Acta Med. Okayama, 2020
Vol. 74, No. 5, pp. 407-413


Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

*Original Article*

# Comprehensive Prospective Analysis of the Factors Contributing to Aspiration Pneumonia Following Endoscopic Submucosal Dissection in Patients with Early Gastric Neoplasms

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**Endoscopic submucosal dissection (ESD) has become the first-line treatment for early gastric neoplasms; however, a subset of patients treated by this method develop aspiration pneumonia. We conducted a comprehensive prospective analysis of the factors contributing to post-ESD aspiration pneumonia in early gastric neoplasms in this study, with special focus on whether pre-treatment oral care can prevent aspiration pneumonia. Sixty-one patients who underwent ESD for gastric neoplasms were randomly assigned to the oral care or control groups. ESD was performed under deep sedation. Of 60 patients whose data were available for analysis, 5 (8.3%) experienced pneumonia confirmed either by chest radiography or computed tomography. Although no difference in the rate of pneumonia was found between the control and oral care groups, the post-oral care bacteria count was significantly higher in the saliva of patients who developed pneumonia compared to those without pneumonia. In addition, the presence of vascular brain diseases and the dose of meperidine were also significantly associated with the occurrence of pneumonia. These results suggest that the number of oral bacteria as well as pre-existing vascular brain diseases and high-dose narcotics can affect the incidence of post-ESD pneumonia.**

**Key words:** endoscopy, oral bacteria, respiratory disease, pneumonia, sedation

Endoscopic submucosal dissection (ESD) has emerged as the primary treatment option for early gastric neoplasms. However, approximately 3-11% of patients treated by this method develop post-procedural aspiration pneumonia [1,2]. Although this complication may occur more frequently than post-ESD bleeding and perforation [3], its prevention has received less attention.

There have been studies indicating that higher age, male sex, and long procedure time may increase the rate of post-ESD pneumonia [1,2]. Professional cleaning of the oral cavity by dental hygienists, including cleaning of the dentures, oral mucous membrane, and

Received February 17, 2020; accepted June 22, 2020.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

tongue, has been shown to reduce the levels of *oropharyngeal* microorganisms and decrease the incidence of pneumonia in various groups of patients, including neonates in intensive care units and elderly in nursing homes [4-6]. Professional oral care treatment prior to surgery requiring general anesthesia was also found to be effective in reducing the rates of post-operative pneumonia [7,8]. This randomized control study aimed to analyze the factors contributing to post-ESD aspiration pneumonia, with special focus on the potential prophylactic effect of pre-procedural professional oral care.

## Materials and Methods

***Patients and study design.*** The present study included the patients who underwent upper ESD for early gastric carcinoma or adenoma at Nagasaki University Hospital and Isahaya General Hospital between December 2016 and December 2019. The study was approved by the Ethics Committee of the Nagasaki University (16092604), UMIN000024259. Patients under 20 years of age and those not able to give informed consent were excluded from the study. All patients provided written informed consent after receiving sufficient explanation of the study aims and methods.

The patients were randomized to the oral care group or control group using a sealed opaque envelope to conceal the random allocation sequence until interventions were assigned [9]. Patients from the oral care group were instructed to visit a dental care unit to receive professional oral care (cleaning of teeth, dentures, oral mucous membrane, and tongue) before admission for the ESD procedure. A uniform oral care protocol was devised and was shared with the dentists of the two institutions in order to ensure uniformity. The number of oral bacteria was measured before and after the oral care. The bacteria count was expressed as colony forming units (CFU)/ml. Patients in the control group did not receive oral care.

Before and after the procedure, body temperature, peripheral blood oxygen saturation ($SpO_2$), and inflammatory markers, including the C-reactive protein (CRP) level, were examined. Thoracic radiography was performed when the patient had one or more of the following conditions: respiratory symptoms, such as cough or sputum, fever > 37.5°C, $SpO_2$ < 94% or $SpO_2$ drop > 3% compared to the pre-procedural level, positive lung murmur, or CRP level > 2 mg/l [10,11]. If chest radiograph showed signs of consolidation, pneumonia was diagnosed. If radiography was inconclusive, computed tomography (CT) was performed to exclude pneumonia. Age, sex, underlying diseases, smoking, procedure time, history of stomach surgery, size of the lesion, and sedation medications were all considered to be potential risk factors for the development of post-ESD pneumonia. Thus, this information was also gathered and was analyzed to determine the association with post-ESD pneumonia.

***Statistics.*** Statistical analysis was performed by a statistician (HK). The statistical significance of differences in quantitative parameters between the two groups (oral care vs. control or pneumonia vs. no pneumonia) was assessed by Wilcoxon's test. Fisher's exact test was used to detect the statistical difference between 2 nominal variables. Differences in the value between the 2 time periods for each patient were assessed using the paired Wilcoxon test. Cochran-Armitage test was employed to assess the relationship between the dose of meperidine and the rate of pneumonia. A $p$ value < 0.05 was considered statistically significant. All calculations were performed using SAS software (version 9.3; SAS Institute, Cary, NC, USA).

## Results

Only 61 of 302 preplanned patients were enrolled, and thus the trial had to be terminated due to poor accrual. The 61 patients were randomized to the oral care group ($n = 33$) or control group ($n = 28$) using a sealed opaque envelope to conceal the random allocation sequence until interventions were assigned (Fig. 1). Among the 61 patients, 1 patient who was randomized to the oral care group but did not complete the ESD procedure due to fibrosis and the subsequent requirement of surgical resection was excluded. Thus, the remaining 60 patients were subjected to further analysis (Fig. 1). The mean age of the enrolled patients was 73.5 ± 7.9 years. Fifty were men and 10 were women. No significant differences in age, sex, or other underlying conditions were detected between the control and oral care groups (Table 1). Depending on the patient's oral hygiene, the number of visits ranged from 1 to 4. It was not possible to determine the oral bacterial count of 1 of the 33 patients who underwent oral care, due to

significant dryness of the oral mucosa. The bacteria count of 28 patients decreased after oral care, while the bacteria counts increased in 4 patients. The overall bacterial count decreased significantly after oral care (median: 15,000,000 CFU/ml before and 2,255,000 CFU/ml after oral care, $p < 0.001$, paired Wilcoxon test) (Fig. 2).

Among the 60 patients, 18 (30%) had respiratory symptoms or body temperature ≥ 37.5℃, and 10 (16.7%) had $SpO_2 < 94\%$ and/or $SpO_2$ drop > 3% compared to the pre-ESD value. After examination by chest radiography and CT, 5 (8.3%) patients were diagnosed with post-ESD pneumonia. Of them, 1 was diagnosed by chest radiography, while in the other 4 patients only CT could detect the pneumonia. All patients with pneumonia received antibiotic therapy and were discharged after full recovery. Among patients from the oral care group, 4 (12.5%) developed pneumonia, whereas in the control group, 1 (3.6%) patient developed pneumonia (Table 1). Pneumonia rates were not statistically different between the oral care and control groups (Table 1).

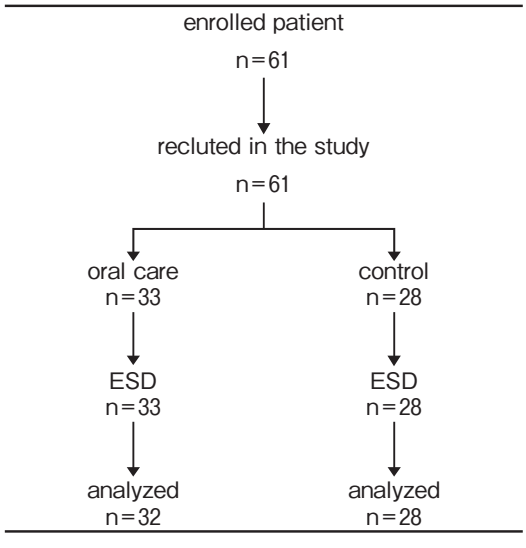


**Fig. 1** Design of the current study.

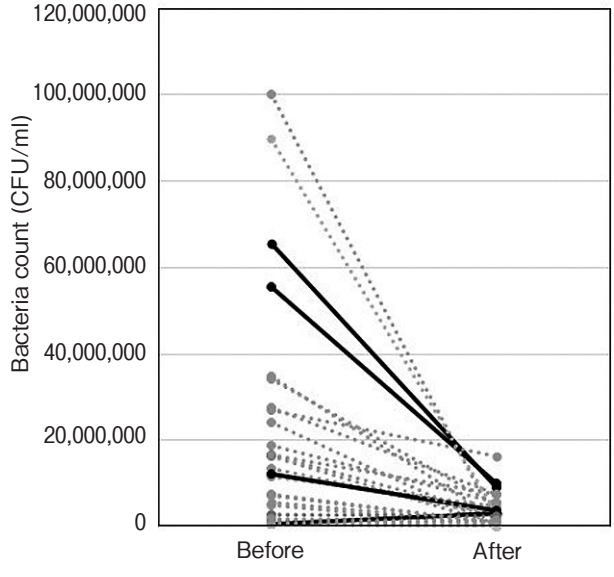


**Fig. 2** Oral bacteria count before and after oral care. Black lines and dotted gray lines indicate the patients who did and did not develop pneumonia, respectively. $P < 0.05$, before oral care vs. after oral care. CFU: colony forming units.

**Table 1** Background and occurrence of pneumonia in included patients

| | Oral care (n = 32) | Control (n = 28) | *P* value |
|---|---|---|---|
| Sex, n | | | |
| Male | 27 | 25 | 0.71 |
| Female | 5 | 3 | |
| Age (years), mean ± SD | 72 ± 1.12 | 76 ± 9.11 | 0.32 |
| History of gastric surgery, n (%) | 4 (12.5) | 3 (11.7) | 1 |
| Respiratory disease, n (%) | 4 (12.5) | 3 (11.7) | 1 |
| Cerebrovascular disease, n (%) | 4 (12.5) | 0 | 0.12 |
| Diabetes mellitus, n (%) | 8 (25.0) | 8 (28.6) | 0.79 |
| Post -ESD pneumonia | 4 (12.5) | 1 (3.6) | 0.36 |

Control group included patients who did not receive oral care
SD, standard deviation; ESD, endoscopic submucosal dissection;
Age differences between Oral care and control care groups were assessed by Wilcoxon test. Fisher's exact test was used to detect the statistical difference between two nominal variables

Table 2 summarizes the background characteristics of patients with pneumonia. Significant increases in WBC count and CRP level were detected in patients with pneumonia the day after ESD (Table 3). The overall medical cost was significantly higher in patients who developed pneumonia compared to those who did not, whereas no significant difference in admission duration was found between the 2 groups (Table 3).

Among the 4 patients in the oral care group who developed pneumonia, the bacteria count in saliva was decreased in 3 patients and increased in 1 patient after the oral care (Fig. 2). Interestingly, the bacteria count after the oral care was significantly higher in the patients who developed pneumonia than in those who did not (median: 7,550,000 vs. 2,980,577 CFU after oral care in the groups with and without pneumonia, respectively; $p<0.001$, Wilcoxon test) (Fig. 3).

Next, we sought to identify factors that potentially contributed to the occurrence of post-ESD pneumonia. Although patients with pneumonia were all men, male sex was not a statistically significant factor for pneumonia occurrence (Table 4). The presence of cerebrovascular disease was significantly associated with the occurrence of pneumonia ($p=0.03$), whereas neither

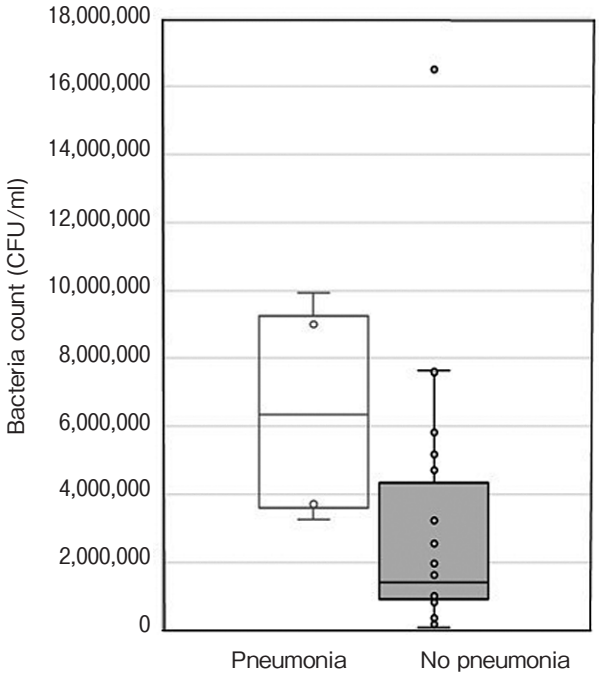


**Fig. 3** Comparison of bacteria count after oral care in the patients according to the presence or absence of pneumonia. $p<0.05$, pneumonia vs. no pneumonia. CFU, colony forming units.

**Table 2** Characteristics of patients who developed post-ESD pneumonia

| Case | Sex | Age (years) | Oral care | History of gastric surgery | Respiratory disease | Cerebrovascular disease | Diabetes mellitus |
|---|---|---|---|---|---|---|---|
| 1 | Male | 70 | + | − | − | − | − |
| 2 | Male | 69 | + | − | + | + | + |
| 3 | Male | 87 | − | + | − | − | − |
| 4 | Male | 65 | + | − | + | + | − |
| 5 | Male | 85 | + | − | − | − | − |

"+" indicates the presence of the disease and "−" indicates absence of the disease.

**Table 3** Comparison patients' characteristics between pneumonia and non-pneumonia groups

| | Pneumonia (n=5) | No pneumonia (n=55) | *P* value |
|---|---|---|---|
| CRP level (mg/l) | 3.77 ± 2.44 | 0.934 ± 1.12 | 0.00005* |
| WBC count (/μl) | 11,920 ± 2,163 | 8,650 ± 2,693 | 0.02* |
| Days of admission | 14.8 ± 4.96 | 11.7 ± 5.57 | 0.22 |
| Medical cost (yen) | 831,312 ± 197,676 | 622,980 ± 128,083 | 0.002* |

**P* value < 0.05

Significance between the groups were assessed by assessed by Wilcoxon's test.

Numbers indicate mean values ± SD. CRP, C-reactive protein, WBC, white blood cell.

diabetes mellitus nor smoking status was associated with pneumonia occurrence (Table 4). The incidence of underlying pulmonary diseases was higher in the pneumonia group (40% vs. 9.1%, pneumonia vs. non-pneumonia), but the difference did not reach the level of statistical significance ($p = 0.09$) (Table 4). Although the procedure time tended to be longer in the pneumonia group, the difference was not statistically different.

We then analyzed the medications used for sedation. When patients were divided into categories according to whether they received ≤70 mg, 71-105 mg, 106-140 mg, or ≥141 mg meperidine, the incidences of pneumonia in these groups were 0% (0/9), 7.8% (1/13), 18.2% (2/11), and 25.0% (2/8), respectively, revealing a significant increase of pneumonia incidence with increasing dose of meperidine (Table 5). In contrast, the use of pentazocine, midazolam, and diazepam were not significantly different between the pneumonia and non-pneumonia groups.

## Discussion

The current study showed that the presence of underlying cerebrovascular diseases and the drug used for sedation may have affected the incidence of post-ESD pneumonia, although the results did not fully clarify whether the impact of oral care affected the incidence of pneumonia under deep-sedation conditions.

The initial aim of the study was to determine whether oral care could prevent aspiration pneumonia. In 2015, the post-ESD pneumonia rate was 10.0% at Nagasaki University Hospital. Based on this fact, we estimated that the pneumonia detection rate would be approximately 15.0% over the first year of the study period with increased chest X-ray and CT. We also estimated that oral care would reduce the pneumonia rate to approximately 4.0%. Given these predictions, we estimated that 302 cases would be needed to attain a statistical power of 80% and derive statistically relevant results. The primary endpoint of this study was the rate

**Table 4** Potential factors related to pneumonia development

| | Pneumonia (n = 5) | No pneumonia (n = 55) | *P* value |
|---|---|---|---|
| Sex, n | | | |
| Male | 5 (100) | 47 (85.5) | 0.57 |
| Female | 0 (0.00) | 8 (14.5) | |
| Age (years), mean ± SD | 75.2 ± 10.1 | 73.4 ± 7.6 | 0.93 |
| History of gastric surgery, n (%) | 1 (20.0) | 6 (11.3) | 0.47 |
| Respiratory disease, n (%) | 2 (40.0) | 5 (9.09) | 0.09 |
| Cerebrovascular disease, n (%) | 2 (40.0) | 2 (3.67) | 0.03* |
| Diabetes mellitus, n (%) | 1 (20.0) | 15 (27.3) | 1.00 |
| Presence of oral care, n (%) | 4 (80.0) | 23 (41.8) | 0.36 |
| Procedure time (min), mean ± SD | 206 ± 222 | 135 ± 70.7 | 0.09 |

*$P$ value < 0.05

Age differences between Oral care and control care groups were assessed by Wilcoxon test. Fisher's exact test was used to detect the statistical difference between two nominal variables.

**Table 5** Association between meperidine dose and rate of post-ESD pneumonia

| | | Meperidine dose (mg) | | | |
|---|---|---|---|---|---|
| | | ≤70 | 71–105 | 106–140 | ≥141 |
| Pneumonia (n) | − | 9 | 12 | 9 | 6 |
| | + | 0 | 1 | 2 | 2 |
| Rate of pneumonia | | 0.00% | 7.80% | 18.2% | 25.0% |

$P = 0.04$, Cochran-Armitage test

"+" indicates the presence of the disease and "−" indicates absence of the disease

ESD, endoscopic submucosal dissection

of post-ESD pneumonia. However, only 61 patients agreed to enroll. Due to the low rate of case entry, enrollment was terminated at 3 years without further registration. The number of patients was not sufficient to effectively determine whether oral care could influence the incidence of pneumonia after ESD. The principle reason for refusal to participate was that the patients declined to visit the hospital multiple times for oral care, and the rate of such non-compliance was underestimated during the initial planning. Therefore, before applying a protocol of oral care for patients undergoing ESD at larger medical centers, the problem of non-compliance must be addressed, since patients visiting major medical centers often travel from remote areas and have underlying diseases that make multiple visits to the hospital difficult. To overcome these issues, more locally located dental clinics could offer comprehensive oral care in cooperation with the medical centers. To address these issues, another multi-center prospective study is being planned based on the current results.

There was no significant difference in pneumonia rate between the oral and non-oral care groups in this study. However, the bacteria count after oral care tended to be higher in those who developed pneumonia. Although additional studies are required, supplementary methods such as post-ESD oral care may ensure the optimal oral hygiene of patients.

Patients are not intubated in the case of deep sedation. Thus, the ability to eliminate saliva from the airway, *e.g.*, the extent of the gag reflex, may also largely determine the amount of aspiration. This study showed that pneumonia rates increased proportionally with meperidine dose. Meperidine is a widely used narcotic analgesic in Japan and can be efficiently used alone or with other sedative drugs, such as midazolam or other benzodiazepines [8]. In our study, although the dose of benzodiazepine did not affect the rate of pneumonia, that of meperidine did. Notably, the majority of patients with pneumonia received more than 105 mg of meperidine. In addition, 25% of patients who received more than 140 mg of meperidine presented with pneumonia. Previous research suggested a relationship between opioid use and the incidence of aspiration pneumonia after upper gastrointestinal ESD [12]. Meperidine is known to have a relatively strong inhibitory effect on gag reflexes, which may increase the risk of aspiration [13-15]. Our results suggest that endoscopists should be cautious regarding the extended use of opioids, especially meperidine [15, 16].

Generally, the dose of narcotics increases proportionally with the resection time during ESD performed under deep sedation. Akasaka *et al.* [17] have reported that a procedure time of > 5 h was an independent risk factor for post-procedural aspiration pneumonia. In another retrospective study, a procedure time of > 2 h was reported to be an independent factor for aspiration pneumonia after ESD performed under deep sedation [12].

Together with the results reported in previous studies, our present findings raise the question of whether all upper gastrointestinal ESD procedures should be performed under general anesthesia in order to avoid excessive use of narcotics and decrease the risk of aspiration. Indeed, in a study comparing the impact of general anesthesia and deep sedation on pneumonia occurrence during esophageal ESD [2], the rates of aspiration pneumonia were lower in the general anesthesia group, although not significantly so [2]. Given the inherent risk and the high cost of the medicines, the potential use of general anesthesia in ESD procedures will require further assessment.

Age > 75 years and male sex have been reported to be independent risk factors of aspiration pneumonia after ESD performed under deep sedation [12]. Although this study did not show significant differences in age or sex between the pneumonia and non-pneumonia groups, the absence of these relations may have been related to the relatively small number of subjects and the fact that 80% were men [12]. In this study, consistent with the results of previous studies, the presence of cerebrovascular disease was related to pneumonia occurrence [18]. Vascular brain disease is a known cause of dysphagia and aspiration [19]; thus, these patients require special attention as a high-risk group for post-ESD pneumonia.

In conclusion, this study did not prove that oral care is effective to prevent ESD-related pneumonia in deep sedative states. However, our results did underscore that patients with underlying cerebrovascular diseases and those requiring higher doses of sedative drugs should be monitored carefully for the occurrence of respiratory complications.

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