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## Propofol sedation during endoscopic treatment for early gastric cancer compared to midazolam

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### Abstract

Endoscopic submucosal dissection (ESD) has been proposed as the gold standard in the treatment of early gastric cancer because it facilitates a more accurate histological assessment and reduces the risk of tumor recurrence. However, the time course of ESD for large gastric tumors is frequently prolonged because of the tumor size and technical difficulties and typically requires higher doses of sedative and pain-controlling drugs. Sedative or anesthetic drugs such as midazolam or propofol are used during the procedure. Therapeutic endoscopy of early gastric cancers can often be performed with only moderate sedation. Compared with midazolam, propofol has a very fast onset of action, short plasma half-life and time to achieve sedation, faster time to recovery and discharge, and results in higher patient satisfaction. For overall success, maintaining safety and stability not only during the procedure but also subsequently in the recovery room and ward is necessary. In obese patients, it is recommended that the injected dose be based on a calculated

standard weight. Cooperation between gastroenterologists, surgeons, and anesthesiologists is imperative for a successful ESD procedure.

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**Key words:** Sedation; Gastric cancer; Endoscopic submucosal dissection; Endoscopic resection; Propofol

**Core tip:** According to the literature, endoscopic submucosal dissection (ESD) has been proposed as the gold standard in the treatment of early gastric cancer. However, ESD requires safe sedation management. This review covers safe sedation using propofol and other sedative drugs in the context of the available literature. Moreover, understanding safe sedation could be important in managing perioperative patients with gastric ESD. To this end, we suggest that sedation using propofol is safe and results in patient satisfaction after endoscopic gastric treatment for ESD.

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### INTRODUCTION

The importance of endoscopic procedures in the diagnosis and treatment of digestive disease is increasing. Furthermore, safe and painless endoscopic procedures have recently been requested. Conscious sedation is an effective technique in reducing pain and improving satisfaction during the endoscopic examination.

For early gastric cancer (EGC) without metastasis, in-

**Table 1** Comparison studies of sedation for gastric endoscopic submucosal dissection

Ref.	Year	Propofol	Midazolam	Combination	General anesthesia	Other	Anesthesiologist present	Conclusion
Sasaki <i>et al</i> <sup>[7]</sup>	2012	•	•					P > M
Chun <i>et al</i> <sup>[8]</sup>	2012	•		•				Combination > P
Rong <i>et al</i> <sup>[9]</sup>	2012		• <sup>1</sup>		•		•	GA > M
Yamagata <i>et al</i> <sup>[10]</sup>	2011	•	•					P > M
Uesato <i>et al</i> <sup>[11]</sup>	2010		•		•		•	GA > M
Takimoto <i>et al</i> <sup>[12]</sup>	2010	•	•			DEX		DEX
Kiriya <i>et al</i> <sup>[13]</sup>	2010	•	•					P > M

<sup>1</sup>Diazepam. About drug names (propofol/midazolam/combination/general anesthesia/pentazocine/fentanyl), “•” means that the drug were “used”. And about the line of Anestheologist, “•” means that anesthesiologists “managed” sedation. Combination: Propofol and midazolam; DEX: Dexmedetomidine hydrochloride; P: Propofol; GA: General anesthesia; M: Midazolam.

cluding lymph node metastasis, complete curative resection is possible with endoscopic treatment. Therefore, higher quality endoscopic examination and diagnosis are important in the detection and treatment of earlier stage gastric cancers.

Therapeutic endoscopy, routine esophagogastroduodenoscopy (EGD), and colonoscopy can often be performed with minimal or moderate sedation; these sedation practices vary widely throughout the world. In the United States, more than 98% of EGDs and colonoscopies are performed with sedation<sup>[1,2]</sup>. On the other hand, in many European and Asian countries, routine EGD is often performed under pharyngeal local anesthesia without intravenous sedation or general anesthesia, and colonoscopy is performed without sedation<sup>[3-5]</sup>. Currently, per os endoscopic examinations under conscious sedation and per nasal thin endoscopic examinations without sedation are often performed<sup>[6]</sup>. In cases where sedative or anesthetic drugs are required, drugs such as midazolam or propofol are the drugs of choice.

## SELECTION METHODS FOR LITERATURE TO BE REVIEWED

We reviewed the literature published until December 2013 to identify studies of gastric cancer patients treated with endoscopic treatment procedures. Studies were identified by searching the Medline and PubMed databases using the terms “gastric cancer”, “endoscopy”, “treatment”, and “sedation”. Research articles on hypopharyngeal cancer, submucosal tumors, screen endoscopy, metallic stenting, and gastronomy procedure were excluded in this review. In total, 41 potential articles were identified during the primary evaluation. Thereafter, 19 articles that met the inclusion criteria were selected for evaluation on this topic. Of these, 7 comparison studies published after 2010 showed that propofol alone, propofol combined, or general anesthesia provided more benefits than midazolam<sup>[7-13]</sup> (Table 1).

In the 12 studies concerning endoscopic treatment of gastric cancer that are not comparative studies on sedation, propofol sedation was used in 9 articles (75%)<sup>[14-25]</sup> (Table 2), and the use of midazolam alone was reported in 3 articles (50%) prior to 2009; however, this number

decreased after 2010. Therefore, the literature suggests that propofol is most commonly used for sedation during endoscopic treatment for gastric cancer.

## ENDOSCOPIC TREATMENT FOR GASTRIC CANCER

Endoscopic resection for gastric cancer is performed on the tumor lesions without risk of metastasis<sup>[26,27]</sup>. The number of endoscopic procedures for treatment of EGC is increasing<sup>[28]</sup>.

Patients with EGC are often in good general health compared to patients with advanced gastric cancer. Most of these patients are able to complete their activities of daily living without symptoms or weight loss. Therefore, these patients are relatively low-risk candidates for sedation and endoscopic treatment.

Endoscopic mucosal resection (EMR) has traditionally been used to treat mucosal gastric cancers. This procedure is often performed quickly and therefore does not require a long sedation time. Recently, endoscopic submucosal dissection (ESD) was initially intended to treat large EGCs and produced higher rates of en bloc resections and tumor-free margins compared to the conventional EMR technique<sup>[29,30]</sup>. As a result, ESD has been proposed as the gold standard in the treatment of EGC<sup>[31-33]</sup>.

ESD for the resection of large tumors is frequently prolonged because of the tumor size and related technical difficulties requiring higher doses of sedative and pain-controlling drugs such as midazolam and pentazocine. Therefore, a method of safe sedation is necessary. In EMR, the procedure time is short and may be possible using only a benzodiazepine, such as midazolam, for sedation. However, midazolam may not be sufficient for ESDs that require a longer treatment time, and can be dangerous for the patient. Therefore, safe but long-acting sedation is necessary for these ESDs. In addition, ESDs have a higher rate of complications such as perforation causing peritonitis, delayed bleeding, and other perioperative complications<sup>[34,35]</sup>.

More invasive treatments, including emergency surgical procedures, may be necessary depending on the degree of complications post-ESD. Therefore, preopera-

**Table 2 Relationship between sedation and endoscopic gastric treatment**

Ref.	Year	Propofol	Midazolam	Combination	Petizine/pentazocine	Fentanyl	Anesthesiologist present
Sohara <i>et al</i> <sup>[14]</sup>	2013	•			•		
Park <i>et al</i> <sup>[15]</sup>	2013			•		•	•
Schumacher <i>et al</i> <sup>[16]</sup>	2012			•	NA		
Takano <i>et al</i> <sup>[17]</sup>	2011			•	•		
Lee <i>et al</i> <sup>[18]</sup>	2011	•	•		NA		
Nonaka <i>et al</i> <sup>[19]</sup>	2010			•	NA		
Hata <i>et al</i> <sup>[20]</sup>	2009	•			•		•
Gotoda <i>et al</i> <sup>[21]</sup>	2009		•		•		
Kiriyaama <i>et al</i> <sup>[22]</sup>	2009		•		•		
Imagawa <i>et al</i> <sup>[23]</sup>	2008	•			•		
von Renteln <i>et al</i> <sup>[24]</sup>	2008			•	NA		
Kondo <i>et al</i> <sup>[25]</sup>	2004		•		•		

About drug names (propofol/midazolam/combination/general anesthesia/pentazocine/fentanyl), “•” means that the drug were “used”. And about the line of Anesthesiologist, “•” means that anesthesiologists “managed” sedation. Combination: Propofol and midazolam; NA: Not applicable.

tive examination and management are important, and endoscopic treatment should not be performed without proper preparation; in fact, the perioperative management for ESD should be similar to that for a surgical procedure.

## NEED FOR SEDATION

The endoscopic treatment of EGC is mainly performed as ESD. For large tumors, it is usually a prolonged procedure requiring higher doses of sedative and pain-controlling drugs such as midazolam and pentazocine. To perform an ESD safely, the movement of the patient during treatment must be controlled, as the operator must be able to focus on the procedure for its success.

ESD has a high risk of complications that may require emergency surgical procedures, making sufficient preoperative management necessary. ESD treatment can take a long time; therefore, if securing adequate doctors and operating room hours is an issue, treatment under general anesthesia is recommended.

In clinical practice, this can be problematic because of the difficulty in securing anesthesiology support and medical insurance coverage. Therefore, regardless of the indications, ESD is commonly performed in the endoscopic room. Additionally, staff who are familiar with the procedure are generally present in the endoscopy unit and can assist with the procedure. ESD is possible under sedation as opposed to an open surgery that requires general anesthesia. If safe and stable sedation can be maintained, ESDs for most cases of EGC can be performed under sedation.

Spirometry, electrocardiography, and blood laboratory examination are necessary aspects of the preoperative examination. The use of propofol and monitoring of vital signs (blood oxygen saturation, blood pressure, and electrocardiography) during the procedure are performed as per the American Society of Anesthesiologists (ASA)<sup>[36]</sup> and American Society of Gastrointestinal Endoscopy guidelines<sup>[37]</sup>.

## SAFE MANAGEMENT AFTER THE ENDOSCOPIC PROCEDURE

For overall success, maintaining safety and stability not only during the procedure but also subsequently in the recovery room and ward is necessary. If perforation occurs, serious complications can be prevented if the symptoms are detected early. However, over-sedation inhibits the patient from communicating their complaints. Therefore, it is necessary for consciousness to be recovered as soon as possible after treatment.

During the ESD procedure, it is preferable that a gastroenterologist or surgeon focuses on treatment and performs the procedure. Therefore, staff who specialize in this area can control the sedation management. Post-operatively, a delayed complication can occur owing to a prolonged sedation effect; therefore, safe management of sedation is necessary both during and after the procedure. A local analgesic such as lidocaine can be used to control postoperative pain<sup>[22]</sup>.

## PROPERTIES OF PROPOFOL

Benzodiazepines (midazolam, diazepam), narcotics (fentanyl, meperidine), propofol, neuroleptic tranquilizers (droperidol) are all acceptable choices for sedation. Recently, propofol has been used more frequently as the sedative drug of choice for endoscopic procedures<sup>[38,39]</sup>. It was originally used for general anesthesia, but is now also used in endoscopic procedures. Propofol is a very short-acting sedative<sup>[40]</sup> that can be administered by continuous infusion or bolus administration; stable sedation is generally maintained by continuous infusion. It is a lipid-soluble drug for which the quantity of fat in the body influences the dose. If actual body weight is used to determine dosage in patients with a high body mass index, it is likely that over-sedation will occur. In obese patients, it is recommended that the injected dose be based on a calculated standard weight. Propofol has a quicker recovery profile than other sedative drugs; patients re-

gain consciousness more quickly after administration is withdrawn. There is no antagonist for propofol, unlike midazolam with flumazenil; therefore, prevention of over-sedation is necessary. Nurses who received training in advanced cardiac life support manage the propofol sedation under the guidance of a supervising gastroenterologist<sup>[41]</sup>.

## METHOD OF SEDATION USING PROPOFOL AND MIDAZOLAM

In sedation using propofol, a continuous infusion dosed at 3-5 mg/kg per hour is appropriate. The exclusive pump (Telfusion pump, TERUMO, Japan) allows for easy setting and management of the infusion. Using this method, patients receive not only the sedative agent but also an analgesic (such as pethidine, pentazocine, or fentanyl) before treatment. At the initial stage of sedation, a bolus injection is often given at a dose of 0.5-0.8 mg/kg for patients  $\geq$  70 years of age and 0.8-1.0 mg/kg for patients < 70 years of age<sup>[13,41]</sup>. After ensuring that the sedation level is equal to a score of 5-6 on the Ramsey scale, the endoscopic procedure can be performed<sup>[13,42]</sup>. Patients with a higher risk of sedation, such as those > 85 years of age or who are ASA class IV, must be managed carefully.

When using midazolam for sedation, an initial bolus of 2-4 mg is administered. After injection, the sedation level is evaluated and another 1-2 mg is administered if the level is unsatisfactory. Additional sedation and analgesia is titrated at the discretion of the physician or nurse. Incremental increases in midazolam administration are necessary if the patient shows signs of discomfort, restlessness, or agitation.

Midazolam has an additive sedating effect; however, this accumulation can result in an overdose. Originally, midazolam was used for short-term sedation, but has now been used for longer-term sedation in procedures such as ESD. There is, however, no evidence in the literature that midazolam is safe for long-term sedation. Recently, the usefulness and safety of propofol sedation for endoscopic procedures has been compared with that of midazolam, showing that propofol is more useful, particularly in respect to the recovery time after sedation<sup>[40]</sup>.

## MONITORING

Monitoring is important during ESD procedures carried out in an endoscopy room. Standard vital sign monitoring with an automated blood pressure cuff, electrocardiography, and pulse oximetry is recommended. Additionally, a specialized monitor for sedation and anesthesia with a bispectral index monitor, capnography, and a respiratory monitor is necessary. Careful monitoring can improve the safety of sedation, but continued training on sedation for doctors, assisting nurses, and other medical staff remains necessary<sup>[37]</sup>.

## CONTRAINDICATIONS FOR PROPOFOL USE

Contraindications for propofol use include pregnancy and egg or soy allergy, hypotension (a baseline systolic blood pressure < 90 mmHg), psychiatric or neurologic disease, difficult airway management (limited opening of the mouth, short neck, or low cervical spine mobility), severe obstructive pulmonary disease (bronchial asthma or emphysema), and ASA class V physical status<sup>[43]</sup>.

## IMPROVING QUALITY OF LIFE THROUGH CHOICE OF SEDATION AND ANESTHESIA

According to the literature on sedation during endoscopic procedures, the safety and usefulness were investigated through evaluation by medical staff such as gastroenterologists and assisting nurses, and there were few reports on patient satisfaction<sup>[44]</sup>.

This review has certain limitations. It was difficult to elucidate evidence levels and the grade of recommendations from the article on early gastric cancer, endoscopic treatment, and sedation management referred to in the present review. It is thought that safe sedation using propofol, which demonstrates a quicker recovery profile, confers better patient satisfaction<sup>[45]</sup>.

## CONCLUSION

Safe and curative gastric endoscopic treatments are more commonly performed under sedation. Propofol has been increasingly used as the preferred sedation drug and is both safe and useful. However, further evaluation is necessary for safe sedation management.

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