

A comparison of sedation protocols for gastric endoscopic submucosal dissection: moderate sedation with analgesic supplementation vs analgesia targeted light sedation

Y. C. Yoo^{1†}, C. H. Park^{2†}, S. Shin¹, Y. Park², S. K. Lee^{2‡*} and K. T. Min^{1‡*}

¹ Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute and ² Division of Gastroenterology, Department of Internal Medicine, Yonsei Institute of Gastroenterology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea

* Corresponding author. E-mail: sklee@yuhs.ac (S.K.L.); kmin501@yuhs.ac (K.T.M.)

Editors' key points

- This retrospective study compared two sedation methods using propofol and remifentanyl—moderate sedation with analgesic supplementation (MSAS) and analgesia targeted light sedation (ATLS)—during endoscopic submucosal dissection (ESD).
- The ATLS protocol reduces the incidence of oxygen desaturation events without affecting ESD performance compared with the MSAS protocol.
- This should be investigated with an appropriately powered, prospective, randomized controlled trial.

Background. Moderate to deep sedation has been recommended during endoscopic submucosal dissection (ESD). However, it is often accompanied by adverse events such as respiratory depression or aspiration pneumonia. This study investigated the respiratory complications and ESD outcomes of two sedation protocols: moderate sedation with analgesic supplementation (MSAS) and analgesia targeted light sedation (ATLS).

Methods. The clinical data of 293 patients who underwent ESD between May and December 2012 were reviewed. During the first 4 months, 155 patients were managed by moderate sedation [Modified Observer Assessment of Alertness/Sedation (MOAA/S) at 2–3] with the MSAS protocol. During the latter period, 138 patients were managed using the ATLS protocol (MOAA/S at 4–5). For both protocols, propofol and remifentanyl were infused for sedation and pain control, respectively.

Results. The ATLS protocol required less propofol [22.9 (SD 17.3) vs 88.1 (44.0) $\mu\text{g kg}^{-1} \text{min}^{-1}$, $P < 0.001$] and more remifentanyl [6.8 (SD 3.1) vs 4.9 (3.0) $\mu\text{g kg}^{-1} \text{hr}^{-1}$, $P < 0.001$] than the MSAS protocol. The desaturation events during the procedure occurred significantly less often (2.2 vs 12.9%, $P = 0.001$) and recovery was significantly faster [19.7 (SD 4.8) vs 27.9 (16.0) min, $P < 0.001$] with the ATLS protocol than with the MSAS protocol. The incidence of aspiration pneumonia with the ATLS protocol was 1.4% compared with 5.2% with the MSAS protocol ($P = 0.109$). There were no differences in outcomes and complications of ESD.

Conclusion. The ATLS protocol reduced the incidence of desaturation events without affecting ESD performance compared with the MSAS protocol. There was also a trend towards a low incidence of aspiration pneumonia with the ATLS protocol.

Keywords: aspiration pneumonia; conscious sedation; endoscopy; moderate sedation

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Today, endoscopic submucosal dissection (ESD) has become the standard care for treatment of early gastric neoplasia.¹ Due to the prolonged procedure time and intense pain caused by distension, incision, and dissection of the gastric wall during ESD, a deeper sedation level than conventional endoscopic procedures has been recommended.² Sedation, however, has a risk of adverse events, including respiratory depression and aspiration pneumonia. Our previous study with 1367 patients who underwent ESD demonstrated that continuous propofol and remifentanyl infusion by the anaesthetist

increased the en bloc and complete resection rate, but unfortunately it also increased the incidence of aspiration pneumonia compared with intermittent midazolam and propofol injection by endoscopists.¹ Although post-sedation aspiration pneumonia is usually easily resolved, cases of mortality have been reported.³ Our other previous study that evaluated sedation methods during therapeutic endoscopy, including gastrointestinal stenting and endoscopic retrograde cholangiopancreatography, demonstrated that combining fentanyl with propofol reduced the risk of respiratory events compared with propofol

[†]Y.C. Yoo and C. H. Park contributed equally to this work as first authors.

[‡]S. K. Lee and K. T. Min contributed equally to this work as co-corresponding authors.

monosedation.⁴ In this regard, anaesthetists and endoscopists are faced with a dilemma in selecting the appropriate sedation and analgesic levels for successful ESD. Although it is unknown whether light sedation with sufficient analgesia would interfere with the procedure, moderate to deep sedation is generally accepted for ESD.^{5–6} The first aim of our study was to see if a change in anaesthesia practice resulted in a difference in respiratory outcome, including aspiration pneumonia. The second aim of the study was to explore how successful the ESD procedure was in terms of the endoscopist being able to excise the tumour according to the sedation technique.

Methods

Study population and design

This retrospective study analysed data from 293 patients who received ESD for gastric lesions under sedation with either moderate sedation with analgesic supplementation (MSAS, $n=155$) or analgesia targeted light sedation (ATLS, $n=138$). ESD for early gastric cancer was performed based on the expanded indication proposed by Gotoda and colleagues.⁷ In addition, patients who were diagnosed with adenoma underwent ESD when there was a chance of foci of malignancy. In cases of gastric subepithelial lesions, including gastrointestinal stromal tumours and neuroendocrine tumours, ESD was performed when the lesions originated from the submucosal layer upon endoscopic ultrasonography. The databases analysed for this study were collected prospectively for hospital quality control between May and December 2012 at a tertiary university hospital in Seoul, Korea. The protocol was changed from MSAS to ATLS in September 2012 as part of an effort to reduce aspiration pneumonia.

All ESD cases included in this study were those performed under sedation by experienced attending anaesthetists. Sedation depth was targeted at 2 or 3 on the Modified Observer Assessment of Alertness/Sedation (MOAA/S) scale in the MSAS protocol and at 4 or 5 in the ATLS protocol (Table 1).⁸ Sedation was carried out with an initial bolus and subsequent infusion of propofol (Pofol®, Dongkook Pharmaceutical, Seoul, Korea). Remifentanyl (Ulitiva®, GlaxoSmithKline, Genval, Belgium) was infused continuously to control pain. The regimens for

initiation of sedation, basal, and adjustment for maintenance in both protocols are described in Table 1. Sedation depth was essentially assessed by verbal and tactile stimulation at at least four time points: just before the insertion of the endoscope, after insertion of the endoscope and before the first incision, immediately after the first incision, and at the end of dissection. In the MSAS group, additional assessments of sedation depth and adjustment of the regimens were done when patients showed signs of undersedation or reactions to discomfort and/or pain. In the ATLS group, additional assessments of sedation depth were done as follows. The patient was asked to raise his or her hand when the patient felt discomfort. Then we discriminated painful and unpainful discomfort by asking the patient to squeeze the hand of the anaesthetist. If the patient complained of pain, the infusion rate of remifentanyl was increased by $0.4 \mu\text{g kg}^{-1} \text{hr}^{-1}$ until the pain disappeared. If a patient was just anxious or demanded deeper sedation, the infusion rate of propofol was increased by $5 \mu\text{g kg}^{-1} \text{min}^{-1}$. To rapidly reach the targeted level of sedation, 0.25 mg kg^{-1} of propofol could be injected at the anaesthesiologist's discretion.

The databases of sedation methods included actual administered doses of sedatives and analgesics. Collected baseline characteristics of the patients included age, sex, height, weight, and ASA physical status. Recorded data for the lesions included the number of lesions, histology, macroscopic appearance, location, lesion size and presence of ulceration. Sedation-related outcomes such as sedation time, recovery time, desaturation events during the procedure, hyper/hypotension, and outcomes of ESD, including en bloc resection, complete resection, procedure time, and complications such as bleeding, perforation, and aspiration pneumonia, were analysed. We also recorded the number of patients who needed a deeper sedation level than MOAA/S 4 in the ATLS group.

Patient monitoring

Endoscopic procedures were all performed in an endoscopy procedure room fully equipped with advanced cardiac life support. All patients were to arrive at the endoscopy room with secured intravenous access and were administered normal saline or Hartmann solution as appropriate. Supplemental nasal oxygen was provided at 3 litre min^{-1} . Procedural

Table 1 Sedation protocol. MOAA/S 2, responds only after mild prodding or shaking; MOAA/S 3, responds only after name is called loudly and/or repeatedly; MOAA/S 4, lethargic response to name spoken in normal tone; MOAA/S 5, responds readily to name spoken in normal tone (alert).⁸ MSAS, moderate sedation with analgesic supplementation; ATLS, analgesia targeted light sedation; MOAA/S, Modified Observer Assessment of Alertness/Sedation

Protocol	Targeted sedation	Basal regimen	Adjustment regimen
MSAS	2–3 on the MOAA/S scale	Propofol: initial bolus (1.0 mg kg^{-1}) + infusion ($60 \mu\text{g kg}^{-1} \text{min}^{-1}$) Remifentanyl infusion: $3 \mu\text{g kg}^{-1} \text{hr}^{-1}$	Increase propofol infusion rate by $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ to reach target depth. Thereafter, increase remifentanyl infusion rate by $0.4 \mu\text{g kg}^{-1} \text{hr}^{-1}$ for any movement or discomfort.
ATLS	4–5 on the MOAA/S scale	Propofol: initial bolus (0.5 mg kg^{-1}) + infusion ($30 \mu\text{g kg}^{-1} \text{min}^{-1}$) Remifentanyl infusion: $5 \mu\text{g kg}^{-1} \text{hr}^{-1}$	Increase propofol infusion rate by $5 \mu\text{g kg}^{-1} \text{min}^{-1}$ for unpainful discomfort. Increase remifentanyl infusion rate by $0.4 \mu\text{g kg}^{-1} \text{hr}^{-1}$ for painful discomfort.

monitoring included non-invasive blood pressure (NIBP) measurements every 5 min and continuous monitoring of pulse oximetry and electrocardiography (ECG) along with respiratory activity via thoracic leads. Capnography was not routinely used for patient monitoring. At the end of the procedure, patients were transferred to the recovery room, where they were monitored by pulse oximetry, ECG, and NIBP. The recovery profiles were assessed by dedicated nursing staff using the modified Aldrete score in the recovery room. Patients were discharged when they reached a score of 10.

Patient' satisfaction

After the protocol was changed from MSAS to ATLS, we started to check the patients' satisfaction regarding sedation done according to the ATLS protocol by interview. The first question was 'Did you feel discomfort during the procedure?' The second question was 'Are you willing to be sedated with the same protocol in the future?' The interview was done by one of the authors (Y.C.Y.) after full recovery in the endoscopy recovery unit.

Definitions

Sedation time was defined as the time from the bolus sedative injection to the end of sedative infusion. The length of stay in the recovery room was considered as recovery time.⁹ Desaturation was defined as a decrease in oxygen saturation ($\text{SpO}_2 < 90\%$) that required an airway modification including chin lift, jaw thrust manoeuvre, or assisted mask ventilation. Hypertension was defined as an increase in systolic or mean arterial pressure $> 20\%$ from baseline and hypotension as a decrease in systolic blood pressure $> 20\%$ or a mean arterial pressure < 60 mm Hg. En bloc resection was defined as tumour removal in a single piece without fragmentation. Complete resection was defined as complete tumour removal including sufficient tumour-free margins on histologic examination. The procedure time was the time from marking to complete removal, including the time required for haemostasis. Bleeding was defined as the occurrence of clinical symptoms such as melena or hematemesis after ESD. All suspected bleeding events were confirmed by performing emergency endoscopy. A diagnosis of perforation required direct endoscopic observation of mesenteric fat or the presence of free air on an abdominal radiography or computed tomography scan. Pneumonia was defined as new or progressive consolidation accompanied by a new cough, new purulent sputum or a change in the character of the sputum, or new rales or dullness to percussion on physical examination of chest.¹⁰

Statistical analysis

Statistical tests used to compare results included *t*-test, χ^2 test, and Fisher's exact test. Descriptive statistics of continuous variables are presented as mean (SD). $P < 0.05$ was regarded as a significant difference between groups. All statistical procedures were conducted with SPSS for Windows (version 20.0; SPSS, Chicago, IL, USA).

Results

Baseline characteristics of patients and lesions

The baseline characteristics of enrolled patients, including age, sex, height, weight, and ASA physical status, did not differ between the ATLS and MSAS groups (Table 2).

The type of histology, macroscopic appearance, tumour location, and presence of ulcer did not differ between groups. The lesion size in the ATLS group was larger than that in the MSAS group [14.1 (SD 8.2) vs 11.6 (5.7) mm, $P = 0.001$].

Administered doses of drugs according to the sedation protocol

The infusion rate of propofol in the ATLS group was lower than in the MSAS group [22.9 (SD 17.3) vs 88.1 (44.0) $\mu\text{g kg}^{-1} \text{min}^{-1}$, $P < 0.001$]. The infusion rate of remifentanyl in the ATLS group was higher than in the MSAS group [6.8 (SD 3.1) vs 4.8 (3.0) $\mu\text{g kg}^{-1} \text{hr}^{-1}$, $P < 0.001$]. Only five patients (3.6%) in the ATLS group demanded a deeper sedation level than MOAA/S 4.

Sedation-related outcomes and adverse events

The ATLS group had a longer sedation time but shorter recovery time than the MSAS group (Table 3). The incidence of desaturation events was significantly lower in the ATLS group than the MSAS group (20/155 patients vs 3/138 patients, $P = 0.001$). The incidences of hyper- or hypotension were comparable between the two groups. In addition, only four patients reported discomfort during the procedure and refused to be sedated with the ATLS protocol in the future.

ESD performance and complications

Table 4 shows ESD outcomes and complications. En bloc and complete resection rates did not differ between groups. The procedure time was significantly longer in the ATLS group than the MSAS group [41.7 (SD 34.4) vs 34.1 (28.0) min, $P = 0.039$]. In addition, the incidence of bleeding or perforation in the ATLS group did not differ from that in the MSAS group.

Table 2 Baseline characteristics of enrolled patients. MSAS, moderate sedation with analgesic supplementation; ATLS, analgesia targeted light sedation

Variable	MSAS	ATLS	P-value
Patients, <i>n</i>	155	138	
Age, mean (range), years	63.4 (28–83)	63.3 (35–88)	0.965
Male, <i>n</i> (%)	101 (65.2)	97 (70.3)	0.349
Height, mean (SD), cm	161.7 (9.0)	162.4 (11.7)	0.583
Weight, mean (SD), kg	64.6 (10.1)	65.8 (10.5)	0.328
ASA physical status, <i>n</i> (%)			0.549
I	60 (38.7)	49 (35.5)	
II	67 (43.2)	68 (49.3)	
III	24 (15.5)	20 (14.5)	
IV	4 (2.6)	1 (0.7)	

Table 3 Sedation-related outcomes and adverse events. MSAS, moderate sedation with analgesic supplementation; ATLS, analgesia targeted light sedation

Variable	MSAS (n=155)	ATLS (n=138)	P-value
Sedation time, mean (SD), min	44.6 (27.3)	53.7 (37.6)	0.020
Recovery time, mean (SD), min	27.9 (16.0)	19.7 (4.8)	<0.001
Desaturation, n (%)	20 (12.9)	3 (2.2)	0.001
Hypertension, n (%)	2 (1.3)	2 (1.4)	>0.999
Hypotension, n (%)	2 (1.3)	0 (0.0)	0.500

Table 4 Outcomes and complications of endoscopic submucosal dissection. MSAS, moderate sedation with analgesic supplementation; ATLS, analgesia targeted light sedation. *The proportion of this variable was calculated based on the number of patients

Variable	MSAS (n=175)	ATLS (n=162)	P-value
Outcome			
En bloc resection, n (%)	171 (97.7)	160 (98.8)	0.686
Complete resection, n (%)	166 (94.9)	157 (96.9)	0.345
Procedure time*, mean (SD), min	34.1 (28.0)	41.7 (34.4)	0.039
Complication*, n (%)			
Bleeding	9 (5.1)	5 (3.1)	0.345
Perforation	2 (1.1)	3 (1.9)	0.674
Aspiration pneumonia	8 (5.2)	2 (1.4)	0.109

Although there was no statistical difference, the incidence of aspiration pneumonia was 1.4% in the ATLS group compared with 5.2% of the MSAS group ($P=0.109$).

Discussion

At present, the generally accepted sedation level for ESD is moderate to deep sedation.^{4,5} Our present study found that light sedation using propofol (ATLS) along with adequate pain control achieved by remifentanyl infusion reduced the incidence of oxygen desaturation events during the procedure without affecting procedural performance. However, we could find only a trend of low incidence of post-procedural aspiration pneumonia without statistical significance.

Incision, dissection, haemostasis, or even air insufflation and rotation of the scope during ESD is inevitably accompanied by pain. However, commonly used sedatives during ESD such as propofol or midazolam have no analgesic effects. This aspect seems to be occasionally overlooked. For the ATLS protocol, we tried to uncouple the components of analgesia and hypnosis in procedural sedation, and sedation was targeted at 4 or 5

on the MOAA/S scale to reflect the patient's need more exactly and carefully.

ESD requires an elaborate technique and carries the risk of gastric perforation or other complications with even slight movements of the patient. In order to minimize the patient's movement, deep sedation is applied for ESD, thus respiratory support may be required.^{2,11,12} In contrast, the procedural performance under the ATLS protocol was comparable to that under the MSAS protocol in our study.

When we first applied the ATLS protocol, we were concerned about the patients' subjective complaints (painful vs unpainful discomfort) as well as procedural performance. Although we did not compare the patients' satisfaction between the MSAS and ATLS protocols, only five patients in the ATLS group demanded a sedation level as deep as MOAA/S 2 or 3 during the study period. From a previous report concerning the satisfaction of patients undergoing carotid endarterectomy during carotid clamping, when anaesthesia was maintained only with high-dose remifentanyl for monitoring response to verbal statements and performing neurological examinations,¹³ 98.8% of 181 patients felt satisfied with the procedure. All patients in the ATLS protocol group were asked whether they would be willing to undergo another procedure with the ATLS protocol. Only four patients reported discomfort during the procedure and refused to be sedated with the ATLS protocol in the future.

In our study, the patients sedated with the ATLS protocol were able to respond to questions regarding the appropriateness of pain and anxiety control. As a result, required propofol use was significantly reduced and remifentanyl use was significantly increased. Complete analgesia by remifentanyl infusion might enable the patients to be comfortable under anxiolytic levels of sedation and prevent the overuse of sedative. Although our previous study¹ showed that the involvement of anaesthesiologists in ESD improved procedural performance, but also increased the incidence of aspiration pneumonia, the exact pathophysiology of aspiration pneumonia in the sedated but spontaneously breathing patient is still unclear. In a study by Savilampi and colleagues¹⁴ that was done in healthy volunteers with a crossover design, the incidence of aspiration pneumonia was 48% under target controlled infusion of remifentanyl at the 3.0 ng ml⁻¹ effect site concentration compared with 12% with placebo, which suggested the possible contribution of remifentanyl to the aspiration pneumonia. When we simulated the effect site concentrations of remifentanyl in this study with the computerized program Orchestra (Base Primea, Fresenius Vial, France, Minto model), the effect site concentrations of remifentanyl in the ATLS and MSAS protocols approached 3.2 ng ml⁻¹ and 2.4 ng ml⁻¹, respectively. In contrast, we found a lower incidence of aspiration pneumonia with the ATLS protocol compared with the MSAS protocol ($P=0.109$). The relatively high incidence of aspiration pneumonia found by Savilampi and colleagues¹⁴ is not comparable to our finding for the following reasons: different diagnostic criteria for aspiration pneumonia, healthy volunteers in a supine position vs patients undergoing ESD in a lateral position, without vs with co-use of propofol, and so on. According to

computer simulation of the effect site concentrations of propofol (modified Schnider model) in the ATLS and MSAS protocols at steady state, they approached 0.59 mg ml^{-1} and 2.4 mg ml^{-1} , respectively. Therefore we suggest that the sedation level might be more important than analgesia for aspiration pneumonia after ESD since our previous study¹ showed a higher incidence of aspiration pneumonia in patients sedated by anaesthesiologists (relatively deep sedation) compared with those sedated by endoscopists. Moreover, the incidence of desaturation events ($\text{SpO}_2 < 90$) was significantly lower in the ATLS protocol than the MSAS protocol.

The ATLS protocol prolonged sedation time compared with the MSAS protocol. This prolongation may be due to the 2.5 mm difference in lesion size and longer procedure time in the ATLS group compared with the MSAS group. The relatively longer time required to titrate analgesics and hypnotics according to the patient's demand might also explain in part this difference in sedation time. As a second aim of this study, we were able to find similar procedural performance between the two protocols.

There are several limitations to this study. First, our data were abstracted from a quality control database and not collected in real time by an observer using a prospective design. Therefore we need a prospective, randomized controlled study to clarify our results. Second, with regard to the respiratory depressive effects of our sedation protocols, we did not assess the severity of oxygen desaturation using the area under the curve method,¹⁵ but only recorded the desaturation events ($\text{SpO}_2 < 90\%$) requiring an airway modification, including chin lift, jaw thrust manoeuvre, or assisted mask ventilation. Also, no capnography was utilized, so the adequacy of ventilation was indeterminate despite differences in hypoxemia. Third, sedation levels in our study were defined according to the subjective tool of the MOAA/S, thus sedation assessment may not be consistent. However, experienced attending anaesthesiologists involved in hospital quality control for the endoscopic sedation unit as well as in this study would recognize the protocols well. Fourth, the shorter recovery time under the ATLS protocol does not necessarily represent the time to readiness for discharge. Finally, we did not compare the satisfaction scores of the patients and endoscopists between the two protocols.

In conclusion, the ATLS protocol reduced the incidence of oxygen desaturation events without affecting ESD performance compared with the MSAS protocol. These data suggest that the ATLS protocol may be superior to the MSAS protocol for ESD. This should be investigated with an appropriately powered, prospective, randomized controlled trial.

Authors' contributions

Y.C.Y. and C.H.P.: designed and analysed patient data and wrote the manuscript. Y.P.: participated in data collection. S.S.: reviewed the manuscript and helped create the outline of the

article. S.K.L. and K.T.M.: participated as corresponding authors and supervised the overall study and construction of the manuscript. All authors contributed to the manuscript and read and approved of the final version.

Declaration of interest

None declared.

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