World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v18.i27.3595

World J Gastroenterol 2012 July 21; 18(27): 3595-3601
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Sedation-associated hiccups in adults undergoing gastrointestinal endoscopy and colonoscopy

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Received: October 8, 2011 Revised: December 12, 2011
Accepted: May 6, 2012
Published online: July 21, 2012

Abstract

AIM: To investigate whether the incidence of hiccups in patients undergoing esophagogastroduodenoscopy (EGD) or same-day bidirectional endoscopy (EGD and colonoscopy; BDE) with sedation is different from those without sedation in terms of quantity, duration and typical onset time.

METHODS: Consecutive patients scheduled for elective EGD or same-day BDE at the gastrointestinal endoscopy unit or the health examination center were allocated to two groups: EGD without sedation (Group A) and BDE with sedation (Group B). The use of sedation was based on the patients' request. Anesthesiologists participated in this study by administrating sedative drugs as usual. A single experienced gastroenterologist performed both the EGD and the colonoscopic examinations for all the patients. The incidence, duration and onset time of hiccups were measured in both groups. In addition, the association between clinical variables and hiccups were analyzed.

RESULTS: A total of 435 patients were enrolled in the study. The incidences of hiccups in the patients with and without sedation were significantly different (20.5% and 5.1%, respectively). The use of sedation for patients undergoing endoscopy was still significantly associated with an increased risk of hiccups (adjusted odds ratio: 8.79, $P < 0.001$) after adjustment. The incidence of hiccups in males under sedation was high (67.4%). The sedated patients who received 2 mg midazolam developed hiccups more frequently compared to those receiving 1 mg midazolam ($P = 0.0028$). The patients with the diagnosis of gastroesophageal reflux disease (GERD) were prone to develop hiccups ($P = 0.018$).

CONCLUSION: Male patients undergoing EGD or BDE with sedation are significantly more likely to suffer from hiccups compared to those without sedation. Midazolam was significantly associated with an increased risk of hiccups. Furthermore, patients with GERD are prone to develop hiccups.

Key words: Anesthesia; Midazolam; Hiccup; Gastroesophageal reflux disease; Esophagogastroduodenoscopy; Bidirectional endoscopy

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Liu CC, Lu CY, Changchien CF, Liu PH, Perng DS. Sedation-associated hiccups in adults undergoing gastrointestinal endoscopy and colonoscopy. *World J Gastroenterol* 2012; 18(27): 3595-3601 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i27/3595.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i27.3595

INTRODUCTION

Esophagogastroduodenoscopy (EGD) and colonoscopy are important diagnostic tools for evaluating gastrointestinal diseases or for the early detection of malignant lesions. Although same-day bidirectional endoscopy (EGD and colonoscopy; BDE) has many advantages, including shorter hospital stays and expedited decision making for patient care[1], BDE remains a difficult and longer endoscopic procedure. Sedation is usually used to alleviate patient discomfort. Several regimens are available for inducting moderate sedation, but the combination of propofol with an opioid[2-4] and/or a benzodiazepine[5,6] is most commonly used. The combined regimens could improve the safety profile of propofol by reducing its dose-dependent potential to induce deep sedation[7], in which patients may develop inadequate spontaneous ventilation and may require assistance to maintain a patent airway. In addition to hemodynamic or respiratory depression, the other frequently encountered clinical situation during endoscopic procedures with sedation is hiccups.

Hiccups are an involuntary spasmodic contraction of the diaphragm and accessory muscles followed by the sudden closure of the glottis[8]. Hiccups during an endoscopic procedure are commonly acute and temporary, but the intermittent involuntary contraction of the diaphragm may interfere with spontaneous breathing and hamper endoscopic investigations and interventions[9]. In addition, this powerful reflex can result in markedly negatively intrathoracic pressures and increased abdominal pressures[8]. Accompanied by gastric distension due to the air inflation that is required during EGD, hiccups can induce reflux of gastric contents into the esophagus and can cause regurgitation and aspiration, particularly in sedated patients[10,11].

Although their exact mechanism remains unknown, hiccups may be induced by stimulating the postulated hiccup reflex arc, which is a complex interaction mainly composed of the phrenic and vagus nerves, the sympathetic chain and accessory nerves connecting to the glottis and the inspiratory intercostal muscles[12-14]. Vagus and phrenic nerve irritation, central nervous system disorders, toxic-metabolic disorders, and psychogenic factors are 4 possible mechanisms leading to hiccups[12,14,15]. As described above, gastric distention during endoscopy stimulates the phrenic nerve and causes hiccups. Drug-induced hiccups are uncommon, but anesthetics and sedative agents, such as benzodiazepines, opioids, and intravenous general anesthesia drugs, are suspected agents in cases of drug-induced hiccups[15]. On the other hand, the sedation of patients to relieve anxiety and discomfort appears to decrease the incidence of hiccups during endoscopic procedures[12]. Therefore, whether sedation can protect the patients undergoing endoscopic procedures against the onset of hiccups is unknown and requires further investigation.

Gastroesophageal reflux disease (GERD) is a common outpatient gastroenterology problem[16,17]. Patients with GERD may present a variety of symptoms, ranging from typical symptoms, such as heartburn or regurgitation, to atypical symptoms, such as chest pain, asthma, laryngitis, or chronic cough[16]. Hiccups represent an atypical symptom of GERD, with a prevalence of 4.5% to 9.5% in GERD patients[18,19]. The major pathophysiology of GERD includes increased episodes of transient lower esophageal sphincter (LES) relaxations, ineffective esophageal motility, and reduced LES tone[20-22]. Interestingly, hiccups could also induce the transient decrease of LES tone[8,20] and even the loss of LES tone[23]. Therefore, the increased probability of hiccups in GERD patients during sedation requires further investigation.

The goals of this study were to determine the incidence of hiccups in patients undergoing EGD or BDE with or without sedation, the possible causes of hiccups in sedated patients and the association of hiccups with GERD in sedated patients.

MATERIALS AND METHODS

Patient selection

This prospective study was approved by the Institutional Review Board of the E-DA hospital (EMRP-098-125). Consecutive adult (18 years or older) patients scheduled for outpatient EGD or same-day BDE at the gastrointestinal endoscopy unit or the health examination center were included. The exclusion criteria included history of esophageal, gastric or colorectal cancer; history of esophageal or gastric surgery; esophageal or gastric varices; allergy to propofol or eggs; and American Society of Anesthesiology risk Class 3 or higher.

The participating patients were allocated into 2 groups: EGD without sedation (Group A) and BDE with sedation (Group B). Sedation used for endoscopic examination was based on the patient's explicit request. The sample size was calculated from the results of our pilot study of patients who underwent EGD without sedation. We assumed that the patients with sedation would show a different (approximately 15%) prevalence of hiccups than the nonsedated patients. Therefore, 195 patients per group were required [where $\alpha = 0.05$ (two-tailed), $\beta = 0.2$]. At least 400 patients were studied to allow for any loss of follow-up.

Study design

After consent was obtained, demographic, medical and drug history data were recorded for each patient. On arrival in the endoscopy room, each patient was routinely given supplemental oxygen (4 L/min) thorough a nasal cannula. In addition, an intravenous route was set up in patients of Group B, and no intravenous fluids were given before the initiation of sedation. Routine patient monitoring included electrocardiography, noninvasive arterial blood pressure measurement, and pulse oximetry.

In all the participating patients (Group A and Group B), 20 mg hyoscine *N*-butyl bromide (Buscopan) was administrated intravenously as premedication except in those with glaucoma, obstructive uropathy, coronary heart diseases, or a history of allergies to anticholiner-

gic drugs. Anesthesiologists participated in this study by administrating sedative drugs. Fifty microgram of fentanyl plus midazolam were given, followed by the administration of propofol approximately 1 to 2 min later. However, the choice of whether to use midazolam as an adjuvant and the administration dosage were determined by the anesthesiologists without further input from the researchers. To avoid any pain from injecting propofol, lidocaine was mixed with propofol before administration (1 mL of 2% lidocaine in every 20 mL of 1% propofol). An initial bolus of 1.5 mg/kg of propofol was given and then titrated in 10- to 20-mg increments to achieve an adequate level of sedation.

A single experienced gastroenterologist performed both the EGD and the colonoscopic examinations for all the patients. The EGD started when an adequate level of sedation (in which the patient was asleep, not responding verbally but ventilating spontaneously) was achieved. Once the EGD was finished, the subsequently colonoscopy was preformed immediately. During the endoscopic procedure, the need to add more propofol was estimated by the patient's pain response (i.e., moans, grimaces, gag reflex, and movements).

Predefined complications (hypotension, bradycardia, airway obstruction, hypoventilation, and hypoxia) were managed according to the hospital's routine protocol. At the end of the procedure, the patients were transferred to the recovery room. The time when the patient was ready for discharge according to hospital criteria (oxygen saturation > 95% on air, heart rate > 60 beats/min, systolic blood pressure ± 30 mmHg from preoperative values, orientated, pain score < 4/10, and no nausea or vomiting) was recorded.

Measurements

Demographic data were recorded, including each patient's age, gender and body weight. Medical data were collected, including diabetes, hypertension, cigarette smoking/alcohol consumption, cerebrovascular diseases, gastrointestinal disorders, GERD-like syndromes, liver diseases, psychological disorders, and history of intractable hiccups. The patients' drug histories regarding agents suspected of causing hiccups [i.e., non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines and aminophylline] was also recorded. Sedative regimens, midazolam and propofol dose titrated to an adequate level of sedation for EGD insertion and total propofol dose were recorded. Oxygen saturation, heart rate and arterial blood pressure were recorded every 5 min during sedation. All the times were recorded from a continuously running stopwatch. Endoscopy time was defined as the time from the insertion and until withdrawal of the colonoscope from the anus. If hiccups occurred during the procedure, the time hiccups occurred, the time hiccups subsided and the administrated doses of propofol were recorded. After the endoscopic examinations, the patients with a diagnosis of GERD and other gastrointestinal disease revealed by the EGD were collected.

Statistical analysis

All the continuous data were tested for normality. Normally distributed continuous data were expressed as the mean ± SD, and *t* tests were used to compare the means of continuous data. Skewed data were expressed with medians and ranges and were compared using Wilcoxon's ranked sum test. Categorical data were analyzed using the Pearson χ^2 test with Yates' correction or Fisher's exact probability test. When there were more than two groups, normally distributed data were compared using analysis of variance, and skewed data were compared using the Kruskal-Wallis test.

In all tests, a 2-tailed $P < 0.05$ was considered statistically significant. The relative magnitudes of the associations between individual (categorical and continuous) variables and the likelihood of the occurrence of hiccups was compared using crude odds ratios (ORs). The precision of the estimated ORs was assessed by examining the 95% confidence intervals (CIs). A multivariate logistic regression model containing all the candidate variables was used to examine the independent contribution made by each variable, while controlling for all the variables. This resulted in an adjusted OR and a calculated 95% CI. The statistical analyses were performed with SPSS for Mac version 19.0 (SPSS Inc., Chicago, IL).

RESULTS

A total of 435 patients were invited to participate in our study. Ten patients were excluded from the analysis because of incomplete data collection. Therefore, a total of 425 data sets were eligible for analysis: 215 data sets were from the non-sedation group, and 210 were from the sedation group. Table 1 summarizes the baseline characteristics of the patients in this study. There was no significant difference between the 2 groups regarding gender, body weight, hypertension, psychological disorders, or aminophylline intake history. However, there were more patients in Group A who took NSAIDs and benzodiazepines and had histories of diabetes, cigarette smoking/alcohol consumption, cerebrovascular diseases, gastrointestinal disorders, GERD-like syndromes and liver diseases than in Group B.

Though the indications for endoscopic examination in our patients were including epigastralgia, abdominal fullness, dysphagia, change in bowel habit, positive fecal occult blood test, and bloody stool *etc*., the indication in most patients was for heath check-up. Hence, these significant differences in baseline characteristics were because most Group B participants undergoing endoscopic examination were for health check-up.

Assessment for the association between sedation and hiccups

The incidences of hiccups in Group B (under sedation) and Group A (without sedation) were 20.5% and 5.1%, respectively. The ORs and 95% CI for the occurrence of hiccups induced by sedation were calculated. The use of sedation for patients undergoing endoscopy was

Table 1 Baseline characteristics of patients in the study *n* (%)

	Group A (*n* = 215)	Group B (*n* = 210)	*P* value
Gender (male)	118 (54.9)	111 (52.9)	0.675
Body weight (kg)	63.6 ± 12.4	64.3 ± 17.6	0.675
Age (yr)	53.1 ± 15.3	48.9 ± 11.6	0.002
Diabetes	28 (13.0)	12 (5.7)	0.012
Hypertension	47 (21.9)	33 (15.7)	0.109
Cigarette smoking/ alcohol consumption	72 (33.5)	36 (17.1)	< 0.001
Cerebrovascular diseases	18 (8.4)	6 (2.9)	0.019
Gastrointestinal diseases	130 (60.5)	30 (14.3)	< 0.001
GERD-like syndromes	103 (47.9)	17 (8.1)	< 0.001
Liver diseases	48 (22.3)	22 (10.5)	0.001
Psychological disorders	2 (0.9)	4 (1.9)	0.445
Drug history			
NSAIDs	36 (16.7)	6 (2.9)	< 0.001
Benzodiazepines	22 (10.2)	7 (3.3)	0.006
Aminophylline	7 (3.3)	2 (1)	0.175

The data are presented as the mean ± SD (normally distributed data), or *n* (%) (categorical data). Group A: Esophagogastroduodenoscopy (EGD) without sedation; Group B: Bidirectional endoscopy (BDE) with sedation; NSAIDs: Non-steroid anti-inflammatory drugs; GERD: Gastroesophageal reflux disease.

Table 2 Baseline characteristics of patients in the sedation group (Group B) *n* (%)

	Hiccups (*n* = 43)	No hiccups (*n* = 167)	*P* value
Gender (male)	29 (67.4)	82 (49.1)	0.032
Body weight (kg)	66.0 ± 10.1	63.9 ± 19.0	0.524
Age (yr)	47.3 ± 11.5	49.3 ± 11.5	0.306
Diabetes	4 (9.3)	8 (4.8)	0.256
Hypertension	7 (16.3)	26 (15.6)	0.909
Cigarette smoking/ alcohol consumption	6 (14.0)	30 (18.0)	0.534
Cerebrovascular diseases	2 (4.7)	4 (2.4)	0.428
Gastrointestinal diseases	7 (16.3)	23 (13.8)	0.675
GERD-like syndromes	5 (11.6)	12 (7.2)	0.341
Liver diseases	4 (9.3)	18 (10.8)	0.778
Psychological disorders	1 (2.3)	3 (1.8)	0.821
Drugs history			
NSAIDs	3 (7.0)	3 (1.8)	0.069
Benzodiazepines	1 (2.3)	6 (3.6)	0.680
Aminophylline	0 (0)	2 (1.2)	0.471
Premedication			
Buscopan	37 (86.0)	121 (76.5)	0.066

The data are presented as the mean ± SD (normally distributed data) or *n* (%) (categorical data). NSAIDs: Non-steroid anti-inflammatory drugs; GERD: Gastroesophageal reflux disease.

significantly associated with an increased risk of hiccups (OR, 4.78; 95% CI: 2.39-9.56). This association remained significant and independent after adjustment for age, diabetes, cigarette smoking/alcohol consumption, cerebrovascular diseases, gastrointestinal disorders, GERD, liver diseases, and the use of NSAIDs or benzodiazepines (adjusted OR, 8.79; 95% CI: 3.27-23.60).

Comparison of the contributing factors to hiccups

Table 2 summarizes the characteristics of the patients who developed hiccups and those who did not during sedation. Gender was the only significant difference between these groups ($P < 0.05$). The majority of the patients who developed hiccups during sedation were male (67.4%).

Comparison of the effect of sedative drugs on hiccups

The onset time (counted from the insertion of EGD) of hiccups was 6 min (1-21 min) [median (range)], and their duration was 1 min (1-19 min) [median (range)]. All the hiccups occurred before the end of the EGD in sedated patients, except in 3 patients who suffered from hiccups after the insertion of the colonoscope (onset time was 21, 17 and 16 min). Two patients suffered from hiccups that lasted for 19 and 15 min.

In the pharmaceutical characteristics of the development of hiccups, the effect of the midazolam dose was observed (Table 3). The patients who received 2 mg midazolam (1-2 mg) (range) developed hiccups more frequently compared with patients who received 1 mg midazolam (range: 0-2.5 mg, $P = 0.028$).

Assessment for the association between diagnostic findings of endoscopy and hiccups

Diagnostic findings of endoscopy were listed in Table 3. The patients with diagnosed GERD were more prone to develop hiccups ($P = 0.018$).

DISCUSSION

To the best of our knowledge, this is the first study to examine the prevalence of hiccups in patients undergoing EGD or BDE. In this prospective study, sedation was associated with a significantly increased occurrence of hiccups. Midazolam, which was used in our combined sedation regimens, was associated with the onset of hiccups. In addition, the patients diagnosed with GERD revealed by EGD were more prone to develop hiccups while undergoing endoscopic procedures with sedation.

Clinically, most hiccup episodes begin with an acute onset, are benign, and are self-limited, typically ceasing within minutes[24]. However, the sudden onset of hiccups may become a safety hazard while patients are sedated. Hiccup-associated acute negative intrathoracic pressure may occur, resulting in hypotension and bradycardia[24]. This effect is attributed to decreased vascular resistance resulting from increased dilation and volume of the thoracic aorta[25]. In our study, no statistically significant changes occurred in any hemodynamic measure following the onset of hiccups. Whether hiccup-associated systolic hypotension is deleterious to cardiovascular function in adults is unclear, but it remains a plausible etiology of pathological hemodynamic changes in those patients with underlying heart disease[26].

Hiccups could influence the respiration of the patient during anesthesia. Unexpected pulmonary aspiration has been diagnosed in positron emission tomography (PET) screening following panedoscopy under conscious sedation[27]. In our patients, we observed no respiratory

Table 3 Intra- and post-procedure study parameters of patients in the sedation group (Group B) *n* (%)

	Hiccups (*n* = 43)	No hiccups (*n* = 167)	*P* value
Endoscopy time (min)	16 (5-40)	15 (0-35)	0.186
Sedation regimens, mean (range)			
Fentanyl (μg)	50	50	-
Midazolam (mg)	2 (0-2)	1 (0-2.5)	0.028
2% Lidocaine (mg)	40 (0-60)	40 (0-60)	0.453
Propofol (mg)	70 (50-150)	80 (40-200)	0.955
Diagnostic findings of endoscopy, *n* (%)			
Superficial gastritis	41 (95.3)	163 (97.6)	0.428
Gastric ulcer	3 (7.0)	18 (10.8)	0.459
Duodenal ulcer	4 (9.3)	14 (8.4)	0.848
Gastric polyp	3 (4.7)	10 (6.0)	0.736
Esophageal diverticulum	0 (0.0)	2 (1.2)	0.471
GERD	11 (25.6)	19 (11.4)	0.018
Internal hemorrhoid	20 (46.5)	68 (40.7)	0.492
Colon polyp	4 (9.3)	7 (4.2)	0.180
Rectal polyp	4 (9.3)	7 (4.2)	0.180
Cecal diverticulosis	1 (2.3)	3 (1.8)	0.821

The data are presented as median (range) (skewed data) or *n* (%) (categorical data). GERD: Gastroesophageal reflux disease.

distress associated with cyanosis or desaturation on pulse oximetry in patients with hiccups during the endoscopic examinations or in the recovery room. Although aspiration during sedation may be silent and uneventful, hiccups in sedated patients do carry clinical risks[10,28].

Acute gastric distention due to air inflation during endoscopy might result in hiccups by stimulating gastric vagal afferent activity[24]. To avoid any influence of the gas inflation that is required during a colonoscopy, we conducted EGD before colonoscopy in the patients of Group B. Furthermore, to avoid inter-observer variation, a single physician performed all the EGD and colonoscopy procedures. In the sedation group, the hiccups all occurred during the EGD, and almost all of the hiccups ceased before the initiation of colonoscopy. Further, the incidence was significantly greater than in the nonsedated group (Group A). Therefore, causes other than this mechanical factor could have induced hiccups. Psychogenic factors (e.g., anxiety, stress, and excitement) are other possible causes of hiccups[12]. Therefore, sedation for EGD or BDE relieves patient anxiety and seems to decrease the incidence of hiccups. However, Group B did not show a lesser incidence of hiccups than Group A. In fact, the use of sedative drugs during endoscopic procedures favored the onset of hiccups.

Although there was insufficient evidence in Thompson's[15] review to conclude that any specific drug induces drug-related hiccups, corticosteroids and benzodiazepines are the most frequently suspected agents in cases of drug-induced hiccups[15,29]. Midazolam is a benzodiazepine with rapid onset, brief duration of action and an amnestic effect[30], and it is commonly administered in combination with an opiate and/or propofol to achieve adequate sedation for an EGD or colonoscopy. In addition, midazolam has gained popularity for use in procedural sedation and anxiolysis in pediatric patients. Midazolam is water-soluble and can be safely administered in a variety of ways. Marhofer *et al*[31] had investigated that the incidence of hiccups in pediatric patients who were pre-medicated with two different doses of rectally administrated midazolam for minor surgery. Their patients in group A received 0.5 mg/kg of midazolam, while their patients in group B were treated with 1 mg/kg. Twenty-four percent of the children developed hiccups, but no statistically significant difference was noted between the two doses (22% in group A *vs* 26% in group B). Hiccups were more common among younger children (i.e., those aged 5-6 mo *vs* 20 mo). In our sedated patients, the total incidence of hiccups was similar, but age was not a statistically significant variable. In addition, the development of hiccups was associated with higher doses of midazolam.

Interestingly, drug-induced hiccups are reported more commonly in men than women[29]. In our study, the majority of patients who developed hiccups during sedation were male. This finding is consistent with recent studies revealing a significant male predominance of hiccups in patients receiving cytotoxic chemotherapy[32,33]. However, the mechanisms for the male predominance of hiccups and the midazolam-induced hiccups are still unknown. Hiccups might be induced by the influence of midazolam on a supraspinal hiccup center localized in the brain stem[34]. Another factor causing midazolam-induced hiccups could be a direct stimulation of the inspiratory muscles, specifically on diaphragm contractility[35]. By contrast, Fujii *et al*[36] indicated that midazolam decreases the contractility of the diaphragm in a dose-dependent manner in an animal study. Furthermore, intravenously administered midazolam has been successfully used in patients with terminal hiccups[37]. The discrepancies among these results perhaps reflect the complicated etiology of hiccups; further studies are required to improve our understanding of their etiology. Nevertheless, our study provides further evidence for the association of midazolam administration with the onset of hiccups.

Graham[23] showed that there is no detectable LES tone during a hiccup attack. Hiccups add tension to the phrenoesophageal ligament and thus have the same sphincter-dilating effect. Therefore, hiccups could induce episodes of transient decrease of LES tone[8,20] that result in reflux both in normal subjects and in esophagitis patients[38]. Furthermore, LES function can be overcome by the transient peritoneal-pleural gradient created during hiccups[39]. In the study of Werlin *et al*[40], 27% transient increases in intra-abdominal pressure, such as would be caused by a hiccup, were associated with reflux. According to Vanner[11], approximately 40% of patients who hiccup after induction of anesthesia develop detectable gastroesophageal reflux.

The most important aspect of the pathophysiology of GERD is the competency of the anti-reflux barriers[22]. Factors contributing to their integrity include the

LES pressure, the presence or absence of a hiatal hernia, and the occurrence of transient LES relaxation[22,41]. Transient LES relaxation is considered the most common pathophysiologic event at the time of a reflux episode[22,41]. Hence, the fact that patients with GERD are prone to develop hiccups during sedation might be due to previous abnormalities of LES.

This study had several weaknesses. Because of the use of sedation is a self-pay service and based on the patients' request, it is difficult to perform a randomized controlled trial to detect the incidence of hiccups in patients undergoing EGD or BDE with or without sedation. Though there is potential for bias in our prospective and cross sectional study, the study design could examine the association among the variables (e.g., sedation *vs* hiccups in our study)[42]. In addition, the fact that the choice of midazolam as an adjuvant was not random limits the ability to draw conclusions about its hiccup-inducing effect, but it raises interesting hypotheses and provides pilot data for testing in the future.

In conclusion, sedation was associated with the occurrence of hiccups in patients undergoing gastrointestinal endoscopic procedures, and hiccups occurred primarily in males. Midazolam, a sedative drug, was significantly associated with an increased risk of hiccups. Furthermore, patients with GERD were prone to develop hiccups.

ACKNOWLEDGMENTS

The authors thank Hon-Yi Shi, PhD for revising the manuscript.

COMMENTS

Background

During esophagogastroduodenoscopy (EGD) and colonoscopy procedure, sedation is usually used to alleviate patient discomfort. In addition to hemodynamic and respiratory depression, hiccups are the other frequently encountered clinical situation during endoscopic procedures with sedation. Hiccups, though commonly acute and temporary, may interfere with spontaneous breathing and hamper endoscopic investigations and interventions. However, the exact mechanism of hiccups remains unknown.

Research frontiers

There are 4 possible mechanisms leading to hiccups, including vagus and phrenic nerve irritation, central nervous system disorders, toxic-metabolic disorders, and psychogenic factors. Anesthetics and sedative agents are suspected agents in cases of drug-induced hiccups. On the other hand, the sedation of patients to relieve anxiety and discomfort appears to decrease the incidence of hiccups during endoscopic procedures. Therefore, whether sedation can protect the patients undergoing endoscopic procedures against the onset of hiccups is unknown and requires further investigation. In addition, hiccups represent an atypical symptom of gastroesophageal reflux disease (GERD), the increased probability of hiccups in GERD patients during sedation also requires further investigation.

Innovations and breakthroughs

To the best of our knowledge, this is the first study to examine the prevalence of hiccups in patients undergoing EGD or colonoscopy. Sedation for endoscopic procedures relieves patient anxiety and seems to decrease the incidence of hiccups. However, in this prospective study, the use of sedative drugs during endoscopic procedures favored the onset of hiccups. Although there was insufficient evidence to conclude that any specific drug induces drug-related hiccups, benzodiazepines are the most frequently suspected agents in cases of drug-induced hiccups. Midazolam, a benzodiazepine with rapid onset and brief duration of action, was associated with the development of hiccups, especially in higher doses. In addition, the study also shows that patients with GERD are prone to develop hiccups during sedation.

Applications

The study results suggest that the development of hiccups was associated with higher doses of midazolam. Therefore, avoid using midazolam or decreasing the midazolam dosage in combined sedation regimen for endoscopic procedure can decrease the incidence of onset of hiccups.

Terminology

Hiccups: Hiccups are an involuntary spasmodic contraction of the diaphragm and accessory muscles followed by the sudden closure of the glottis; GERD: Patients with GERD may present a variety of symptoms, ranging from typical symptoms, such as heartburn or regurgitation, to atypical symptoms, such as chest pain, asthma, laryngitis, chronic cough, or hiccups. The major pathophysiology of GERD includes increased episodes of transient lower esophageal sphincter (LES) relaxations, ineffective esophageal motility, and reduced LES tone.

Peer review

The results of the study are interesting and it was well written. Nevertheless, there are some major points of concern.

REFERENCES

1 **Triadafilopoulos G**, Aslan A. Same-day upper and lower inpatient endoscopy: a trend for the future. *Am J Gastroenterol* 1991; **86**: 952-955
2 **Külling D**, Fantin AC, Biro P, Bauerfeind P, Fried M. Safer colonoscopy with patient-controlled analgesia and sedation with propofol and alfentanil. *Gastrointest Endosc* 2001; **54**: 1-7
3 **Rudner R**, Jalowiecki P, Kawecki P, Gonciarz M, Mularczyk A, Petelenz M. Conscious analgesia/sedation with remifentanil and propofol versus total intravenous anesthesia with fentanyl, midazolam, and propofol for outpatient colonoscopy. *Gastrointest Endosc* 2003; **57**: 657-663
4 **Moerman AT**, Struys MM, Vereecke HE, Herregods LL, De Vos MM, Mortier EP. Remifentanil used to supplement propofol does not improve quality of sedation during spontaneous respiration. *J Clin Anesth* 2004; **16**: 237-243
5 **Sipe BW**, Rex DK, Latinovich D, Overley C, Kinser K, Bratcher L, Kareken D. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Gastrointest Endosc* 2002; **55**: 815-825
6 **Paspatis GA**, Manolaraki M, Xirouchakis G, Papanikolaou N, Chlouverakis G, Gritzali A. Synergistic sedation with midazolam and propofol versus midazolam and pethidine in colonoscopies: a prospective, randomized study. *Am J Gastroenterol* 2002; **97**: 1963-1967
7 **VanNatta ME**, Rex DK. Propofol alone titrated to deep sedation versus propofol in combination with opioids and/or benzodiazepines and titrated to moderate sedation for colonoscopy. *Am J Gastroenterol* 2006; **101**: 2209-2217
8 **Marshall JB**, Landreneau RJ, Beyer KL. Hiccups: esophageal manometric features and relationship to gastroesophageal reflux. *Am J Gastroenterol* 1990; **85**: 1172-1175
9 **Kranke P**, Eberhart LH, Morin AM, Cracknell J, Greim CA, Roewer N. Treatment of hiccup during general anaesthesia or sedation: a qualitative systematic review. *Eur J Anaesthesiol* 2003; **20**: 239-244
10 **McVey FK**, Goodman NW. Gastro-oesophageal reflux and hiccough on induction of anaesthesia. *Anaesthesia* 1992; **47**: 712
11 **Vanner RG**. Gastro-oesophageal reflux and hiccup during anaesthesia. *Anaesthesia* 1993; **48**: 92-93
12 **Friedman NL**. Hiccups: a treatment review. *Pharmacotherapy* 1996; **16**: 986-995
13 **Samuels L**. Hiccup; a ten year review of anatomy, etiology, and treatment. *Can Med Assoc J* 1952; **67**: 315-322
14 **Lembo AJ.** Overview of hiccups. In: Basow DS, editor. UpToDate. Waltham, MA: UpToDate Inc., 2012

15 **Thompson DF**, Landry JP. Drug-induced hiccups. *Ann Pharmacother* 1997; **31**: 367-369
16 **Lacy BE**, Weiser K, Chertoff J, Fass R, Pandolfino JE, Richter JE, Rothstein RI, Spangler C, Vaezi MF. The diagnosis of gastroesophageal reflux disease. *Am J Med* 2010; **123**: 583-592
17 **Chait MM**. Gastroesophageal reflux disease: Important considerations for the older patients. *World J Gastrointest Endosc* 2010; **2**: 388-396
18 **Dore MP**, Pedroni A, Pes GM, Maragkoudakis E, Tadeu V, Pirina P, Realdi G, Delitala G, Malaty HM. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. *Dig Dis Sci* 2007; **52**: 463-468
19 **Bor S**, Mandiracioglu A, Kitapcioglu G, Caymaz-Bor C, Gilbert RJ. Gastroesophageal reflux disease in a low-income region in Turkey. *Am J Gastroenterol* 2005; **100**: 759-765
20 **Dent J**, Dodds WJ, Friedman RH, Sekiguchi T, Hogan WJ, Arndorfer RC, Petrie DJ. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. *J Clin Invest* 1980; **65**: 256-267
21 **Kahrilas PJ**. Clinical practice. Gastroesophageal reflux disease. *N Engl J Med* 2008; **359**: 1700-1707
22 **Herbella FA**, Patti MG. Gastroesophageal reflux disease: From pathophysiology to treatment. *World J Gastroenterol* 2010; **16**: 3745-3749
23 **Graham DY**. Esophageal motor abnormality during hiccup. *Gastroenterology* 1986; **90**: 2039
24 **Rousseau P**. Hiccups. *South Med J* 1995; **88**: 175-181
25 **Mathew OP**. Effects of transient intrathoracic pressure changes (hiccups) on systemic arterial pressure. *J Appl Physiol* 1997; **83**: 371-375
26 **Marinella MA**. Diagnosis and management of hiccups in the patient with advanced cancer. *J Support Oncol* 2009; **7**: 122-127, 130
27 **Wang CH**, Sun SS, Hsieh TC, Yen KY, Wu YC, Lin YY, Kao CH. Unexpected left-sided pulmonary aspiration misdiagnosed as malignancy in PET cancer screening following panendoscopy cancer screening under conscious sedation. *Clin Nucl Med* 2010; **35**: 604-606
28 **Brouillette RT**, Thach BT, Abu-Osba YK, Wilson SL. Hiccups in infants: characteristics and effects on ventilation. *J Pediatr* 1980; **96**: 219-225
29 **Bagheri H**, Cismondo S, Montastruc JL. [Drug-induced hiccup: a review of the France pharmacologic vigilance database]. *Therapie* 1999; **54**: 35-39
30 **Reves JG**. Intravenous anesthetics. In: Miller RD editor. Miller's Anesthesia. 6th ed. Philadelphia: Churchill Livingstone, 2005: 736-738
31 **Marhofer P**, Glaser C, Krenn CG, Grabner CM, Semsroth M. Incidence and therapy of midazolam induced hiccups in paediatric anaesthesia. *Paediatr Anaesth* 1999; **9**: 295-298
32 **Liaw CC**, Wang CH, Chang HK, Liau CT, Yeh KY, Huang JS, Lin YC. Gender discrepancy observed between chemotherapy-induced emesis and hiccups. *Support Care Cancer* 2001; **9**: 435-441
33 **Takiguchi Y**, Watanabe R, Nagao K, Kuriyama T. Hiccups as an adverse reaction to cancer chemotherapy. *J Natl Cancer Inst* 2002; **94**: 772
34 **Davis JN**. An experimental study of hiccup. *Brain* 1970; **93**: 851-872
35 **Aldrich TK**, Prezant DJ. Adverse effects of drugs on the respiratory muscles. *Clin Chest Med* 1990; **11**: 177-189
36 **Fujii Y**, Hoshi T, Uemura A, Toyooka H. Dose-response characteristics of midazolam for reducing diaphragmatic contractility. *Anesth Analg* 2001; **92**: 1590-1593
37 **Wilcock A**, Twycross R. Midazolam for intractable hiccup. *J Pain Symptom Manage* 1996; **12**: 59-61
38 **Dodds WJ**, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK, Egide MS. Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med* 1982; **307**: 1547-1552
39 **Borromeo CJ**, Canes D, Stix MS, Glick ME. Hiccupping and regurgitation via the drain tube of the ProSeal laryngeal mask. *Anesth Analg* 2002; **94**: 1042-1043
40 **Werlin SL**, Dodds WJ, Hogan WJ, Arndorfer RC. Mechanisms of gastroesophageal reflux in children. *J Pediatr* 1980; **97**: 244-249
41 **Waring JP**. Gastroesophageal reflux disease (GERD). In: Johnson LR, editor. Encyclopedia of gastroenterology. Amsterdam, Boston: Elsevier Academic Press, 2004: 203-204
42 **Mann CJ**. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J* 2003; **20**: 54-60

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