Randomized Clinical Trial - Necessity of Pharyngeal Anesthesia in Pharyngeal Observation during Transoral Upper Gastrointestinal Endoscopy: A Randomized Clinical Trial

Tomoyuki Hayashi (hayasix0917@gmail.com)
Kanazawa University
Yoshiro Asahina
Kanazawa University
Yasuhito Takeda
Kanazawa University
Masaki Miyazawa
Kanazawa University
Hajime Takatori
Kanazawa University
Hidenori Kido
Kanazawa University
Jun Seishima
Kanazawa University
Noriho Iida
Kanazawa University
Kazuya Kitamura
Kanazawa University
Takeshi Terashima
Kanazawa University
Sakae Miyagi
Kanazawa University
Tadashi Toyama
Kanazawa University
Eishiro Mizukoshi
Kanazawa University

Article

Keywords: Anesthesia, Endoscopy, Gastrointestinal, Midazolam, Randomized Controlled Trial

Posted Date: May 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1643576/v1

Abstract

BACKGROUND

Pharyngeal anesthesia's role in improving observational ability during upper gastrointestinal endoscopy is controversial. No randomized controlled trials have evaluated observational ability with and without pharyngeal anesthesia (PA + vs. PA- group) under sedation with midazolam. We report the non-inferiority of the PA- group in the pharyngeal observation success rate.

METHODS

This prospective, single-blinded, randomized study included 500 patients, randomly allocated to PA + or PA- groups (250 cases/group), undergoing transoral upper gastrointestinal endoscopy under intravenous sedation with midazolam.

RESULTS

The pharyngeal observation success rate was 72.0% and 84.0% in the PA- and PA + groups, respectively; non-inferiority in PA- group was not observed (p = 0.707). In the PA- group, observable sites were fewer (8.33 vs 8.86, p = 0.006), time was longer (67.2 vs. 58.2 s, p = 0.001), and pain scores were higher. Image quality at the posterior wall of oropharynx, vocal fold and pyriform sinus was significantly inferior in PA- group. Subgroup analysis showed a higher sedation level (Ramsay score ≥ 5); no differences in the pharyngeal observation success rate were observed between the groups.

CONCLUSION

Pharyngeal anesthesia may improve pharyngeal observation ability in the hypopharynx and reduce pain. However, this difference may be reduced with deeper sedation.

Introduction

Patients usually experience severe discomfort during transoral upper gastrointestinal endoscopy (UGE) because of the pain and strong gag reflex when the endoscope passes through the pharynx [1–3]. Topical pharyngeal anesthesia, such as lidocaine (spray or viscous solution), reduces transoral UGE-induced pain and the gag reflex [4–7].

According to a survey report, 0.0028% of UGE-related complications were due to pretreatment, and 0.00005% were fatal. The culprit drugs were sedative/analgesic-related and pharyngeal anesthesia-related in 46.5% and 8.3% of cases, respectively [8]. Thus, sedation/analgesic-related adverse events are more common than pharyngeal anesthesia-related ones. However, sedation alleviates anxiety and

discomfort in patients and improves their receptiveness and satisfaction with UGE [9]. Although the frequency of side effects of lidocaine is lower, anaphylactoid reactions and lidocaine toxicity caused by increased blood concentration, resulting in death, have been reported [10]. Therefore, lidocaine's side effects are not negligible. Several studies on the use of pharyngeal anesthesia under sedation with propofol have reported that pharyngeal anesthesia did not reduce the amount of propofol required, improve endoscopists' satisfaction, or improve pharyngeal discomfort or patient satisfaction [11–14]. However, currently, benzodiazepines are more commonly administered than propofol to obtain optimal sedation during UGE [9], as they do not require management by an anesthesiologist.

Considering these factors, the necessity of pharyngeal anesthesia in UGE under sedation with benzodiazepines is controversial. As previously reported, pharyngeal anesthesia before UGE improved endoscopy ease and patient tolerance [3]. However, the number of cases was small in each study, and the sedation method was not consistent. With advances in endoscopic instruments, narrow-band imaging (NBI) has helped improve early superficial pharyngeal carcinomas detection, resulting in a better prognosis [15–17]. Therefore, the importance of pharyngeal observation is increasing. However, endoscopic pharyngeal observation is difficult and careful observation of the pharynx while avoiding the gag reflex is essential to reduce the incidence of undetected cancers.

Experienced doctors can observe 86–90% of the sites without blind spots [18–19]. However, there are no reports on whether pharyngeal anesthesia affects pharyngeal observation in patients sedated with benzodiazepines.

Based on these considerations, we conducted a prospective, single-blinded, randomized clinical trial to compare the groups undergoing transoral endoscopy with and without pharyngeal anesthesia under sedation with benzodiazepines. In addition to evaluating the degree of pain, we assessed the pharyngeal observation quality between the two groups. If the observation quality in the group not being administered pharyngeal anesthesia was not inferior to the group to which it was administered, pharyngeal anesthesia would be considered unnecessary. Therefore, a non-inferiority trial was appropriate to test this hypothesis. Randomized controlled trials evaluating the patients' pain and pharyngeal observation ability with and without pharyngeal anesthesia under sedation with benzodiazepines are required.

Results

Figure 2 shows a flow chart of patient selection and allocation. Five hundred patients were enrolled and randomly allocated to the PA- and PA + groups. Coincidentally, 250 cases were assigned to each group. Patient demographics and clinical characteristics are shown in Table 1. Patients in both groups were similar. No statistically significant differences were observed for age, sex, height, weight, BMI, PS, drinking and smoking habits, the number of endoscopic procedures, and Ramsay score at sedation.

Table 1
Patient demographics and clinical characteristics

	PA- group (n = 250)	PA + group (n = 250)	p value
Age, years	65.1 ± 11.4	63.7 ± 12.6	0.295
Sex (male:female)	133:117 (53.2:46.8)	130:120 (52.0:48.0)	0.789
Body mass index	22.6 ± 3.9	23.0 ± 3.6	0.228
ECOG PS (0:1:≥2)	160:74:16 (64.0:29.6:6.4)	164:77:9 (65.6:17.6:3.6)	0.356
Drinking habit (never: sometimes: one or more times per week: every day)	119:48:34:49 (47.6:19.3:13.6:19.6)	127:54:24:45 (50.8:21.6:9.6:18.0)	0.474
Smoking habit (no: yes)	128:122 (51.2:48.8)	129:121 (51.6:48.4)	0.929
Number of endoscopies (1: 2–4: ≥5)	9:121:120 (3.6:48.4:48.0)	12:128:110 (4.8:51.2:44.0)	0.589
Ramsay score (≤ 2:3,4:≥5)	19:93:138 (7.6:37.2:55.2)	22:83:145 (8.8:33.2:58.0)	0.619
Values are expressed as the mean ± SD or n (%).			

The agreement rate between the two endoscopists was 97.2%, and the Kappa statistic was 0.916.

The pharyngeal observation success rate in the PA- group was 72.0% (95% confidence interval [CI]: 66.4–77.6%), while that in the PA + group was 84.0% (95% CI: 79.5–88.5%). The difference was − 19.2–-4.8% (p = 0.707, non-inferiority), and the non-inferiority of the PA- group was not demonstrated (Table 2). In the PA- group, one oropharyngeal cancer, and one hypopharyngeal cancer were detected. Table 3 shows the difference in the situation during endoscopy. The PA- group was inferior to the PA + group in the number of observable parts (0–10) (8.33 ± 2.32 vs. 8.86 ± 1.94, p = 0.006), pharyngeal observation time (67.2 ± 33.7 vs. 58.2 ± 27.1 s, p = 0.001), pain evaluated by VAS (1.21 ± 2.37 vs. 0.68 ± 1.78, p = 0.004), and the number of gag reflexes (3.83 ± 3.15 vs. 2.11 ± 2.49, p < 0.001). There were non-significant differences in adverse events, decrease in SpO_2 (12.0% vs. 10.0%, p = 0.475), decrease in blood pressure (1.2% vs. 0.4%, p = 0.623), and bradycardia (0.4% vs. 1.2%, p = 0.623) between the two groups.

Table 2
Non-inferiority test of the difference in the success rate of pharyngeal observation (based on a risk α of 0.025 [one-sided test], a statistical power of 80%, and a non-inferiority threshold [Δ] of 0.1).

PA- group (95% CI)	PA + group (95% CI)	Difference (95% CI)	p value (Non-inferiority)
72.0% (66.4–77.6%)	84.0% (79.5–88.5%)	-12.0% (-19.2%–-4.8%)	0.707
PA, pharyngeal anesthesia; CI, confidence interval			

Table 3
Differences in pharyngeal observation ability pain and adverse events during endoscopy.

	PA- group (n = 250)	PA + group (n = 250)	p value
Number of observable parts (0–10)	8.33 ± 2.32	8.86 ± 1.94	[a]0.006
Pharyngeal observation time, s	67.2 ± 33.7	58.2 ± 27.1	[b]0.001
Pain on visual analog scale	1.21 ± 2.37	0.68 ± 1.78	[c]0.004
Number of gag reflex	3.83 ± 3.15	2.11 ± 2.49	[d]0.000
Adverse events			
(Decrease in SpO_2)	30 (12.0%)	25 (10.0%)	0.475
(Decrease in blood pressure)	3 (1.2%)	1 (0.4%)	0.623
(Bradycardia)	1 (0.4%)	3 (1.2%)	0.623
PA, pharyngeal anesthesia; Values are expressed as the mean ± SD or n (%). a,b,c,d represent statistically significant figures.			

Table 4 shows the percentages of suitable quality images obtained at the 10 prescribed points. The percentage of suitable quality images at the posterior wall of the oropharynx (92.4% vs. 96.8%, p = 0.030), vocal fold (74.8% vs. 88.8%, p < 0.001), and right (74.4% vs. 88.4%, p < 0.001) and left pyriform sinus (76.4% vs. 88.0%, p = 0.001) were significantly inferior in the PA- than in the PA + group. There were no significant differences at any other points. The subgroup analysis of the lower level of sedation (Ramsay score ≤ 4, 217 cases) revealed that the pharyngeal observation success rate (61.6% vs. 81.9%, p = 0.001), number of pharyngeal observation sites (7.88 ± 2.55 vs. 8.89 ± 1.89, p = 0.001), and number of gag reflexes (3.97 ± 3.07 vs. 2.70 ± 2.73, p = 0.001) were significantly inferior in the PA- than in the PA + group. However, non-significant differences were found in pain evaluated by VAS (1.85 ± 2.91 vs. 1.27 ± 2.42, p = 0.113) and pharyngeal observation time (67.0 ± 32.9 vs. 59.8 ± 31.9 s, p = 0.104) (Table 5).

Table 4
Percentages of suitable quality images obtained at the ten tested points.

		PA- group (n = 250)	PA + group (n = 250)	p value
Uvula		88	91.2	0.241
Arch of the palate	Right	84.4	85.6	0.707
	Left	82.4	85.2	0.270
Wall of the oropharynx	Right	88.4	88	0.890
	Left	87.2	92.4	0.055
	Posterior	92.4	96.8	[a]0.030
Epiglottis		84.4	80.4	0.240
Vocal fold		74.8	88.8	[b]0.000
Pyriform sinus	Right	74.4	88.4	[c]0.000
	Left	76.4	88	[d]0.001
Total		**83.3**	**88.6**	
PA, pharyngeal anesthesia. a,b,c,d represent statistically significant figures.				

Table 5
Subgroup analysis of the level of sedation.

Ramsay score < 5	**PA- group (n = 112)**	**PA + group (n = 105)**	**p value**
Age, years	63.0 ± 11.1	61.3 ± 13.2	0.313
Sex (male:female)	63:49	55:50	0.567
Pharyngeal observation success rate	61.6% (69/112)	81.9% (86/105)	[a]0.001
Pharyngeal observable site	7.88 ± 2.55	8.89 ± 1.89	[b]0.001
Pain on visual analog scale	1.85 ± 2.91	1.27 ± 2.42	0.113
Pharyngeal observation time, s	67.0 ± 32.9	59.8 ± 31.9	0.104
Number of gag reflex	3.97 ± 3.07	2.70 ± 2.73	[c]0.001
Ramsay score ≥ 5	**PA- group (n = 138)**	**PA + group (n = 145)**	**p value**
Age, years	66.9 ± 11.3	65.4 ± 11.8	0.288
Sex (male:female)	70:68	75:70	0.866
Pharyngeal observation success rate	80.4% (111/138)	85.5% (124/145)	0.255
Pharyngeal observable site	8.70 ± 2.05	8.83 ± 1.97	0.562
Pain on visual analog scale	0.70 ± 1.66	0.25 ± 0.77	**[d]0.005**
Pharyngeal observation time, s	67.3 ± 34.4	56.7 ± 23.1	**[e]0.003**
Number of gag reflex	3.70 ± 3.22	1.68 ± 2.20	**[f]0.000**

PA, pharyngeal anesthesia; Values are expressed as the mean ± SD or n (%). a, b,c,d,e,f represent statistically significant figures

The subgroup analysis of the higher level of sedation (Ramsay score ≥ 5, 283 cases) revealed that pain evaluated by VAS (0.70 ± 1.66 vs. 0.25 ± 0.77, p = 0.005), pharyngeal observation time (67.3 ± 34.4 vs. 56.7 ± 23.1 s, p = 0.003), and the number of gag reflexes (3.70 ± 3.22 vs. 1.68 ± 2.20, p < 0.001) were significantly inferior in the PA- than in the PA + group. However, a non-significant difference between the two groups was found in the pharyngeal observation success rate (80.4% vs. 85.5%, p = 0.255) and the number of pharyngeal observation sites (8.70 ± 2.05 vs. 8.83 ± 1.97, p = 0.562) (Table 5). Figure 3 shows the subgroup analysis of patient's characteristics such as sex, age (over or under 70), BMI (over or under 25), alcohol intake (over or under 1 time/week), smoking, performance status (0 or over 1), antihypertensive drugs, psychotropic drugs, Ramsay score (over or under 5), and the number of examinations (over or under 5). In comparing BMI and Ramsay scores, p values were < 0.05.

Discussion

This is the first study to evaluate the pharyngeal observation ability in patients undergoing transoral UGE under sedation with, versus without, administration of topical pharyngeal anesthesia. Our study revealed that non-inferiority of non-pharyngeal anesthesia was not demonstrated in terms of the pharyngeal observation success rate; and the percentage of suitable quality images at the posterior wall of the oropharynx, vocal fold, and pyriform sinus was significantly inferior. However, in the subgroup analysis of a higher level of sedation, almost no differences in the pharyngeal observation success rate between with and without pharyngeal anesthesia were observed.

However, in ad hoc analysis, the PA + group had a significantly higher pharyngeal observation success rate than the PA- group ($p = 0.0012$). Naturally, it is not a preset test; however, the PA + group may have better pharyngeal observation ability than PA- group for patients who were administered intravenous anesthesia with midazolam.

The PA + group was significantly superior to the PA- group in terms of the number of observable pharyngeal parts (0.53 parts), observation time (9.0 s), pain measured using VAS (0.53 points), and the number of gag reflexes (1.72 times) owing to the advantages of pharyngeal anesthesia using lidocaine. These differences were presumably small absolute numerical numbers between groups. However, these were clinically important facts for endoscopists focusing on reducing patients' pain as much as possible. Pharyngeal anesthesia may be tolerated after weighing these differences against the side effects.

In the subgroup analysis of each pharyngeal site, the PA- group was statistically inferior to the PA + group in terms of observation of the posterior wall of the oropharynx, epiglottis, vocal fold, and right and left pyriform sinus. This difference could be attributed to multiple comparisons. It is suspected that the effect of anesthesia in the hypopharynx may be stronger in the PA + group; however, more cases need to be evaluated to prove the theory. Further studies on the relationship between the extent of hypopharyngeal anesthesia and pharyngeal observation ability are desirable because the pyriform sinus is the predilection site of pharyngeal cancer.

In the subgroup analysis for each variable, obese patients ($BMI \geq 25$) and patients with low sedation levels (Ramsay score < 5) may have low pharyngeal observation success rates in the PA- group. To clarify these differences, it is necessary to evaluate additional cases.

Detailed subgroup analysis of each sedation level revealed that the pharyngeal observation success rate and the number of observable sites were low in the PA- group at the low sedation level (Ramsay score $<$ 5). However, these differences were not observed at the high sedation level (Ramsay score ≥ 5). Based on our study findings, it is reasonable to presume that deep sedation reduces the disadvantage of not using pharyngeal anesthesia. This would be beneficial for patients who cannot use pharyngeal anesthesia because of allergies. Although the possibility of chance by multiple analyses cannot be ruled out, as deep sedation with propofol has shown that pharyngeal anesthesia is unnecessary, the deeper the sedation level, the lesser the pharyngeal anesthesia that might be required.

In the deep sedation group, pharyngeal anesthesia may further reduce pain and pharyngeal observation time. Although difficult to explain theoretically, this may be because pharyngeal anesthesia reduces the patients' pain and the difficulty in observation. Alternatively, considering that there is a similar tendency without significant difference in the low sedation group, it may not be relevant to sedation. A larger study is necessary to investigate this further.

Diagnostic transnasal endoscopy is proven to be more tolerable than the transoral approach (23,24). Furthermore, during the COVID-19 pandemic, transnasal endoscopy has proven to be beneficial in terms of less aerosol spreading (25). However, transoral endoscopy models have magnification and better image quality. Therefore, many endoscopists prefer it.

This study had some limitations. First, it was carried out at a single institution. Second, it was single-blind because the patients knew whether they were administered pharyngeal anesthesia or not. The PA- group did not receive a placebo intervention because of the difficulty of creating a placebo with a flavor similar to lidocaine. Thus, awareness of whether pharyngeal anesthesia was administered or not, might have altered their mental state and affected the outcome. Third, our study did not evaluate the postcricoid area. The nasal Valsalva or sniffing position was reported to improve examination in transoral endoscopy (26,27); however, we did not adopt such methods. Future studies are needed to explore these methods. Fourth, no synthetic opioid analgesics such as pethidine were used as a premedication. However, our findings will be important for facilities still unable to use them. Fifth, high-risk patients with pharyngeal cancer often have a history of alcohol drinking and may be tolerant to sedation. Such patients are considered to be more suitable for participation. Sixth, the definition of successful pharyngeal observation formulated by us may seem controversial among experts. Thus far, no consensus exists among experts in this regard. Hence, it is desirable to establish clear criteria for future clinical research

Conclusion

Not administering pharyngeal anesthesia did not demonstrate non-inferiority of pharyngeal observation ability. Pharyngeal anesthesia may improve pharyngeal observation ability, especially in the hypopharynx, and reduce the patients' pain. However, with deeper sedation, this difference may be reduced.

Methods

Study design

This single-center prospective, single-blinded, randomized study was conducted in Kanazawa University Hospital, Ishikawa, Japan. Patients were randomized into groups with or without pharyngeal anesthesia by computer-generated numerical codes by the information manager (simple randomization, allocation ratio 1:1).

After adopting the pharyngeal anesthesia protocols mentioned below, the first image upon insertion of the endoscope was captured, followed by six and four endoscopic images of the oropharynx and

hypopharynx, respectively. The last image was captured before insertion into the esophagus. Overall, 12 NBI images were obtained per patient. We also measured the time from the first image to insertion into the esophagus. Once it became impossible to obtain images owing to the continuous gag reflex, the endoscope was inserted into the esophagus. Hence, the first and the last images were used only for time measurement.

The physicians were required to undergo more than half a year of pharyngeal observation training. Two endoscopists (T.H. and Y.A.) assessed whether the 10 images were appropriate (Fig. 1). They were blinded to the allocation group and were independent of the examining physicians. Regarding previous reports [18–19], the definition of an appropriate image required fulfillment of three criteria. The first is that the image was taken at the appropriate location; second, that the image was focused; and third, that the mucus had been removed, and the pharyngeal mucosa color in the images could be evaluated. A consensus was reached upon discussion among other expert endoscopists in case of disagreement.

The following data were recorded for each patient after endoscopy: age, sex, body mass index (BMI), performance status (PS) of Eastern Cooperative Oncology Group, drinking and smoking habits, and the number of endoscopic experiences. Subjective pain symptoms were evaluated using an 11-point visual analog scale (VAS), where 10 points indicated the most severe pain, and 0 indicated no pain.

Patients

Patients aged ≥ 20 years undergoing transoral UGE under intravenous sedation with midazolam between July 2019 and July 2020 were asked for written informed consent before the endoscopy. We excluded patients who refused to participate in the study, who had previously undergone surgical resection for pharyngeal or laryngeal cancer, or those with a severely damaged, difficult-to-evaluate pharynx. Other exclusion criteria were lesions in the pharynx requiring biopsy or magnified observation, emergency endoscopy such as gastrointestinal bleeding or food impaction, lidocaine allergy, psychosis or psychotic symptoms, and those deemed unfit to participate in the study by the investigator.

Anesthesia protocols

Patients who received pharyngeal anesthesia (PA + group) were asked to swallow 40 mg (five puffs) of lidocaine (Xylocaine Pump Spray 8%; AstraZeneca, Osaka, Japan), while the PA- group were not asked to swallow anything. The examining physicians were blinded to the randomization. To maintain a single-blind format, they entered the room only after premedications, including pharyngeal anesthesia, were administered.

Endoscopic examinations

All endoscopic procedures were carried out using a magnifying endoscope (GIF-H290Z; Olympus Medical Systems, Tokyo, Japan) with a hood attachment (MAJ-1990; Olympus Medical Systems). The video endoscopy system used in this study comprised a video processor (EVIS LUCERA ELITE CV-290; Olympus Medical Systems) and a light source (EVIS LUCERA ELITE CLV-290SL; Olympus Medical Systems). Afterward, pharyngeal anesthesia was administered as described in “Anesthesia protocols.”

Procedures were carried out under sedation with midazolam (Midazolam Injection; Sandoz, Tokyo, Japan). It was administered at 0.05 mg/kg or with reference to the information regarding previous benzodiazepine consumption if it existed. This amount was determined by examining physicians who were blinded to allocation results. The pharynx was assessed at the beginning of each examination, and standard endoscopy was carried out after the pharyngeal examination. In case pharyngeal lesions were detected, the lesions were evaluated by magnification after the pharyngeal examination because it is necessary to measure the pharyngeal observation time. The number of gag reflex events was counted during pharyngeal observation by the examining physicians and recorded promptly after endoscopy.

Outcome measures

The main outcome was the difference in the pharyngeal observation success rate between the PA- and PA + groups. We defined successful pharyngeal observation as being able to take appropriate images in 8 or more of the 10 sites within 120s. When experienced endoscopists observe the pharynx, an average of 9.0 [18] and 8.6 [19] will be observed out of 10 sites. In a previous study, when still images and videos were compared in cases with ≥ 8 imaging sites, almost all the test sites could be confirmed in the video. However, with ≤ 7 imaging sites, significantly lower sites could be examined [20]. Moreover, the assessments of the two evaluator endoscopists were significantly different in such cases. Therefore, pharyngeal observation could not be defined as successful [20].

Hence, the quality of pharyngeal observations might improve when the observation time is longer. However, a longer time results in a significant delay in the examination, which is unacceptable in routine screening. There is no absolute standard for pharyngeal observation time; therefore, we postulated that 15 UGEs would be performed in 3 hours (12 min/UGE), considering a reported average time for pharyngeal observation of 69s [18]. If the examination time/case was extended by 51s, only 14 UGEs/hour would be possible, which is not acceptable. Hence, a successful pharyngeal observation could be completed within 69 + 51 = 120s.

The secondary outcomes were as follows: (1) a difference in the number of observable pharynx sites; (2) a difference in endoscopy-associated pain; (3) a difference in the pharyngeal observation time; (4) subgroup analysis of the level of sedation by Ramsay score; (5) adverse effects of lidocaine including decreased SpO_2 (< 90% or decrease of more than 4% for < 94%), decreased blood pressure (systolic blood pressure < 90mmHg), and bradycardia (< 60 / bpm or decrease of more than 10%) [21]; and (6) the percentages of suitable quality images obtained at the 10 prescribed points.

Statistical analysis

The non-inferiority of the PA- group to the PA + group was examined. An 81.8% success rate was reported when the pharyngeal observation success was defined as above [19]. In this study, we referred to the Food and Drug Administration standard [22]; therefore, the non-inferiority threshold [Δ] was set to 10%. It was estimated that at least 468 cases were required to detect statistically significant differences, admitting a

type I error rate of 0.025 (one-sided test) and statistical power of 80%. Therefore, we have determined that it was necessary to include a total of 500 cases in consideration of dropouts.

Continuous variables are expressed as mean (standard deviation [SD]), and comparisons between groups were performed using the Student's t-test or Mann Whitney U test (not approximately, normally distributed). Categorical variables are expressed as percentages, and comparisons between groups were performed using Fisher's exact tests. The level of statistical significance was defined as a P-value < 0.05. Only the researchers performed the collection and aggregation of data. All statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC) and Stata 17 (Stata Corp, College Station, TX).

Declarations

Clinical Trial Number: jRCTs041190031

Acknowledgments

The authors thank all the endoscopy medical staff at Kanazawa University Hospital.

Author Contribution

Conception or design of the work: Tomoyuki Hayashi; Data collection: Tomoyuki Hayashi; Data analysis and interpretation: Tomoyuki Hayashi, Sakae Miyagi, Tadashi Toyama; Drafting the article: Tomoyuki Hayashi; Critical revision of the article: Tomoyuki Hayashi. All authors have reviewed the article and approved the submitted final draft.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Conflict of Interest Statement

The authors have no conflicts of interest to declare."

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki, Clinical Trials Act, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and all other applicable laws and guidelines in Japan. The protocol of this study was approved by the Institutional Review Board at Kanazawa University Hospital on April 25, 2019. We registered this study at the Japan Registry of Clinical Trials (jRCTs041190031).

Funding Sources

None

References

1. Leslie, K. & Stonell, C. A. Anaesthesia and sedation for gastrointestinal endoscopy. Curr Opin Anaesthesiol **18**, 431–436 (2005).
2. Campo, R. et al. Identification of factors that influence tolerance of upper gastrointestinal endoscopy. Eur J Gastroenterol Hepatol **11**, 201–204 (1999).
3. Mogensen, S. et al. New lidocaine lozenge as topical anesthesia compared to lidocaine viscous oral solution before upper gastrointestinal endoscopy. Local Reg Anesth **5**, 17–22 (2012).
4. Shaoul, R., Higaze, H. & Lavy, A. Evaluation of topical pharyngeal anaesthesia by benzocaine lozenge for upper endoscopy. Aliment Pharmacol Ther **24**, 687–694 (2006).
5. Evans, L. T., Saberi, S., Kim, H. M., Elta, G. H. & Schoenfeld, P. Pharyngeal anesthesia during sedated EGDs: is "the spray" beneficial? A meta-analysis and systematic review. Gastrointest Endosc **63**, 761–766 (2006).
6. Hwang, S. H., Park, C. S., Kim, B. G., Cho, J. H. & Kang, J. M. Topical anesthetic preparations for rigid and flexible endoscopy: a meta-analysis. Eur Arch Otorhinolaryngol **272**, 263–270 (2015).
7. Watanabe, J. et al. Lidocaine spray versus viscous lidocaine solution for pharyngeal local anesthesia in upper gastrointestinal endoscopy: Systematic review and meta-analysis. Dig Endosc **33**, 538–548 (2021).
8. Furuta, T., Kato, M., Ito, T., Inaba, T., Komura, N., Katanuma, A., et al. 6th report of endoscopic complications: results of the Japan Gastroenterological Endoscopy Society Survey from 2008 to 2012. Gastroenterol Endosc. **58**, 1466–91 (2016).
9. Guidelines for sedation in gastroenterological endoscopy. Dig Endosc **27**, 435–449 (2015).
10. Bahar, E. & Yoon, H. Lidocaine: A Local Anesthetic, Its Adverse Effects and Management. Medicina (Kaunas) **57**, 782 (2021).
11. Jeong, J. et al. Propofol alone prevents worsening hepatic encephalopathy rather than midazolam alone or combined sedation after esophagogastroduodenoscopy in compensated or decompensated cirrhotic patients. Eur J Gastroenterol Hepatol **32**, 1054–1061 (2020).
12. Kim, D. B. et al. Propofol compared with bolus and titrated midazolam for sedation in outpatient colonoscopy: a prospective randomized double-blind study. Gastrointest Endosc **93**, 201–208 (2021).
13. de la Morena, F. et al. Usefulness of applying lidocaine in esophagogastroduodenoscopy performed under sedation with propofol. World J Gastrointest Endosc **5**, 231–239 (2013).
14. Sun, X. et al. Topical pharyngeal anesthesia provides no additional benefit to propofol sedation for esophagogastroduodenoscopy: a randomized controlled double-blinded clinical trial. Sci Rep **8**, 6682 (2018).
15. Muto, M. et al. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer **101**, 1375–1381 (2004).

16. Muto, M., Katada, C., Sano, Y. & Yoshida, S. Narrow band imaging: a new diagnostic approach to visualize angiogenesis in superficial neoplasia. Clin Gastroenterol Hepatol **3**, S16-20 (2005).
17. Muto, M. et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol **28**, 1566–1572 (2010).
18. Tsuji, K. et al. Use of transoral endoscopy for pharyngeal examination: cross-sectional analysis. Dig Endosc **26**, 344–349 (2014).
19. Hayashi, T. et al. Lidocaine spray alone is similar to spray plus viscous solution for pharyngeal observation during transoral endoscopy: a clinical randomized trial. Endosc Int Open **5**, E47-E53 (2017).
20. Hayashi, T., Kitamura, K., Kaneko, S., Nakagawa, H., Nio, K., Horii, R., et al. Comparison of still and moving image of pharyngeal observation in upper gastrointestinal endoscopy. Gastroenterol Endosc. 63, 901 (2021).
21. Collinsworth, K. A., Kalman, S. M. & Harrison, D. C. The clinical pharmacology of lidocaine as an antiarrhythymic drug. Circulation **50**, 1217–1230 (1974).
22. Chow, S.C., Shao, J., Wang, H., Lokhnygina, Y. Sample size calculations in clinical research. 3rd ed. Chapman & Hall/CRC, (2017).
23. Sami, S. S. et al. Performance characteristics of unsedated ultrathin video endoscopy in the assessment of the upper GI tract: systematic review and meta-analysis. Gastrointest Endosc **82**, 782–792 (2015).
24. Parker, C., Alexandridis, E., Plevris, J., O'Hara, J. & Panter, S. Transnasal endoscopy: no gagging no panic. Frontline Gastroenterol **7**, 246–256 (2016).
25. Phillips, F., Crowley, J., Warburton, S., Gordon, G., Parra-Blanco, A. Quantifying aerosol and droplet generation during upper and lower gastrointestinal endoscopy: whole procedure and event-based analysis. COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv.
26. Draper, M.R., Blagnys, B., Premachandra, D.J. To 'EE' or not to 'EE'. J Otolaryngol. **36**(**3**), 191–5 (2007).
27. Mori, S., Yokoyama, A., Matsui, T., Maruyama, K., Omori, T., Kawakubo, H., et al. Endoscopic screening for upper aerodigestive tract cancer in alcoholics using wide visualization of the pharynx and esophageal iodine staining procedures. Gastroenterol Endosc. 53: 1426–34 (2011).

Figures

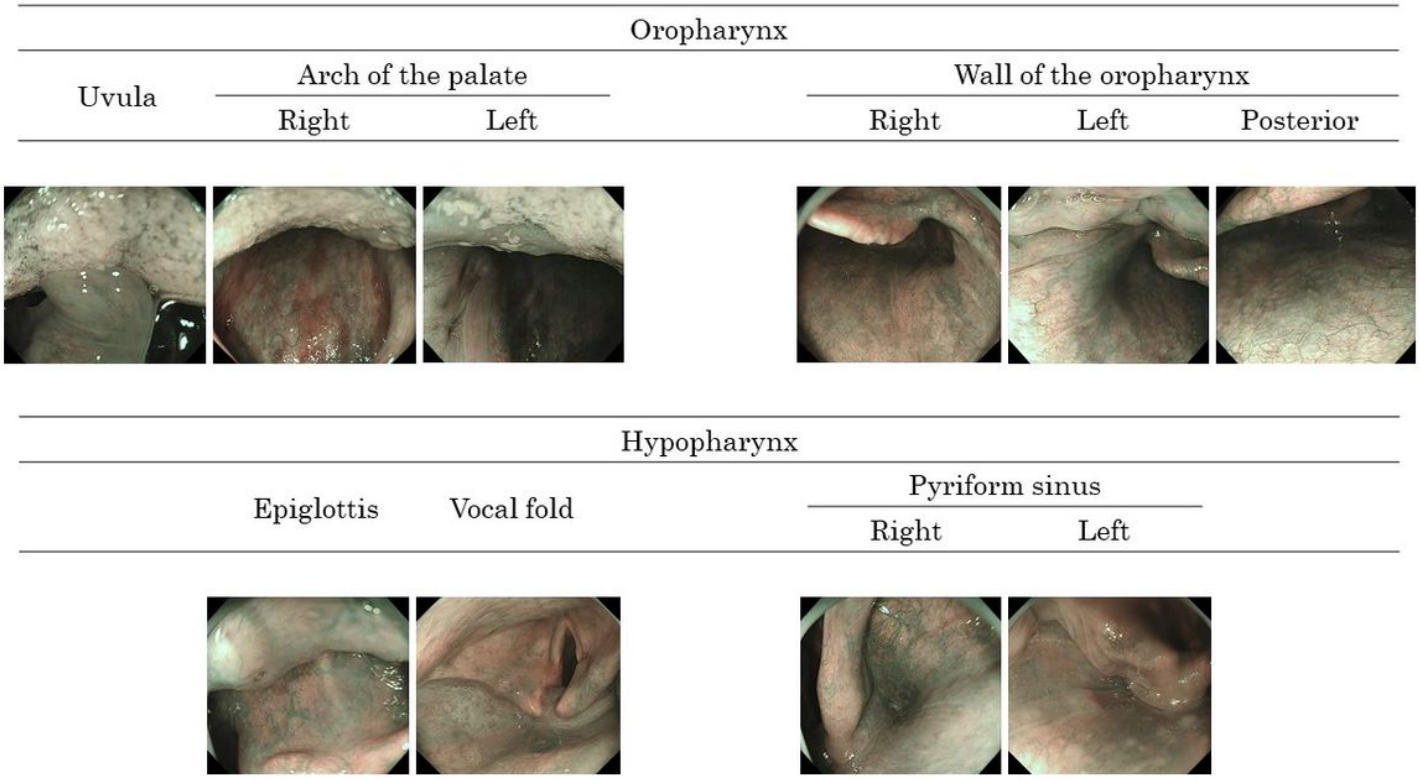

Figure 1

The ten images of the oropharynx and hypopharynx. The definition of a high-quality image required three criteria: 1) the image was taken at the appropriate location; 2) the image was focused; 3) mucus had been removed, and it was possible to evaluate the color of the pharyngeal mucosa.

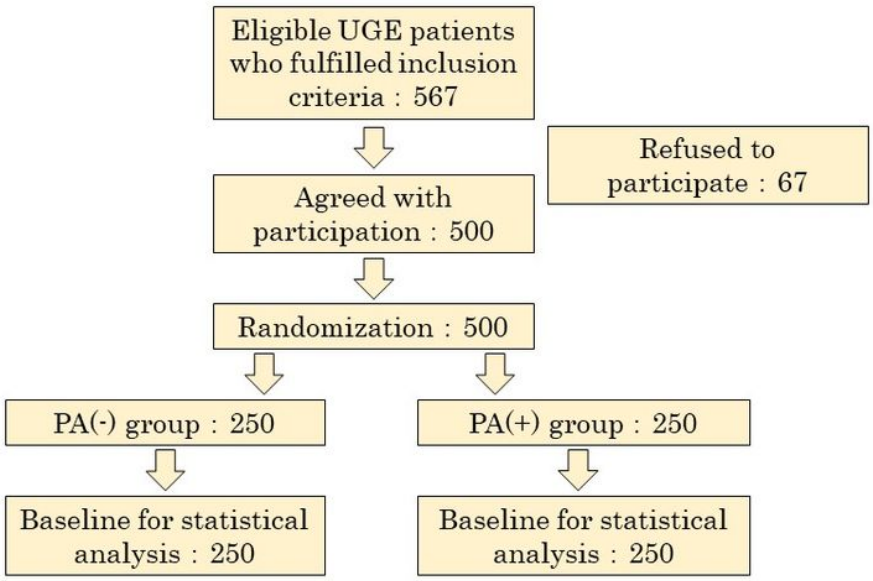

Figure 2

Flow chart of patient enrollment.

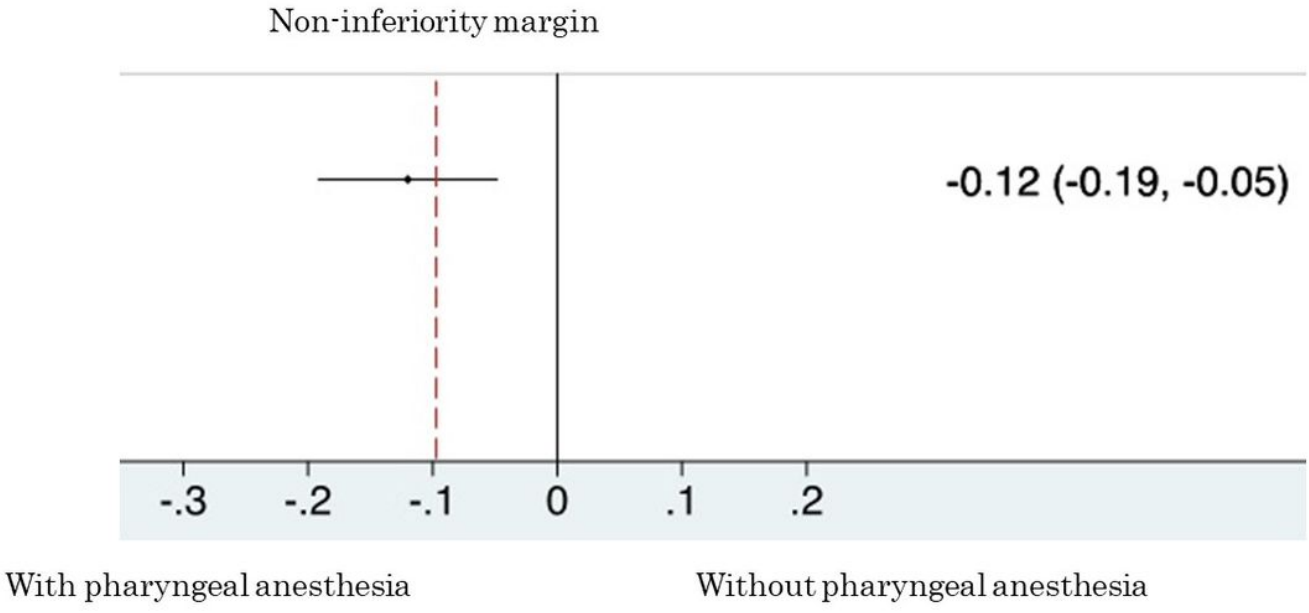

Figure 3

Subgroup analysis of patients’ characteristics.