



Pain Intensity at Injection Site during Esophagogastroduodenoscopy Using Long- and Medium-Chain versus Long-Chain Triglyceride Propofol: A Randomized Controlled Double-Blind Study

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Background/Aims: The intensities of injection pain resulting from the use of long- and medium-chain triglyceride (LCT/MCT) propofol and conventional LCT propofol during esophagogastroduodenoscopy (EGD) have yet to be compared. We aimed to determine the pain intensity caused by different formulations of propofol and to evaluate the formulation that would be preferred by patients as a sedative agent during their next procedure.

Methods: This study was a single-center, randomized, controlled, and double-blind trial. Pain intensity was estimated 30 seconds after propofol injection by an examiner who was blinded to the group assignment using a numeric (0–10) pain rating scale (NPRS). After 1 week, the patients were asked whether they could recall the pain and were willing to receive the same agent for their next EGD.

Results: One hundred twenty-nine patients were randomly assigned to LCT/MCT or LCT group. Although there was no significant difference in pain incidence between the LCT/MCT and LCT groups (52.9% vs 65.6%, $p=0.156$), the pain intensity was significantly lower in the LCT/MCT group (NPRS median [interquartile range]; 1 (0–2) vs 2 (0–5), $p=0.005$). After 1 week, fewer patients in the LCT/MCT group recalled the pain (19.1% vs 63.9%, $p<0.001$) and more patients in the LCT/MCT group were more willing to use the same agent for their next procedure (86.8% vs 72.1%, $p=0.048$) than in the LCT group.

Conclusions: LCT/MCT propofol significantly reduced injection pain intensity compared to LCT propofol during EGD and preferred by patients as a sedative agent during their next EGD. (*Gut Liver* 2021;15:562-568)

Key Words: Endoscopy; Medium chain triglyceride; Propofol; Pain

INTRODUCTION

Sedation is considered an integral factor during gastrointestinal (GI) endoscopy to improve the examination accuracy and increase the patients' willingness to undergo the procedure.¹ Although several agents are administered during endoscopy including propofol, benzodiazepines, and opioids, propofol is considered an essential agent during this process owing to its pharmacokinetic characteristics along with its sedative and amnestic properties.²⁻⁴ Propofol can cross the blood brain barrier rapidly due to

its high lipophilic activity, leading to an onset of action within 30 to 60 seconds.⁵ It also has a short recovery profile due to rapid metabolism, with effects lasting for 4 to 8 minutes.⁶ Several meta-analyses have shown that propofol provides clear benefits including better sedation, higher patient satisfaction, and comparable or lower cardiopulmonary complications compared with other agents during GI endoscopy.⁷⁻¹⁰ In addition, propofol improves the diagnostic accuracy of esophagogastroduodenoscopy (EGD), which can lead to higher quality endoscopy from the examiner's perspective.¹¹ Many studies have demonstrated

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the tolerability and safety of propofol administered by non-anesthesiologists during GI endoscopy.¹²⁻¹⁵

One of the main drawbacks of propofol is that it may cause local pain at the injection site, with an incidence rate of over 60% in patients.¹⁶ The intensity of the pain is severe enough to be unpleasant for patients and some patients consider the induction of anesthesia to be the most painful part of the perioperative period.¹⁷ Since propofol is water insoluble, it is conventionally prepared as a 1% solution in a fat emulsion containing 10% soybean oil comprised of long-chain triglycerides (LCTs), which provoke pain on injection.¹⁶ A formulation with a long- and medium-chain triglyceride (LCT/MCT) emulsion was introduced to diminish the injection pain, incorporating 10% LCT/MCT propofol formulated at a 1:1 ratio in the carrier emulsion.¹⁸ It has been reported that LCT/MCT propofol reduces pain and has equivalent efficacy to LCT propofol during general anesthesia, which requires a deeper and longer sedation period than GI endoscopic procedures.^{19,20} However, the pain severity and patient preferences for LCT/MCT propofol during GI endoscopy have yet to be studied.

EGD is commonly performed for the diagnosis of various GI diseases and cancer screening, especially in regions with a high incidence of gastric cancer such as China, Japan, and Korea.^{21,22} Individuals in these areas may undergo EGD repeatedly as nationwide screening programs recommend the procedure every 2 to 3 years.^{23,24} Therefore, it is considered clinically relevant to evaluate the injection site pain when propofol is used and to evaluate patients' willingness to repeat the procedure with propofol. This study aimed to evaluate the provocation rate and intensity of injection pain for different propofol formulations as well as the influence of injection pain on patient sedative preferences for their next EGD.

MATERIALS AND METHODS

1. Population

Patients over the age of 18 who were scheduled to undergo EGD under sedation at a tertiary referral hospital in Daegu, South Korea between January 2016 and April 2017 were eligible for the study. The exclusion criteria were as follows: significant systemic disease in accordance with the American Society of Anesthesiologists classification III-IV; history of allergic reactions to any of the study drugs (eggs and soybeans); chronic opioid analgesic use; psychiatric disorder; arrhythmia; pregnancy; and/or difficult venous cannulation at the dorsal hand. Patients who declined to participate were also excluded. This study was approved by the Institutional Review Board of Keimyung University

Hospital (IRB number: DSMC 2014-08-026-001) and all patients provided written informed consent before participating in the study. The study protocol was registered by the principal investigator (E.S.K.) at ClinicalTrials.gov (October 5, 2015, NCT02567916) prior to patient enrollment.

2. Study design and randomization

This study was a single-center, randomized-control, and double-blind trial. On arrival at the endoscopy suite, patients were randomly assigned to the LCT/MCT (1% Fresofol®; Fresenius Kabi, Graz, Austria) or LCT (Pofol®; Jeil, Seoul, Korea) propofol groups according to a random number generated using Excel (Microsoft, Redmond, WA, USA). All endoscopists and nurses in the endoscopy unit were trained and followed sedation guidelines for the Accreditation of Qualified Endoscopy Units issued by the Korean Society of Gastrointestinal Endoscopy.²⁵ One specialized nurse prepared the drug and knew of the patient assignments; however, the endoscopists and nurses involved in the study were blinded. The patients in the trial did not receive premedication before arrival at the endoscopy unit. A 20-gauge cannula was inserted into the largest dorsal vein in the non-dominant hand, and propofol was injected by registered nurses under endoscopist supervision. The initial dose of propofol was measured at 0.5–1 mg/kg (administered for 10 seconds) and additional injection doses (10–20 mg) were administered intermittently as required for adequate endoscopic study.²

Patients from both groups received supplemental oxygen (2 L/min) via a nasal cannula. The heart rate and oxygen saturation were monitored using a pulse oximeter. Arterial blood pressure was measured with a sphygmomanometer every three minutes during the procedures and in the recovery room. Following the procedure, full recovery from sedation was confirmed based on the Aldrete Scores by dedicated nurses in the recovery room.²⁶ One week after the procedure, the patients revisited the outpatient clinic and a nurse who was blinded to group allocation asked whether they could recall the pain (yes or no) and their willingness to receive the same sedative agent for their next EGD (yes or no). If the patients could not visit the hospital, the same question was asked via a phone call.

3. Outcome measures

Pain intensity was estimated 30 seconds after propofol injection using a numeric (0–10) pain rating scale (NPRS) by an examiner (Y.J.L.) who was blinded to the group assignment. A score of zero was considered indicative of no pain while scores of 1–10 were indicative of pain (pain provocation). Overall, the sedation degree for optimal EGD examination was assessed during the procedure with

a five-point scale (excellent, does not respond to deep stimulus; good, responds only after mild prodding or shaking; moderate, responds only after name is called; poor, alert state with responds readily to name spoken; unacceptable, difficulty in proceeding the examination due to agitated state) by an endoscopist (K.B.C.) who was blinded to the group assignment.²⁷ A heart rate of less than 50 beats per

minute, a systolic blood pressure below 90 mm Hg, and/or oxygen saturation below 85% during EGD were considered to be adverse events related to sedation.

4. Statistical analysis

Sample size was calculated based on a previous study that reported a 26% difference in pain incidence between

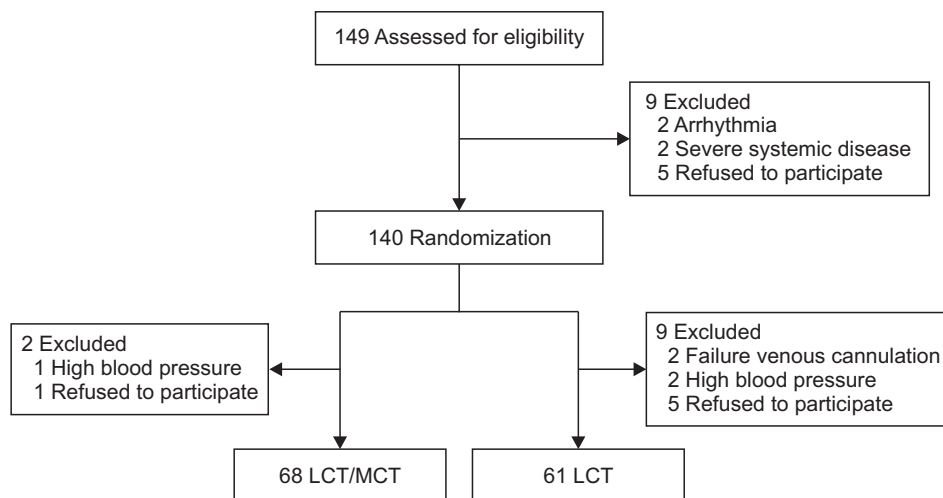


Fig. 1. Patient flowchart. LCT, long-chain triglycerides; MCT, medium-chain triglycerides.

Table 1. Baseline Characteristics between the LCT/MCT Propofol Group and the LCT Propofol Group

Characteristics	LCT/MCT (n=68)	LCT (n=61)	p-value
Age, yr	56.40±11.80	58.25±11.48	0.374
Male sex	33 (48.5)	28 (45.9)	0.860
Height, cm	162.21±9.14	160.97±8.03	0.417
Weight, kg	61.28±9.90	60.54±11.06	0.692
Underlying disease			
Hypertension	16 (23.5)	14 (23.0)	1.000
Diabetes mellitus	7 (10.3)	9 (14.8)	0.594
Chronic kidney disease	1 (1.5)	1 (1.6)	1.000
Ischemic heart disease	6 (8.8)	2 (3.3)	0.279
Heart failure	1 (1.0)	2 (3.3)	0.602
Liver cirrhosis	4 (5.9)	1 (1.6)	0.369
Cerebral vascular attack	0	3 (4.9)	0.103
Others	11 (16.2)	14 (23.0)	0.377
Indication			0.605
Screening	39 (57.4)	29 (47.5)	
Follow up of ESD for gastric tumor	16 (23.5)	18 (29.5)	
Follow up of peptic ulcer	2 (2.9)	3 (4.9)	
Gastrointestinal symptoms	9 (13.2)	11 (18.0)	
Anemia	2 (2.9)	0	
ASA classification			0.101
I	60 (88.2)	59 (96.7)	
II	8 (11.8)	2 (3.3)	
Experience of previous sedative EGD	62 (91.2)	57 (93.4)	0.748
Administered dosage, mg			
Initial dose	45.44±16.43	48.52±18.69	0.321
Total dose	128.32±32.96	139.02±39.36	0.100

Data are presented as mean±SD or number (%).

LCT, long-chain triglyceride; MCT, medium-chain triglyceride; ESD, endoscopic submucosal dissection; ASA, American Society of Anesthesiologists; EGD, esophagogastroduodenoscopy.

LCT and LCT/MCT propofol (62% vs 37%) under general anesthesia.¹⁸ Considering a 10% dropout rate and 80% power to detect such as difference at a two-sided significance level of 0.05, a total of 60 patients were needed per group. Statistical analyses were performed using R package version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Values are expressed as mean±standard deviation or median with interquartile range (IQR). The chi-square test was used to analyze categorical variables and the Student t-test was used to analyze differences in the continuous variables. Fisher exact test was used to calculate differences in pain recall and willingness, and the Mann-Whitney U-test was used to evaluate NPRS differences. Two-way analysis of variance was used to adjust confounders that might affect the pain score. All tests were two-sided and $p < 0.05$ was regarded as statistically significant.

RESULTS

1. Baseline characteristics and dosage

The patient flowchart is presented in Fig. 1. Among 149 eligible patients, 129 were randomly allocated to the LCT/MCT (n=68) and LCT (n=61) groups. There was no significant difference between the groups in age, sex, height,

Table 2. Degree of Sedation and Occurrence of Adverse Events during Esophagogastroduodenoscopy in the LCT/MCT Propofol Group and the LCT Propofol Group

Efficacy and safety of propofol injection	LCT/MCT (n=68)	LCT (n=61)	p-value
Degree of sedation			0.170
Excellent	23 (33.8)	31 (50.8)	
Good	38 (55.9)	22 (36.1)	
Moderate	5 (7.4)	7 (11.5)	
Poor	1 (1.5)	1 (1.6)	
Unacceptable	1 (1.5)	0	
Hypoxemia (SpO ₂ <85%)	2 (2.9)	2 (3.3)	0.999

Data are presented as number (%).

LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

Table 3. The Provocation Rate and Pain Score after the Administration of LCT/MCT and LCT Propofol during Esophagogastroduodenoscopy

Injection pain of propofol	LCT/MCT (n=68)	LCT (n=61)	p-value
Provocation of pain, No. (%)	36 (52.9)	40 (65.6)	0.156
Pain score			
Median (IQR)	1 [0–2]	2 [0–5]	0.005
Mean±SD	1.43±1.97	2.93±3.13	0.002

LCT, long-chain triglyceride; MCT, medium-chain triglyceride; IQR, interquartile range.

body weight, comorbidities, indication of EGD, and American Society of Anesthesiologists classification (Table 1). Half of the patients underwent EGD for the screening of gastric cancer (LCT/MCT 57.4% vs LCT 47.5%, $p=0.605$). Most patients had undergone EGD under sedation previously (LCT/MCT 91.2% vs LCT 93.4%, $p=0.748$). The initial and total dosage of propofol did not differ between the groups (Table 1).

2. Outcomes between different propofol formulations

Most patients exhibited excellent or good sedation levels with no significant differences between the LCT/MCT and LCT groups (89.7% vs 86.9%, $p=0.170$) (Table 2). Four patients experienced hypoxemia (SpO₂ <85%) during the procedure, with no difference between the groups (Table 2). The number of patients with pain provocation seemed to be lower in the LCT/MCT group than in the LCT group (52.9% vs 65.6%, $p=0.156$) (Table 3) but there was no statistical significance. Pain intensity was significantly lower in the LCT/MCT group than in the LCT group, indicated by the median (IQR) NPRS (1 [0–2] vs 2 [0–5], $p=0.005$) (Table 3, Fig. 2) and mean±standard deviation NPRS (1.43 ± 1.97 vs 2.93 ± 3.13 , $p=0.002$) (Table 3).

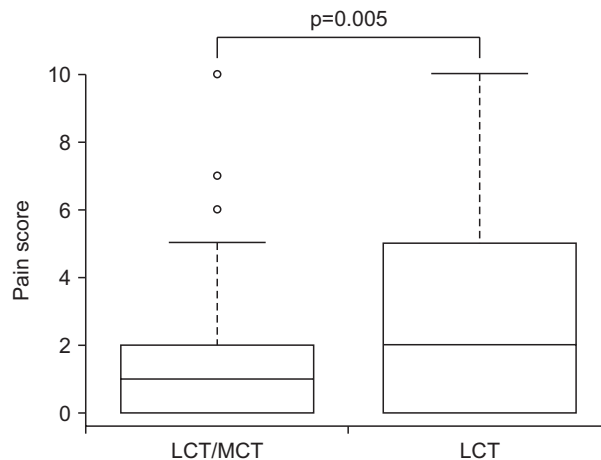


Fig. 2. Pain scores between LCT/MCT and LCTs propofol groups. LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

Table 4. Recall of Pain and Willingness to Use the Same Agent during the Next Examination

Patient's preference of propofol	LCT/MCT (n=68)	LCT (n=61)	p-value
Recall of pain	13 (19.1)	39 (63.9)	0.001
Willingness to use the same agent for the next examination	59 (86.8)	44 (72.1)	0.048

Data are presented as number (%).

LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

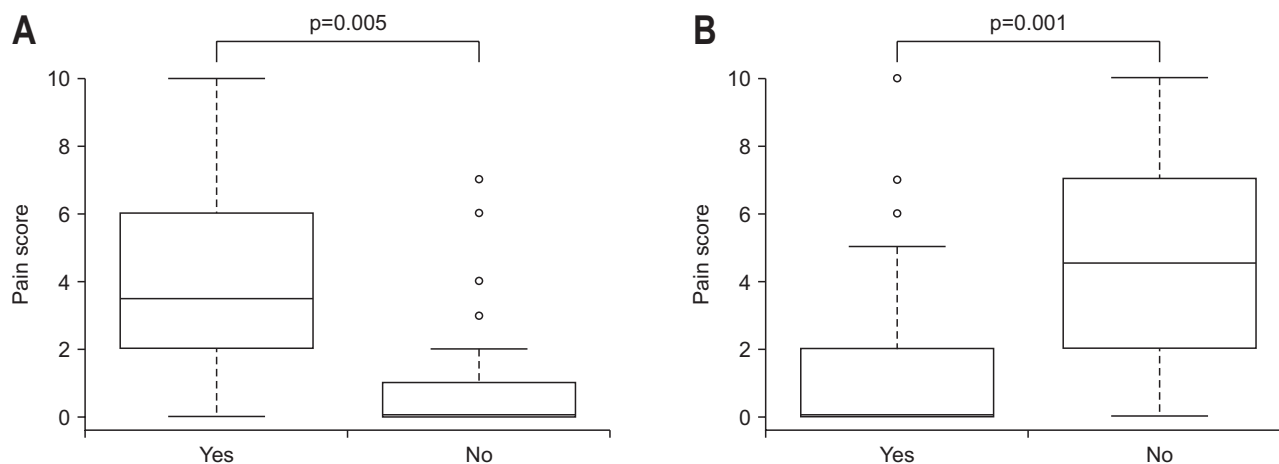


Fig. 3. Association of the pain score with the answers to the questions “Do you remember the pain?” (A) and “Are you willing to use the same sedative agent for the next examination?” (B). Comparison was conducted after adjustment for confounders, including age, sex, comorbidities, indication for endoscopy, propofol formulation (LCT and LCT/MCT), body weight, and American Society of Anesthesiologists classification. LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

3. Patients’ recall of pain perception and willingness to receive the same propofol formulation for next EGD

The patients’ recall of pain perception 1 week following the procedure was evaluated as a part of this study. Patients in the LCT group were significantly more likely to remember the injection pain than those in the LCT/MCT group (63.9% vs 19.1%, $p < 0.001$) (Table 4). The proportion of patients who were willing to receive the same sedative agent for their next EGD was significantly higher in the LCT/MCT group than in the LCT group (86.8% vs 72.1%, $p = 0.048$) (Table 4). Pain recall and the preference for a sedative agent may be associated with the intensity of injection pain as the pain score was significantly higher among patients who recalled pain than among those who did not (NPRS median [IQR]; 4 [2–6] vs 0 [0–1], $p = 0.005$) (Fig. 3A). In addition, the pain score was significantly lower among patients who showed a willingness to use the same agents than among those who did not (NPRS median [IQR]; 0 [0–2] vs 5 [2–7], $p = 0.001$) (Fig. 3B). These differences were statistically significant after the adjustment of other confounding factors including age, sex, comorbidities, indication of EGD, propofol formulation (LCT and LCT/MCT), body weight, and American Society of Anesthesiologists classification.

DISCUSSION

This single-center, randomized-control, and double-blind trial showed that LCT/MCT propofol significantly decreased the intensity of injection pain compared with conventional LCT propofol with no changes in the seda-

tion level or adverse events during EGD. Patients administered with LCT/MCT propofol were less likely to recall the injection pain 1 week following the procedure and were more willing to use the same sedative agent for their next EGD. Patients who were willing to use the same sedative agents for their next EGD reported significantly lower pain scores than those who were not, suggesting that the injection pain from propofol may affect the preference for the sedative agent in further examinations. To the best of our knowledge, the current study is the first of its kind to compare injection pain and patient preference between LCT/MCT and LCT propofol during EGD in a GI endoscopy unit under a condition other than general anesthesia.

Although the precise mechanism for propofol-induced pain remains unclear, the aqueous phase of free propofol is considered to be one of the main causes of the pain.²⁸ A potential solution to reduce the injection pain from LCT/MCT propofol is to use a unique lipid component that ameliorates the aqueous phase of propofol.¹⁷

A previous study has shown that the incidences of pain caused by LCT/MCT and LCT propofol under general anesthesia were 36.7% and 61.8%, respectively, which were lower than those observed in this study (52.9% and 65.6%).¹⁸ This difference was unexpected given that the initial dose of propofol in the previous study (1.5 mg/kg) was high compared with that in the present study (0.5–1 mg/kg). This could be explained, in part, by differences in the intravenous site location as the large vein in the antecubital area of the forearm reduces injection pain compared to the small vein in the hand.¹⁷ The injection was administered in the dorsal hand of patients in this study, whereas the injection was administered in the forearm of patients in the former study, which could have resulted in different

degrees of pain perception.

It should be noted that propofol can induce short-term retrograde amnesia including no recall of word which was read before administering propofol.²⁹ Among 76 patients who reported pain at the administration of propofol, 24 (31.6%) did not remember the pain 1 week following the procedure, consistent with a previous study that reported amnesia in 30.5% of cases following injection pain after EGD.³⁰ In this study, significantly more patients in the LCT/MCT group presented with no recalling of injection pain compared to the corresponding number of patients in the LCT group (23/36 [63.8%] vs 1/40 [2.5%]). Considering the same dose of propofol was used in both groups, pain intensity may affect this difference in the recall of pain perception after 1 week. The significantly higher pain score reported by patients who recalled the pain after adjusting for other confounders supports this hypothesis. However, this data should be interpreted cautiously because no recall of pain does not necessarily mean the amnesia. As there is no universal assessment tool of amnesia related with propofol, it is hard to consider no recall of pain as the evidence of retrograde amnesia.

Injection pain related to propofol is a common problem during both general anesthesia and non-operational room anesthesia for procedures like GI endoscopy.^{30,31} In contrast to general anesthesia administered in the operation room, sedation for EGD may be performed multiple times over a patient's lifetime, particularly in East Asian countries. More than 90% of patients had previously undergone EGD under sedation in the present study. Given that propofol is the most commonly used agent for sedation during GI endoscopy, it is crucial to address the common limitation of propofol to improve patients' satisfaction during the procedure.^{3,4} The findings from this study demonstrate a greater willingness to use the same sedative agents for the next EGD in the LCT/MCT group compared to that in the conventional LCT group. This indicates that reducing pain may improve patients' satisfaction during EGD and is supported by the fact that lower pain intensity was associated with higher willingness to utilize the same sedative agent. Another strategy for reducing the injection pain of propofol would be preinjection of intravenous lidocaine.^{30,31}

Our study has some limitations. We did not evaluate the patient's perception of sedation depth and painful memory of procedure. Furthermore, we did not obtain the short-term and long-term side effects in patients' perspective. We surmised that these factors might also influence patients' preference for a sedative agent in further procedures.

In conclusion, LCT/MCT propofol reduces injection pain intensity compared with conventional LCT propofol with no changes in the sedation level and adverse events

during EGD. Patients that receive LCT/MCT propofol are less likely to remember the pain and more willing to use the same agent for the next EGD. As pain intensity is associated with later pain recall and the preference for sedative agents in further examinations, methods to reduce propofol-related pain may improve patients' satisfaction during EGD under sedation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: E.S.K. Data curation: E.S.K. Formal analysis: E.S.K., J.S.L. Methodology: E.S.K. Patient enrollment: E.S.K., K.B.C., K.S.P., Y.J.L., J.Y.L. Writing - original draft: J.S.L. Writing - review & editing: E.S.K. Approval of final manuscript: all authors.

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REFERENCES

1. Cohen LB, Ladas SD, Vargo JJ, et al. Sedation in digestive endoscopy: the Athens international position statements. *Aliment Pharmacol Ther* 2010;32:425-442.
2. Nishizawa T, Suzuki H. Propofol for gastrointestinal endoscopy. *United European Gastroenterol J* 2018;6:801-805.
3. Lee CK, Dong SH, Kim ES, et al. Room for quality improvement in endoscopist-directed sedation: results from the first nationwide survey in Korea. *Gut Liver* 2016;10:83-94.
4. Dumonceau JM, Riphaus A, Schreiber F, et al. Non-anesthesiologist administration of propofol for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates Guideline: updated June 2015. *Endoscopy* 2015;47:1175-1189.
5. Shafer A, Doze VA, Shafer SL, White PF. Pharmacokinetics

- and pharmacodynamics of propofol infusions during general anesthesia. *Anesthesiology* 1988;69:348-356.
6. Moon SH. Sedation regimens for gastrointestinal endoscopy. *Clin Endosc* 2014;47:135-140.
 7. Qadeer MA, Vargo JJ, Khandwala F, Lopez R, Zuccaro G. Propofol versus traditional sedative agents for gastrointestinal endoscopy: a meta-analysis. *Clin Gastroenterol Hepatol* 2005;3:1049-1056.
 8. Wang D, Chen C, Chen J, et al. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. *PLoS One* 2013;8:e53311.
 9. Sethi S, Wadhwa V, Thaker A, et al. Propofol versus traditional sedative agents for advanced endoscopic procedures: a meta-analysis. *Dig Endosc* 2014;26:515-524.
 10. Nishizawa T, Suzuki H, Hosoe N, Ogata H, Kanai T, Yahagi N. Dexmedetomidine vs propofol for gastrointestinal endoscopy: a meta-analysis. *United European Gastroenterol J* 2017;5:1037-1045.
 11. Meining A, Semmler V, Kassem AM, et al. The effect of sedation on the quality of upper gastrointestinal endoscopy: an investigator-blinded, randomized study comparing propofol with midazolam. *Endoscopy* 2007;39:345-349.
 12. Rex DK, Deenadayalu VP, Eid E, et al. Endoscopist-directed administration of propofol: a worldwide safety experience. *Gastroenterology* 2009;137:1229-1237.
 13. Vargo JJ, Cohen LB, Rex DK, Kwo PY. Position statement: nonanesthesiologist administration of propofol for GI endoscopy. *Gastrointest Endosc* 2009;70:1053-1059.
 14. Poincloux L, Laquière A, Bazin JE, et al. A randomized controlled trial of endoscopist vs. anaesthetist-administered sedation for colonoscopy. *Dig Liver Dis* 2011;43:553-558.
 15. Rex DK, Heuss LT, Walker JA, Qi R. Trained registered nurses/endoscopy teams can administer propofol safely for endoscopy. *Gastroenterology* 2005;129:1384-1391.
 16. Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. *Anesth Analg* 2000;90:963-969.
 17. Jalota L, Kalira V, George E, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. *BMJ* 2011;342:d1110.
 18. Ohmizo H, Obara S, Iwama H. Mechanism of injection pain with long and long-medium chain triglyceride emulsive propofol. *Can J Anaesth* 2005;52:595-599.
 19. Suzuki H, Miyazaki H, Andoh T, Yamada Y. Propofol formulated with long-/medium-chain triglycerides reduces the pain of injection by target controlled infusion. *Acta Anaesthesiol Scand* 2006;50:568-571.
 20. Theilen HJ, Adam S, Albrecht MD, Ragaller M. Propofol in a medium- and long-chain triglyceride emulsion: pharmacological characteristics and potential beneficial effects. *Anesth Analg* 2002;95:923-929.
 21. Zhang X, Li M, Chen S, et al. Endoscopic screening in Asian countries is associated with reduced gastric cancer mortality: a meta-analysis and systematic review. *Gastroenterology* 2018;155:347-354.
 22. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87-108.
 23. Fock KM, Talley N, Moayyedi P, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol* 2008;23:351-365.
 24. Suh YS, Lee J, Woo H, et al. National cancer screening program for gastric cancer in Korea: nationwide treatment benefit and cost. *Cancer* 2020;126:1929-1939.
 25. Lee JK, Lee YJ, Cho JH, et al. Updates on the sedation for gastrointestinal endoscopy. *Clin Endosc* 2019;52:451-457.
 26. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg* 1970;49:924-934.
 27. Cohen LB, Delegee MH, Aisenberg J, et al. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007;133:675-701.
 28. Nakane M, Iwama H. A potential mechanism of propofol-induced pain on injection based on studies using nafamostat mesilate. *Br J Anaesth* 1999;83:397-404.
 29. Miner JR, Bachman A, Kosman L, Teng B, Heegaard W, Birros MH. Assessment of the onset and persistence of amnesia during procedural sedation with propofol. *Acad Emerg Med* 2005;12:491-496.
 30. Kwon JS, Kim ES, Cho KB, et al. Incidence of propofol injection pain and effect of lidocaine pretreatment during upper gastrointestinal endoscopy. *Dig Dis Sci* 2012;57:1291-1297.
 31. Borazan H, Sarıtaş TB, Sarkılar G. Incidence of propofol injection pain and effect of lidocaine pretreatment during upper gastrointestinal endoscopy. *Dig Dis Sci* 2012;57:1725-1726.