

## Safety and Effectiveness of Propofol Sedation during Endoscopic Retrograde Cholangiopancreatography

Minami T<sup>1\*</sup>, Sasaki T<sup>1</sup>, Serikawa M<sup>1</sup>, Ishigaki T<sup>1</sup>, Ishii Y<sup>1</sup>, Mouri T<sup>1</sup>, Yoshimi S<sup>1</sup>, Shimizu A<sup>1</sup>, Tsuboi T<sup>1</sup>, Kurihara K<sup>1</sup>, Tasugawa Y<sup>1</sup>, Miyaki E<sup>1</sup>, Nakamura R<sup>2</sup> and Chayama K<sup>1</sup>

<sup>1</sup>Department of Gastroenterology and Metabolism, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan

<sup>2</sup>Department of Anesthesiology and Critical Care, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan

\*Corresponding author: Minami T, Department of Gastroenterology and Metabolism, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan, Tel: +81-82-257-5192; Fax: +81-82-257-5194; E-mail: [char-aznable@hiroshima-u.ac.jp](mailto:char-aznable@hiroshima-u.ac.jp)

Received date: Jan 30, 2015, Accepted date: Mar 19, 2015, Published date: Mar 21, 2015

Copyright: © 2015, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

**Objectives:** Evidence of the safety and usefulness of propofol sedation during endoscopic retrograde cholangiopancreatography is presently insufficient; our study aimed to add such information.

**Methods:** Patients were sedated using propofol or midazolam during endoscopic retrograde cholangiopancreatography. The safety and utility of the sedatives were compared. Safety parameters included examination cancellation rate, circulatory depression, and respiratory depression. Utility parameters included pain level, sedation tolerability rate, and bispectral index sedation level.

**Results:** The propofol and midazolam groups contained 30 and 27 patients, respectively. No patient had an examination cancelled for sedation-related reasons. Blood pressure reduction (mmHg) was  $24.1 \pm 19.7$  and  $28.1 \pm 20.7$  in the midazolam and propofol groups, respectively, showing no significant difference. Pulse rate decrease (beats/min) was  $2.4 \pm 5.6$  and  $1.7 \pm 4.5$  in the propofol and midazolam groups, respectively, with no significant difference. Arterial carbon dioxide tension (mmHg) increased by  $10.2 \pm 6.5$  and  $10.8 \pm 7.2$  in the propofol and midazolam groups, respectively, showing no significant difference. Arterial oxygen saturation reduced by  $2.9 \pm 2.2\%$  and  $1.5 \pm 1.7\%$  in the midazolam and propofol groups, respectively. The percentage of patients with  $<92\%$  oxygen saturation showed no significant difference. The pain level was  $0.9 \pm 1.3$  in the propofol group, and significantly lower than  $2.4 \pm 2.7$  in the midazolam group. The sedation tolerability rate was 93.3% for propofol, and significantly higher than 74.1% for midazolam. The bispectral index (mean value/minimum value) was  $75.1 \pm 10.6/63.9 \pm 12.1$  for propofol, and significantly lower than  $80.5 \pm 4.2/72.0 \pm 5.0$  for midazolam.

**Conclusions:** Propofol sedation had similar safety and superior efficacy to midazolam. Stepwise adjustments of propofol dosage likely result in safer sedation.

**Keywords:** Cholangiopancreatography; Endoscopic retrograde; Conscious sedation; Drug-related; Adverse reactions; Midazolam; Propofol

### Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a procedure useful for the diagnosis and treatment of diseases of the biliary system and pancreas. However, ERCP causes various levels of pain to patients. In addition, the pain induced occasionally causes vigorous body motion, preventing safe examination and treatment. Currently in Japan, sedation is mainly performed using a benzodiazepine such as midazolam, and has been adopted for the reduction of ERCP-caused pains [1]. Although these sedatives can be safely used, their problems include an occasional insufficient effect, leading to an insufficient reduction in patient pain and disinhibition, promoting body motion [2]. In recent years, a number of reports have stated the usefulness and safety of propofol as a sedative in medical care during endoscopy [3-13]. According to these reports, propofol has a superior sedative effect and safety to midazolam in upper endoscopy, colonoscopy, and endoscopic therapy for early gastric

cancer. Sedation with propofol is expected to allow for a safe examination and therapy with less pain during ERCP as well. However, clinical evidence of the safety and usefulness of propofol sedation is insufficient, because previous reports have used various administration methods and doses [13-20]. In the present study, we compared patients sedated with propofol during ERCP to those sedated with midazolam, as is used conventionally. We sought to clarify whether propofol allows for safe sedation and if it can improve patient tolerability by reducing pain during ERCP.

### Methods

#### Patients

The subjects were patients who were sedated with propofol or midazolam during ERCP and could be evaluated regarding pain and sedation during and after the ERCP examination from among patients who underwent ERCP for a detailed examination or treatment of a disease of the biliary system or pancreas at our hospital during the period between September 2012 and April 2014 (Figure 1). Written informed consent was obtained from all participants. This study was

approved by the Human Ethics Review Committee of Hiroshima University and conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

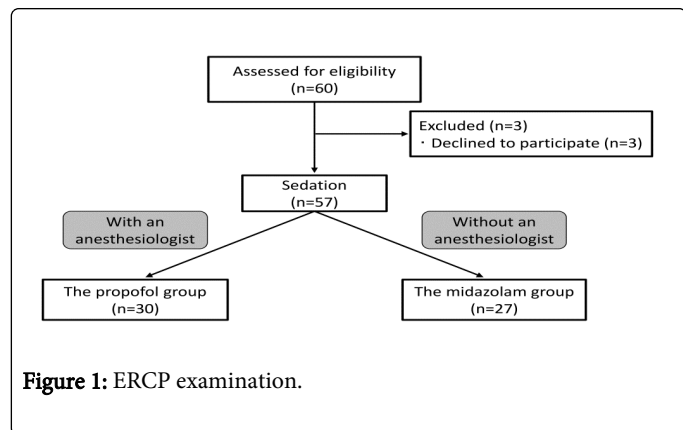


Figure 1: ERCP examination.

### Monitoring

During ERCP, blood pressure, pulse rate, PtcCO<sub>2</sub>, SpO<sub>2</sub>, ECG, and BIS were monitored. Blood pressure was measured intermittently every 5 min, while the other parameters were monitored continuously.

### Sedation regimens

Propofol and midazolam were used in the presence and absence of an anesthesiologist, respectively. Sedation was controlled by a full-time gastroenterologist in all cases. In the midazolam group, 0.06 mg/kg of midazolam and 7.5 mg of pentazocine were intravenously (i.v.) injected at the start of ERCP (Figure 2A). In cases where sedation was considered poor, as manifested by significant body motion, 0.02 mg/kg of midazolam or 7.5 mg of pentazocine was additionally injected as necessary. In the propofol group, sedation was desired to be at level-3 on the Richmond agitation-sedation scale (RASS), and the dose was adjusted in three steps. At the start of ERCP, 0.5 mg/kg of propofol and 7.5 mg of pentazocine were i.v. injected slowly followed by a continuous propofol infusion of 2.0 mg/kg/h (Figure 2B). In cases where the desired sedation could not be obtained in a few minutes, the same doses of propofol and pentazocine were slowly i.v. injected followed by maintenance of the propofol level at 4.0 mg/kg/h. In cases where the desired sedation could not be obtained in another few minutes, 0.5 mg/kg of propofol was slowly i.v. injected followed by maintenance of the propofol level at 6.0 mg/kg/h. Pentazocine was i.v. injected at a dose of 7.5 mg every 30 min, with a maximum dose of 45 mg. In both groups, oxygen was provided nasally at 2 L/min from the start of the examination. Timepidium bromide hydrate or glucagon was administered as an antispasmodic agent.

### Parameters

#### Safety and efficacy

Safety was evaluated using the cancellation rate of examinations for sedation-related reasons, as well as hemodynamic and respiratory kinetic changes. The hemodynamic changes were evaluated using changes in blood pressure and pulse rate as indicators, whereas respiratory kinetic changes were evaluated using changes in PtcCO<sub>2</sub> and SpO<sub>2</sub> as indicators.

Efficacy was evaluated using pain level, sedation level, and sedation tolerability rate. The pain level was evaluated on the day following the examination using the 0–10 numerical rating scale (NRS) (0 refers to no pain and 10 to maximum pain). The sedation level was evaluated using the BIS value during the examination as an indicator. The sedation tolerability rate was evaluated the day following the examination using an either-or question (tolerable or intolerable).

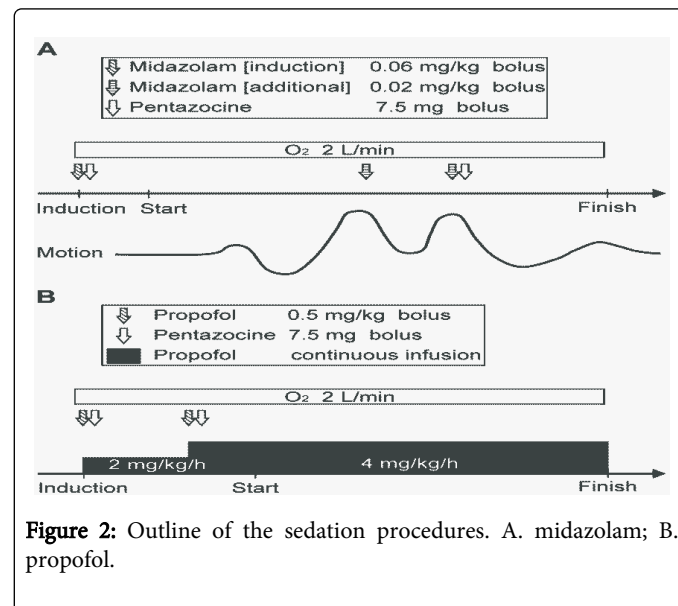


Figure 2: Outline of the sedation procedures. A. midazolam; B. propofol.

### Data collection

Patient data regarding age, sex, body height, body weight, alcohol consumption, smoking history, the presence of the regular use of benzodiazepines, and primary disease were extracted from hospital medical records. Hospital records also provided the ERCP procedure time. Information was also collected on the occurrence of cholangiography, pancreatography, biliary drainage, pancreatic duct drainage, papillotomy, lithotripsy, cholangioscopy, and intraductal ultrasonography of the bile duct.

### Statistical analysis

Sample size was estimated focused on the adverse event rate. Assuming that the adverse event rate in the propofol group was 3% based on our clinical data, when the data were analyzed with a non-inferiority margin of 10% and a power of 0.8, and the adverse event rate in the midazolam group was 10%, 26 patients were needed for each group to claim non-inferiority of propofol-midazolam. Accordingly, 60 patients (propofol, 30; midazolam, 30) were planned to be included in this trial.

All results were expressed as the mean ± standard deviation. For the statistical analysis, Wilcoxon's test or the chi-squared test were used as necessary. The difference was considered significant at P<0.05. JMP 9 (SAS Institute Inc., Cary, NC, USA) was used for the data analysis.

### Results

The propofol and midazolam groups contained 30 and 27 patients, respectively. No significant difference was seen in patient characteristics between the two groups (Table 1). The ERCP-related

procedures were not significantly different between the two groups, except that the propofol group lacked lithotripsy (Tables 2 and 3).

Cases (n)	Midazolam	Propofol	P-value
		27	30
Age (years)	65.6 ± 14.8	66.4 ± 11.8	0.713
Male : Female (n)	14:13	21:09	0.16
Body height (cm)	159.9 ± 8.1	163.3 ± 9.6	0.137
Body weight (kg)	55.2 ± 9.3	60.7 ± 14.1	0.143
Alcohol consumption>50 g/day (n)	5	10	0.205
Smoker (n)	11	15	0.483
Benzodiazepine user (n)	7	6	0.594
Disease	-	-	-
Pancreatic disease (n)	13	16	0.696
Biliary disease (n)	14	14	0.696

**Table 1:** Patient characteristics.

	Midazolam (n=27)	Propofol (n=30)	P-value
Procedure duration (min)	39.7 ± 20.6	40.2 ± 17.3	0.737
Cholangiography (n)	17	19	0.977
Pancreatography (n)	22	18	0.077
Biliary drainage (n)	12	12	0.734
Pancreatic duct drainage (n)	10	8	0.400
Papillotomy (n)	3	1	0.251
Lithotripsy (n)	4	0	0.029
Cholangioscopy (n)	2	2	0.913
IDUS† (n)	5	4	0.592
Procedure discontinuation (n)	0	0	1.000

**Table 2:** Endoscopic retrograde cholangiopancreatography procedures.

	Midazolam	Propofol	P-value
Initial	97.5 ± 0.8	97.6 ± 1.0	0.391
Mean	80.5 ± 4.2	75.1 ± 10.6	0.012
Minimum	72.0 ± 5.0	64.9 ± 12.1	0.005

**Table 3:** Sedation level (bispectral index).

### Safety

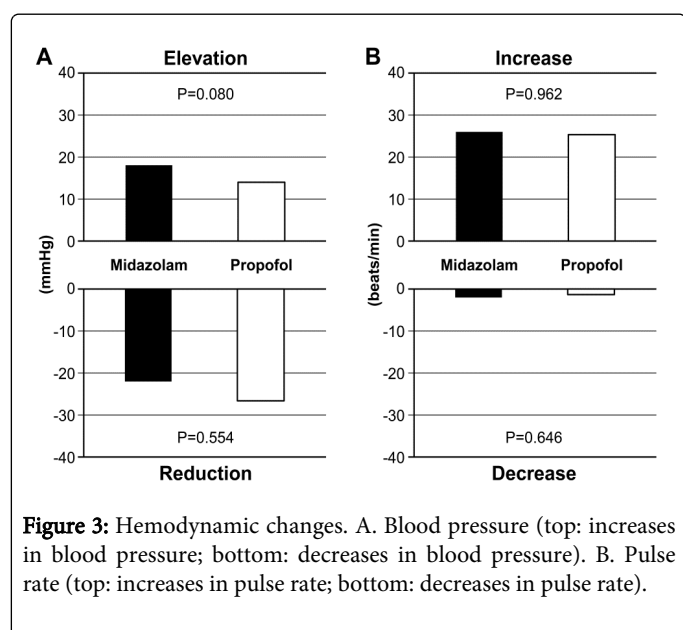
There was no patient whose examination was cancelled for a sedation-related reason in either group (Table 2). Regarding circulatory depression, changes in blood pressure (increase/decrease [mmHg]) were 17.8 ± 15.6/24.1 ± 19.7 and 14.3 ± 22.2/28.1 ± 20.7 in

the midazolam and propofol groups, respectively, showing no significant differences in values (P=0.080, 0.554) (Figure 3A). Changes in pulse rate (increase/decrease [beats/min]) were 26.4 ± 17.9/1.7 ± 4.5 and 25.5 ± 15.2/2.4 ± 5.6 in the midazolam and propofol groups, respectively, showing no significant differences in values (P=0.962, 0.646) (Figure 3B). Regarding respiratory depression, the increase in PtcCO<sub>2</sub> (mmHg) was 10.8 ± 7.2 and 10.2 ± 6.5 in the midazolam and propofol groups, respectively, with no significant difference (P=0.833) (Figure 4A). The percentages of patients with PtcCO<sub>2</sub>>50 mmHg were 44.4% and 43.5% in the midazolam and propofol groups, respectively, with no significant difference (P=0.951) (Figure 4B). The reduction in SpO<sub>2</sub> (%) was 2.9 ± 2.2 in the midazolam group, and higher (P=0.015) than that of 1.5 ± 1.7 in the propofol group (Figure 4C), whereas the percentage of patients with less than 92% SpO<sub>2</sub> showed no significant difference (P=0.940) (Figure 4D), as both groups included one such

patient (3.7% and 3.3% in the midazolam and propofol groups, respectively).

### Efficacy

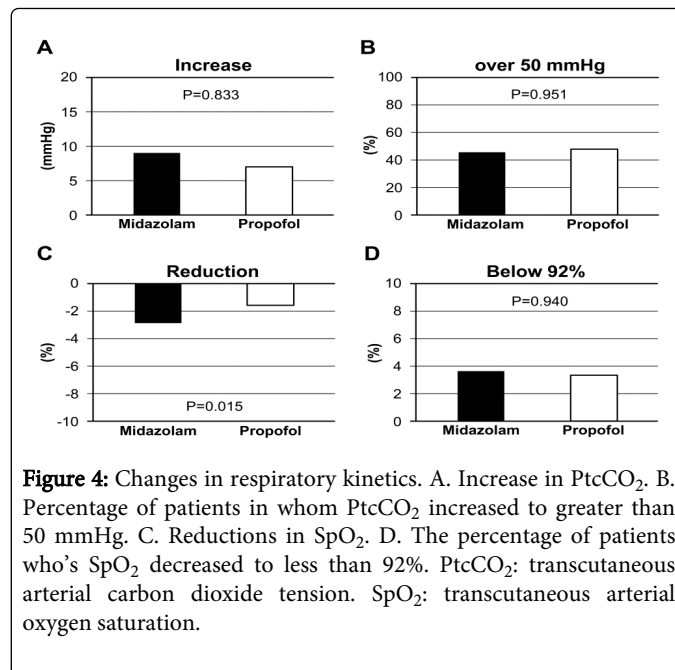
The level of patient pain evaluated using the 0–10 NRS was  $0.9 \pm 1.3$  in the propofol group, and significantly lower than the value of  $2.4 \pm 2.7$  in the midazolam group ( $P=0.030$ ) (Figure 5A). The sedation tolerability rate was 93.3% in the propofol group, and significantly higher than the 74.1% rate in the midazolam group ( $P=0.047$ ) (Figure 5B). The BIS values (initial value/mean value/minimum value) used as indicators of sedation level were  $97.5 \pm 0.8/80.5 \pm 4.2/72.0 \pm 5.0$  and  $97.6 \pm 1.0/75.1 \pm 10.6/64.9 \pm 12.1$  in the midazolam and propofol groups, respectively, showing no significant difference in the initial values, but significantly lower mean and minimum values in the propofol group ( $P=0.391/0.012/0.005$ ).



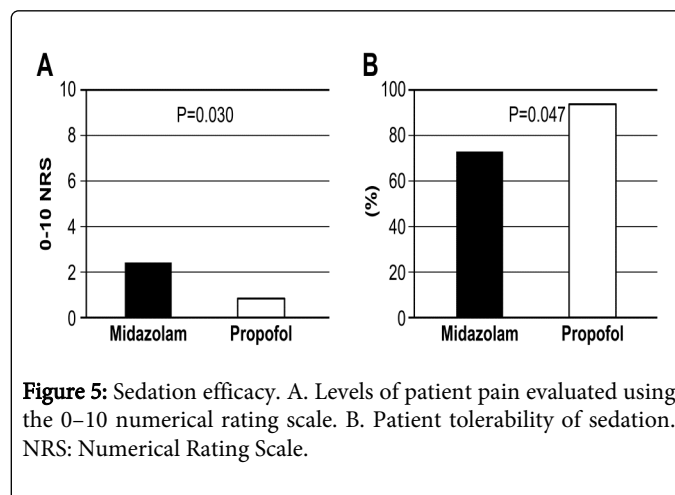
**Figure 3:** Hemodynamic changes. A. Blood pressure (top: increases in blood pressure; bottom: decreases in blood pressure). B. Pulse rate (top: increases in pulse rate; bottom: decreases in pulse rate).

### Discussion

Propofol is classified as a general anesthetic and characterized by the early development and short duration of its effect [4]. Midazolam also develops an effect relatively early, but has a longer duration than propofol, and has the problem that dosage adjustment for proper sedation requires time. On the other hand, propofol is also an agent with a narrow range between sedation and anesthesia is therefore not necessarily recommended for sedation during endoscopy. However, propofol with its strong sedating effect is likely to be useful during painful ERCP procedures because the duration of effect is short and the time required for dosage adjustment can also be shortened compared to midazolam. However, it is stipulated in Japan that the use of propofol shall be controlled by an anesthesiologist. However, it is currently impossible to administer sedatives under an anesthesiologist's control at all times during ERCP. In cases where an anesthesiologist is unavailable, the gastroenterologist engaged in ERCP must control the sedation.



**Figure 4:** Changes in respiratory kinetics. A. Increase in PtcCO<sub>2</sub>. B. Percentage of patients in whom PtcCO<sub>2</sub> increased to greater than 50 mmHg. C. Reductions in SpO<sub>2</sub>. D. The percentage of patients who's SpO<sub>2</sub> decreased to less than 92%. PtcCO<sub>2</sub>: transcutaneous arterial carbon dioxide tension. SpO<sub>2</sub>: transcutaneous arterial oxygen saturation.



**Figure 5:** Sedation efficacy. A. Levels of patient pain evaluated using the 0–10 numerical rating scale. B. Patient tolerability of sedation. NRS: Numerical Rating Scale.

For that reason, in the present study, a gastroenterologist provided sedation using propofol during ERCP in the presence of an anesthesiologist. Our sedation regimen using propofol attempts to reduce the risk of overdose by adjusting the dose in a stepwise manner and is simplified as much as possible to avoid the risk of human error. In our present study, no patient developed a sedation-related adverse event so serious that we could not avoid cancelling the examination. Regarding influences on hemodynamics, propofol caused blood pressure reductions, but minor pulse rate decreases, both of which showed no significant differences from those of midazolam. Regarding respiratory kinetics, an increase in PtcCO<sub>2</sub> was seen, likely indicating the occurrence of respiratory depression, whereas SpO<sub>2</sub> reduction remained mild. In addition, a few patients showed a large reduction in SpO<sub>2</sub>. Wehmann et al. reported that 99 patients for whom they used propofol for sedation during ERCP showed 18%, 5% and 5% average reductions in systolic blood pressure, heart rate, and SpO<sub>2</sub>, respectively and no serious reduction in blood pressure or heart rate requiring treatment, whereas a patient required temporary assisted ventilation because of respiratory depression [14]. Vargo et al. reported that

sedation using propofol during ERCP or endoscopic ultrasonography led to 13.8%, 5.9% and 6.2% average reductions in blood pressure, heart rate and SpO<sub>2</sub>, respectively and no serious reduction in these parameters requiring treatment occurred [6]. The reductions in blood pressure, pulse rate and SpO<sub>2</sub> reported in the present study were similar to the reductions in these reports. Therefore, we consider that sedation using propofol has a level of safety similar to conventional sedation using midazolam because it caused only non-serious circulatory and respiratory depression. Although propofol has a narrow range between sedation and anesthesia, serious circulatory and respiratory depression events are likely avoidable by a stepwise dose adjustment, as was used in the present study. On the other hand, propofol also showed superior usefulness to midazolam in the present study. One of the objectives of sedation is a reduction in patient pain. Sedation using propofol reduced the pain level of the patients to a greater extent than midazolam. Propofol was also superior to midazolam in terms of tolerability to sedation. Wehmann et al. reported that tolerability to propofol sedation was rated as 9 out of 10 [14]. Our result can also be interpreted to be similar to approximately 90% tolerability, indicating the high utility of propofol sedation. In the present study, the evaluation was performed on the day following ERCP. Given that midazolam can cause anterograde amnesia, propofol was shown to have a much greater effect than midazolam. The BIS measured in the present study supports the above assertions. The initial BIS value, which is the value before sedation induction, showed no significant difference, indicating no difference in the baseline state of consciousness between propofol and midazolam. On the other hand, the mean and minimum values were significantly lower, indicating deeper sedation in the propofol group than in the midazolam group. Although Kissin et al. mentioned that the BIS do not necessarily reflect the sedated condition; it is used as a specific indicator of the level of anesthesia/sedation. Johansen et al. reported that it is desirable to maintain a BIS of 45–65 in general anesthesia, whereas Hata et al. reported it is desirable to maintain a BIS of 70–75 in endoscopic therapy for early cancer of the esophagus, stomach, or colon [21–23]. The BIS of the propofol group in our present study was in a similar range to the optimal range reported above, despite the fact that we did not adjust the dose of sedatives according to the BIS in the present regimen. Moreover, we barely adjusted the dose of propofol once a proper sedation depth was induced, although changes in respiratory kinetics and hemodynamics were seen to some extent. Thus, the sedation procedure with propofol used in this study is likely to enable a stable sedation effect with small changes in respiratory kinetics and hemodynamics. The propofol administration regimen used in the present study is considered appropriate for sedation during ERCP.

In conclusion, sedation during ERCP using propofol has similar safety and superior efficacy to sedation using midazolam. The stepwise adjustment of propofol dosage makes it possible to enable safer sedation.

## References

1. Yoshino J, Igarashi Y, Ohara H, Komura N, Kato M, et al. (2010) 5th report of endoscopic complications: results of the Japan Gastroenterological Endoscopy Society survey from 2003 to 2007. *Gastroenterological Endoscopy* 52: 95-103.
2. Magni VC, Frost RA, Leung JW, Cotton PB (1983) A randomized comparison of midazolam and diazepam for sedation in upper gastrointestinal endoscopy. *Br J Anaesth* 55: 1095-1101.
3. Oei-Lim VL, Kalkman CJ, Bartelsman JF, Res JC, van Wezel HB (1998) Cardiovascular responses, arterial oxygen saturation and plasma catecholamine concentration during upper gastrointestinal endoscopy using conscious sedation with midazolam or propofol. *Eur J Anaesthesiol* 15: 535-543.
4. Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS (2000) Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol* 95: 1476-1479.
5. Krugliak P, Ziff B, Rusabrov Y, Rosenthal A, Fich A, et al. (2000) Propofol versus midazolam for conscious sedation guided by processed EEG during endoscopic retrograde cholangiopancreatography: a prospective, randomized, double-blind study. *Endoscopy* 32: 677-682.
6. Vargo JJ, Zuccaro G Jr, Dumot JA, Shermock KM, Morrow JB, et al. (2002) Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. *Gastroenterology* 123: 8-16.
7. Tohda G, Higashi S, Sakumoto H, Sumiyoshi K, Kane T (2006) Efficacy and safety of nurse-administered propofol sedation during emergency upper endoscopy for gastrointestinal bleeding: a prospective study. *Endoscopy* 38: 684-689.
8. Meining A, Semmler V, Kassem AM, Sander R, Frankenberger U, et al. (2007) The effect of sedation on the quality of upper gastrointestinal endoscopy: an investigator-blinded, randomized study comparing propofol with midazolam. *Endoscopy* 39: 345-349.
9. Froehlich F, Milliet N (2008) Propofol sedation during endoscopic procedures in private practice: the case for capnography to make 1-nurse endoscopy acceptable. *Gastrointestinal endoscopy* 67: 1008.
10. Nayar DS, Guthrie WG, Goodman A, Lee Y, Feuerman M, et al. (2010) Comparison of propofol deep sedation versus moderate sedation during endoscopy. *Dig Dis Sci* 55: 2537-2544.
11. Correia LM, Bonilha DQ, Gomes GF, Brito JR, Nakao FS, et al. (2011) Sedation during upper GI endoscopy in cirrhotic outpatients: a randomized, controlled trial comparing propofol and fentanyl with midazolam and fentanyl. *Gastrointest Endosc* 73: 45-51, 51 e1.
12. Riphaut A, Geist C, Schrader K, Martchenko K, Wehrmann T (2012) Intermittent manually controlled versus continuous infusion of propofol for deep sedation during interventional endoscopy: a prospective randomized trial. *Scand J Gastroenterol* 47: 1078-1085.
13. Sethi S, Wadhwa V, Thaker A, Chuttani R, Pleskow DK, et al. (2013) Propofol versus traditional sedative agents for advanced endoscopic procedures: A meta-analysis. *Dig Endosc* 26: 515-524.
14. Wehrmann T, Kokabpick S, Lembcke B, Caspary WF, Seifert H (1999) Efficacy and safety of intravenous propofol sedation during routine ERCP: a prospective, controlled study. *Gastrointest Endosc* 49: 677-683.
15. Jung M, Hofmann C, Kiesslich R, Brackertz A (2000) Improved sedation in diagnostic and therapeutic ERCP: propofol is an alternative to midazolam. *Endoscopy* 32: 233-238.
16. Chen WX, Lin HJ, Zhang WF, Gu Q, Zhong XQ, et al. (2005) Sedation and safety of propofol for therapeutic endoscopic retrograde cholangiopancreatography. *Hepatobiliary Pancreat Dis Int* 4: 437-440.
17. Riphaut A, Stergiou N, Wehrmann T (2005) Sedation with propofol for routine ERCP in high-risk octogenarians: a randomized, controlled study. *Am J Gastroenterol* 100: 1957-1963.
18. Kongkam P, Rerknimitr R, Punyathavorn S, Sitthi-Amorn C, Ponauthai Y, et al. (2008) Propofol infusion versus intermittent meperidine and midazolam injection for conscious sedation in ERCP. *J Gastrointest Liver Dis* 17: 291-297.
19. Paspatis GA, Chainaki I, Manolaraki MM, Vardas E, Theodoropoulou A, et al. (2009) Efficacy of bispectral index monitoring as an adjunct to propofol deep sedation for ERCP: a randomized controlled trial. *Endoscopy* 41: 1046-1051.
20. Wehrmann T, Grotkamp J, Stergiou N, Riphaut A, Kluge A, et al. (2002) Electroencephalogram monitoring facilitates sedation with propofol for routine ERCP: a randomized, controlled trial. *Gastrointestinal endoscopy* 56: 817-824.

- 
21. Johansen JW, Sebel PS (2000) Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology* 93: 1336-1344.
  22. Hata K, Andoh A, Hayafuji K, Ogawa A, Nakahara T, et al. (2009) Usefulness of bispectral monitoring of conscious sedation during endoscopic mucosal dissection. *World J Gastroenterol* 15: 595-598.
  23. Kissin I (2000) Depth of anesthesia and bispectral index monitoring. *Anesth Analg* 90: 1114-1117.