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MINIREVIEWS

Burgeoning study of sentinel-node analysis on management of early gastric cancer after endoscopic submucosal dissection

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Abstract

Endoscopic submucosal dissection (ESD) represents an organ-preserving alternative to surgical resection of early gastric cancer. However, even with ESD yielding en-bloc resection specimens, there are concerns regarding tumor spread such as with larger lesions, ulcerated lesions, undifferentiated pathology and submucosal invasion. Sentinel node navigational surgery (SNNS) when combined with ESD offers a minimally invasive alternative to the traditional extended gastrectomy and lymphadenectomy if lack of lymph node spread can be confirmed. This would have a clear advantage in terms of potential complications and quality of life. However, SNNS, though useful in other malignancies such as breast cancer and melanoma, may not have a sufficient sensitivity for malignancy and negative predictive value in EGC to justify this as standard practice after ESD. The results of SNNS may improve with greater standardization and more involved dissection, technological innovations and more experience and validation such that the paradigm for post-ESD resection of EGC may change and include SNNS.

Key words: Early gastric cancer; Sentinel node; Sentinel node navigation surgery; Expanded criteria; Endoscopic submucosal dissection; Function-preserving gastrectomy; Organ preserving surgery; Lymphadenectomy

Core tip: Sentinel node navigation surgery after endoscopic submucosal dissection represents a minimally invasive approach to gastric cancer. However, this approach is controversial because it is not standardized nor has it been well validated outside of few

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centers in Asia. We will discuss these controversies and the potential of sentinel node navigational surgery to become an accepted diagnostic modality for select early gastric cancer patients.

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INTRODUCTION

Gastric cancer (GC) is a common and lethal malignancy ranking fifth and second in global prevalence and cancer-related mortality, respectively[1]. There are mass screening programs in Asia but not the West. Mortality after gastrectomy for cancer is lower in Asia compared to the West; largely due to predominance of earlier stages representation[2]. Early GC (EGC) is defined as intramucosal cancer (T1a) or limited to mucosa and submucosa (T1b). Figure 1 Similar to other luminal GI malignancies, prognosis relates largely to stage of disease with post-surgical groups for EGC having a respective 5-year survival rate for T1a and T1b of 96% and 83%[3]. Endoscopic submucosal dissection (ESD) has become the standard mode of resection for T1a lesions with expanded criteria also considered from Japanese centers[4]. However, additional surgery is recommended for subjects undergoing ESD for these expanded indications (larger diameter, ulcerated, submucosal invasion, undifferentiated histology); especially for Western subjects[5]. Table 1 Concerns regarding oncologic cure linger even after apparent en-bloc resections.

A sentinel node resection is removal of draining lymph nodes that are deemed likely to first receive lymph flow from the area of the resected gastric lesion and is examined by a pathologist to determine presence of metastasis. Lack of noted metastasis can infer no likely spread of the gastric malignancy to other lymph nodes or organs. Sentinel node navigation surgery (SNNS) is combined with ESD (ESN) with the premise that this will ensure complete resection for EGC with organ preservation and assessment of pathological nodes. However, the SNNS concept was first described almost 20 years ago but has not been well validated subsequently; currently its implementation has been concentrated in a few Asian centers and there is sparse Western use. Moreover, though the minimal invasiveness and organ-preservation concept is attractive, doubts linger as to sensitivity of malignant lymph node detection and negative predictive value.

Surgical approach to EGC: Surgery for invasive EGC is involved with either total or subtotal gastrectomy depending on tumor localization. Lymphadenectomy is mandated with local (D1) or extended (D2) resection. There was a trend favoring the D1 resection in European studies in terms of lesser postoperative complications and similar outcomes[6,7], but 15-year follow-up for the Dutch group noted better survival in the D2 cohort[8]. D2 lymphadenectomy remains the standard in Japan for advanced cancer[9]. However, GC is prevalent in Japan and there has been an impetus for less drastic surgeries to improve quality of life and the concept of "function-sparing gastrectomy" including pylorus-sparing gastrectomy, local tumor resection and segmental gastrectomy in conjunction with SNNS[10]. Laparoscopic gastrectomy yields similar technical and oncological results as open gastrectomy with less invasiveness, and robotic gastrectomy has promise[11].

Sentinel Node Navigational Surgery: SNNS has been used been used extensively for staging in breast cancer and malignancy, and sporadically in a variety of other solid tumors including thyroid tumors, head/neck squamous cancer and pelvic tumors[12]. The goal of SNNS is to avoid the morbidity of extensive gastric resection with preservation of gastric function and goal of likely complete cancer resection. Sentinel node navigational surgery for EGC was described in 2001 with concerns that continue today including micrometastases, aberrant lymph drainage, accuracy of frozen section and criteria for sentinel node[13].

Techniques for detecting sentinel lymph nodes: The premise of SN dissection is the status of the sentinel node (*i.e.*, tumor-free or not) determines the status of the adjacent draining nodes as well. The primary draining peri-gastric LN stations usually can be defined though there is variability and challenges for the surgeon. Larger tumors may

Table 1 Guidelines for endoscopic submucosal dissection of gastric cancer

Histology	Depth					
	Mucosal cancer				Submucosal cancer	
	No ulceration		Ulcerated		SM1	SM2
	≤ 20	> 20	≤ 30	> 30	≤ 30	Any size
Differentiated	-	--	--	---	--	---
Undifferentiated	----	---	---	---	---	---

Guideline and expanded criteria for endoscopic submucosal dissection in early gastric cancer. -: Guideline criteria for ESD; --: Expanded criteria for ESD; ---: Surgery (gastrectomy + lymph node dissection); ----: Surgery or ESD. ESD: Endoscopic submucosal dissection.

have multidirectional lymph flow and post-ESD scarring may alter flow[14,15] (Figure 2).

The most commonly used tracers are indocyanine green, carbon nanoparticles and blue dyes (patent, sulfan, isosulfan) which are injected into the submucosa at endoscopy done just prior to surgery or sub-serosally during surgery. Radioisotopes such as Technetium can be injected solely or in addition to the tracer. Tracers usually delineate draining LN's well (Figure 3, Figure 4) but adiposity can be an obstacle. Injection should be done optimally intraoperatively to allow the surgeon to well delineate lymphatic drainage. Imaging is enhanced by a variety of electronic systems including some packaged into the laparoscope such as a florescence imaging system for indocyanine green (ICG) or using electronic infrared filtering where there is less concern for adiposity[16]. Probably, the greatest challenge to considering SNNS in EGC to be standard practice is the issue of how metastases in retrieved LN's are verified[17]. Typically, this is done *via* frozen section using hematoxylin-eosin staining. The "lymphatic basin" concept of dissection has been advanced where LN dissection is dictated by the apparent path of the tracer during the surgery to cover the entire area of drainage[18]. This concept allows for more LN dissection than a "pick-up" approach of dissecting only obviously involved nodes but less than a gastrectomy-associated lymphadenectomy. LB dissection is superior to the "pick-up" method in terms of micrometastases detection[19].

The surgeon is tasked with potentially sampling multiple LN's including possibly those in the second tier of gastric drainage, and the pathologist would be required to do the LN analysis (requiring multiple slices) which would be a tedious endeavor! Moreover, the accuracy of H&E staining for malignancy is suspect with a reported false-negative rate of 46% in one study which was therefore terminated[20]. This was felt to be largely due to insufficient sectioning of LN's. One study noted that almost a quarter of ultimately positive LN's were not identified in real time by H&E staining[21]. One experienced Japanese group noted a 10% intraoperative and 3% ultimate false negative rate using ICG alone[22]. Most other studies using dye tracer alone report lesser results[17,21,23].

Combined dye and radiotracer use is clearly superior to dye alone in terms of detection of involved LN's and undetected pathology was associated with higher T stage and undifferentiated histology[23,24]. Micrometastases are a prime concern for SNNS in EGC; there is no accepted biomarker for GC, but there is a concerted effort to improve pathologic analysis of LN's. This includes reverse transcriptase-PCR with CEA as mRNA rather than standard immunohistochemistry[25,26]. RT-PCR for MUC2 and CEA demonstrated good sensitivity and specificity[27]. Using real-time RT-PCR for specific cytokeratins and CEA demonstrated high sensitivity and no false negative LN's[28]. More work in this area is awaited.

DIAGNOSTIC EFFECTIVENESS OF SNNS

Despite its attractiveness in concept and prior scrutiny, SNNS remains relatively unvalidated for EGC with concern for patient outcome in terms of oncological cure and dubious QOL benefits with lesser resections[29]. A basic concern again is the complexity and variability of gastric drainage after ESD and in relation to the original lesion with the possibility of "skip" metastases[30]. One small Korean study noted a skip metastases rate of 17%[31]! The difficulty of accurate real-time LN analysis has been noted[21]. Nonetheless, the SNNS concept has been validated at least in some Japanese centers. This was demonstrated by a multicenter study where subgroup analysis of D2 lymphadenectomy subjects with EGC showed SNNS sensitivity and

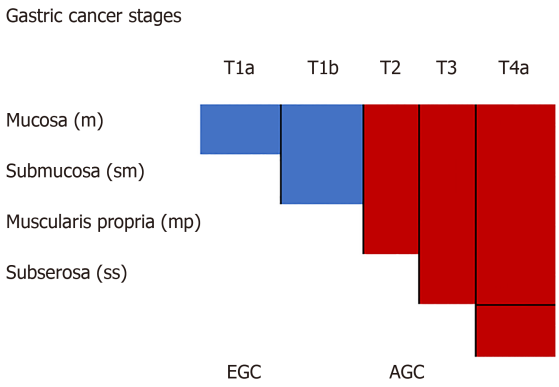

Figure 1 Gastric cancer staging. EGC: Early gastric cancer; AGC: Advanced gastric cancer.

accuracy of 93% and 99%, respectively[21]. Only 4 patients (1%) had false negative SN dissection and ¾ of these were in the lymphatic basin with the fourth having a primary lesion > 4 cm[21]. The authors affirmed a LBD strategy rather than simple SND. The extrapolation of this study is limited however as these were very experienced operators with both EGC and SNNS.

An earlier meta-analysis also suggested that SNNS alone was inadequate to support limited lymphadenectomy for EGC, and a minimum of 4 LN's should be harvested to ensure adequate sensitivity-overall sensitivity and negative predictive value was 98% and 92%, respectively[32]. Another meta-analysis had similar favorable results[24]. Limited results outside Asia showed lesser results likely reflecting less experience and issues with technique[33]. One American study noted a false-negative rate of 17%[34].

SNNS in the West/our experience

There is much less SNNS experience outside Asia and very little in the Americas[34-36]. The greatest obstacle to pursuing SNNS for EGC in the West is that GC-especially EGC- is generally less prevalent in the West and relatedly ESD is not commonplace. The potential solutions include multicenter trials to garner enough cases and to extrapolate the SNNS after ESD concept to GEJ tumors including Barrett's esophagus. Siewert II and III GEJ tumors are probably best treated as GCs[37,38]. Surgeons beginning SNNS should consider travel to Asia for instruction or at least converse with surgeons who perform this for other entities (breast cancer). They probably should follow the typical path noted in Asian studies of performing SNNS prior to a planned gastrectomy and extended lympadenectomy to familiarize themselves before embarking on a SNNS directed strategy. The learning curve for SNNS has been suggested to be 25-30 cases[21,39].

Our experience included SNNS performed on 10 elderly patients with comorbid disease and early foregut cancers (7 Barrett's, 3 EGC). Staging was as follow: T1a-mm(5), T1b(5) Mean lesion diameter was 4.0(2.2-8.6)cm-histology was G1(4), G2(5), G4(1). R0 resection and curative resection noted in 8 and 5 patients, respectively. SNNS was performed with a median of 9 (4-20) LN's resected. Four had (+) SN's with staging N1(1), N2(2), N3(1). These four received adjuvant chemotherapy; 2 with radiation. None of N_0 subjects received chemotherapy. After a median follow-up of 30 months, 8 patients (including the 6 N_0 patients) were in remission. Two patients with (+) SN's died. We used endoscopic submucosal injection of ICG intra-operatively and unenhanced tracer detection. Of note, diagnostic laparoscopy with SNNS was the goal at onset and any gastric resection was to be performed at another time. Again, real time pathologic analysis is challenging and yield may increase with delayed assessment. SN analysis was useful in our multidisciplinary conference to direct management. Our experience suggests that SNNS is best reserved for those who value potential minimal resection, lesser postoperative complications and better global QOL over oncological safety. These would include the elderly including those with significant comorbid disease.

Challenges for SNND

Skipped metastases: Skipped metastases refers to the discontinuous spread of malignancy with uninvolved contiguous lymph nodes interspersed among those harboring malignancy. This phenomenon runs counter to the sentinel node concept and would mandate extended lymphadenectomy if skipped metastases were common after ESD for EGC. Risk factors for LN spread with EGC surgery or ESD include

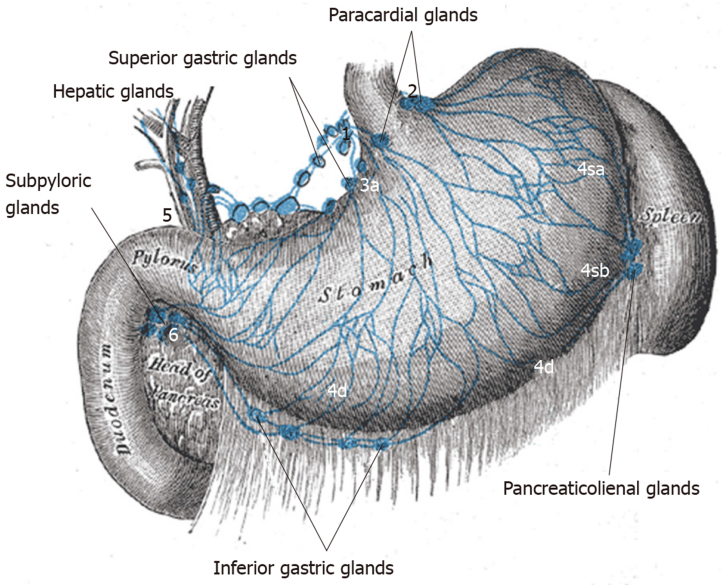

Figure 2 D1 nodal stations.

tumor > 2 cm, submucosal invasion, undifferentiated histology and lymphovascular invasion and these are also risk factors for skipped metastases[40]. It is not entirely clear whether a skip metastases relates to direct spread from the resection site to second-tier LN's or that spread to the first tier of LN's is simply undetected[27]. This is academic and emphasizes the fragility of the SNNS concept; especially for lesions in the expanded criteria group, and also highlights that although SNNS is a multidisciplinary endeavor, the major onus is on the surgeon to adequately dissect appropriate and sufficient LN's. The surgeon could be aided by enhanced technical aspects-dual dye and radiolabel tracer (gamma probe in abdomen and on resected LN's on back table), IR electronic endoscopy and fluorescence imaging with improved as well as dedicated pathologic analysis (not simple H&E and one slice, but rather multiple slices and use of nuclear amplification, immunohistochemistry, imprint cytology). Lymphatic basin dissection rather than simple SND is essential[31]. A consideration is to have a dedicated SNNS independent of findings and have subsequent time for pathological analysis.

Lesion location: Lesion location has a significant impact on variability of LN drainage and possibility of missed or skipped metastases. GC anywhere can have atypical metastases but this is more likely for distal tumors and those on the lesser curvature[41]. Proximal tumors extending towards the middle of the stomach often have drainage to multiple LN basins[42]. Antral location may be a predictor of LN metastases after non-curative EGC resection[43].

Beginning a SNND program: There are many obstacles to initiating a SNND program and this includes both direct and indirect costs. Surgical faculty may need to be recruited. SNND would potentially also require more faculty, time, efforts and costs for gastroenterology, nuclear medicine and pathology. Formal cost analysis of gastric SNND has not been described but is likely a significant barrier; especially in the West where EGC is less common.

New techniques with SNNS: Endoscopist and laparoscopic surgeons can "cooperate" to effect removal of gastric lesions; this has been done widely for gastric GIST's and described for a 6 cm lateral spreading GC[44]. Conceptually, this approach could include SNND for treating EGC[45]. A further enhancement of this cooperation is laparoscopic sero-muscular incision and suturing to evert a GC with endoscopic performance of ESD (EFTR) and preventing tumor seeding into the peritoneum; the specimen is removed orally, and SNNS is actually performed initially to assess for LN spread[46]. Finally, a NOTES (transvaginal entry) approach to EGC and SNNS has been described[47].

Current perspective

A Korean study analyzing SNNS with subsequent extended gastrectomy and D2 lympadenectomy noted 100% sensitivity and accuracy with dual tracer and radiolabel in detecting metastatic LN's, but > 20% of cases were technical failures due to inability

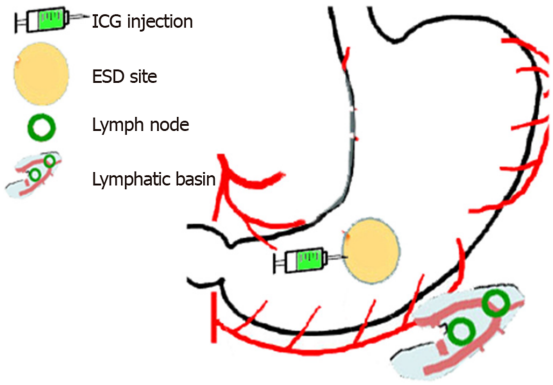

Figure 3 Indocyanine green injection into endoscopic submucosal dissection site. ICG: Indocyanine green; ESD: Endoscopic submucosal dissection.

to dissect at least five SB LN's[48]. These results together with the recent Japanese study[21] suggest that the treatment paradigm for EGC may change and incorporate SNNS use. Nonetheless, it is apparent that there will always be a chance of missed micrometastases so the sentinel node concept is imperfect and both the patient and surgeon have to realize this. The attraction of organ and function preservation has to be balanced with oncologic safety. One Japanese surgeon opined: "endoscopic and laparoscopic limited gastrectomy combined with SLN navigation surgery has the potential to become the standard minimally invasive surgery in EGC[29]." This optimism runs counter to the current swing back to extended lymphadenectomy[8] in GC surgery and number of LN's dissected regarded as a quality measure[49]. An optimistic outcomes study of patients after SNNS for EGC noted that none of 93 subjects with (-) SNNS LN exam died of gastric cancer with follow-up of up to 15 years and a 5 year survival rate > 98%; metachronous GC developed in 6 patients with "diminished" gastrectomy emphasizing the need for continued gastric surveillance[50]. We are hopeful for similar positive outcomes regarding SNNS in future studies.

CONCLUSION

SNNS was first conceptualized almost 20 years ago but remains controversial and only recently has gained traction as a plausible option for patients with EGC. It is only performed routinely in a handful of select Japanese and Korean centers, where experience has increased confidence in the technique and as a stratifying modality. SNNS is more recently conceptualized as the surgical complement to ESD for the treatment and potential cure of EGC. Prolonged disease-free survival after successful ESD for EGC has been noted. SNNS after ESD is part of the continuum of minimal resection with organ and function preservation. However, SNNS as a technique has not been well validated outside of these centers, nor has the technique been standardized. Experience to date favors a lymphatic basin resection approach based on intraoperative determination of lymph drainage as opposed to a dedicated sentinel node dissection or "pick-up" approach. Dual use of both injected dye tracer in the ESD site and radiolabeled injection is superior to dye injection alone. The benefit of minimal resection including SNNS has to be balanced with oncological safety; specifically, likelihood of missed dissemination of malignancy and related lesser prognosis. These issues have to be explained to the patient giving informed consent. Western centers are handicapped by relative lack of EGC and ESD operators. A reasonable path to acquire SNNS experience and expertise is to perform this prior to extended gastrectomy and lymphadenectomy in order to gain experience without risking missed malignancy. It is inevitable that SNNS following ESD becomes an option in the management of EGC; especially for patients who are older, have significant comorbid disease and prefer avoidance of significant organ resection. We also expect that subsequent to more studies on the standardization and validation of sentinel node navigational surgery, the technique will be widely utilized globally.

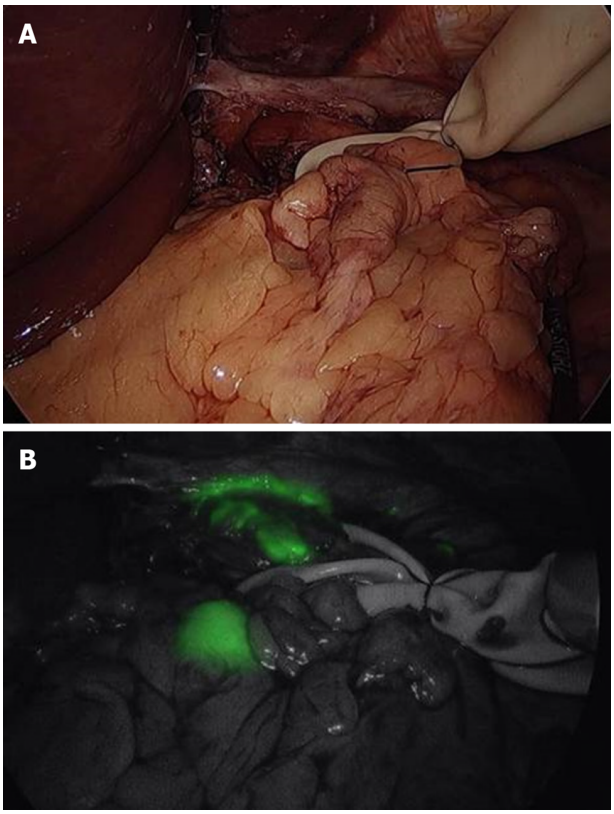

Figure 4 Perigastric area in subject post-endoscopic submucosal dissection of endoscopic submucosal dissection prior to indocyanine green injection (A) and same area post indocyanine green injection with noted uptake (B).

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ORIGINAL ARTICLE

Observational Study

Causative factors of discomfort in esophagogastroduodenoscopy: A large-scale cross-sectional study

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Abstract

BACKGROUND

It is important to reduce patient discomfort in esophagogastroduodenoscopy. Remedial measures can be taken to alleviate discomfort if the causative factors are determined; however, all the factors have not been elucidated yet.

AIM

To clearly determine the factors influencing discomfort in transoral esophagogastroduodenoscopy using a large-size cross-sectional study with readily available data.

METHODS

Consecutive patients who underwent screening transoral esophagogastroduodenoscopy consecutively between August 2017 and October 2017 at a health check-up center were included. Discomfort was evaluated using a face scale between 0 and 10 with a 6-level questionnaire. Univariate and multiple regression analyses were performed to investigate the factors related to the discomfort in esophagogastroduodenoscopy. Univariate analysis was performed in both the unsedated and sedated study groups. Age, sex, height, body mass index, smoking status, alcohol intake, hiatal hernia, history of gastrectomy, biopsy during examination, Lugol's solution usage, administration of butylscopolamine with/without a sedative (pethidine, midazolam, or both), endoscope model, history of endoscopy, and endoscopists were considered as possible factors of discomfort.

RESULTS

Finally, 1715 patients were enrolled in this study. Overall, the median discomfort score was 2 and the interquartile range was 2-4. High discomfort (score ≥ 6) was recorded in 18% of the participants. According to univariate analysis, in the

checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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unsedated group, young age ($P < 0.001$), female sex ($P < 0.001$), and no history of endoscopy ($P < 0.001$) were factors associated with increased discomfort. Significant differences were also noted for height ($P = 0.007$), smoking status ($P = 0.003$), and endoscopists ($P < 0.001$). In the sedation group, young age ($P < 0.001$), female sex ($P < 0.001$), and no history of endoscopy ($P = 0.004$) were associated with increased discomfort; additionally, significant differences were found in smoking status ($P < 0.001$), type of sedation ($P < 0.001$), and endoscopists ($P = 0.027$). There was also a marginal difference due to alcohol intake ($P = 0.055$). Based on multiple regression analysis, young age, female sex, less height, current smoking status, and presence of hiatal hernia [regression coefficients of 0.08, $P < 0.001$ (for -1 years); 0.45, $P = 0.013$; 0.02, $P = 0.024$ (for -1 cm); 0.35, $P = 0.036$; and 0.34, $P = 0.003$, respectively] were factors that significantly increased discomfort in esophagogastroduodenoscopy. Alternatively, sedation significantly reduced discomfort and pethidine (regression coefficient: -1.47, $P < 0.001$) and midazolam (regression coefficient: -1.63, $P = 0.001$) significantly reduced the discomfort both individually and in combination (regression coefficient: -2.92, $P < 0.001$). A difference in the endoscopist performing the procedure was also associated with discomfort.

CONCLUSION
Young age, female sex, and smoking are associated with esophagogastroduodenoscopy discomfort. Additionally, heavy alcohol consumption diminished the effects of sedation. These factors are easily obtained and are thus useful.

Key words: Esophagogastroduodenoscopy; Discomfort; Smoking; Alcohol; Pethidine; Endoscopy

Core tip: It is essential to reduce discomfort in esophagogastroduodenoscopy. The present study clearly identified the factors associated with discomfort in esophagogastroduodenoscopy using a large-size cross-sectional study. Young age, female sex, and current smoking were identified as the contributive factors. Smoking status was a newly identified predictor of this study. Furthermore, heavy alcohol consumption was noted to diminish the effect of the sedative(s). These factors are useful because they can be easily obtained, and we can take remedial measures for reducing discomfort.

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INTRODUCTION

Esophagogastroduodenoscopy often causes discomfort in patients. Discomfort due to the endoscope contributes to a negative experience and reduces the patient's satisfaction[1,2]. Therefore, it is important to reduce discomfort as much as possible. Sedation is mainly considered as a method to reduce such discomfort; however, due to the cost and risk of complications, the consensus is to perform endoscopy without sedation in appropriately selected patients[3]. To identify the patients who are likely to have marked discomfort, so that they can be considered for sedation, the predictive factors of discomfort must be ascertained. In previous studies, young age[4-7], female sex[4,5,8,9], anxiety before the examination[4,5,6,9], and pharyngeal sensitivity[6,7] were identified as factors that increased the discomfort of transoral esophagogastroduodenoscopy; however, all factors have not yet been elucidated. Most previous studies have conducted investigations only in several hundred subjects, which is a relatively small sample. The aim of this study was to elucidate the

contributing factors of discomfort in transoral esophagogastroduodenoscopy by a large-scale cross-sectional study, using easily available information from a regular endoscopy examination practice.

MATERIALS AND METHODS

Ethical considerations

This study was reviewed and approved by the Institutional Review Board of Kameda Medical Center. Since this was a retrospective observational study, using already existing data, and did not include invasive interventions, the requirement for informed consent from the study participants was waived by the Institutional Review Board. However, written informed consent for endoscopy was obtained at the time of the procedure. The study protocol was published on the hospital's website. This study's methods are in accordance with the Japanese "Ethical Guidelines for Medical and Health Research Involving Human Subjects".

Study population and methods

All consecutive patients who had undergone screening transoral esophagogastroduodenoscopy at a health check-up center associated with a general hospital between August 2017 and October 2017 were included. The discomfort experienced by the patients during examination was evaluated using a questionnaire subsequent to either completion of the examination or recovery from sedation. Originally, the questionnaires were intended for the improvement of hospital services to the patients; the questionnaire results and medical records of the patients were utilized for this study. Accordingly, participants with inadequate responses in the questionnaire were excluded. In order to increase the statistical accuracy of this study, the data was collected from the largest sample size possible.

In preparation for endoscopy, dimethicone (Barugin antifoam solution; Kaigen Pharmaceutical Co., Ltd.; Osaka, Japan) containing pronase (PronaseMS; Kaken Pharmaceutical Co., Ltd.; Tokyo, Japan) and sodium bicarbonate (Yoshida Pharmaceutical Co., Ltd.; Tokyo, Japan) were administered orally. For topical pharyngeal anesthesia, 8% lidocaine spray (Xylocaine Pump Spray 8%; Aspen Japan Co., Ltd.; Tokyo, Japan) was administered. The decision to administer an antispasmodic agent depended on the endoscopist; when administered, intravenous injection of 10 mg butylscopolamine (Scopolamine butylbromide; Nichi-Iko Pharmaceutical Co., Ltd.; Tokyo, Japan) was used. Sedatives were administered upon the request of the patients and with the permission of the doctor; accordingly, an intravenous injection of pethidine (Takeda Pharmaceutical Company Ltd.; Tokyo, Japan) was predominantly used, sometimes in combination with midazolam (Sandoz Co., Ltd.; Tokyo, Japan); however, midazolam was rarely used alone. Sedation was induced prior to scope insertion. Patients expected to drive were not administered any sedatives, even upon request. The endoscope used either the GIF-PQ260, GIF-Q260, or GIF-H290 (Olympus Corporation, Tokyo, Japan). The number of endoscopists who conducted the examination was 27. The esophagus, stomach, and partial duodenum were endoscopically observed. The mouthpiece for endoscopic examination had a tube capable of aspirating saliva continuously.

The questionnaire was distributed to the patients at a different location from the endoscopy unit, by staff other than the ones who performed the endoscopy. Discomfort was evaluated on a face scale of 0 to 10 on a 6-level questionnaire (Figure 1).

Statistical analysis

Since the discomfort scores had a non-normal distribution, the median and interquartile ranges were calculated for all cases. In addition, the proportion of high discomfort (score ≥ 6) was calculated. Age, sex, height, body mass index, smoking status, alcohol intake, hiatal hernia, history of gastrectomy, biopsy performed during examination, administration of Lugol's solution, administration of butylscopolamine with/without a sedative (pethidine, midazolam, or both), endoscope model, history of endoscopy, and endoscopists were considered as probable factors of discomfort. Based on the smoking status to the participants were classified as current-smoker, past-smoker and non-smoker. Classification based on alcohol consumption included non-drinker, never to rare drinking; heavy drinker, ≥ 40 mg/d of alcohol for ≥ 3 d/wk; and the rest as normal drinker. GIF-Q260 and GIF-H290 with a diameter of 9.2 mm and 8.9 mm, respectively, defined as a normal diameter, and GIF-PQ260 with 7.9 mm, defined as a small diameter, were the endoscope models used. The participants were divided into subgroups: Sedated and non-sedated, which was expected to be

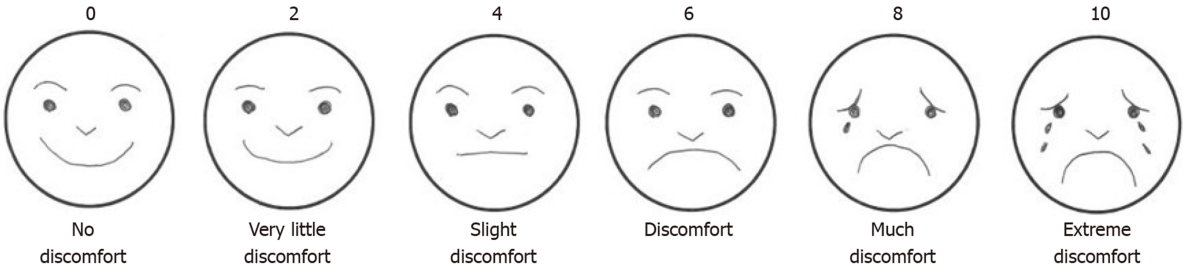

Figure 1 Discomfort rating scale.

strongly related to discomfort. The median discomfort score and the proportion of high discomfort (score ≥ 6) were calculated for each factor, and a univariate analysis was performed.

Furthermore, as an adjustment for bias, we implemented multiple regression analysis to clarify the factors associated with discomfort for the primary outcome. In this analysis, the objective variable was the discomfort score, and the explanatory variables were the probable factors relating to the discomfort.

In order to investigate the effect of heavy alcohol consumption on sedation, multiple regression analysis adjusted for the factors of discomfort was performed in the subgroups with and without sedation as an additional analysis. All statistical analyses were performed using EZR (ver1.37; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). P value < 0.05 was considered as statistically significant.

RESULTS

The number of participants were 1792. Seventy-seven patients were excluded due to inadequate questionnaire responses; finally, 1715 patients were enrolled in this study. Table 1 includes the demographics of all participants by possible factors relating to discomfort. We were able to obtain all the data for the factors without any gaps. Overall, the median discomfort score and the interquartile range were 2 and 2-4, respectively, and 18% of the participants had high discomfort levels (score ≥ 6).

According to the univariate analysis in the non-sedated group, the factors associated with increased discomfort were young age (P < 0.001), female sex (P < 0.001), and no history of endoscopy (P < 0.001); additionally, significant differences were also found for height (P = 0.007), smoking status (P = 0.003), and endoscopist (P < 0.001) (Table 2). With reference to the proportion of high discomfort (score ≥ 6) in the non-sedated group, young age (P < 0.001), female sex (P = 0.03), and no history of endoscopy (P < 0.001) were the factors related to increased discomfort; significant differences were also found for smoking status (P = 0.033) and endoscopists (P = 0.011) (Table 2). For the sedated group, young age (P < 0.001), female sex (P < 0.001), and no history of endoscopy (P = 0.004) were the factors associated with increased discomfort; significant differences were also found for smoking status (P < 0.001), type of sedation (P < 0.001), and endoscopist (P = 0.027). There was a marginal difference based on alcohol consumption (P = 0.055) (Table 3). Additionally, for the proportion of high discomfort in this group, young age (P < 0.001) and no history of endoscopy (P = 0.018) were the factors associated with increased discomfort. Significant differences were also found based on alcohol intake (P = 0.001). However, there was only a marginal difference based on the smoking status (P = 0.055) (Table 3).

Based on multiple regression analysis (Table 4), young age (regression coefficient for -1 years: 0.08, P < 0.001), female sex (regression coefficient: 0.45, P = 0.013), shorter height (regression coefficient for -1 cm: 0.02, P = 0.024), current smoking status (regression coefficient: 0.35, P = 0.036), and presence of hiatal hernia (regression coefficient: 0.34, P = 0.003) were the factors that significantly increased the discomfort in esophagogastroduodenoscopy. The use of sedation significantly reduced discomfort. Pethidine (regression coefficient: -1.47, P < 0.001), midazolam (regression coefficient: -1.63, P = 0.001), and their combination (regression coefficient: -2.92, P < 0.001) were found to significantly reduce the discomfort. The individual endoscopist performing the procedure was also associated with the discomfort (regression coefficient estimates: Maximum 2.78 differences). According to the multiple regression analysis performed in both groups, the regression coefficient of heavy

Table 1 Participants' demographics (*n* = 1715)

Possible factors relating to discomfort	Mean (SD)
Age	59 (11)
BMI	23.5 (3.6)
Height	163.1 (8.8)
Possible factors relating to discomfort number (%)	
Age	
≤ 39	80 (4.7)
40-49	308 (18.0)
50-59	431 (25.1)
60-69	610 (35.6)
≥ 70	286 (16.7)
Male sex	950 (55%)
BMI ≥ 25	503 (29.3)
Height	
< 150 cm	114 (6.7)
150-160 cm	546 (31.8)
160-170 cm	644 (37.6)
≥ 170 cm	411 (24.0)
Smoking status	
Non-smoker	988 (57.6)
Past-smoker	487 (28.4)
Current-smoker	240 (14.0)
Alcohol consumption	
Non-drinker	761 (44.4)
Normal drinker	812 (47.4)
Heavy-drinker	142 (8.3)
History of endoscopy	1602 (93.4)
History of gastrectomy	30 (1.8)
Butylscopolamine administration	511 (29.8)
Biopsy performed	49 (2.9)
Lugol's solution use	7 (0.4)
Small diameter endoscope	1657 (96.6)
Hiatal hernia	775 (45.2)
Sedative	
None	774 (45.1)
Pethidine	797 (46.5)
Midazolam	19 (1.1)
Pethidine and midazolam	125 (7.3)

BMI: Body mass index.

alcohol consumption was 0.90 (P = 0.001) in the sedation group and 0.008 (P = 0.78) in the non-sedation group. Therefore, under sedation, the discomfort experienced by a heavy drinker was greater than that experienced by a non-heavy drinker.

DISCUSSION

Based on the multiple regression analysis, the factors associated with increased discomfort in esophagogastroduodenoscopy were young age, female sex, short height, current smoking status, and hiatal hernia. Individual endoscopists were also related to the discomfort. Additionally, heavy alcohol consumption diminished sedation. This is consistent with the previous report that revealed young[4-7] and female patients[4,5,8,9] have higher levels of discomfort. The high discomfort in younger patients is considered to be mainly due to gag reflex[10]. The high discomfort in women

Table 2 Discomfort for each factor in the group without sedation (*n* = 774) and univariate analysis results

Discomfort score value median (quartile ranges)			Proportion of high discomfort (score ≥ 6)	
Age				
≤ 39	6 (4-8)	$P < 0.001$	60.5% (23/38)	$P < 0.001$
40-49	4 (4-6)	Kruskal-Wallis test	45.1% (51/113)	χ^2 test
50-59	4 (2-6)		34.7% (66/190)	
60-69	4 (2-4)		18.3% (48/262)	
≥ 70	2 (0-4)		9.9% (17/171)	
Male sex	4 (2-4)	$P < 0.001$	23.5% (130/554)	$P = 0.003$
Female sex	4 (2-6)	Mann-Whitney *U* test	34.1% (75/220)	χ^2 test
BMI				
≥ 25	4 (2-6)	$P = 0.796$	27.2% (62/228)	$P = 0.773$
< 25	4 (2-6)	Mann-Whitney *U* test	26.2% (143/546)	χ^2 test
Height				
< 150 cm	4 (2-5)	$P = 0.007$	25.7% (9/35)	$P = 0.219$
150-160 cm	4 (2-6)	Kruskal-Wallis test	29.4% (53/180)	χ^2 test
160-170 cm	4 (2-4)		22.7% (75/330)	
≥ 170 cm	4 (2-6)		29.7% (68/229)	
Non-smoker	4 (2-6)	$P = 0.003$	26.5% (104/393)	$P = 0.033$
Past smoker	4 (2-4)	Kruskal-Wallis test	22.4% (57/255)	χ^2 test
Current smoker	4 (2-6)		34.9% (44/126)	
Non-drinker	4 (2-6)	$P = 0.098$	29.4% (91/309)	$P = 0.291$
Normal drinker	4 (2-4)	Kruskal-Wallis test	24.9% (96/386)	χ^2 test
Heavy drinker	4 (2-4)		22.8% (18/79)	
History of endoscopy (+)	4 (2-4)	$P < 0.001$	24.8% (180/727)	$P < 0.001$
History of endoscopy (-)	6 (4-7)	Mann-Whitney *U* test	53.2% (25/47)	χ^2 test
History of gastrectomy (+)	2 (2-4)	$P = 0.202$	16.7% (3/18)	$P = 0.428$
History of gastrectomy (-)	4 (2-6)	Mann-Whitney *U* test	26.7% (202/756)	Fisher's exact test
Butylscopolamine (+)	2 (2-4)	$P = 0.115$	20.6% (14/68)	$P = 0.249$
Butylscopolamine (-)	4 (2-6)	(Mann-Whitney *U* test	27.1% (191/706)	χ^2 test
Biopsy performed (+)	4 (2-6)	$P = 0.461$	39.1% (9/23)	$P = 0.163$
Biopsy performed (-)	4 (2-6)	Mann-Whitney *U* test	26.1% (196/751)	χ^2 test
Lugol's solution (+)	4 (2-6)	$P = 0.950$	40.0% (2/5)	$P = 0.612$
Lugol's solution (-)	4 (2-6)	(Mann-Whitney *U* test	26.4% (203/769)	Fisher's exact test
Endoscope				
Normal diameter	4 (2-6)	$P = 0.737$	28.6% (6/21)	$P = 0.826$
Small diameter	4 (2-6)	Mann-Whitney *U* test	26.4% (199/753)	χ^2 test
Hiatal hernia (+)	4 (2-6)	$P = 0.257$	27.6% (113/410)	$P = 0.472$
Hiatal hernia (-)	4 (2-6)	Mann-Whitney *U* test	25.3% (92/364)	χ^2 test
Sedation agent				
No use	4 (2-6)	-	26.5% (205/774)	-
Pethidine alone	-		-	
Midazolam alone	-		-	
Pethidine and Midazolam	-		-	

Number of endoscopists: 27. Range of median score: 0 to 6. Proportion of high discomfort responses: 0 to 60% (details are omitted). Kruskal-Wallis test result for median score: $P < 0.001$. χ^2 test result for proportion of high discomfort: $P = 0.011$. BMI: Body mass index.

is considered due to a low pain threshold[11]. Additionally, it is reported that vomiting, belching, or retching increases significantly in patients with hiatal hernia[10], which can be the cause of the high levels of discomfort in such cases.

The results of the present study suggest that current smokers have increased discomfort due to esophagogastroduodenoscopy. Although smoking is considered a

Table 3 Discomfort for each factor in the sedation group (*n* = 941) and univariate analysis results

Discomfort score value median (quartile ranges)			Proportion of high discomfort (score 6 or higher)	
Age				
≤ 39	4 (2.5-6)	$P < 0.001$	40.5% (17/42)	$P < 0.001$
40-49	2 (2-4)	Kruskal-Wallis test	17.9% (35/195)	χ^2 test
50-59	2 (0-4)		10.8% (26/241)	
60-69	2 (0-4)		6.0% (21/348)	
≥ 70	2 (0-2)		3.5% (4/115)	
Male sex	2 (0-4)	$P < 0.001$	10.9% (43/396)	$P = 0.942$
Female sex	2 (2-4)	Mann-Whitney *U* test	11.0% (60/545)	χ^2 test
BMI				
≥ 25	2 (0-4)	$P = 0.155$	11.3% (31/275)	$P = 0.837$
< 25	2 (0-4)	Mann-Whitney *U* test	10.8% (72/666)	χ^2 test
Height				
< 150 cm	2 (1-4)	$P = 0.185$	13.9% (11/79)	$P = 0.109$
150-160 cm	2 (0-4)	Kruskal-Wallis test	9.6% (35/366)	χ^2 test
160-170 cm	2 (0-4)		9.2% (29/314)	
≥ 170 cm	2 (0-4)		15.4% (28/182)	
Non-smoker	2 (0-4)	$P < 0.001$	10.1% (60/595)	$P = 0.055$
Past smoker	2 (0-4)	Kruskal-Wallis test	9.9% (23/232)	χ^2 test
Current smoker	2 (2-4)		17.5% (20/114)	
Non-drinker	2 (0-4)	$P = 0.055$	9.5% (43/452)	$P = 0.001$
Normal drinker	2 (0-4)	Kruskal-Wallis test	10.3% (44/426)	χ^2 test
Heavy drinker	2 (1-5)		25.4% (16/63)	
History of endoscopy (+)	2 (0-4)	$P = 0.004$	10.3% (90/875)	$P = 0.018$
History of endoscopy (-)	2 (2-4)	Mann-Whitney U test	19.7% (13/66)	χ^2 test
History of gastrectomy (+)	2 (0-2.5)	$P = 0.477$	16.7% (2/12)	$P = 0.631$
History of gastrectomy (-)	2 (0-4)	Mann-Whitney *U* test	10.9% (101/929)	Fisher's exact test
Butylscopolamine (+)	2 (0-4)	$P = 0.187$	10.6% (47/443)	$P = 0.755$
Butylscopolamine (-)	2 (0-4)	Mann-Whitney *U* test	11.2% (56/498)	χ^2 test
Biopsy performed (+)	2 (0-3.5)	$P = 0.287$	11.5% (3/26)	$P = 0.757$
Biopsy performed (-)	2 (0-4)	Mann-Whitney *U* test	10.9% (100/915)	Fisher's exact test
Lugol's solution (+)	1 (0.5-1.5)	$P = 0.35$	0.0% (0/2)	$P = 1.00$
Lugol's solution (-)	2 (0-4)	Mann-Whitney *U* test	11.0% (103/939)	Fisher's exact test
Endoscope				
Normal diameter	2 (2-4)	$P = 0.197$	10.8% (4/37)	$P = 1.00$
Small diameter	2 (0-4)	Mann-Whitney *U* test	11.0% (99/904)	Fisher's exact test
Hiatal hernia (+)	2 (0-4)	$P = 0.891$	12.3% (45/365)	$P = 0.279$
Hiatal hernia (-)	2 (0-4)	Mann-Whitney *U* test	10.1% (58/576)	χ^2 test
Sedation agent				
No use	-		-	
Pethidine alone	2 (0-4)	$P < 0.001$	11.7% (93/797)	$P = 0.186$
Midazolam alone	2 (0-4)	Kruskal-Wallis test	10.5% (2/19)	Fisher's exact test
Pethidine and Midazolam	0 (0-2)		6.4% (8/125)	

Number of endoscopists: 27. Range of median score: 0 to 4. Range of proportion of high discomfort responses: 0 to 27.8% (details are omitted). Kruskal-Wallis test result for median score: $P = 0.027$. χ^2 test result for proportion of high discomfort: $P = 0.216$. BMI: Body mass index.

cause of gag reflex[12], smoking was not identified as a significant factor of discomfort in the previous studies[7,9,10]. Thus, current smoking status associated with increased discomfort has been newly identified in the present study, which may be due to the larger sample size of the present study. It is reported that smokers have chronic laryngitis[13]; hence, chronic irritation to the throat may be the cause of gag reflex in

Table 4 Multiple regression analysis and impact of each factor for discomfort

	Regression coefficient	Upper limit of 95%CI	Lower limit of 95%CI	*P* value
Age (+ 1)	-0.08	-0.09	-0.07	< 0.001
Sex (male)	-0.45	-0.79	-0.10	0.013
BMI (+ 1)	-0.002	-0.03	0.03	0.903
Height (+ 1)	-0.02	-0.04	-0.003	0.024
Smoking status				
Past smoker	-0.06	-0.32	0.20	0.638
Current smoker	0.35	0.02	0.67	0.036
Alcohol consumption				
Normal drinker	-0.05	-0.27	0.18	0.680
Heavy drinker	0.20	-0.21	0.61	0.337
Has no endoscopic experience	0.22	-0.20	0.65	0.300
History of gastrectomy	0.36	-0.41	1.14	0.362
Butylscopolamine use	-0.04	-0.35	0.27	0.802
Biopsy performed	0.11	-0.51	0.72	0.729
Lugol's solution use	1.02	-0.61	2.64	0.221
Normal diameter endoscope	0.48	-0.09	1.05	0.101
Hiatal hernia	0.34	0.11	0.57	0.003
Sedation agent				
Pethidine alone	-1.47	-1.71	-1.22	< 0.001
Midazolam alone	-1.63	-2.61	-0.66	0.001
Pethidine and midazolam	-2.92	-3.36	-2.49	< 0.001

Maximum difference in discomfort among endoscopists (regression coefficient): 2.78 (details of each endoscopist were omitted). BMI: Body mass index.

smokers. Additionally, since there was no difference in the discomfort experienced between past-smokers and non-smokers, smoking cessation could help eliminate the increasing discomfort. Although previous studies only investigated the discomfort or gag reflex based on body mass index as a body-type factor in[5,9,10]; short height may be related to high discomfort levels because the scope diameter is relatively large. Therefore, in this study, height was also included as a factor and was found to be significantly related to discomfort. Although this is a new finding of interest, univariate analysis for high discomfort was not significantly different, and the regression coefficient in multiple regression analysis is relatively small and, therefore, has less clinical relevance.

Sedation was useful as it significantly reduced discomfort, and the use of either pethidine, midazolam, or their combination was effective. However, heavy alcohol consumption reduced the effect of sedation. Sedation is reported to be less effective in heavy drinkers[14]. Previous studies have shown that the requisite doses of benzodiazepines and the combination of benzodiazepine and opioid are higher for heavy drinkers than for others[15,16]. Unlike previous reports, in the majority of the cases in the present study, pethidine was used and was found to be less effective in heavy drinkers. Therefore, we believe that discomfort can be predicted from age, sex, smoking status, and alcohol consumption, which can be easily obtained before examination.

The limitation of this study is the possibility of a selection bias since it is a retrospective cross-sectional study from a single facility. However, various information was analyzed in connection with the health check-up data in many participants. Additionally, anxiety and pharyngeal sensitivity, which were identified as factors of discomfort in the previous studies, could not be analyzed before the examination[4-7,9]. However, anxiety and pharyngeal sensitivity are rarely evaluated in general practice; therefore, it is meaningful to investigate the factor of discomfort by the information obtained ordinarily in daily practice. The strengths of the present study are that it is a large-size study, and smoking status was identified for the first time as a contributing factor to discomfort in esophagogastroduodenoscopy.

In conclusion, young and female patients experience more discomfort in esophagogastroduodenoscopy. Furthermore, the discomfort in current smokers may increase. Additionally, heavy alcohol consumption reduces the effect of sedatives. These factors are useful because they can be easily obtained, and we can take remedial

measures for reducing discomfort.

ARTICLE HIGHLIGHTS

Research background

Discomfort due to esophagogastroduodenoscopy contributes to a negative experience and reduces the patients' satisfaction. Therefore, it is important to reduce discomfort as much as possible. By identifying the factors that cause discomfort, we can take remedial measures such as using sedation.

Research motivation

However, not all factors of discomfort have been elucidated yet. Most previous studies have conducted investigations only in several hundred subjects, which is a relatively small sample.

Research objectives

The aim of this study was to elucidate the contributing factors of discomfort in transoral esophagogastroduodenoscopy by a large-scale cross-sectional study.

Research methods

This study was a retrospective observational study using a questionnaire for the improvement of hospital services. Discomfort was evaluated using a face scale between 0 and 10 with a 6-level questionnaire. Univariate and multiple regression analyses were performed to investigate the factors related to the discomfort in esophagogastroduodenoscopy. The primary outcome was the result of a multiple regression. In this analysis, the objective variable was the discomfort score and the explanatory variables were age, sex, height, body mass index, smoking status, alcohol intake, hiatal hernia, history of gastrectomy, biopsy during examination, Lugol's solution usage, administration of butylscopolamine with/without a sedative (pethidine, midazolam, or both), endoscope model, history of endoscopy, and endoscopists.

Research results

Finally, 1715 patients were enrolled in this study. Based on multiple regression analysis, young age, female sex, shorter height, current smoking status, and presence of hiatal hernia [regression coefficients of 0.08, $P < 0.001$ (for -1 years); 0.45, $P = 0.013$; 0.02, $P = 0.024$ (for -1 cm); 0.35, $P = 0.036$; and 0.34, $P = 0.003$, respectively] were factors that significantly increased the discomfort in esophagogastroduodenoscopy. Alternatively, sedation significantly reduced discomfort; pethidine (regression coefficient: -1.47, $P < 0.001$) and midazolam (regression coefficient: -1.63, $P = 0.001$) both individually and in combination (regression coefficient: -2.92, $P < 0.001$) significantly reduced the discomfort. A difference in the endoscopist performing the procedure was also associated with discomfort. Additionally, for the proportion of a high discomfort level (score ≥ 6) in the sedated group, significant differences were also found based on alcohol intake in univariate analyses ($P = 0.001$).

Research conclusions

The present study clearly identified the factors associated with discomfort in esophagogastroduodenoscopy using a large-size cross-sectional study. Young age, female sex, and current smoking were identified as the contributive factors. Smoking status was a newly identified predictor of this study. Furthermore, heavy alcohol consumption was noted to diminish the effect of the sedative(s). These factors are useful because they can be easily obtained, and we can take remedial measures for reducing discomfort.

Research perspectives

Prospective research is needed to clarify whether predicting discomfort and taking measures to alleviate it can effectively increase patient satisfaction.

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