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OPINION REVIEW

Effectiveness and safety of sedation in gastrointestinal endoscopy: An opinion review

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Abstract

Although endoscopy is a less invasive procedure than surgery, patients can experience pain without sedation. Patients expect reduced pain during endoscopies from effective and safe sedatives. Midazolam and propofol are used for endoscopic sedation in many countries and regions. Midazolam is a widely available benzodiazepine, and many clinical trials have shown it to be an effective sedative. However, patients who are sedated with midazolam require rest in the recovery room due to its relatively long half-life, and an antagonist such as flumazenil may need to be administered in cases of deep or prolonged sedation. Propofol is a short-acting sedative with a short half-life and a quick recovery time. Therefore, the use of propofol has been increasing. However, propofol has a narrow margin of safety and often induces adverse effects such as respiratory depression. Also, propofol has no specific antagonist, and should be administered by an anesthesiologist or an endoscopist familiar with anesthesia. Remimazolam, which is a novel ultra-short-acting benzodiazepine, has recently gained attention. Remimazolam has a short half-life and an antagonist. Both effective and safe sedation is desired in accordance with the increasing need for sedative endoscopies. Therefore, in this review each sedative is summarized.

Key words: Gastrointestinal endoscopy; Conscious sedation; Propofol; Midazolam; Remimazolam; Benzodiazepine

Core tip: The need for sedation during gastrointestinal endoscopies is ever increasing. Currently, benzodiazepines such as midazolam and the short acting propofol are the most commonly used sedatives for an endoscope. However, midazolam requires the patient to have an extended recovery period and in cases of a deep sedation an antagonist administered. Although short acting, propofol must be administered by an anesthesiologist due to its potential side effects and does not have an antagonist. Remimazolam is ultra-short acting and has both a short half-life and if required an

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antagonist. In this review we discuss the advantages and disadvantages of each sedative.

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INTRODUCTION

Recently, the advances in gastrointestinal endoscopy is remarkable. Gastrointestinal endoscopy has been applied to not only endoscopic diagnoses of gastrointestinal tract cancers including stomach, esophagus and colon, but also endoscopic treatment for gastrointestinal diseases such as endoscopic submucosal dissection and endoscopic retrograde cholangiopancreatography[1-4]. The need for endoscopic treatment for gastrointestinal disease has been gradually increasing, because this is a less invasive procedure than surgery. Sedation during endoscopic treatment is essential considering its time consumption. Although endoscopic examination is less invasive and less time-consuming than endoscopic treatment, patients often experience pain and discomfort without sedation. Conscious sedation is considered effective for gastrointestinal endoscopic examinations[5,6]. Both patient satisfaction and re-examination compliance are superior in those patients who received sedation compared to those who did not have sedation[7,8]. Only 65% of patients who underwent upper gastrointestinal endoscopy without sedation were willing to have a repeat examination. Effective sedation is not only important for pain reduction in patients, but also for endoscopists to facilitate a successful examination[9]. In elderly patients or patients with various comorbidities, the risk of adverse events associated with sedation is increased[10]. Sedation is required not only to increases the completion rates of endoscopic examinations and reduces pain in patients, but also to create a safer system.

CURRENT STATUS IN THE USAGE OF SEDATIVES

Although sedation during endoscopic treatment is essential, the use of conscious sedation, without tracheal intubation, during endoscopic examination varies greatly by country and region, depending on the endoscopic facilities or insurance systems. Sedation is used during 98% of upper gastrointestinal endoscopies and colonoscopies in the United States, and in 90% of these procedures in Canada[11-13]. While in Europe, the use of sedation during endoscopy was lower than in the Unites States and Canada. However, its rate is gradually increasing. Sedation during endoscopy is already standard practice in Italy[14]. In Greece, the rates of sedation are 64% in upper gastrointestinal endoscopies and 78% in colonoscopies[15]. In Germany, sedation is used in 74% of upper gastrointestinal endoscopies and 87% of colonoscopies[16]. In Japan, the rate of sedation during endoscopy has been increasing. Sedation is used during upper endoscopies in up to 75% of 544 institutions. Sedation will be increasingly required during endoscopic examinations in the future.

Midazolam, which has the shortest half-life out of all of the conventional benzodiazepines, is administered either alone or with opioids such as fentanyl or pethidine in many countries. Recently, the use of propofol has been increasing because endoscopists are satisfied with its rapid onset of action and quick recovery time.

MIDAZOLAM'S CHARACTERISTICS AND CLINICAL TRIALS

Midazolam, as well as other benzodiazepines, enhances the effect of gamma-aminobutyric acid, a suppressive neurotransmitter in the central nervous system, at its receptor. Therefore, hypnotic, sedative, anxiolytic, amnesic, anti-convulsive, and muscle-relaxing effects are achieved. The active duration of midazolam is the shortest (2-6 h) out of all the conventional benzodiazepines, which is metabolized *via* the liver. Severe adverse effects include respiratory depression, hypotension, and bradycardia

depending on the dosage. There is no vascular pain at the time of intravenous injection[17].

Various clinical trials have been conducted on the use of midazolam for endoscopic sedation. A randomized controlled trial that compared endoscopies using either midazolam or a placebo, showed that the midazolam group had higher rates of procedural success, patient satisfaction, and compliance with re-examination. There was no significant difference in the rate of severe hypoxemia between the two groups[7,18].

Benzodiazepines are sometimes used in combination with analgesics such as fentanyl and pethidine hydrochloride. A randomized controlled trial that compared endoscopies using a benzodiazepine alone and a benzodiazepine in combination with an analgesic, showed that there were no significant differences in the patient satisfaction or cardiorespiratory depression between the two groups, but a higher endoscopist satisfaction was achieved in the benzodiazepine combined with an analgesic group[19,20]. However, unpredicted deep sedation was reported to occur in the benzodiazepine combined with an analgesic group[21]. The combination of a benzodiazepine and an analgesic might be limited for elderly patients or those patients with comorbidities.

PROPOFOL CHARACTERISTICS AND CLINICAL TRIALS

Propofol is a short-acting intravenous anesthesia, which is a phenol derivative that easily crosses the blood-brain barrier due to its high fat solubility. Rapid induction and a short recovery time can be achieved with propofol compared with conventional Benzodiazepines. Propofol's sedative effect can be achieved within 30-60 s after administration. The half-life of propofol in the blood is 1-4 min. A 15%-30% reduction in systolic blood pressure as a cardiovascular side-effect of this drug occurred in 53% of patients following induction of anesthesia with propofol because of cardiovascular depressant and dilation of the peripheral vessels[22].

Various randomized controlled trials have been conducted to compare sedation using a benzodiazepine such as midazolam, and propofol[23-26]. Although patient satisfaction differed from report to report, the recovery time from sedation was shorter in the propofol groups than in the benzodiazepines groups in all reports. The recovery time with propofol was significantly shorter than with midazolam, and without the increase of cardiorespiratory adverse effects according to a meta-analysis[27-29].

Several studies have shown the efficacy and safety of propofol compared with the benzodiazepines, regardless of whether an anesthesiologist or gastroenterologist (non-anesthesiologist) administered the propofol sedation[30,31]. However, propofol has a narrow range between sedation and anesthesia, therefore sometimes adverse effects can be induced such as respiratory and cardiac depression. Furthermore, there is no specific antagonist for propofol[32,33]. The written information inside the packaging of propofol cautions that sedation with propofol should be inducted by an anesthesiologist or independent physician familiar with anesthesia for safety, and that patients should be carefully monitored until they have completely recovered. Although the American Gastroenterological Association proposed to remove this caution, this proposal was rejected by the Food and Drug Administration.

WHICH DRUG IS MORE EFFECTIVE FOR SADATION MIDAZOLAM OR PROPOFOL?

An endoscopic examination is a relatively short procedure and is usually conducted without admission to the hospital. Endoscopists must conduct many endoscopic examinations per day, while responding to the needs of patients to eliminate pain. Therefore, sedatives that are safe, have a rapid onset of action, rapid recovery, and have an antagonist are desired.

Due to Midazolam's half-life, recovery takes approximately 30 min-1 h after the endoscope. Patients can usually return home once they are able to walk unaccompanied. There are various medical costs associated with endoscopic sedation such as securing a large recovery space in the hospital and medical staff to watch over patients. Flumazenil acts as a midazolam antagonist and is sometimes used to reduce recovery time in patients who are either in a deep or prolonged sedation. However, re-sedation might occur after reversing sedation because the active duration of flumazenil (approximately 50 min) is shorter than that of Midazolam, and some active metabolites profoundly contribute to the sedative profile of midazolam[34,35].

However, appropriate monitoring and observation of those sedated with propofol is required because it has a narrow therapeutic range with the potential to cause cardiorespiratory depression. Although propofol acts *via* gamma-aminobutyric acid receptors, similar to the benzodiazepines, there is no antagonist for propofol unlike the benzodiazepines. Lack of an amnestic effect and pain during administration is a disadvantage of propofol sedation. Furthermore, at the time of writing propofol can only be administered by an anesthesiologist or independent physician familiar with anesthesia.

For the above reasons, propofol is currently only used in institutions where independent anesthesiologists or endoscopists can administer the drug and monitor the patient's sedation. In other institutions, midazolam is used as a sedative.

REMIMAZOLAM: A NEW SEDATIVE

Remimazolam is an ultra-short-acting intravenous novel benzodiazepine sedative, with a shorter half-life (approximately 40 min) compared with other conventional benzodiazepines. It can rapidly pass through the blood-brain barrier and provide a rapid effect because it is a fat-soluble drug. Remimazolam is rapidly metabolized by carboxylic acid elastase, which does not involve the liver enzyme CYP3A4, and shows organ-independent metabolism. Its organ-independent metabolism makes it less likely to impair liver and kidney function. Remimazolam's metabolites are pharmacologically inactive. Therefore, the adjustability of remimazolam seems to be superior to Midazolam.

Remimazolam is safer than propofol because it can be reversed with flumazenil to rapidly terminate sedation, similar to other benzodiazepines if necessary. Furthermore, remimazolam's half-life is as short as flumazenil's and therefore, there is low risk of re-sedation unlike other benzodiazepines.

In a phase IIa study conducted in the United States, the induction times from drug administration to sedation was 1.5-2.5 min in remimazolam (0.10-0.20 mg/kg) and 5 min in midazolam (0.075 mg/kg) in upper gastrointestinal endoscopies[36]. The time to recover from sedation (3 consecutive Modified Observer's Assessment of Alertness and Sedation scores of 5) was significantly shorter in remimazolam than that in midazolam (6.8-9.9 min *vs* 11.5 min, respectively). These results suggest that remimazolam had a faster onset of action and a faster recovery time after endoscopic examination/treatment compared with midazolam.

In a phase IIb study conducted in the United States, remimazolam (5.0 mg, 7.0 mg, and 8.0 mg) achieved a lower rate of additional administrations compared with Midazolam (2.5 mg) during colonoscopies[37].

Similarly in a phase III study conducted in the United States, remimazolam (5 mg) achieved a higher procedural completion rate without the requirement for additional fixed doses (5 doses in any 15-min interval), compared with placebo (5 doses in any 15-min interval) and midazolam (3 doses in any 12-min interval; aged < 60 years, 1.75 mg; aged ≥ 60 years, 1.0 mg) in outpatient colonoscopies[38].

All studies have suggested that remimazolam was as safe as Midazolam as a sedative for gastrointestinal endoscopy. Remimazolam, has the combined advantage of a short half-life, similar to propofol and an antagonist like midazolam. Furthermore, it can be managed by non-anesthesiologists. Therefore, remimazolam may increasingly be used as a sedative for gastrointestinal endoscopies.

The use of Remimazolam in clinical practice remains insufficient. New issues might arise after clinical administration. To the best of our knowledge, there are no studies comparing the clinical outcomes of remimazolam with propofol. There is a lack of clinical data on Remimazolam. Various additional clinical studies to improve the efficacy and safety of remimazolam as a sedative for endoscopic procedures is desired in the future. Preparation for clinical trial for insurance coverage are currently in progress in Japan.

CONCLUSION

Conscious sedation, without tracheal intubation, during endoscopy differs greatly depending on the country and region. Endoscopic examination using sedation should be safely completed without pain. Currently, benzodiazepine sedatives and propofol are the predominant drugs administered during endoscopic examinations. Propofol might be useful for patients in countries or regions with sufficient anesthesiologists. While a novel benzodiazepine sedative, remimazolam, could be a desired option in countries or regions without adequate numbers of anesthesiologists to attend

endoscopic procedures.

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