Comparison of intraoperative ketamine vs. fentanyl use decreases postoperative opioid requirements in trauma patients undergoing cervical spine surgery


Background: Postoperative airway compromise following cervical spine surgery is a potentially serious adverse event. Residual effects of anesthesia and perioperative opioids that can cause both sedation and respiratory depression further increase this risk. Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist that provides potent analgesia without noticeable respiratory depression. We investigated whether intraoperative ketamine administration could decrease perioperative opioid requirements in trauma patients undergoing cervical spine surgery.

Methods: We retrospectively reviewed anesthesia records identifying cervical spine surgeries performed between March 2014 and February 2015. All patients received a balanced anesthetic technique utilizing sevoflurane 0.5 minimum alveolar concentration (MAC) and propofol infusion (50-100 mcg/kg/min). For intraoperative analgesia, one group of patients received ketamine (N=25) and a second group received fentanyl (N=27). Cumulative opioid doses in the recovery room and until 24 hours postoperatively were recorded.

Results: Fewer patients in the ketamine group (11/25 [44%] vs. 20/27 [74%], respectively; p = 0.03) required analgesics in the recovery room. Additionally, the total cumulative opioid requirements in the ketamine group decreased postoperatively at both 3 and 6 hours (p = 0.01).

Conclusion: Ketamine use during cervical spine surgery decreased opioid requirements in both the recovery room and in the first 6 hours postoperatively. This may have the potential to minimize opioid induced respiratory depression in a population at increased risk of airway complications related to the surgical procedure.

Keywords: Ketamine, Opioids, Postoperative Analgesia, Fentanyl, Cervical Spine Surgery

* MD, Department of Anesthesiology, Nassau University Medical Center.
** BS, Department of Anesthesiology, Nassau University Medical Center.
*** MD, MPH, Department of Surgery, Nassau University Medical Center.
**** MPH, Department of Surgery, Nassau University Medical Center.
***** MD, PhD, Department of Anesthesiology, Nassau University Medical Center.

Corresponding author: Dov B. Ginsburg, MD, PhD, Department of Anesthesiology, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, Phone: 516-572-6813, Fax: 516-572-5019. E-mail: dov.ginsburg@gmail.com
Introduction

Cervical spine surgery is associated with the potential for postoperative airway compromise due to laryngopharyngeal edema, hematoma, and abscess formation. Patients are especially vulnerable to this highly dangerous complication in the acute postoperative period due to the residual effects of anesthesia, as well as due to perioperative opioid use, which can cause both sedation and respiratory depression. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that has potent analgesic properties even at small sub-anesthetic doses. It is postulated that by blocking the NMDA receptor, ketamine decreases nociceptive pain pathways and may prevent the development of hyperalgesia as well as opioid tolerance, which is a common problem with this class of medications. Ketamine also has a significant benefit over other analgesics, such as opioids, in that it does not cause respiratory depression. Several clinical studies have been conducted to test whether intraoperative ketamine administration can minimize perioperative opioid requirements in a variety of surgical procedures and have produced conflicting results. However, the consequence of intraoperative use of ketamine as the primary analgesic during cervical spine surgery is largely unknown, and patients may stand to benefit much from elucidation of this issue. We hypothesized that intraoperative ketamine administration can minimize perioperative opioid requirements while still providing effective analgesia, thereby minimizing the risk of airway compromise in a class of patients who are already at particularly increased risk of this complication.

Materials and Methods

After obtaining institutional review board approval, we retrospectively reviewed anesthesia records identifying cervical spine surgeries in trauma patients performed between March 2014 and February 2015. These cases were cross-referenced with the electronic medical records of our institution to determine opioid consumption in the postoperative period.

Basic patient information including age, height, weight, body mass index (BMI), sex, American Society of Anesthesiology Health Classification Status (ASA status), presence of diabetes and hypertension, as well as operative and perioperative data including number of spinal levels, repair with or without instrumentation, surgical duration, hospital length of stay, and incidence of postoperative nausea or postoperative mechanical ventilation were collected for analysis. Patients were divided into two groups based on those that exclusively received either intraoperative ketamine or fentanyl.

All patients had received a relatively standardized anesthesia induction that included 2 mg midazolam, either 0.5 mg/kg ketamine (ketamine group) or approximately 1.5 mcg/kg fentanyl (fentanyl group), 2 mg/kg propofol, and neuromuscular blocking agents (typically succinylcholine or cisatracurium) to facilitate intubation and surgical exposure as requested by the surgeon. After induction, all patients received a balanced anesthetic technique for anesthesia maintenance utilizing sevoflurane 0.5 MAC and propofol infusion (50-100 mcg/kg/min). Patients who received ketamine (N=25) were placed on a continuous intraoperative infusion of 10 mcg/kg/min (ketamine group) and the patients who received fentanyl (N=27) were placed on a continuous infusion of approximately 2 mcg/kg/hr (fentanyl group). All anesthesia providers were asked by the surgeon to administer 10 mg of dexamethasone intravenously upon anesthesia induction to all patients. All patients in the study had intraoperative neuromonitoring analyzing somatosensory evoked potentials (SSEPs) by a trained neurophysiologist. The cumulative doses of opioids in the recovery room and up to 24 hours postoperatively were recorded.

Statistical Analysis

Descriptive statistics were performed on all variables in this study. Categorical variables were described as frequency distributions and percentages of the study population. Continuous variables were
summarized as means ± standard deviations. Chi-square test and Fisher exact test were used to compare categorical binary outcomes when appropriate. The total cumulative morphine equivalents at different time intervals were compared using an unpaired Student t test. A p-value of <0.05 was considered significant. SAS version 9.4 (SAS Institute Inc. Cary, NC) was used as the statistical tool in this study.

Results

Fifty-two patients undergoing cervical spine surgery were included in this study. Patient characteristics were similar in both the ketamine and fentanyl groups (Table 1), and there was no significant difference found between the two groups in terms of the number of spine levels involved, duration of surgery, and hospital length of stay (Table 2).

In evaluating the opioid requirements in the recovery room (post anesthesia care unit [PACU]; Table 3) for each patient, we found that there were significantly fewer patients in the ketamine group than in the fentanyl group who required pain medication (44% vs. 74%, p = 0.03). Similarly, the average cumulative morphine consumption in the PACU was lower in the ketamine group (3.4 mg ± 4.6 mg vs. 8.6 mg ± 7.1, p = 0.03).

We also recorded the average cumulative morphine requirements of each patient during the first 24 hours after surgery (Table 4). The average cumulative morphine consumption was significantly decreased in the ketamine group at 3 hours (5.8 mg ± 5.8 mg vs. 11.0 mg ± 8.5, p = 0.01) and at 6 hours (8.9 mg ± 7.1 mg vs. 17.4 mg ± 8.3 mg, p = 0.01). The significant difference between the two groups did not appear at 24 hours.

Differences in the incidence of post-operative nausea and/or vomiting (PONV) and the number

| Table 2 | Operative and Perioperative Details by Group |
|------------------|------------------|------------------|
| Spinal Levels, No. % | Ketamine | Fentanyl | p-value |
| One | 16 (64.0%) | 21 (77.8%) | 0.43 |
| Two | 9 (36.0%) | 6 (22.2%) | - |
| Duration of Surgery, min | 96.4 ± 29.7 | 89.3 ± 18.8 | 0.30 |
| Hospital LOS, days | 1.8 ± 0.9 | 2.0 ± 0.7 | 0.37 |

Data are presented as mean ± SD or as a percentage.

| Table 3 | Analgesic Requirements in the Post-anesthesia Care Unit |
|------------------|------------------|------------------|
| Number of Patients  | Ketamine | Fentanyl | p-value |
| Requiring Analgesia, % | 11 (44.0%) | 20 (74.0%) | 0.03 |
| Morphine, mg | 3.4 ± 4.6 | 8.6 ± 7.1 | 0.01 |

Data are presented as a percentage or as mean ± SD.

| Table 4 | Postoperative Analgesic Requirements |
|------------------|------------------|------------------|
| Cumulative Morphine, mg | Ketamine | Fentanyl | p-value |
| 3 hr | 5.8 ± 5.7 | 11.0 ± 8.5 | 0.01 |
| 6 hr | 8.9 ± 7.1 | 17.4 ± 8.3 | 0.01 |
| 24 hr | 33.4 ± 17.1 | 37.6 ± 18.0 | 0.39 |

Data are presented as mean ± SD.

Table 1

Patient Characteristics by Group

<table>
<thead>
<tr>
<th></th>
<th>Ketamine</th>
<th>Fentanyl</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>25</td>
<td>27</td>
<td>-</td>
</tr>
<tr>
<td>Age, yr</td>
<td>41.2 ± 12.3</td>
<td>43.9 ± 10.6</td>
<td>0.39</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.6 ± 10.1</td>
<td>165.5 ± 12.8</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.4 ± 23.6</td>
<td>78.3 ± 14.7</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.8 ± 6.4</td>
<td>28.6 ± 3.8</td>
<td>0.41</td>
</tr>
<tr>
<td>Female, %</td>
<td>11 (44.0%)</td>
<td>12 (44.4%)</td>
<td>0.97</td>
</tr>
<tr>
<td>ASA Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>21 (84.0%)</td>
<td>24 (88.9%)</td>
<td>0.70</td>
</tr>
<tr>
<td>III</td>
<td>4 (16.0%)</td>
<td>3 (11.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (16.0%)</td>
<td>4 (14.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (28.0%)</td>
<td>6 (22.2%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or as a percentage.

BMI = body mass index; ASA = American Society of Anesthesiologists.
of patients requiring post-operative mechanical ventilation were also evaluated. No significant difference was found in either parameter up to 24 hours after surgery (Table 5).

Table 5

<table>
<thead>
<tr>
<th></th>
<th>Ketamine</th>
<th>Fentanyl</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td>1 (4%)</td>
<td>3 (11.1%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Post-operative Mechanical Ventilation</td>
<td>0 (0%)</td>
<td>1 (3.7%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data are presented as number and percentages.

Discussion

The intraoperative use of ketamine as the primary analgesic in trauma patients undergoing cervical spine surgery and its effects on postoperative opioid requirement has not been previously studied. We have demonstrated that intraoperative ketamine use can reduce both the number of patients requiring pain medication during recovery in the PACU, as well as decrease the cumulative morphine requirements up to 6 hours following surgery (Tables 3 and 4).

The benefit of an intraoperative opioid sparing anesthetic technique is especially valuable because due to the increasing use of intraoperative neuromonitoring to monitor spinal cord function, patients often receive larger than typical total opioid dosages. Anesthetic agents typically employed during surgery can affect the ability to effectively monitor and record signal responses. In particular, inhalational anesthetic agents are known to have a significant effect on the neuromonitoring signal responses. In contrast, intravenous anesthetic agents such as propofol, ketamine, and opioids have a significantly lesser effect. A typical balanced anesthetic technique for spine surgery will often incorporate infusions of propofol and opioids, resulting in larger than typical total intraoperative opioid administration. As mentioned previously, all patients in this study had intraoperative neuromonitoring recordings (SSEPs) throughout the surgical procedure.

It is well known that opioids are the class of drugs that most significantly depresses ventilation through their actions at the μ-opioid receptors on respiratory neurons in the brainstem [8]. Opioid-induced respiratory depression is potentially life threatening and has been the cause of substantial morbidity and mortality. It is of clinical importance to note that patients with risk of airway obstruction, such as obstructive sleep apnea may be more sensitive to the respiratory depressant effect of opioids and thus should have their doses adjusted accordingly. In light of the above, the use of intraoperative ketamine in patients undergoing cervical spine surgery to minimize perioperative opioid requirements while still providing effective analgesia is particularly beneficial. This is of particular clinical importance in this class of patients, as they are already at increased risk of airway compromise due to surgical manipulation of the cervical spine.

Previous studies have shown that the use of intraoperative ketamine not only decreases pain acutely but has also demonstrated a reduction in pain intensity at 6 weeks. In our study, ketamine use demonstrated a significant decrease of cumulative opioid requirements up to 6 hours, but there did not appear to be any significant decrease at 24 hours. This may be attributed to our smaller sample size, and requires further evaluation. Based on the findings of the present study, the next logical step is to systematically evaluate the use of ketamine as a primary analgesic in patients undergoing surgery where opioids should be minimized, such as patients who may be susceptible specifically to the adverse effects of opioids and those who are opioid tolerant or are at risk of potential airway compromise either due to inherent patient characteristics or surgical manipulation. Among these, ketamine may be particularly beneficial in chronic pain patients who consume large amounts of opioid medications and who may be somewhat resistant to the analgesic effects of opioids in the acute postoperative setting.

The benefit of intraoperative low dose ketamine in our study was without an apparent increase in side effects such as hallucinations, PONV, and need for postoperative mechanical ventilation (Table 5). Although the literature has mentioned cases of
hallucinations following ketamine administration, the use of hypnotic doses of propofol has been shown to block ketamine-induced hallucinations\textsuperscript{27}. One patient in the fentanyl group did require postoperative mechanical ventilation as they did not meet extubation criteria, which was presumed to be due to opioid induced respiratory depression and sedation. Of note, this patient did not receive any further opioids for several hours until they were safely extubated. For these reasons, low dose ketamine administration can be considered as a useful primary analgesic for patients undergoing surgery with potential for airway compromise.

The findings of this study substantially add to the existing body of literature regarding the efficacy of intraoperative ketamine in comparison to opioid administration during cervical spine surgery with the goal of improving patient safety and satisfaction. A limitation to our study was that it relied on the use of retrospective data collection and analysis and we were not able to study if ketamine specifically caused a reduction in respiratory depression. Future prospective studies will hopefully determine if intraoperative ketamine administration can reduce opioid induced respiratory depression and airway compromise in patients undergoing cervical spine surgery.
References

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- 97% of BRIDION patients recovered to a TOF ratio of 0.9 from 1 to 2 PTCs\(^-\) within 5 minutes\(^3\)

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BRIDION is not recommended in patients with severe renal impairment. Studies in patients with severe renal impairment have not been conducted and, therefore, patients with severe renal impairment should be treated with caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.

If neuromuscular blockade is required within 24 hours of BRIDION administration, a muscle relaxant neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dyspnea (chest or labored respiration) and anesthetic complications (movement, coughing, grimacing, or straining on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain in a few individuals, allergic reactions (e.g., flushing, erythematous rash). Following BRIDION were reported. Children should be prepared for the possibility of allergic reactions and have the necessary medications. In a trial of patients with a history of coronary artery disease, atrial fibrillation was reported in 2 patients and a causal relationship could not be fully excluded.

Volunteer studies have demonstrated a slight (17%-21%) prolongation of the phytohemagglutinin-stimulated lymphocytes in vitro. In vitro, BRIDION has no effect on the renin-angiotensin system. BRIDION has no effect on the renin-angiotensin system. BRIDION may interact in vitro with other drugs that have a similar effect on the renin-angiotensin system. Although formal interaction studies have not been conducted, drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of tachycardia, pheochromocytoma, and the renin-angiotensin system.

\(^{1}\) Brain of four
\(^{2}\) Phase 3/4 studies
\(^{3}\) Second switch


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