

Effect of dexmedetomidine in the prophylactic endoscopic injection sclerotherapy for oesophageal varices: a study protocol for prospective interventional study

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ABSTRACT

Background: Dexmedetomidine (DEX) is a novel, highly selective α_2 -adrenoceptor agonist that elicits sedative, amnestic, sympatholytic and analgesic effects in patients. Several Japanese investigators have reported the clinical usefulness of DEX for sedation in endoscopic therapies for gastrointestinal malignancies; however, there have been limited data regarding the usefulness and safety of DEX for sedation during endoscopic procedures for oesophageal varices (OVs), such as endoscopic injection sclerotherapy (EIS). In this prospective, single-arm interventional study, we aimed to elucidate these issues.

Methods: Patients who require two or more sessions of prophylactic EIS for the treatment of OVs will be enrolled in this prospective interventional study. EIS procedures include two methods: (1) sedation during endoscopic procedures will be performed using conventional methods (pentazocine (PNZ) and midazolam (MDZ)), and (2) sedation during endoscopic procedures will be performed using PNZ, low-dose MDZ and DEX. These two methods were randomly assigned in the first and second EIS. The effect and safety of these two procedures with respect to patient sedation are to be compared with the degree of sedation evaluated using the Bispectral Index monitoring system (Aspect Medical Systems, Norwood, Massachusetts, USA).

Ethics and dissemination: This study received approval from the Institutional Review Board at Hyogo College of Medicine (approval no. 2324). The authors are committed to publishing the study results as widely as possible in peer-reviewed journals, and to ensuring that appropriate recognition is provided to everyone who is working on this study.

Trial registration number: UMIN000026688;
Pre-results.

INTRODUCTION

Endoscopic procedures are of great benefit for the diagnosis and treatment of various

diseases, including upper gastrointestinal bleeding, early gastric cancer, hepatobiliary-pancreatic diseases and oesophageal varices (OVs).¹⁻⁴ However, anxiety, pain, fear and adverse gastrointestinal reactions may cause subjects to be less cooperative during endoscopic procedures, and may even cause harmful cardiovascular adverse events.⁵⁻⁷ Thus, the role of sedation in endoscopy is therefore very important, with various sedative agents commonly used during endoscopic procedures.⁵⁻⁷

Midazolam (MDZ, Dormicum; Astellas Pharma, Tokyo, Japan), the most common agent used for sedation, is a benzodiazepine with a rapid onset of action and short duration of sedative effect.⁸⁻⁹ However, it has several unfavourable side effects, including delayed recovery of memory, long-term behavioural changes such as long-term cognitive dysfunction, and respiratory suppression.¹⁰

Dexmedetomidine (DEX, Precedex; Hospira Japan Co., Osaka, Japan) is a novel, highly selective α_2 -adrenoceptor agonist characterised by its ability to elicit sedative, amnestic, sympatholytic and analgesic effects.¹¹⁻¹³ DEX was globally first approved for its use in intensive care unit (ICU) in 1999, and its application has been extended since to several other clinical situations.¹³⁻¹⁴ In a phase III study of DEX, the administration of 0.2–0.7 $\mu\text{g}/\text{kg}$ per hour of DEX resulted in clinically effective sedation and significantly reduced the analgesic requirements for ventilated patients in the ICU.¹³ A previous investigation has also demonstrated that DEX may be a possible alternative to MDZ for sedation.¹⁵ In general, DEX is

preferred over MDZ, and seems to provide a more stable profiling, based on the observation of cardiopulmonary condition.¹⁶ Thus, DEX is being increasingly used in the sedation of patients in various clinical situations.^{15–21} In our country, DEX was first approved for health insurance for use in the ICU in 2004. In the field of endoscopic therapy, the demand for sedation methods that offer safety during local anaesthesia procedures has been increasing because most endoscopic procedures do not require general anaesthesia, and in 2013, the use of DEX was additionally approved for use in endoscopic therapies under local anaesthesia in Japan.¹⁵ Several Japanese investigators have reported on the clinical usefulness of DEX for sedation in endoscopic submucosal dissection (ESD) for the treatment of early gastric or oesophageal cancers, or in endoscopic retrograde cholangiopancreatography (ERCP) for hepatobiliary and pancreatic diseases.^{15 22 23} To the best of our knowledge, however, there are no data on the usefulness and safety of DEX for sedation during endoscopic procedures for the treatment of OV, such as during endoscopic injection sclerotherapy (EIS).

Thus, the aim of the current study is to prospectively examine the safety and usefulness of DEX for sedation during prophylactic EIS (as a primary prophylaxis) for patients with OV.

INDICATION FOR PROPHYLACTIC ENDOSCOPIC THERAPIES FOR OV

Based on the findings of oesophagogastrroduodenoscopy, OV were graded in accordance with scores established in a previous report: specifically, F1 (small), F2 (medium) and F3 (large).²⁴ Red colour signs (RC signs) on oesophageal were evaluated by the presence of cherry red spots, haematocystic spots or red whale markings, as reported previously.²⁴ In Japan, for patients with OV that test positive for RC signs or a level of F2 or more, prophylactic endoscopic therapies are typically considered.²⁴ In patients with well-preserved liver function, EIS monotherapy or EIS and endoscopic variceal ligation (EVL) combination therapy are considered, while in cases of patients with poor liver function, such as those with ascites or hyperbilirubinemia or hypoalbuminemia, EVL monotherapy is considered.^{25–29} The time required for one endoscopic treatment for EIS is generally about 30 min. In EIS therapy, ethanolamine oleate is routinely used as a sclerosant. In patients who receive EIS, two or more sessions of EIS therapy per hospitalisation are often required, depending on the severity of OV. After endoscopic procedures, close observation of the patient, for fear of developing serious procedure-related complications, such as oesophageal perforation, liver failure and renal failure, is performed.

PATIENT ELIGIBILITY CRITERIA

- The inclusion criteria for this study are the following:

1. patients with liver cirrhosis (LC) (diagnosed by liver histology or radiologic findings) who will require prophylactic EIS for OV; presence or absence of past history for endoscopic treatments for OV are not required, and causes of LC are not limited;
 2. patients who are considered to require two or more sessions of EIS for OV;
 3. patients aged 20 years or more;
 4. patients with 7 Child-Pugh points or less;
 5. patients with a medical history for underlying liver diseases, such as antiviral therapies or liver-supporting therapies; and/or
 6. patients who provide written informed consent after full explanation about participation in the study are also to be included. Each attending physician will inform the patients about the voluntary nature of participation in the study, and the involved risks and benefits.
- Patients will be excluded if they meet one or more of the following criteria:
1. patients with poor liver function (Child-Pugh points of 8 or more);
 2. patients with severe comorbid diseases; and/or
 3. patients deemed unsuitable as study subjects.

STUDY PROTOCOL

- Study design: single-arm and open-label trial

Our study participants are subjects who will receive two or more sessions of EIS for OV. In our country, it has been conventionally practised to insert an endoscope after intravenously injecting 3 mg of MDZ and 7.5–15 mg of pentazocine (PNZ), and then to inject MDZ intravenously into the patient while observing their condition as they undergo treatment.³⁰

EIS procedures in this study include two methods: (1) sedation during endoscopic procedures will be performed using conventional methods (PNZ and MDZ), and (2) sedation during endoscopic procedures will be performed using PNZ, low-dose MDZ and DEX. These two methods were randomly assigned in the first and second EIS. The effect and safety of these two procedures on sedation will be compared. As for endoscopic treatments, the same endoscopist, who has sufficient experience in endoscopic treatments, will perform endoscopic therapies in the first and second treatments. As for the use of DEX, an infusion of 6.0 µg/kg per hour over 10 min followed by continuous infusion at 0.4 µg/kg per hour will be performed on the basis of the recommendations of manufacturers (<https://medley.life/medicine/item/1129400A1046>). Just before the continuous infusion of DEX, an intravenous infusion of PNZ (7.5–15 mg) and low-dose MDZ (1–2 mg) will be performed, and conventional procedures will be completed for the purpose of decreasing the patients' discomfort.

Case registration period

Patients will be enrolled from September 2016 to December 2017 (there may be a change depending on

registration status). At the time of manuscript submission, no patient has yet been registered.

OUTCOME MEASURES

- The primary outcome measures of this study include the following:
 - a decreasing rate in SpO₂ during endoscopic procedures;
 - increasing or decreasing rates in blood pressure during endoscopic procedures;
 - pulse fluctuation during endoscopic procedures;
 - the rate of complications, including disturbance or others;
 - Ramsey Sedation Scale values.

The degree of sedation will be totally evaluated using the Bispectral Index (BIS) monitoring system (Aspect Medical Systems, Norwood, Massachusetts, USA). The BIS monitoring system (Aspect Medical Systems) is an EEG-based assessment method that quantifies the depth of anaesthesia by analysing the EEG attached to the forehead of patients, and relies on a complex algorithm to generate an index score, which provides an objective measurement of the consciousness level in sedated subjects.^{31 32} The BIS monitoring system (Aspect Medical Systems) displays the degree of sedation as a numerical value between 0 and 100. A higher value of BIS monitoring means arousal, with the sedation state becoming deeper as the value of BIS monitoring becomes lower.^{31 32} The most appropriate value in BIS monitoring for sedation is known to be 40–60.^{31 32} In the current study, participants will be assessed using the BIS monitoring system (Aspect Medical Systems) throughout endoscopic treatments. As for body movements during endoscopic procedures, the actigram will also be used. The actigram is a device that records movement by means of an accelerometer. It is the size of a wristwatch, and can be worn without interfering with the normal activity of daily life.^{33–36}

DATA COLLECTION

A research assistant will collect data elements from patient medical records, including the following at baseline (figure 1):

- gender, date of birth and age;
- height and body weight;
- preoperative diagnosis (the severity of OV);
- previous treatments;
- information on comorbid conditions;
- results from baseline laboratory tests;
- the presence or absence of hepatic encephalopathy; and
- the presence or absence of ascites on radiologic findings.

At first endoscopic therapy

On days 1 and 3 after the first EIS, laboratory testing will be repeated. In principle, this study will be performed on an inpatient basis. Thus, we will observe the general conditions of the study participants strictly (figure 1).

At second endoscopic therapy

On days 1 and 3 after the second EIS, laboratory testing will be similarly repeated. In principle, this study will be performed on an inpatient basis, and we will observe the general conditions of the study participants strictly (figure 1).

STATISTICAL ANALYSIS

Descriptive statistics

Data will be transferred to JMP V.11 software (SAS Institute, Cary, North Carolina, USA), and all data will be checked to ensure their integrity. Data from the first and second endoscopic procedures will be compared. Quantitative variables will be compared by unpaired *t*-test or Mann-Whitney U test as appropriate. Categorical variables will be compared using the Pearson χ^2 test or Fisher's exact tests as appropriate.

Sample size

From the previous reports of Zhang *et al*¹² and Nishizawa *et al*,¹⁵ the number of patients can be set based on a significance level of 5% on two side and a statistical power of 80%. Referring to the data stated above, the estimated number of patients is set at 50.

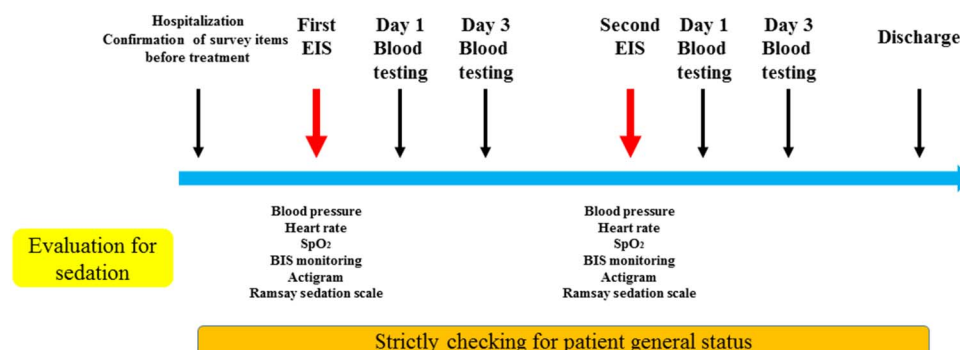


Figure 1 Study protocol. BIS, Bispectral Index; EIS, endoscopic injection sclerotherapy.

DISCUSSION

As described earlier, DEX has been increasingly preferred for the sedation of patients in various clinical situations, especially in the field of drug-induced sleep endoscopy.^{15–21} Japan is a country that actively enforces the performance of ESD and ERCP due to the large number of target patients and, thus, the usefulness of DEX during ESD or ERCP has been well verified.^{15 22 23} However, few data exist regarding the safety and usefulness of this sedative agent in EIS therapy for patients with OVs. In other words, preliminary results for these issues are currently lacking. DEX has the advantage of a more stable profiling based on cardiopulmonary status.¹⁶ To the best of our knowledge, this is the first prospective interventional study comparing the effects of MDZ and DEX on sedation for patients with OVs receiving EIS therapy. One study limitation is that this study will be based on a Japanese population, and additional studies involving other ethnic populations are necessary to further validate the efficacy of DEX and to extrapolate results to non-Japanese populations. Another limitation is that it is likely that the duration and complexity of the second EIS will be shorter and simpler than the first EIS. However, if the superiority of DEX over MDZ in terms of sedation is confirmed in this trial, sedative methods in EIS therapy for patients with OVs will be dramatically changed.

RESEARCH ETHICS APPROVAL AND DISSEMINATION

This study has received approval from the Institutional Review Board at Hyogo College of Medicine (approval no. 2324). The study protocol, informed consent forms and other submitted documents were reviewed and approved. The trial registration number is UMIN000026688 (<https://upload.umin.ac.jp/>). The authors are committed to publishing the study results as widely as possible in peer-reviewed journals, and to ensuring that appropriate recognition is provided to everyone who works on this study.

CONFIDENTIALITY

On patient recruitment, the research assistant will provide a unique scrambled identification number to each patient. Only the identification number will be used to identify patients. Sheets for data collection and any printout of electronic files will be kept in a locked filing cabinet in a secure office in the Department of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan, with limited access given.

Contributors HN, YI and HE will analyse data and have written the paper. SN is supervising this study. The other authors are collecting data. YI participated in the design of this study.

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Patient consent Obtained.

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