The Effect of Perioperative Intravenous Lidocaine and Ketamine on Recovery After Abdominal Hysterectomy

Martin V. Grady, MD, Edward Mascha, PhD, Daniel I. Sessler, MD, and Andrea Kurz, MD

BACKGROUND: Perioperative ketamine infusion reduces postoperative pain; perioperative lidocaine infusion reduces postoperative narcotic consumption, speeds recovery of intestinal function, improves postoperative fatigue, and shortens hospital stay. However, it is unknown whether perioperative IV lidocaine and/or ketamine enhances acute functional recovery. We therefore tested the primary hypothesis that perioperative IV lidocaine and/or ketamine in patients undergoing open abdominal hysterectomy improves rehabilitation as measured by a 6-minute walk distance (6-MWD) on the second postoperative morning.

METHODS: Women having open hysterectomy were anesthetized with sevoflurane, followed by patient-controlled morphine. Patients were factorially randomized to one of the following groups: (1) lidocaine and placebo, (2) placebo and ketamine, (3) placebo and placebo, or (4) lidocaine and ketamine. Lidocaine was given as a bolus (1.5 mg/kg), followed by lidocaine infusion of 2 mg/kg/h for the first 2 hours, and then 1.2 mg/kg/h for 24 postoperative hours. Ketamine was given as a bolus (0.35 mg/kg), followed by ketamine infusion of 0.2 mg/kg/h for the first 2 hours, and then 0.12 mg/kg/h for 24 postoperative hours. The primary double-blind outcome was 6-MWD on the second postoperative morning; secondary outcomes included pain scores, opioid consumption, postoperative nausea and vomiting, and fatigue score.

RESULTS: The study was stopped after a planned interim analysis of 64 patients showed that lidocaine crossed the preplanned futility boundary, with mean ± SD of 202 ± 66 m versus 202 ± 73 m for lidocaine versus placebo, respectively, and mean difference (interim adjusted 97.5% confidence interval) of 0.93 m (−52, 54) (P = 0.96); the ketamine effect also crossed the futility boundary, with mean ± SD of 193 ± 77 m versus 210 ± 61 m for ketamine versus placebo, respectively, and mean difference (interim adjusted 97.5% confidence interval) of −11 m (−65, 44) (P = 0.54). No interaction between the 2 intervention effects was observed (P = 0.96). Neither intervention significantly influenced any of the secondary outcomes.

CONCLUSION: Our results do not support use of lidocaine or ketamine for improving 6-MWD on the second postoperative day after open hysterectomy. (Anesth Analg 2012;115:1078–84)

Inflammation is necessary for recovery of normal structure and function after tissue injury. However, postoperative inflammation is often excessive and thereby maladaptive. L2 Potential consequences of an excessive systemic inflammatory response include reduced functional capacity such as impaired ambulation, fatigue, and pain. Ll Lido- caine is a prototypic local anesthetic, but it also has systemic effects that are mediated by inhibitory effects on N-methyl-d-aspartate receptors and leukocyte priming. Consequently, systemic lidocaine is antiinflammatory, analgesic, and anti-hyperalgesic. Randomized clinical trials, however, have produced mixed results. Several studies have shown reduction in postoperative opioid consumption and pain scores, whereas others have failed to show a benefit. Favorable and negative results have been observed in recovery of bowel function, fatigue scores, and length of hospitalization.

Ketamine, also an N-methyl-d-aspartate receptor antagonist, is antiinflammatory, analgesic, and anti-hyperalgesic. As with lidocaine, however, randomized studies have demonstrated inconsistent results. Improved pain scores and reduced opioid consumption have been observed in some studies but not in others. Similarly, inconsistent results have been observed with ketamine versus controls in inflammatory markers and postoperative ambulation.

Lidocaine and ketamine both moderate the inflammatory response to surgery. However, the clinical consequences remain controversial, in particular whether either improves 6-minute walk distance (6-MWD). We therefore tested the hypothesis that lidocaine and/or ketamine improves ambulation, as measured by 6-MWD, after open abdominal hysterectomy for fibroid disease.

METHODS

With approval of the IRB at the Cleveland Clinic and written informed patient consent, we enrolled 64 ASA physical status I to III patients between the ages of 18 and 75 years who were scheduled for elective open abdominal hysterectomy for fibroid disease or uterine myomelec- tomy with general anesthesia. Patients were enrolled from September 2008 to October 2010 (ClinicalTrials.gov, number NCT00721110).

Exclusion criteria included preexisting chronic pain at any site requiring treatment, contraindication to ketamine or lidocaine, history of significant axis I psychiatric disease,
substantial hepatic (alanine aminotransferase or aspartate aminotransferase >2 times normal) or renal (serum creatinine >2 mg/dL) impairment, seizure disorder requiring medication within the previous 2 years, and planned spinal or epidural anesthesia or analgesia.

**Protocol**

General anesthesia was induced with propofol (1.5–2.5 mg/kg), fentanyl (1.5 µg/kg), and midazolam (1–2 mg). Anesthesia was maintained with sevoflurane in 50% oxygen, titrated to a Bispectral Index (Covidien, Dublin, Ireland) near 50. The lungs were mechanically ventilated to maintain end-tidal Pco₂ near 35 mm Hg. Normothermia was maintained with a forced-air cover. Neither ketorolac nor dexamethasone was given. All patients were given ondansetron 4 mg IV before emergence.

Treatment assignments were based on computer-generated, randomized assignments that were maintained in sequentially numbered, sealed opaque envelopes. Study medications were prepared by our hospital pharmacy, and all clinicians and investigators were blinded to treatment. Patients were factorially randomized to either lidocaine or placebo, and also to either ketamine or placebo. Specifically, patients were randomized to one of the following groups: (1) lidocaine and placebo, (2) placebo and ketamine, (3) placebo and placebo, or (4) lidocaine and ketamine. Lidocaine was given as a bolus (1.5 mg/kg), followed by lidocaine infusion of 2 mg/kg/h for the first 2 hours, and then 1.2 mg/kg/h for 24 postoperative hours. Ketamine was given as a bolus (0.35 mg/kg), followed by ketamine infusion of 0.2 mg/kg/h for the first 2 hours, and then 0.12 mg/kg/h for 24 postoperative hours. Medication doses were based on actual patient body weight to a maximum of 150% of ideal body weight based on the following formula: 49 kg + 0.6 kg for each centimeter of height exceeding 152 cm.

Initial postoperative pain was treated with bolus IV morphine and then with IV patient-controlled morphine (bolus = 1 mg, lockout interval = 6 minutes, basal rate = 0). Fentanyl or hydromorphone was substituted in morphine-intolerant patients. Patients transitioned on the first postoperative day (POD) to oral acetaminophen 325 mg with oxycodone 5 mg every 4 hours as needed.

**Measurements**

Demographic variables (age and race), ASA physical status, and morphometric measurements (weight and height) were recorded. Patients were specifically queried about undesirable effects potentially attributable to ketamine (dysphoria, hallucinations, disorientation) or lidocaine (tinnitus, metallic taste, perioral numbness) on the first and second postoperative mornings.

Our primary outcome was the 6-MWD measured on the day of planned hospital discharge POD 2. The 6-minute walk test (6-MWT) objectively assesses functional exercise capacity by measuring the distance that a patient can walk on a flat, hard surface over a period of 6 minutes. By integrating responses from the pulmonary and cardiovascular systems, systemic and peripheral circulations, and neuromuscular system, it provides a global assessment of exercise.

The 6-MWD correlates well with requirements for activities of daily living and has been used to assess functional capacity in patients recovering from cardiac, thoracic, colon surgery, and major abdominal surgery (the latter on POD 5).33–37

We evaluated 6-MWD preoperatively on the day of surgery after patients changed into hospital attire, but before insertion of an IV catheter. The test was repeated on the second postoperative morning. If an IV catheter was in place, it was capped so there would be no impediment to free movement. The patient was instructed to walk at a normal, moderate pace with cautions to avoid lightheadedness, shortness of breath, palpitations, or pain beyond slight or moderate incisional discomfort.

Secondary outcomes included pain severity measured by verbal response score (VRS) (0 = no pain; 10 = worst pain) upon admission to the postanesthesia care unit, at discharge from the unit, and on the first and second PODs. The amount of intraoperative opioid use was recorded, as were opioids given in the postanesthesia care unit, and on the first and second PODs. Opioid amounts were converted to morphine sulfate equivalents.38 Patients were queried about postoperative nausea and vomiting upon discharge from the postanesthesia care unit and the next day. Any nausea or vomiting within each timeframe (i.e., the time between measurements) was considered a positive response for that interval. On the first POD, patients were asked to rate their fatigue using a VRS, with 0 = no fatigue and 10 = extreme fatigue.

**Data Analysis**

Randomized groups were assessed for balance on potential baseline confounding variables using the standardized difference (STD), i.e., the difference in means or proportions divided by the pooled standard deviation. Based on the observed sample size, variables with absolute STD >0.49 were considered imbalanced and were adjusted for in all analyses.39

Our primary analysis was modified intention-to-treat, thus including all randomized participants who received any of the interventional treatment, including potential crossovers. We planned to assign missing primary outcome data (6-MWD on the second postoperative morning) to randomized patients who received the study intervention using either their 6-MWD results on the subsequent day, if available, or using a conservative assignment based on their randomized group (i.e., patients randomized to receive both lidocaine and ketamine assigned worst score of any patient, double-placebo patients assigned best of any patient, and patients randomized to one of the drugs assigned the average across patients).

The main effects of lidocaine and ketamine and their interaction on the primary outcome of 6-MWD on the second postoperative morning were assessed using analysis of covariance adjusting for baseline 6-MWD. Given a significant interaction (P < 0.15), the effects of each intervention would have been assessed within levels of the other intervention. Treatment effect estimates were summarized using mean difference between groups, with interim-adjusted 97.5% confidence intervals (CIs) (i.e., using z of 2.97).

The effects of lidocaine and ketamine on secondary outcomes VRS and fatigue scores were assessed using t tests,
on opioid consumption for various time intervals using Wilcoxon rank sum test, and on nausea and vomiting variables using Pearson $\chi^2$ tests.

The significance level was 0.025 for each of the 2 interventions, chosen to maintain an overall $\alpha$ of 0.05 for the primary outcome across interventions. No adjustment was made for assessing several secondary outcomes. All analyses were performed with SAS 9.3 software (SAS Institute Inc., Cary, NC).

**Sample Size Considerations**

We expected the mean 6-MWD to be approximately 300 m$^{36}$ for the group receiving neither lidocaine nor ketamine (the control group). We also assumed a standard deviation of approximately 20% of the mean for each group,$^{34}$ or about 65 m, averaging across groups. Assuming a correlation of 0.5 between baseline and second POD distance, a maximum $n = 128$ total patients (i.e., 32 for each of the 4 groups) was needed to have 80% power at the 0.025 significance level to detect main effects of 36 m$^{34,40}$ or more for lidocaine and ketamine in the 6-MWD versus their respective controls (nonlidocaine and nonketamine). We chose 36 m as being clinically significant because this was the average difference observed in the validation study for the 6-MWD instrument by O’Keeffe et al.$^{40}$ between heart failure patients who claimed to be “much better” versus those who were “about the same” at a repeat clinic visit 3 to 8 weeks later. The study was not powered to detect an interaction between lidocaine and ketamine because we believed they would act independently of each other and thus be additive in their combined effect.

Sample size calculations included adjustment for a single interim evaluation at 50% of the planned maximum enrollment ($n = 64$) to assess efficacy and futility using the $\gamma$ spending function approach ($\gamma$ of $-4$ and $-2$ for efficacy and futility, respectively).$^{41}$

**RESULTS**

A total of 64 patients were randomized between September 2008 and October 2010 (Fig. 1). One patient from the ketamine group and another from the lidocaine/ketamine group withdrew before they received interventions and were thus excluded from the study based on the modified intent-to-treat principle. Of the 62 patients remaining in the study, we achieved good balance between each intervention and its control on baseline characteristics (i.e., all absolute STD <0.49, Table 1).

Two patients refused to walk on the second postoperative morning. One patient, randomized to lidocaine/ketamine, withdrew from the study and was conservatively assigned the shortest observed 6-MWD of any patient. The

![Figure 1. Enrollment of the study participants.](image)
There was no interaction between the effects of lidocaine and ketamine on the primary outcome of 6-MWD ($P = 0.96$). Neither lidocaine nor ketamine increased mean 6-MWD after adjusting for both baseline 6-MWD and interim monitoring, with both treatment effects crossing the futility boundary ($P > 0.531$) (Fig. 2); lidocaine versus nonlidocaine was $202 \pm 66$ m versus $202 \pm 73$ m, with estimated mean

**Table 1. Baseline Characteristics by Lidocaine and Ketamine Interventions**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Lidocaine ($n = 31$)</th>
<th>Nonlidocaine ($n = 31$)</th>
<th>STD a</th>
<th>Ketamine ($n = 30$)</th>
<th>Nonketamine ($n = 32$)</th>
<th>STD a</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA physical status, %</td>
<td>0</td>
<td>6</td>
<td>0.16</td>
<td>7</td>
<td>0</td>
<td>-0.13</td>
</tr>
<tr>
<td>I</td>
<td>46 ± 7</td>
<td>47 ± 9</td>
<td>-0.09</td>
<td>46 ± 8</td>
<td>46 ± 8</td>
<td>0.08</td>
</tr>
<tr>
<td>II</td>
<td>29 ± 6</td>
<td>29 ± 8</td>
<td>0.03</td>
<td>29 ± 8</td>
<td>29 ± 6</td>
<td>0.02</td>
</tr>
<tr>
<td>III</td>
<td>0.06</td>
<td>0.09</td>
<td>-0.09</td>
<td>0.02</td>
<td>-0.13</td>
<td></td>
</tr>
<tr>
<td>Preoperative 6-MWD (m)</td>
<td>319 ± 45</td>
<td>322 ± 49</td>
<td></td>
<td>312 ± 44</td>
<td>329 ± 48</td>
<td>-0.38</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD. BMI = body mass index; 6-MWD = 6-minute walk distance.

a STD = standardized difference = difference in means or proportions divided by pooled standard deviation; we considered as imbalanced any variable with absolute STD $\geq \sqrt{2/n}$ per group = 0.50.27

**Figure 2.** Details of our group sequential design with the predetermined boundaries for efficacy, harm, and futility. The vertical axis is the standardized effect size, $z$ (difference in group means divided by the SE), where a $z > 0$ indicates efficacy, and $z < 0$ means harm. The horizontal axis is the cumulative number of planned ($n = 128$) and observed ($n = 62$) patients. Interim analysis results are shown by the lidocaine (+) and ketamine (×) intervention, with $z$ statistics of 0.054 and -0.611, respectively. Both the lidocaine and ketamine effects crossed into the “futility” region.

other took the 6-MWT the following day and that result was used in the primary analysis.

Three patients remained sedated 2 hours after postanesthesia care unit admission. They aroused to voice easily, conversed normally, but promptly fell back asleep unstimulated. The study infusion was stopped in all 3 patients. Two were fully alert within 20 minutes. The study infusion was resumed at half its previous rate in the recovery room for 2 hours with no change in level of alertness, were transferred to the nursing floor, and recovered uneventfully. The third patient awoke more gradually over an hour or so, and the study infusion was not resumed. This patient was also transferred to the floor and recovered uneventfully. All 3 patients who remained sedated after surgery in the postanesthesia care unit were given both lidocaine and ketamine.

There was no interaction between the effects of lidocaine and ketamine on the primary outcome of 6-MWD ($P = 0.96$). Neither lidocaine nor ketamine increased mean 6-MWD after adjusting for both baseline 6-MWD and interim monitoring, with both treatment effects crossing the futility boundary ($P > 0.531$) (Fig. 2); lidocaine versus nonlidocaine was $202 \pm 66$ m versus $202 \pm 73$ m, with estimated mean

**Table 2. Effects of IV Lidocaine and Ketamine Interventions on Primary Outcome of 6-Minute Walk Distance, in Meters, on the Second Postoperative Morning**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean ± SD (m)</th>
<th>Difference (97.5% CI) a</th>
<th>$P$ value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine ($n = 31$)</td>
<td>202 ± 66</td>
<td>0.93 (−52, 54)</td>
<td>0.96</td>
</tr>
<tr>
<td>Nonlidocaine ($n = 31$)</td>
<td>202 ± 73</td>
<td>0.03 (−29, 29)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ketamine ($n = 30$)</td>
<td>193 ± 77</td>
<td>−11 (−65, 44)</td>
<td>0.54</td>
</tr>
<tr>
<td>Nonketamine ($n = 32$)</td>
<td>210 ± 61</td>
<td>0.54 (−38, 52)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.

a Analysis of covariance adjusted for baseline 6-minute walk distance; $n = 62$ patients included based on modified intent-to-treat (i.e., 2 randomized patients not included because no treatment was received); intent-to-treat used to assign outcome on 2 additional patients; interaction $P$ value between the 2 intervention effects = 0.96; significant if $P < 0.003$ for efficacy and $P > 0.5311$ for futility; 97.5% confidence intervals (CIs) adjusted for group sequential design (using confidence coefficient of 2.97) to maintain the overall $\alpha$ of 0.025 for each intervention and 0.05 for the trial.

**Figure 3.** Six-minute walk distance by each intervention. The solid gray line shows the change in 6-minute walk distance from baseline to postoperative day 2 for individual patients; the dashed dark line shows the mean change by group for each intervention.
Table 3. Effects of IV Lidocaine and Ketamine Interventions on Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lidocaine (n = 31)</th>
<th>Nonlidocaine (n = 31)</th>
<th>Mean difference (97.5% CI)</th>
<th>P value</th>
<th>Ketamine (n = 30)</th>
<th>Nonketamine (n = 32)</th>
<th>Mean difference (97.5% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain severity (VRS: 0–10 scale)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PACU admitt</td>
<td>6.2 ± 3.3</td>
<td>7.1 ± 2.5</td>
<td>−1.0 (−3.3, 1.3)</td>
<td>0.20</td>
<td>6.4 ± 3.4</td>
<td>6.9 ± 2.5</td>
<td>−0.5 (−2.8, 1.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>PACU discharge</td>
<td>4.0 ± 2.3</td>
<td>4.9 ± 1.9</td>
<td>−0.9 (−2.5, 0.8)</td>
<td>0.11</td>
<td>4.6 ± 2.4</td>
<td>4.3 ± 1.9</td>
<td>0.3 (−1.4, 2.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>POD 1</td>
<td>4.0 ± 1.8</td>
<td>3.3 ± 2.2</td>
<td>0.6 (−0.9, 2.2)</td>
<td>0.20</td>
<td>3.7 ± 2.2</td>
<td>3.6 ± 1.7</td>
<td>0.1 (−1.4, 1.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>POD 2</td>
<td>3.1 ± 1.7</td>
<td>2.9 ± 1.9</td>
<td>0.3 (−1.1, 1.7)</td>
<td>0.55</td>
<td>3.1 ± 2.1</td>
<td>2.8 ± 1.4</td>
<td>0.3 (−1.1, 1.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>Opioid consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(morphine sulfate equivalents in mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative</td>
<td>20 [15, 30]</td>
<td>20 [19, 30]</td>
<td>0 (−7, 7)</td>
<td>0.63</td>
<td>20 [15, 26]</td>
<td>23 [20, 30]</td>
<td>−2 (−10, 5)</td>
<td>0.27</td>
</tr>
<tr>
<td>PACU</td>
<td>20 [7, 27]</td>
<td>23 [18, 27]</td>
<td>−3 (−15, 5)</td>
<td>0.28</td>
<td>20 [7, 27]</td>
<td>23 [19, 27]</td>
<td>−4 (−15, 4)</td>
<td>0.22</td>
</tr>
<tr>
<td>POD 1</td>
<td>23 [15, 48]</td>
<td>22 [13, 50]</td>
<td>2.5 (−13, 21)</td>
<td>0.76</td>
<td>21 [12, 48]</td>
<td>23 [17, 47]</td>
<td>−3 (−19, 14)</td>
<td>0.66</td>
</tr>
<tr>
<td>POD 2</td>
<td>10 [3, 18]</td>
<td>6 [2, 15]</td>
<td>2.5 (−5, 10)</td>
<td>0.30</td>
<td>9 [3, 20]</td>
<td>8 [3, 14]</td>
<td>0 (−5, 8)</td>
<td>0.79</td>
</tr>
<tr>
<td>Fatigue POD 1 (VRS: 0–10 scale)</td>
<td>7.2 ± 2.5a</td>
<td>7.2 ± 2.4b</td>
<td>0.03 (−2.14, 2.2)</td>
<td>0.96</td>
<td>7.4 ± 2.6</td>
<td>7.0 ± 2.3</td>
<td>0.3 (−1.80, 2.57)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Relative risk (97.5% CI)

Nausea, %

<table>
<thead>
<tr>
<th></th>
<th>Relative risk</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(97.5% CI)</td>
<td>(97.5% CI)</td>
</tr>
<tr>
<td>PACU</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>0.06 (−0.28, 0.41)</td>
<td>0.58</td>
</tr>
<tr>
<td>POD 1</td>
<td>55</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>0.06 (−0.31, 0.44)</td>
<td>0.61</td>
</tr>
</tbody>
</table>
| Vomiting, %
|          | Relative risk | Relative risk |
| POUC     | 6             | 19            |
|          | −0.13 (−0.38, 0.12) | 0.26 |
| POD 1    | 23            | 16            |
|          | 0.06 (−0.23, 0.36) | 0.52 |

Data are presented as means ± SD, median (quartiles), or percent. P values from t test for pain variables and fatigue score, Wilcoxon rank-sum test for opioid variables, and Pearson χ² test for nausea and vomiting variables; 97.5% confidence intervals (CIs) adjusted for group sequential design (using confidence coefficient of 2.97) to maintain the overall α of 0.025 for each intervention and 0.05 for the trial.

VRS = verbal response score; PACU = postoperative care unit; POD = postoperative day.

* n = 5 missing values.

† n = 6 missing values.

difference (97.5% CI) of 0.93 m (−52, 54) (P = 0.96); ketamine versus nonketamine was 193 ± 77 m versus 210 ± 61 m, with estimated mean difference (97.5% CI) of −11 m (−65, 44) (P = 0.54) (Table 2, Fig. 3). The Executive Committee thus decided to stop the trial.

No difference was found for either intervention in mean postoperative pain severity, opioid consumption, fatigue, or postoperative nausea and vomiting (Table 3).

DISCUSSION

Our major results are that neither lidocaine nor ketamine improved the 6-MWD, fatigue, or pain. That lidocaine did not improve functional capacity is largely consistent with reports in patients having smaller operations, but differs from reports in patients having major open abdominal surgery. Our results thus support the proposal by Wu and Liu that the extent of surgery determines the success or failure of lidocaine. Thus, lidocaine is more effective for open than laparoscopic prostatectomy, presumably because the former requires more tissue dissection and provokes a greater inflammatory response. An additional potential explanation is that lidocaine is especially effective for visceral abdominal pain and intestinal function, which may explain the comparable benefit of lidocaine in open and laparoscopic colon surgery.

Ketamine also failed to improve the 6-MWD or any of our secondary outcomes. Ketamine could influence functional recovery directly, via its antiinflammatory effect, or indirectly, by reducing pain, hyperalgesia, and opioid consumption. Each of these mechanisms is more likely to be clinically apparent after larger than smaller operations. For example, 3 studies involving 269 joint replacement patients randomized to ketamine bolus and infusion versus placebo demonstrated acute reduction in opioid consumption and improved joint flexion after knee replacement and improved amputation after hip replacement. Similarly, a recent meta-analysis indicates that ketamine is most effective for large operations. The operation we evaluated, open hysterectomy, is substantial but involves far less tissue injury, physiologic stress, and postoperative pain than upper abdominal or thoracic surgery. Thus, although our results are negative for ketamine in hysterectomy, they do not preclude a clinically significant benefit for ketamine in larger operations.

Three patients given the combination of lidocaine and ketamine were excessively sedated during the initial phase of anesthetic recovery. With half the maximum number of patients enrolled, results for both lidocaine and ketamine passed the futility boundary for the 6-MWD, which was our primary outcome. The Executive Committee thus stopped the trial. Our study nonetheless enrolled a substantial number of patients, and it seems unlikely that enrolling additional patients would result in either treatment being concluded better than placebo.

Based on the validation study for the 6-MWT by O’Keeffe and others, we a priori specified that a treatment effect of ≥36 m in the 6-MWT would be clinically significant. Although neither treatment effect was significant, it is important to note that the CIs for the change in 6-MWD for the lidocaine effect (−52 m, 54 m) and the ketamine effect (−65 m, 44 m) were consistent with treatment effects larger than 36 m, implying that the true effects may well be clinically significant.
Larger studies with narrower CIs would be helpful in more precisely estimating the true effects of these interventions.

Believing that ability to walk is an important element in attaining independent function at home after surgery, we chose the 6-MWT as a continuous measure of walking ability on the day of planned hospital discharge, POD 2. In a recent study, use of an abdominal binder after major abdominal surgery prolonged 6-MWD on POD 5.37 We thus thought it reasonable to look for an improvement in ambulation earlier after hysterectomy, a more modest surgery with less tissue dissection, a less painful incision, and a shorter hospital stay. In addition, conducting the 6-MWT on POD 3 or later would have required a return to the hospital very shortly after discharge for most patients, which we thought impractical. Prior studies, however, have not performed the 6-MWT this early after surgery. Thus, the 6-MWD data from this study may not be comparable to previous studies.

Our 6-MWT results were lower than anticipated. The patients did not wear shoes and were accompanied by a clinical research nurse during the 6-MWT. Both may be associated with reduction in 6-MWD. Other variations in conduct of the 6-MWT such as length of hospital corridors and number of turns may also account for observed differences although previous studies in similar patient groups have shown up to 30% variation in 6-MWT results.33,47 In this study, the results were internally consistent. All 6-MWTs were conducted by the same clinical research nurse. The preoperative and postoperative 6-MWTs were conducted in different parts of the hospital resulting in two separate layouts. The two 6-MWT layouts while different from each other were the same for all patients within each 6-MWT.

The dose of ketamine we used was on the high end of that used in previous studies. The lidocaine dose was more typical, and similar to that used in previous studies showing benefit. It is probable that higher doses of each would produce greater effect, but at the expense of potential toxicity. Although lidocaine and ketamine were well tolerated when given individually, 3 of our 16 patients given lidocaine and ketamine together experienced mild toxicity. And finally, our study was restricted to women by nature of the surgery, although there is no reason to believe that results would differ in men.

In summary, neither lidocaine nor ketamine improved functional capacity, pain scores, opioid consumption, fatigue, or nausea and vomiting in patients undergoing abdominal hysterectomy. Furthermore, the combination of lidocaine and ketamine provoked excessive sleepiness in several patients. We thus conclude that neither drug improves recovery profile after abdominal hysterectomy. Our study results therefore do not support the use of lidocaine or ketamine in women having open abdominal hysterectomy.


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