Antiemetic Effects of Midazolam Added to Fentanyl–Ropivacaine Patient-Controlled Epidural Analgesia After Subtotal Gastrectomy: A Prospective, Randomized, Double-Blind, Controlled Trial

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ABSTRACT

BACKGROUND: Nausea and vomiting are frequent adverse effects of patient-controlled epidural analgesia (PCEA) with opioids.

OBJECTIVE: This study was designed to assess the antiemetic effect of midazolam added to fentanyl–ropivacaine PCEA.

METHODS: In a prospective, randomized, double-blind, controlled trial, smoking patients with gastric cancer undergoing elective subtotal gastrectomy were evenly allocated to 1 of 2 treatment groups to manage postoperative pain: 0.2% ropivacaine mixed with fentanyl 4 μg/mL and midazolam 0.2 mg/mL (test group) or 0.2% ropivacaine mixed with fentanyl 4 μg/mL (control group). The PCEA infusion was set to deliver 4 mL/h of the study solution, with a bolus of 2 mL per demand and a 15-minute lockout time. The incidence of postoperative nausea and vomiting (PONV), pain intensity, sedation score, usage of rescue analgesia and rescue antiemetic, respiratory depression, urinary retention, and pruritus were recorded at 2, 6, 12, 24, 48, and 72 hours after surgery. Total infused volume of PCEA at 72 hours after surgery was measured.

RESULTS: A total of 60 patients were approached and randomized to treatment. No patients were excluded by exclusion criteria and all enrolled patients completed this study. Incidence of nausea (7% vs 33%; P = 0.02) in the test group was significantly lower than in the control group. The overall frequency of PONV in the test group was significantly less than that of the control group (7% vs 40%; P = 0.006). In addition, the mean (SD) infused volume of PCEA in the test group was significantly lower than that in the control group (392.3 [68.9] vs 351.2 [49.8] mL; P = 0.01). However, there were no significant differences in pain intensity, usage of rescue antiemetics and rescue analgesics, and mild pruritus between groups. No patient reported moderate or severe sedation, respiratory depression, or hypoxemia. In addition, there were no severe adverse events.

CONCLUSIONS: Midazolam added to fentanyl–ropivacaine PCEA was associated with a significant reduction in the incidence of PONV compared with fentanyl–

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ropivacaine alone, and a significant decrease in the amount of PCEA administered without
a significant increase in adverse events in these patients who underwent subtotal gastrec-

**KEY WORDS:** fentanyl, midazolam, nausea and vomiting, epidural analgesia.

**INTRODUCTION**

Patient-controlled epidural analgesia (PCEA) has been used to reduce postoperative
pain after major abdominal surgery.1 A combination of local anesthetic with opioid
has been commonly used to improve the quality of pain relief in PCEA, but this treat-
ment increases postoperative nausea and vomiting (PONV) during PCEA.2 PONV
may result in electrolyte abnormalities and dehydration.3 Persistent retching or vomit-
ing following surgery can put tension on suture lines, result in hematomas beneath
surgical flaps, and place the patient at risk for pulmonary aspiration of vomit. There-
fore, these have led to attempts to combine opioid and drugs such as droperidol4,5 and
naloxone6 in PCEA solution in the hope of minimizing the adverse effects (AEs) of
opioids. However, continuous infusion of droperidol did not decrease PONV5 and
naloxone, an opioid antagonist, did not increase analgesia.6

A short-acting water-soluble benzodiazepine, midazolam has been reported to de-
crease the incidence and severity of PONV.7–11 Midazolam has also been found to be
effective in the treatment of established PONV.12 Midazolam administered intrathecal-
ly12–14 or epidurally13–17 has been reported to have an analgesic effect. A prospective,
randomized, double-blind trial by Nishiyama et al16 found that adding midazolam
(10–20 mg for 12 hours) to continuous epidural infusion of bupivacaine (100 mg) for
postoperative pain provided better analgesia than bupivacaine alone without a deep
sedative effect in 80 patients (mean age, 58 years; weight, 56.5 kg). In addition,
Nishiyama et al17 conducted a second prospective, randomized study that investigated
the effects of adding midazolam to the postoperative epidural analgesia with 2 dif-
f erent doses (180 vs 90 mg) of bupivacaine in 100 postgastrectomy patients (age, 40–75
years). It was reported that epidural-infused midazolam (10–20 mg for 12 hours)
with bupivacaine 180 mg provided better analgesia compared with bupivacaine
alone. In a prospective, randomized, double-blind trial of 60 patients (mean age,
26.1 years; weight, 54.5 kg) who underwent spinal anesthesia for cesarean delivery,
intrathecal midazolam 1 mg (5%) and 2 mg (5%) added to bupivacaine appeared to
reduce PONV compared with controls (85%) during cesarean delivery.14 However,
based on a search of the literature on MEDLINE (search terms: epidural analgesia,
midazolam, opioid, and postoperative nausea and vomiting; years, 1990–2009), no pub-
lished data were available for the antiemetic effect of midazolam added to opioid-local
anesthetics–based PCEA. Therefore, we hypothesized that epidural midazolam may
reduce PONV during PCEA and reduce the overall infused volume of PCEA.

The present study assessed the effect of midazolam added to fentanyl–ropivacaine
PCEA on the incidence of PONV in patients having subtotal gastrectomy. In addi-
tion, we investigated total consumed volume of PCEA, pain intensity, sedation level,
respiratory complications, and other AEs.
**PATIENTS AND METHODS**

This prospective, randomized, double-blind, controlled study was approved by the ethics committee of Kyungpook National University Hospital, Daegu, Republic of Korea. We included consecutive American Society of Anesthesiologists Physical Status Classification I (no organic, physiologic, biochemical, or psychiatric disturbance) and II (mild to moderate systemic disturbance that may or may not be related to the reason for surgery) smoking patients with gastric cancer, undergoing elective subtotal gastrectomy. Written informed consent was obtained from all patients. Patients with a history of drug abuse, allergies to any of the drugs, previous PONV or motion sickness, who had complained of nausea or vomiting or received any antiemetic medication within 24 hours before surgery, or who had liver or renal dysfunction were excluded.

The night before surgery, all patients were instructed on how to use the PCEA device. No premedication was administered. The anesthetic regimen and postoperative pain management were standardized in all patients. In the operating room, patients were placed in the sitting position and an epidural catheter was inserted via 18-gauge Tuohy needle at the T8/T9 interspace and was advanced 3 to 4 cm into the epidural space in a cephalad direction. A standard test dose of lidocaine 2% with epinephrine 5 μg/mL was injected to rule out intrathecal or intravascular position of the catheter. Sensory block (loss of pinprick test) covering the area of the proposed incision was induced by injecting 8 to 12 mL of 0.375% ropivacaine. General anesthesia was induced with propofol (2 mg/kg) and rocuronium (1.0 mg/kg) and maintained with 66% nitrous oxide in oxygen with a small concentration (0.5%-0.9%) of isoflurane. Within 30 minutes of induction, a continuous epidural infusion of 0.375% ropivacaine at 0.1 mL/kg/h was initiated. Lungs were mechanically ventilated maintaining an end tidal carbon dioxide concentration of 4.6 kPa. It is standard practice to administer opioids during this surgery. However, intraoperative opioids increase PONV incidence\(^1\); therefore, opioids were not administered during the present surgery.\(^3\) An infusion of Ringer’s solution (10 mL/kg/h) was administered intravenously together with 4-mg boluses of ephedrine to maintain mean arterial pressure within 20% of baseline values throughout surgery. At the end of surgery, glycopyrrolate 7 μg/kg and pyridostigmine 30 μg/kg were administered intravenously for antagonism of residual neuromuscular blockade and the epidural infusion of 0.375% of ropivacaine was stopped.

In the postanesthetic care unit, postoperative pain relief was provided by using PCEA with a standard pump (Abbott Ambulatory Infusion Manager plus, Abbott Laboratories, North Chicago, Illinois). Patients were randomly assigned to receive 0.2% ropivacaine mixed with fentanyl 4 μg/mL and midazolam 0.2 mg/mL (test group) or 0.2% ropivacaine mixed with fentanyl 4 μg/mL (control group). In the present study, midazolam was epidurally administered at a mean rate of 0.98 mg/hr. One anesthesiologist, not involved in the study, generated the randomization sequence. Assignment was double blinded with respect to treatment. Sealed, sequenced envelopes for assignment were opened on arrival in the preoperating room. Another anesthesiologist, not involved in the study, prepared the study medications. These study
drugs were concealed in numbered opaque envelopes, and all study personnel and participants were blinded to treatment assignment for the duration of the study. The PCEA infusion was set to deliver 4 mL/hr of the study solution, with a bolus of 2 mL per demand and a 15-minute lockout time. Based on previous reports,16,17 midazolam 0.2 mg/mL was chosen. Therefore, the patients in this study could receive midazolam at a rate of 0.8 to 1.6 mg/hr.

The primary end point was the incidence of PONV and secondary end points were total consumed volume of PCEA, pain intensity, sedation level, respiratory complication, and any other AEs during PCEA. The epidural catheter was removed at 72 hours after surgery and then total infused volume of PCEA solution for 72 hours after surgery was measured. Assessment of PONV, sedation level, pain intensity, usage of rescue antiemetic and analgesic, and any noted AEs were collected at 2, 6, 12, 24, 48, and 72 hours after the end of surgery by direct questioning by a study-blinded trainee anesthesiologist.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit, while vomiting was defined as the forceful expulsion of gastric contents from the mouth. For the purpose of data collection, retching (defined as the same as vomiting but without expulsion of gastric contents) was considered vomiting. A rescue antiemetic, ondansetron 4 mg IV, was administered if vomiting occurred, or at the patient’s request to treat intolerable nausea.

Sedation levels were assessed using a 4-point scale (0 = awake; 1 = mildly sedated, easy to wake up when spoken to; 2 = moderately sedated, easy to wake up when slightly shaken; and 3 = deeply sedated, difficult to wake up when shaken).18 Pain intensity scores were measured with a visual analog scale (VAS) from 0 (no pain) to 10 (the worst possible pain). If analgesia was inadequate (verbal rate score on coughing >4) and patients ask for more analgesia, ketorolac 50 mg IV was administered as a rescue analgesic.

Using pulse oximetry, oxygen saturation was continuously measured during PCEA. Reduction in oxygen saturation to <92% was treated with supplemental oxygen via face mask, and need for oxygen treatment during the postoperative period was recorded as a minor respiratory complication. However, a patient with hypoxemia refractory to oxygen was regarded as unacceptable in this context and the patient was excluded. In addition, any AEs that occurred during the study were recorded.

**Statistical Analysis**

A power analysis with a pilot study revealed that a group size of 29 would be required to detect a reduction in the incidence of PONV from 55% to 20% (P = 0.05; power = 0.8). Statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, Illinois). The t test was used to compare continuous variables; when data were not normally distributed, the Mann-Whitney U test was used. ANOVA for repeated measures was used to analyze over time. Categorical data were analyzed using the contingency table analysis with the Fisher exact test and the χ² test. Categorical variables are presented as number (%), while continuous variables are presented as mean (SD).
RESULTS
Sixty consecutive patients were enrolled. No patients were excluded by exclusion criteria and all enrolled patients completed this study. There were no significant between-group differences in regard to demographic data or duration of anesthesia (Table I).

Table II shows the incidence of PONV and patients requiring rescue antiemetics. The incidence of nausea was significantly less in the test group than in the control group (2 [7%] vs 10 [33%]; \( P = 0.02 \)). The overall frequency of PONV in the test group was significantly less than that in the control group (2 [7%] vs 12 [40%]; \( P = 0.006 \)). Numerically more patients in the control group received rescue antiemetic medication, but there was no statistically significant difference (4 [13%] vs 0).

Table III shows sedation scores, respiratory complications, pruritus, mean consumed PCEA volume, and rescue analgesic. There was no difference in the level of sedation between the 2 groups. No patients developed deep sedation or hypoxemia requiring oxygen therapy. In addition, no patients were excluded due to severe hypoxemia refractory to oxygen. With respect to pruritus, there was no significant between-group difference. The mean (SD) infused volume of PCEA in the test group was significantly lower (351.2 [49.8] mL vs 392.3 [68.9] mL; \( P = 0.01 \)). However, there were no significant differences in the usage of rescue analgesics (2 [7%] vs 5 [17%]) or VAS pain score on cough during the observation period (Figure).

No patient reported moderate or severe sedation, respiratory depression, or hypoxemia. In addition, there were no severe AEs observed during this study.

Pruritus observed in this study was relatively mild, and there were no severe AEs in the 2 groups.

Table I. Demographic data and duration of anesthesia in smoking patients with gastric cancer undergoing elective subtotal gastrectomy (N = 60). Data are mean (SD) unless otherwise indicated.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ropivacaine–Fentanyl–Midazolam* (n = 30)</th>
<th>Ropivacaine–Fentanyl† (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.6 (2.0)</td>
<td>58.4 (1.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male/female</td>
<td>18/12</td>
<td>20/10</td>
<td>0.79</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.3 (1.4)</td>
<td>164.0 (1.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.0 (2.2)</td>
<td>60.9 (1.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>Duration of anesthesia, min</td>
<td>256.6 (9.1)</td>
<td>253.0 (7.9)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Test: ropivacaine 0.2% + fentanyl 4 μg/mL and midazolam 0.2 mg/mL.
†Control: ropivacaine 0.2% + fentanyl 4 μg/mL.
Table II. Postoperative nausea and vomiting (PONV) and requirement of rescue antiemetics in smoking patients with gastric cancer undergoing elective subtotal gastrectomy (N = 60). Data are number (%) of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ropivacaine–Fentanyl–Midazolam* (n = 30)</th>
<th>Ropivacaine–Fentanyl† (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea only</td>
<td>2 (7)</td>
<td>4 (13)</td>
<td>0.67</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2–6 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea only</td>
<td>0</td>
<td>4 (13)</td>
<td>0.11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6–12 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea only</td>
<td>0</td>
<td>3 (10)</td>
<td>0.23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>2 (7)</td>
<td>0.49</td>
</tr>
<tr>
<td>12–24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea only</td>
<td>0</td>
<td>2 (7)</td>
<td>0.49</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>24–48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea only</td>
<td>0</td>
<td>2 (7)</td>
<td>0.49</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>48–72 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea only</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0–72 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28 (93)</td>
<td>18 (60)</td>
<td>0.006</td>
</tr>
<tr>
<td>Nausea only</td>
<td>2 (7)</td>
<td>10 (33)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>2 (7)</td>
<td>0.49</td>
</tr>
<tr>
<td>Patients requiring rescue antiemetic</td>
<td>0</td>
<td>4 (13)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Test: ropivacaine 0.2% + fentanyl 4 µg/mL and midazolam 0.2 mg/mL.
†Control: ropivacaine 0.2% + fentanyl 4 µg/mL.

**DISCUSSION**

The overall incidence of PONV in patients receiving midazolam–fentanyl–ropivacaine PCEA was significantly reduced compared with fentanyl–ropivacaine PCEA without increasing the occurrence of AEs in these patients who underwent partial gastrectomy. In addition, the total infused volume in the test group was significantly less compared with that in the control group.

PONV is one of the most distressing complications after anesthesia and surgery. In the present study, patients' specific surgical and anesthetic factors that might modify the incidence of PONV were balanced between groups. Opioids increase PONV via stimulating the chemoreceptor zone in the area postrema of the medulla. Therefore, the differences in the incidence of PONV can be attributed to the study drug. In the present study, the incidence of PONV in the control group was 40%. In
Table III. Sedation, hypoxemia, pruritus, infused volume of patient-controlled epidural analgesia (PCEA) solution, and consumption of rescue analgesics in smoking patients with gastric cancer undergoing elective subtotal gastrectomy (N = 60).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ropivacaine–Fentanyl–Midazolam*</th>
<th>Ropivacaine–Fentanyl†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 30)</td>
<td>(n = 30)</td>
<td></td>
</tr>
<tr>
<td>Sedation level,† no. (%)</td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>0</td>
<td>25 (83)</td>
<td>28 (93)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (17)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypoxemia requiring oxygen treatment</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypoxemia refractory to oxygen</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pruritus, no. (%)</td>
<td>8 (27)</td>
<td>14 (47)</td>
<td>0.18</td>
</tr>
<tr>
<td>Infused volume of PCEA, mean (SD), mL</td>
<td>351.2 (49.8)</td>
<td>392.3 (68.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rescue analgesia, no. (%)</td>
<td>2 (7)</td>
<td>5 (17)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*Test: ropivacaine 0.2% + fentanyl 4 µg/mL and midazolam 0.2 mg/mL.  
† Control: ropivacaine 0.2% + fentanyl 4 µg/mL.  
† Sedation level: 0 = awake; 1 = mildly sedated, easy to wake up when spoken to; 2 = moderately sedated, easy to wake up when slightly shaken; 3 = deeply sedated, difficult to wake up when shaken.

In the present study, the incidence of PONV in the test group was significantly less than that in the control group.

The antiemetic effect of midazolam has been demonstrated with various objects of study and various methods of administration. Di Florio and Goucke conducted a prospective, randomized, double-blind study in 20 patients (aged 18–82 years) with persistent PONV refractory to other conventional antiemetics comparing the antiemetic effect of midazolam bolus (1 mg) followed by infusion of 1 mg/hr with placebo. It was reported that cumulative nausea score (26 vs 50; P = 0.04), vomiting frequency (10% vs 70%; P = 0.02), and the use of rescue antiemetic (0% vs 70%; P = 0.003) were significantly less in the midazolam group than those in placebo. Sanjay and Tauro conducted a prospective, randomized, double-blind trial, comparing efficacy of midazolam versus ondansetron, in 200 patients (mean age, 61 years; weight, 68 kg) on the incidence of PONV for 24 hours after cardiac surgery. A 6% incidence of PONV was observed in patients receiving midazolam in a dose of 0.02 mg/kg/hr after 1 mg bolus compared with a 21% incidence rate in patients receiving ondansetron 0.1 mg/kg IV every 6 hours (P < 0.001).

The exact mechanism by which midazolam exerts its antiemetic action is not fully understood. Postulated mechanisms include glycine mimetic inhibitory effects, enhancement of the inhibitory effects of γ-aminobutyric acid, inhibition of dopa-
Figure. Visual analog scale (VAS) scores of pain on coughing in smoking patients with gastric cancer undergoing elective subtotal gastrectomy randomized to receive ropivacaine 0.2% plus fentanyl 4 μg/mL and midazolam 0.2 mg/mL (test) or ropivacaine 0.2% plus fentanyl 4 μg/mL (control) (N = 60).

It has been found that intravenous continuous infusion of midazolam in a dose of about 1 mg/hr was effective for reducing PONV without sedative effects in patients who received opioids for postoperative pain control. The prospective, randomized, double-blind trial by Unlugenc et al. suggested that the antiemetic effect of midazolam lasted longer than the sedative effect in 453 patients (mean age, 44 years; weight, 66 kg). In the present study, there were no additional sedative effects in patients who received midazolam. However, a variety of midazolam doses should be investigated to determine its antiemetic effectiveness and tolerability profile.

Intrathecal midazolam provides segmental analgesia, but conflicting experimental studies have cast doubts on its safety. Malinovsky et al. reported necrosis, hemorrhage, and other histopathologic changes in 2 of 9 spinal cords of rabbits that had
received a single intrathecal injection of midazolam 0.3 mg. However, various other experimental histopathologic studies have found that intrathecal midazolam does not cause any morphologic changes in the spinal cord.\(^{26,27}\) Tucker et al\(^{12}\) suggested that clinically useful doses of intrathecal midazolam 2 mg did not increase adverse neurologic symptoms compared with conventional treatments. Aguilar et al\(^{28}\) found that intrathecal infusion of midazolam for 13 months was tolerable for reducing chronic lower back pain in a patient with chordoma. Borg and Krijnen\(^{29}\) reported cases of long-term (>2.5 years) administration of up to 6 mg/d of intrathecal midazolam in patients with refractory neurogen and musculoskeletal pain. It was found that midazolam did not cause any neurologic deficits. In the present study, midazolam was epidurally administered at a mean rate of 0.98 mg/hr, which was consistent with previous reports.\(^{16,17}\) In addition, no patients who received epidural infusion of midazolam showed neurotoxic effects.

The findings should be considered within the context of the limitation of the study. The sample size of the study was relatively small. This study showed a lack of power to detect significant differences in secondary outcomes. In addition, all patients having a single type of surgery underwent a single type of general anesthesia. Therefore, the results may not be widely applicable to patients undergoing other procedures.

**CONCLUSION**

Midazolam added to fentanyl–ropivacaine PCEA was associated with a significant reduction in the incidence of PONV compared with fentanyl–ropivacaine alone, and a significant decrease in the amount of PCEA administered without a significant increase in AEs in these patients who underwent subtotal gastrectomy.

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Dr. Kim wrote the manuscript. Dr. Seo was involved in data collection and analysis. Dr. Jeon was responsible for the study design and conduct.

**REFERENCES**


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