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Effect of antispasmodic drugs on endoscopic ultrasound/endoscopic ultrasound-guided fine-needle aspiration: A multicenter randomized controlled trial

Masaki Kuwatani¹, Hiroshi Kawakami¹, Tsuyoshi Hayashi², Kazunori Eto³, Hiroaki Yamato⁴, Manabu Onodera⁵, Hirohito Naruse⁴, Koji Oba⁶

¹Department of Gastroenterology and Hepatology, Hokkaido University Graduate School of Medicine, Sapporo 060-8638, ²Department of Medical Oncology and Hematology, Sapporo Medical University School of Medicine, Sapporo 060-8556, ³Department of Gastroenterology, Tomakomai City Hospital, Tomakomai 053-8567, ⁴Department of Gastroenterology and Hepatology, Hakodate Municipal Hospital, Hakodate, 041-8680, ⁵Department of Gastroenterology, Abashiri-Kosei General Hospital, Abashiri 093-0076, ⁶Translational Research and Clinical Trial Center, Hokkaido University Hospital, Sapporo 060-8648, Japan

ABSTRACT

Background and Objective: Antispasmodic drugs (ADs) have been used to reduce examination time or improve the quality of gastrointestinal endoscopy, although the practice is controversial. No evidence about the efficacy of AD for endoscopic ultrasonography/EUS-guided fine-needle aspiration (EUS/EUS-FNA) is available. This study was aimed to evaluate the efficacy of AD in EUS/EUS-FNA. Patients and Methods: A total of 400 patients with pancreaticobiliary, peripancreatic, or peribiliary disease or disorder undergoing EUS/EUS-FNA were prospectively and evenly randomized to undergo EUS/EUS-FNA with AD (w-AD) or without AD (w/o-AD). The primary endpoint was total EUS/EUS-FNA examination time. The secondary endpoints were visual analogue scale (VAS) scores of endoscopists (patient body motion, gastrointestinal peristalsis, and accomplishment of the purpose) and patients (pain, discomfort, and willingness to undergo re-examination), vital sign changes, adverse events, and sedative dose. Results: Two hundred patients in the w-AD group and 197 patients in the w/o-AD group were ultimately analyzed. The total examination time was similar between the groups (2299 ± 937 vs. 2259 ± 1019 s). The difference in total examination time from w/o-AD group to w-AD group was −40 s (95% confidence interval, −234-153 s), which was within the noninferiority margin. No statistical differences were observed in endoscopist and patient VAS scores, changes in vital signs, adverse events, or total sedative dose other than fentanyl between the groups. Conclusion: EUS/EUS-FNA can be effectively and safely performed w/o-AD. Further, randomized controlled trials on EUS/EUS-FNA in various disease entities may be required to confirm the results of this study (UMIN000008047).

Key words: Antispasmodic drug, endoscopic ultrasonography, endoscopic ultrasound-guided fine-needle aspiration, examination time

INTRODUCTION

Endoscopic ultrasonography (EUS) and EUS-guided fine-needle aspiration (EUS-FNA) are efficient modalities for the diagnosis of gastrointestinal diseases and pancreaticobiliary diseases, particularly for determining the depth, localization, internal characteristics, and pathology. In addition, EUS/EUS-FNA is an extension of
esophageal-gastro-duodenoscopy (EGD) or colonoscopy (CS). To lessen the examination time or improve the quality of these examinations, antispasmodic drugs (ADs) such as scopolamine butylbromide, atropine, or glucagon have been used as premedication.

Cattau et al.\[1\] reported that atropine was not more beneficial for the ease of EGD or patients’ assessments of the acceptability of the procedure compared with that without atropine, although it was effective for reducing gastric motility. Qvigstad et al.\[2\] found that glucagon significantly reduced peristalsis compared with both atropine and placebo, but observed no difference about vomiting, opening of the pylorus, feeling of discomfort, or the success of the examination among the three groups. These results suggest that gastric motility is not related to procedural success or patient discomfort in EGD.

In the case of CS, arguments have been made both for and against the use of antispasmodics to decrease cecal intubation or procedure time\[3-7\] or increase the ease of intubation.\[8\] Recent reports have indicated the nonsuperiority\[6\] or disadvantage of AD.\[7\]

Regarding the comparison of scopolamine butylbromide and glucagon, two randomized controlled trials (RCT) in EGD and CS revealed that the use of scopolamine butylbromide significantly increased heart rate compared to glucagon, although examination time and accomplishment rate did not significantly differ between the two drugs.\[9,10\]

In EUS/EUS-FNA, like EGD/CS, although premedication with AD (w-AD) was previously considered natural and indispensable or performed depending on the discretion of an endoscopist, a recent guideline by the American Society for Gastrointestinal Endoscopy has indicated the lack of necessity for anticholinergics in EUS/EUS-FNA as well as in routine diagnostic EGD/CS.\[11\] In addition, we frequently experience easy accomplishment of EUS/EUS-FNA without AD (w/o-AD) in clinical practice. However, no prospective RCT has confirmed the efficacy of AD in EUS/EUS-FNA. Thus, we performed a multicenter, prospective RCT to investigate the effect of AD in EUS/EUS-FNA.

**MATERIALS AND METHODS**

**Study design**
This study was conducted as a prospective multicenter single-blind RCT. Patients were assigned to two groups: EUS/EUS-FNA w-AD and w/o-AD group. The study protocol was approved by the institutional review board of each participating institution (Hokkaido University Hospital, Clinical Research approval number 011-0358; Sapporo Medical University School Hospital, Clinical Research approval number 24-20; the other institutes each received approval without an ID number). This study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN ID: UMIN000008047).

**Patients**
Between May 2012 and March 2013, all consecutive patients with pancreaticobiliary, peripancreatic, or peribiliary disease or disorder (abnormal biliary or pancreatic enzymes) requiring EUS/EUS-FNA for work-up who presented to our departments at Hokkaido University Hospital, Sapporo Medical University Hospital, Tomakomai City Hospital, Hakodate Municipal Hospital, or Abashiri-Kosei General Hospital were screened for recruitment. Patients with gastric or duodenal epithelial lesion were not screened because such lesions require an ultrasonic probe different from an echoendoscope for work-up. The exclusion criteria for patients were as follows:

1. Refusal to provide informed consent;
2. Poor general status (performance status according to Eastern Cooperative Oncology Group 4: Completely disabled, cannot carry out any self-care, and totally confined to the bed);
3. Age under 20 years;
4. Impossibility of endoscopic examination by gastrointestinal stricture or trismus;
5. Severe heart dysfunction (New York Heart Association classification class III or IV) or lung dysfunction;
6. Pregnancy;
7. Use of an AD within 12 h before EUS/EUS-FNA;
8. Tendency to bleed (impossibility of withdrawal of antplatelet or anticoagulation therapy) when EUS-FNA is planned;
9. Contraindications for scopolamine butylbromide (hemorrhagic colitis, glaucoma, prostate hypertrophy, and paralytic ileus) and glucagon (pheochromocytoma); and
10. Judged inappropriate by a doctor.

Written informed consent was obtained from all patients.

**Study protocol**
The enrolled patients were evenly randomized to undergo EUS/EUS-FNA with an AD (w-AD group,
Oxygen supply by nasal tube (2-4 L/min) was also performed appropriately. Patients were routinely monitored by pulse oximeter (SpO₂) to measure oxygen saturation; pulse rate and arterial blood pressure (BP) were recorded every 5 min and when the alarm rang using a bedside monitor (BSM-2301; Nihon Kohden Corporation, Tokyo, Japan). Additional AD was administered according to the judgment of the operator, regardless of the result of randomization. The total dose of sedative drugs and AD during EUS/EUS-FNA was routinely recorded.

**Definitions**

The total examination time(s) of EUS/EUS-FNA was determined as the time from scope insertion into the oral cavity to scope removal from the mouth. Ten-point VAS and modified VAS scores were used to evaluate satisfaction levels of endoscopists and patients in order to quantify, for endoscopists, (1) body motion of the patient during the examination, (2) gastrointestinal peristalsis (0, no motion, not impeditve for examination at all to 10, maximally active, maximally impeditive for examination; score was modified as follows: Modified score = 10 − VAS score), and (3) accomplishment of the purpose of the examination, and for patients, (1) pain, (2) discomfort (distention and nausea) during the examination (0, no pain, no discomfort to 10, maximal pain, maximal discomfort; score was modified as follows: Modified score = 10 − VAS score), and 3) willingness to undergo re-examination after the examination. All scores were considered to be better as they increased. A sheet describing the VAS was handed out to each participant after the procedure, to be filled out and collected within 3 h after EUS/EUS-FNA.

Adverse events were classified essentially using the Cotton classification. On the basis of a consensus meeting held in 1991, the diagnostic criteria for post-EUS/EUS-FNA pancreatitis are abdominal pain lasting >24 h after EUS/EUS-FNA and hyperamylasemia (>3 times the upper limit of the normal range). The Cotton classification was used for the assessment of severity, but on the basis of the medical circumstances in Japan, the time leading to food consumption was used as an indicator of the severity rather than the duration of hospitalization. Hypoxia was defined as a decrease in SpO₂ to ≤90% or ≥10% drop of SpO₂. Hypotension was defined as a decrease in systolic BP to <80 mmHg. Hypertension was defined as continuous increase of systolic BP to >180 mmHg requiring a hypotensor.

**Study outcome**

The primary endpoint was the total examination time of EUS/EUS-FNA. The secondary endpoints were VAS scores and modified VAS scores of endoscopists and patients; changes in BP, pulse rate, and SpO₂ during the examination; adverse events; and total sedative dose.

**Statistical analysis**

In this study, we assessed the noninferiority of EUS/EUS-FNA without AD compared to that with AD with respect to the examination time.

Based on the clinical data on work-up EUS/EUS-FNA or simultaneous EUS and EUS-FNA, both w-AD and w/o-AD groups were speculated to have a similar mean examination time of 30 min (1800 s) and standard deviation (SD) of 1000 s. We set the noninferiority margin as 300 s. To investigate the noninferiority with a power of 0.8 and an alpha of 0.025 (one-sided), complete data were required for at least 176 patients per group. Therefore, assuming some dropouts of the enrolled patients and considering no similar previous report, our recruitment goal was a total of 400 patients.

The primary endpoint was evaluated on whether the difference between w-AD and w/o-AD groups with 95% confidence interval was within the noninferiority...
margin. Categorical data and continuous data were expressed as a proportion and mean ± SD, respectively. Categorical data were examined using the $\chi^2$ test. The Mann-Whitney U-test or $t$-test was used to compare quantitative data. These tests were performed with Microsoft Excel software (Redmond, WA), and the results were regarded as significant if $P < 0.05$.

**RESULTS**

**Patients**

A total of 400 patients were included in the present study. Of these patients, one rejected EUS on the examination day. The remaining 399 patients enrolled in the study underwent EUS/EUS-FNA based on their assignment regarding the use of AD, but two patients were incorrectly administered with AD in contradiction to the allocation. Ultimately, 200 patients in the w-AD group and 197 patients in the w/o-AD group were analyzed [Figure 1]. Patient characteristics were similar in both groups [Table 1]. The most frequent location of the target was the pancreas in both groups (122 vs. 115 cases).

**Total examination time**

The total examination time for EUS/EUS-FNA was similar between groups [2299 ± 937 vs. 2259 ± 1019 s; Table 2]. Median time of EUS/EUS-FNA was 2100 s in both the w-AD and w/o-AD groups. Furthermore, the difference in the time from w/o-AD group to w-AD group was −40 s, with 95% CI of −234-153 s, which was within the noninferiority margin of 300 s. Thus, we observed the noninferiority of EUS/EUS-FNA w/o-AD to that w-AD.

**Visual analogue scale scores and modified visual analogue scale scores**

For endoscopists, modified VAS scores for patient body motion and gastrointestinal peristalsis and VAS score for accomplishment of the purpose did not significantly differ between the w-AD and w/o-AD groups. All scores were very high, exceeding 9.4 points [Table 3]. For patients, modified VAS scores for pain and discomfort and VAS score for willingness to undergo re-examination after the procedure, which were supposed to be partially affected by AD, were similar between the two groups. Although lower than those of endoscopists, all scores exceeded 8.6 points [Table 3].

**Doses of sedative drugs and antispasmodic drugs**

The effect of AD on the doses of sedative administered during EUS/EUS-FNA was also assessed.

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**Table 1. Characteristics of patients**

|          | w-AD  | w/o-AD | P value |
|----------|-------|--------|---------|
| Number   | 200   | 197    |         |
| Age (years) (mean±SD) | 66.4±11.5 | 67.4±11.3 | 0.34    |
| Male/female | 108/92 | 101/96 | 0.59    |
| Location of target |       |        |         |
| Pancreas | 122   | 115    | 0.67    |
| Bile duct | 31    | 24     |         |
| Gallbladder | 16    | 27     |         |
| Ampulla | 8     | 7      |         |
| Lymph node | 10    | 9      |         |
| Others | 13    | 15     |         |

w-AD: With an antispasmodic drug, w/o-AD: Without an antispasmodic drug, SD: Standard deviation

**Table 2. Total examination time**

|          | w-AD (n = 200) | w/o-AD (n = 197) | Difference between w-AD and w/o-AD |
|----------|----------------|-----------------|----------------------------------|
| Time(s) (mean±SD) | 2299±937 | 2259±1019 | −40 (95% CI: −234, 153) |

w-AD: With an antispasmodic drug, w/o-AD: Without an antispasmodic drug, SD: Standard deviation

**Table 3. VAS and modified VAS scores**

|          | w-AD (n = 200) | w/o-AD (n = 197) | P value |
|----------|----------------|-----------------|---------|
| Endoscopists |               |                 |         |
| Patient body motion | 9.4±1.6 | 9.6±1.3 | 0.79    |
| Gastrointestinal peristalsis | 9.6±1.5 | 9.7±1.3 | 0.95    |
| Accomplishment of the purpose | 9.5±1.4 | 9.5±1.3 | 0.61    |
| Patients |               |                 |         |
| Pain | 8.7±2.5 | 8.6±2.7 | 0.76    |
| Discomfort | 8.7±2.5 | 8.6±2.7 | 0.74    |
| Willingness to undergo re-examination | 8.6±2.6 | 8.7±2.7 | 0.43    |

Score 0: Worst, Score 10: Best, Values in the central two columns indicate mean ± SD, SD: Standard deviation, VAS: Visual analogue scale
The sedative drugs fentanyl citrate (50-200 μg) or pethidine (17.5-70 mg) and midazolam (2-13 mg), or diazepam (2.5-40 mg), or pentazocine (7.5-22.5 mg) were used. Fentanyl citrate was the only drug that significantly differed between the two groups [Table 4]. Regarding AD, scopolamine butylbromide was used in 116 patients (average 10.0 ± 0.0 mg), and glucagon was used in 84 patients (average 1.0 ± 0.0 mg). No additional AD was administered [Table 4].

### Changes in blood pressure, pulse rate, and saturation by pulse oximeter

Systolic and diastolic BP, pulse rate, and arterial SpO2 levels were measured in all patients to assess the effect of AD before, during, and 2 h after EUS/EUS-FNA [Table 5]. Changes in diastolic BP, pulse rate, and SpO2 did not significantly differ between the two groups before and after the exam or during the exam [Table 5], and the time courses of these measurements were highly similar between the two groups. However, the change in pulse rate during examination tended to be higher in the w-AD group than in the w/o-AD group (P = 0.061). In addition, changes in the four measurements during the exam were larger than those before and after the exam in both groups.

### Adverse events

Adverse events associated with EUS/EUS-FNA are shown in Table 6. The total number of complications did not differ between the w-AD and w/o-AD groups (7 [3.5%] vs. 4 [2.0%]). Acute pancreatitis, cholangitis, and peritonitis were specific to EUS-FNA. All complications were mild or moderate and resolved by conservative therapies.

### DISCUSSION

The present study revealed that EUS/EUS-FNA can be effectively and safely performed w/o-AD premedication from the viewpoints of total examination time, satisfaction levels of endoscopists and patients, changes in vital signs, and adverse events. This evidence is the first to be generated in a prospective RCT.

American Society for Gastrointestinal Endoscopy has mentioned the lack of necessity of AD for EUS/EUS-FNA as in routine diagnostic EGD/CS,[11] while the European Society of Gastrointestinal Endoscopy (ESGE) has not clearly shown the necessity or lack of necessity of AD. In recent endoscopic settings in the US and European countries, deep sedation with propofol is widespread for relief of patient anxiety and discomfort,[15,16] which can lead to safety and high quality of endoscopy due to complete cessation of patient body motion without AD. Thus, it would be reasonable not to use AD for routine EUS/EUS-FNA without additional procedures in these countries.

### Table 4. Doses of sedative and antispasmodic drugs

| Number (w:w/o)* | w-AD (n = 200) | w/o-AD (n = 197) | P value |
|-----------------|----------------|-----------------|---------|
| Sedative drugs  |                |                 |         |
| Fentanyl citrate (μg) | 54:52 | 103.2±32.6 91.3±29.0 | 0.045  |
| Pethidine (mg)   | 109:106 | 39.5±11.9 40.0±13.5 | 0.99    |
| Midazolam (mg)   | 82:74 | 5.8±2.5 6.1±2.5 | 0.52    |
| Diazepam (mg)    | 136:135 | 12.9±6.8 12.3±6.6 | 0.40    |
| Pentazocine (mg) | 6:8 | 13.8±5.2 12.2±5.2 | 0.57    |
| Antispasmodic drugs |             |                 |         |
| Scopolamine butylbromide (mg) | 116:0 | 10.0±0.0 | –       |
| Glucagon (mg)    | 84:0 | 1.0±0.0 | –       |

| Values in the w-AD and w/o-AD columns indicate mean±SD, w: w-AD group, w/o: w/o-AD group, w-AD: With an antispasmodic drug, w/o-AD: Without an antispasmodic drug, SD: Standard deviation |

### Table 5. Changes in BP, pulse rate and SpO2

| Systolic BP (mmHg) | w-AD (n = 200) | w/o-AD (n = 197) | P value |
|--------------------|----------------|-----------------|---------|
| Before and after exam | 17.1±13.7 | 15.7±12.1 | 0.28    |
| During exam | 30.1±18.9 | 28.3±15.7 | 0.31    |
| Diastolic BP (mmHg) |                |                 |         |
| Before and after exam | 10.6±8.6 | 10.6±8.1 | 0.96    |
| During exam | 16.8±11.4 | 17.7±12.1 | 0.41    |
| Pulse rate (bpm) |                |                 |         |
| Before and after exam | 9.7±8.2 | 9.2±7.6 | 0.57    |
| During exam | 15.6±10.1 | 13.7±9.7 | 0.061   |
| SpO2 (%) |                |                 |         |
| Before and after exam | 1.4±1.5 | 1.4±1.5 | 0.93    |
| During exam | 2.5±2.6 | 2.5±2.8 | 0.85    |

| Values indicate mean of absolute values ± SD, SpO2: Oxygen saturation by pulse oximeter, BP: Blood pressure, SD: standard deviation, w-AD: With an antispasmodic drug, w/o-AD: Without an antispasmodic drug |

### Table 6. Adverse events associated with EUS/EUS-FNA

| Total number of complications | w-AD (n = 200) | w/o-AD (n = 197) | P value |
|------------------------------|----------------|-----------------|---------|
| Acute pancreatitis | 4 | 1 | 0.38    |
| Bradycardia/tachycardia | 1 | 0 | 0.99    |
| Hypertension | 0 | 1 | 0.99    |
| Cholangitis/peritonitis | 2 | 0 | 0.48    |
| Nausea/fever | 0 | 2 | 0.47    |

| *All patients underwent EUS-FNA, *All patients underwent EUS alone, Continuous increase of systolic blood pressure to >180 mmHg requiring a hypotensor, Each complication respectively affected one patient, w-AD: With an antispasmodic drug, w/o-AD: Without an antispasmodic drug, EUS/EUS-FNA: Endoscopic ultrasonography/endoscopic ultrasound-guided fine-needle aspiration |
The most important factor for a successful EUS/EUS-FNA procedure is to eliminate artifacts, especially due to gas in the gastrointestinal tract. Therefore, intermittent aspiration of the gas is usually performed during the procedure. Such a situation in EUS/EUS-FNA led to the similarities in total examination time and the satisfaction level of endoscopists between the w-AD and w/o-AD groups. The lack of necessity for AD was also revealed by the lack of additional administration of AD during examination in both groups. The effect of AD on patients’ satisfaction level was negligible, because patient discomfort during EUS would depend mainly on the level of conscious sedation.[17] The difference in fentanyl dose between the w-AD and w/o-AD groups is most likely to depend on incidental differences in the rate of patients who reacted poorly to sedative drugs.

Vital signs should be carefully monitored during endoscopic examination, especially when using anticholinergic drugs, which can affect the circulatory system. The changes in pulse rate of the w-AD group with intramuscular administration in this study were smaller than those reported in previous studies using intravenous administration.[7,8] Because intramuscular administration of an anticholinergic leads to milder elevation of anticholinergic serum concentration than intravenous administration,[3] this difference could be the cause of the smaller observed changes,[9] although the present study was limited by its low rate of use of scopolamine butylbromide (58%; 116/200).

One report indicated that maximal effects of scopolamine butylbromide on the inhibition of gastroduodenal peristalsis were exerted 2-8 min after intravenous administration, 30 min after subcutaneous administration, and more than 30 min after intramuscular administration.[10] Another report indicated that gastric peristalsis inhibition by intramuscular injection of scopolamine butylbromide and glucagon occurred 10-20 min after administration.[18] Thus, the administration of AD in the present study was appropriate and did not cause bias in our results.

Adverse events in diagnostic EUS/EUS-FNA are reported in approximately 0.03-3% of patients[19] and include gastrointestinal perforation, bleeding, and bacteremia. In addition, general ADs, namely both scopolamine butylbromide and glucagon, can cause adverse effects such as tachycardia, dysuria, hyperglycemia, and hypertension. They were generally rare in this study, and AD was not related to their frequency. Thus, AD would not be necessary for the safety of EUS/EUS-FNA, although the number of participants was small for comparison of adverse events.

The present study has some limitations: It was a single-blind study (to endoscopists, not to patients), without placebo because of affairs in the multiple institutions, had no stratification according to endoscopists, and target lesions consisted of pancreaticobiliary, peripancreatic, or peribiliary disease or disorder alone.

CONCLUSION

Endoscopic ultrasonography/endoscopic ultrasound-guided fine-needle aspiration can be effectively and safely performed without AD. Further RCTs on EUS/EUS-FNA in various disease entities may be required to confirm the results of this study.

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