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Impact of balloon inflation on the insertion of endoscopic ultrasound: a prospective, randomized controlled trial

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ABSTRACT

Background and study aims During endoscopic ultrasound (EUS), patients may experience severe discomfort. The radial echoendoscope has a balloon around its tip. Balloon inflation prior to insertion may reduce contact injury and pharyngeal pain. The purpose of this study was to investigate the effect of balloon inflation on pharyngeal pain during insertion.

Patients and methods Patients who underwent radial EUS for pancreatobiliary disease were randomized into standard insertion or balloon-inflated insertion. The primary outcome was the proportion of moderate-to-severe pharyngeal pain. Secondary outcomes were the degree of pharyngeal pain, risk factors for moderate pharyngeal pain, procedure-related adverse events, and pharyngeal pain depending on the experience of the endoscopist.

Results A total of 481 patients were randomized into two groups: standard insertion (238) and balloon inflation (243). No statistically significant differences in proportion of moderate-to-severe pain were found (26.5 % vs. 20.2 %, $P = 0.107$). Balloon inflation (HR 0.65; 95 % CI (0.42–0.98, $P = 0.041$) was a protective factor against moderate pain. Balloon inflation reduced the proportion of patients with moderate-to-severe pain when performed by physicians with less than 3months of experience with EUS (44.7 % vs. 25.3 %, $P = 0.012$).

Conclusion Balloon inflation did not reduce the absolute degree of post-procedural pain with EUS, but it reduced the number of patients with moderate-to-severe pain when performed by physicians with less than 3 months of experience.

Introduction

Endoscopic ultrasound (EUS) has become an indispensable modality for diagnosis of pancreatobiliary diseases. Studies actively investigating interventional therapy with EUS are expected to widen the clinical application of EUS [1,2]. Echoendoscope is thicker than the conventional upper gastrointestinal endoscope, and the end of the scope with the transducer is rigid, which causes discomfort during insertion. In addition, visibility is poor during insertion due to the nature of the side-view endoscope [3]. Therefore, echoendoscope is more difficult to insert than the conventional endoscope and may be associated with additional complications. In general, upper endoscopy is associated with minor throat discomfort. In a single prospective study, approximately 2.5 % of patients reported seeking medical services due to such discomfort [4]. In the case of endoscopic retrograde cholangiopancreatography (ERCP), one-third to one-half of patients felt pain and discomfort and

6 % reported moderate-to-severe pain in the neck [5]. In the case of echoendoscope with a thicker diameter and side view, more severe and frequent discomfort can be expected.

A balloon is attached around the tip of the probe, which can be inflated with water through an endoscope. Usually, the balloon is inflated after positioning the echoendoscope appropriately. If the balloon is inflated at the time of insertion, it may reduce pharyngeal mucosal injury and subsequent complications caused by the hard tip of the scope. In this study, we evaluated the degree of neck pain after the procedure with balloon inflation, compared with standard insertion.

Patients and methods

Patients

A single-blinded, prospective, randomized study was performed from October 2016 to September 2018 at a single tertiary center in Seoul, Korea. This study was approved by the institutional review board of Seoul National University Hospital and registered in ClinicalTrials.gov (NCT02924948). Patients aged at least 20 years who underwent radial EUS for diagnosis of pancreatobiliary disease were enrolled. Patients who underwent linear EUS were excluded from the study. Informed consent was obtained from all patients.

Absent any previous study of complications with EUS, 6 % of patients with moderate-to-severe pharyngeal pain were estimated based on ERCP study [5]. Balloon inflation was assumed to reduce the rate of moderate-to-severe pain by nearly 67 %. A total of 482 subjects including 241 in each group were calculated to provide a power of 80 % and $\alpha = 0.05$. Randomization was done by assigning patients according to a computer-generated random number list with 1:1 allocation using a random block size of 4 or 6 by personnel not involved in the trial.

Intervention

All interventions were performed by six clinical fellows (A-F) using a radial-array echoendoscope (GF-UE260; Olympus) with a balloon (MH-303; Olympus) applied at the tip. The first 6 months were studied by A and B, the next year by C and D, and the last 6 months by E and F. Since A and B had 6 to 7 months of EUS experience at the time of study participation, the EUS procedure performed by A and B were classified as more than 6 months. C and D had several days of EUS experience when they participated in the study, and about 1 year of experience at the end of the study participation. The procedures, which were performed by C and D for 1 year, were classified into three categories; less than 3 months, 3 to 6 months, and more than 6 months. E and F had several days of experience with EUS at the time of participation. They accumulated about 6 months of experience at the end of the study. The procedures performed by these patients were divided into two categories; less than 3 months and 3 to 6 months.

After conscious sedation with only midazolam (0.05 mg/kg), the randomized assignments were opened by an attending nurse before inserting EUS. In the case of patients who were assigned to the balloon inflation group, the EUS was inserted with a half-inflated balloon. Except for the insertion, the subsequent procedure was no different between the two groups.

After patients recovered from sedation with full consciousness with the ability to engage in adequate conversation. Nurses who did not participate in the endoscopy procedure evaluated the degree of pharyngeal pain with the Numeric Rating Scale (NRS) which is validated in most settings [6, 7].

Outcomes

The primary outcome was the rate of moderate-to-severe pharyngeal pain with an NRS score of 4 or more [8, 9] according to the insertion method. Secondary outcomes included the degree of pharyngeal pain, rates of insertion failure at first attempt and balloon loss according to the insertion method, adverse events (AEs), the difference in pain level according to the physicians' experience. Balloon loss was defined as the balloon not inflating due to damage during insertion. Risk factors for post-procedural pain were also evaluated.

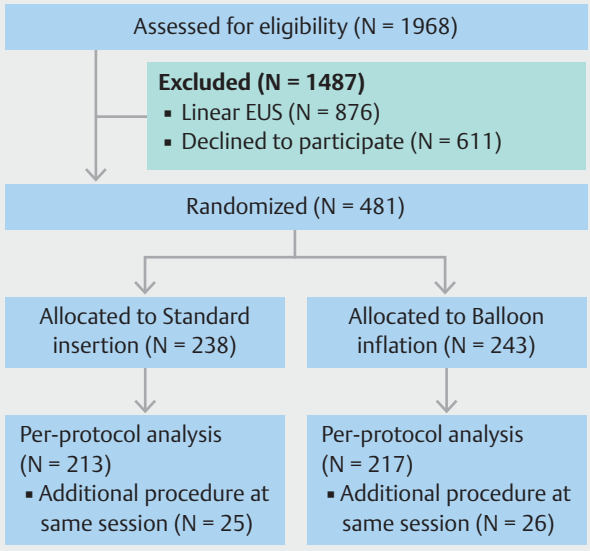
Statistical analysis

The analyses were performed according to intention-to-treat (ITT) analysis and per-protocol (PP) analysis. ITT analysis was performed with all the subjects and PP analysis was performed after exclusion of subjects who underwent additional endoscopy in the same session. Data are expressed as a number and percentage for categorical variables, and as the mean ± standard deviation (SD) or the median for continuous variables. Significance of differences in clinical parameters between groups was assessed using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables distributed normally were analyzed using the *t*-test, otherwise, the Mann-Whitney U test was used. Risk factors for pharyngeal pain were evaluated by logistic regression analysis. Demographic, disease-related, and procedure-related factors were assessed in the analysis. Factors with a significance level of 0.1 based on the univariable analysis were considered in the multivariable analysis. Results were expressed as hazard ratios (HRs) and 95 % confidence interval (CI). Statistical significance was assumed at a confidence level of 0.05. Statistical analyses were performed using SPSS 23 (SPSS, Chicago, Illinois, United States).

Results

Patients' clinical characteristics

From October 2016 to September 2018, a total of 1,092 patients underwent radial EUS for evaluation of pancreatobiliary disease. We obtained informed consent from 481 of these patients and registered 238 for standard insertion and 243 for balloon inflation. These patients constituted the ITT population. Fifty-five patients were excluded from the per-protocol analysis because of additional endoscopy in the same session with radial EUS. The per-protocol analysis included 213 cases in standard insertion and 217 cases in balloon inflation (▶ **Fig. 1**). Demographic, disease-related and procedure-related characteristics of the two groups were not significantly different (▶ **Table 1**).



▶ **Fig. 1** Flowchart of the study.

Primary outcome

One hundred and twelve patients (23.3 %) reported moderate-to-severe pharyngeal pain after the procedure. The ratio of patients reporting moderate-to-severe pain with an NRS score of 4 or more was slightly lower in the balloon insertion group, without any statistical significance (26.5 % vs. 20.2 %; P = 0.107). In PP analysis, the difference in the ratio of moderate-to-severe pain was also lower in the balloon group but was not statistically significant (23.9 % vs. 16.1 %; P = 0.053, ▶ **Table 2**).

Secondary outcomes

Post-procedural pain score was slightly lower in the balloon group, but did not reach statistical significance (2.04 ± 2.39 vs. 1.83 ± 2.11, P = 0.297). Rate of insertion failure at first attempt (standard vs. balloon 8.4 % vs. 5.8 %; P = 0.289) and the rate of balloon loss (standard vs. balloon 8.0 % vs. 6.6 %; P = 0.601) were not significantly different between the two groups. PP analysis did not show any significant differences in those outcomes, either (▶ **Table 3**). During the trial period, no procedure-related AEs such as bleeding, perforation, or subsequent infection occurred.

Risk factors for pharyngeal pain

Risk factors for moderate-to-severe pharyngeal pain were evaluated according to the various characteristics. Gender, age, observation time, patient's prior EUS experience, the endoscopist's experience at time of procedure, and the insertion method were considered as variables in logistic regression analysis. Age and observation time were classified based on interquartile ranges. Female gender and endoscopist's experience with less than 3 months were associated with severe pain, whereas older age (>66 years) and balloon inflation were associated with less pain in multivariable analysis (▶ **Table 4**).

We compared the proportion of patients experiencing moderate-to-severe pharyngeal pain according to the insertion method in patients with identified risk factors. No differences based on the insertion method were found in female (30.7 % vs. 22.8 %, P = 0.177) or younger patients (29.1 % vs. 23.6 %, P =

▶ **Table 1** Baseline characteristics of patients.

	Total	Standard (N = 238)	Balloon (N = 243)	*P* value
Age (mean, range)	57.3 (24–80)	57.1 (26–80)	57.6 (24–80)	0.675
Gender				0.927
Male	228	112 (47.1 %)	116 (47.7 %)	
Female	253	126 (52.9 %)	127 (52.3 %)	
Etiology				0.121
Pancreas	232	124 (52.1 %)	108 (44.4 %)	
Biliary tract	258	119 (50.0 %)	139 (47.2 %)	
Patients' experience				0.581
No	450	221 (92.9 %)	229 (94.2 %)	
Yes	31	17 (7.1 %)	14 (5.8 %)	
Endoscopists' experience				0.865
>6 months	156	78 (32.8 %)	78 (32.1 %)	
3–6 months	170	84 (35.3 %)	86 (35.4 %)	
≤3 months	155	76 (31.9 %)	79 (32.5 %)	
Observation time (min, mean±SD)	6.2 ± 4.2	6.0 ± 3.9	6.5 ± 4.4	0.232

SD, standard deviation

▶ **Table 2** Primary outcome: moderate-to-severe pharyngeal pain according to the insertion method.

ITT analysis	**Standard (N = 238)**	**Balloon (N = 243)**	***P* value**
NRS < 4	175 (73.5 %)	194 (79.8 %)	0.107
NRS ≥ 4	63 (26.5 %)	49 (20.2 %)	
PP analysis	**Standard (N = 213)**	**Balloon (N = 217)**	***P* value**
NRS < 4	162 (76.1 %)	179 (83.9 %)	0.053
NRS ≥ 4	51 (23.9 %)	38 (16.1 %)	

ITT, intention-to-treat; PP, per-protocol; NRS, numeric rating scale

▶ **Table 3** Secondary outcomes according to the insertion method.

ITT analysis	**Standard (N = 238)**	**Balloon (N = 243)**	***P* value**
NRS (mean±SD)	2.04 ± 2.39	1.83 ± 2.11	0.297
Insertion at 1st attempt			0.289
Success	218 (91.6 %)	229 (94.2 %)	
Fail	20 (8.4 %)	14 (5.8 %)	
Loss of balloon			0.601
No	219 (92.0 %)	227 (93.4 %)	
Yes	19 (8.0 %)	16 (6.6 %)	
Procedure-related complications	0	0	ns
PP analysis	**Standard (N = 213)**	**Balloon (N = 217)**	***P* value**
NRS (mean±SD)	1.70 ± 2.17	1.65 ± 2.01	0.651
Insertion at 1st attempt			0.274
Success	194 (91.1 %)	204 (94.0 %)	
Failure	19 (8.9 %)	13 (6.0 %)	
Loss of balloon			0.854
No	197 (92.5 %)	202 (93.1 %)	
Yes	16 (7.5 %)	15 (6.9 %)	
Procedure-related complications	0	0	ns

ITT, intention-to-treat; PP, per-protocol; NRS, numeric rating scale; SD: standard deviation

0.367). In patients who were undergoing EUS by endoscopists with less than 3 months' experience, pain score was significantly higher than in other groups (< 3 months: 2.4, 3 – 6 months: 1.7, > 6 months: 1.7, $P = 0.016$). However, balloon inflation decreased the proportion of patients experiencing moderate-to-severe pharyngeal pain when performed by endoscopists with less than 3 months' experience (44.7 % vs. 25.3 %, $P = 0.012$) (▶ **Fig. 2**).

Discussion

Results of this study indicate that EUS insertion with an inflated balloon was effective in terms of post-procedural pain without disturbing procedure, especially performed by physicians with less than 3 months of experience.

Although there was no statistically significant difference in average pain intensity and rate of moderate-to-severe pain according to insertion method. Balloon inflation tended to be lower than the standard method in both outcomes. In addition, no increase was found in rates of insertion failure or balloon loss with increased diameter due to the inflated balloon. Balloon inflation did not hinder the procedure.

▶ **Table 4** Risk factors for pharyngeal pain.

Factors	N	Univariable		Multivariable	
		HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Gender					
▪ Male	228	1		1	
▪ Female	253	2.263 (1.434–3.572)	<.001	2.168 (1.349–3.483)	0.001
Age					
▪ <50	121	1		1	
▪ 50–58	121	0.960 (0.550–1.678)	0.887	0.945 (0.528–1.691)	0.945
▪ 59–66	121	0.810 (0.458–1.432)	0.469	0.779 (0.429–1.416)	0.413
▪ >66	118	0.414 (0.217–0.790)	0.007	0.341 (0.174–0.671)	0.002
Insertion method					
▪ Standard	238	1		1	
▪ Balloon	243	0.666 (0.427–1.040)	0.074	0.645 (0.423–0.983)	0.041
Patients' experience					
▪ No	450	1			
▪ Yes	31	0.912 (0.383–2.176)	0.836		
Observation time (min)					
▪ ≤3.3	87	1			
▪ 3.4–4.9	119	0.935 (0.523–1.675)	0.822		
▪ 5.0–7.7	116	0.824 (0.452–1.503)	0.528		
▪ >7.7	159	1.057 (0.594–1.882)	0.851		
Endoscopists' experience					
▪ ≥6 months	156	1		1	
▪ 3~6 months	170	1.015 (0.582–1.773)	0.957	1.095 (0.618–1.942)	0.755
▪ <3 months	155	2.409 (1.431–4.054)	0.001	2.861 (1.658–4.938)	<0.001

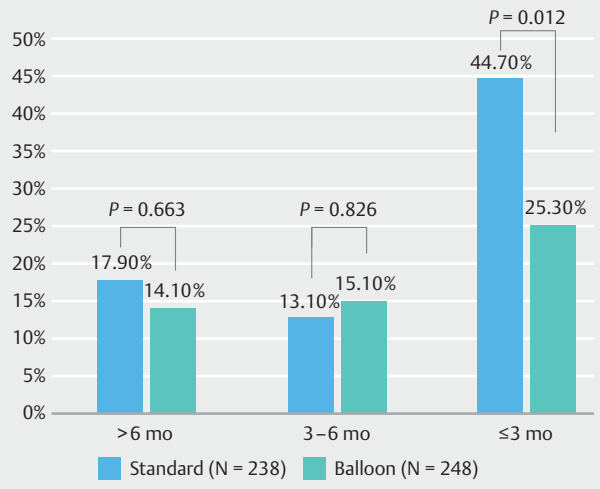
HR, hazard ratio; CI, confidence interval

Compared with results of the referenced study, the rate of moderate-to-severe pharyngeal pain after EUS was much higher than expected, while the average pain level was mild (NRS ≤ 2). Therefore, it is possible that more participants may have been needed to reach statistical significance. There are several reasons for this result. First, the structural difference between endoscope should be considered. Second, the absence of analgesics such as meperidine or fentanyl during conscious sedation may have affected pain level. Third, this study involved a higher proportion of female patients who are known to be more sensitive to pain. In addition, the difference in the proficiency level of the endoscopists may have been influential.

Several factors were identified as associated with pharyngeal pain. Balloon inflation may be a protective factor. During insertion, the portion of the endoscope contacting the mucous membrane is soft and plastic with compliance. Because it has a curved surface, it is expected to reduce mucosal damage due to physical contact. The total force exerted upon insertion and pharyngeal pain caused by force may not be reduced [10, 11] but the possibility of additional pain can be decreased by reduced physical injury.

Younger age was identified as a risk factor for pain. A study showed that younger patients complained of pain after the ERCP procedure [5]. The tone of the upper esophageal sphincter is increased in younger patients, and reflex response to the stimulus is also higher than in the elderly [12]. Therefore, younger patients are more likely to feel greater pain, because greater pressure is needed to offset the elevated muscle tone and reflexes.

Gender was also one of the risk factors for pain. In the study of conventional upper gastrointestinal endoscopy, the rate of pain complaints was higher in women [4]. Higher prevalence of moderate-to-moderate pain in women suggests the effect of gender difference. It is known that women are likely to suffer



▶ **Fig. 2** Rates of moderate-to-severe pharyngeal pain according to the physician's experience with EUS and the insertion method. Fewer patients reported moderate-to-severe pharyngeal pain with inflated balloon when EUS was performed by endoscopists with less than 3 months' experience of EUS.

from more severe pain than men in diseases like irritable bowel syndrome (IBS) [13]. The reason for the lower pain threshold in women is not yet clear. In previous studies, psychosocial factors and behavioral stress related to social learning were the main factors [14, 15]. Recently, the hormonal factor is also postulated as important from a recent gender-specific perspective [13, 16].

Experience level in endoscopy was identified as a major risk factor for pain. The shorter the experience, the harder can be the insertion procedure and greater the risk of complications. In this study, pain associated with insertion was reduced and plateaued after 70 procedures and approximately 3 months of experience. Studies of endoscopy learning curves showed that in the case of EUS, a certain level of technical competence was achieved after 50 to 75 procedures [17–19]. In this study, a comparable level of technical competence was reached in accordance with previous studies.

Based on these results, we examined conditions under which balloon inflation can alleviate pharyngeal pain. It was effective in reducing the rate of moderate-to-severe pain for physicians with less than 3 months of EUS experience. Because balloon inflation did not significantly increase the rate of insertion failure or balloon loss, it may prevent the risk of pain and complications for unexperienced endoscopists.

Our study has several limitations. First, it was a single-blind trial. Although pain evaluation was made by a third-party nurse not related to the study, possible biases from the operators still remained. Second, we did not evaluate factors from a socioeconomic aspect or quality-of-life perspective. Mental health and quality of life may play an important role in pain thresholds [5, 15]. Third, there were no complications, such as clinically important gastrointestinal bleeding or perforation associated with EUS insertion. Therefore, the role of pain as a surrogate marker was limited.

Our study also has some strengths. First, it is the first prospective study of complications associated with EUS. Second, it identified risk factors for pain during EUS insertion. Third, it showed that balloon inflation can be used to prevent complications by novices. Fourth, although the study did not identify learning curves, it indirectly demonstrated that 3 months is needed to become technically competent in echoendoscope insertion, as the pain associated with insertion was significantly reduced after performing 70 procedures.

Conclusion

In conclusion, when performed by physicians with EUS experience of fewer than 3 months, the balloon inflation method can reduce the proportion of patients with moderate-to-severe pharyngeal pain.

Clinical trial

clinicaltrials.gov
NCT02924948
TRIAL REGISTRATION: Single center, Single-blinded randomized prospective study NCT02924948 at clinicaltrials.gov

Competing interests

The authors declare that they have no conflict of interest.

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