enrollment to assess for efficacy and futility using a group sequential design with gamma spending functions, and using gamma of -4 for efficacy and -1 for futility for each intervention. With this design, and assuming the hypothesized

treatment effects (25% reduction in opioid consumption, 2 points in pain score), the cumulative probability of crossing an efficacy or futility boundary at the 1st, 2nd, 3rd or 4th look will be 0.09, 0.40, 0.78, 1.00, respectively.

SAS 9.4 statistical software, Carey, NC, and R statistical software version 3.5.1 for 64-bit Windows operating system (The R Foundation for Statistical Computing, Vienna, Austria) will be used for all analyses.

Sample Size

We base the sample size calculations on being able to claim either lidocaine or ketamine to be effective, and assuming no interaction between the two interventions. Based on the records we have for patients who went through colorectal surgery, opioid consumption through POD2 is approximately lognormally distributed. From these records, we observed means (SD) for pain scores to be 5 (2) and 4 (2), respectively for POD1 and POD2. Total opioid consumption for POD1 and POD2 has a mean (SD) of 257 (186), for an estimated coefficient of variation of 0.72.

We assume similar variability in pain scores and coefficient of variation for opioid consumption for the current study. Sample size calculation is based on 90% power to detect a difference in pain score of 2 points (out of 10) and 25% reduction in mean of opioid consumption with an overall significance level of 0.025 for each outcome. Sample size is driven by opioid consumption. Total sample size needed to detect a 25% reduction in opioid consumption is 272, 420 and 568, respectively, for coefficient of variance of 0.75, 1, and 1.25, adjusting for 2 outcomes (i.e., using significance criterion of 0.0125).

We will assume a CV of 1.0 to begin the study, and re-evaluate the CV during the trial, at the first interim analysis. If a larger CV is estimated, the sample size will be appropriately increased, with no statistical penalty. Therefore, before interim monitoring adjustment a total of 420 patients are needed. With interim monitoring adjustment, a total of 476 is needed.

HUMAN SUBJECTS

Lidocaine and ketamine are both medications commonly used in patient care with well-established safety profiles, as can be seen in previous studies.

We propose to charge the cost of the study medications to study participants as this treatment regimen is currently used in our institution on a routine basis, with 20 out of 23 anesthesiologists (87%) affirming its use for postoperative analgesia. The project should therefore not require any funding sources.

Consent will be obtained at least a day before surgery in the preoperative surgical or anesthesia clinics, where the discussion will be conducted by the research fellows in conjunction with the surgeon or anesthesiologist interviewing the patient.

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