Ambulatory colonoscopy under sedoanalgesia in adult patients with and without irritable bowel syndrome: A prospective, cross-sectional, and double-blind comparison

Bahattin Tuncalı[1] , *Coşkun Araz[2]* , *Arzu Çelebi[3]*

[1]*Department of Anesthesiology, Başkent University Zübeyde Hanım Practice and Research Center, İzmir, Turkey*
[2]*Department of Anesthesiology, Başkent University School of Medicine, Ankara, Turkey*
[3]*Department of Gastroenterology, Başkent University Zübeyde Hanım Practice and Research Center, İzmir, Turkey*

ABSTRACT

Background/Aims: *It is unclear whether patients with irritable bowel syndrome (IBS) require a high dose of sedatives during colonoscopy. In this study, we investigated the pre-procedural anxiety levels, sedative consumption, procedure times, complications, and patient's satisfaction between patients with IBS and controls for ambulatory colonoscopy under sedation.*

Materials and Methods: *Rome III criteria were used in the diagnosis of IBS. Anxiety levels were measured using Spielberger's State-Trait Anxiety Inventory (STAI) and Beck Anxiety Inventory (BAI). Patients received a fixed dose of midazolam (0.02 mg/kg), fentanyl (1 µg/kg), ketamine (0.3 mg/kg), and incremental doses of propofol under sedation protocol. Demographic data, heart rate, blood pressure, and oxygen saturation were measured. Procedure times, recovery and discharge times, drug doses used, complications associated with the sedation, and patient's satisfaction scores were also recorded.*

Results: *The mean Trait (p=0.015), State (p=0.029), Beck anxiety scores (p=0.018), the incidence of disruptive movements (p=0.044), and the amount of propofol (p=0. 024) used were significantly higher in patients with IBS. There was a decline in mean systolic blood pressure at the 6th minute in patients with IBS (p=0.026). No association was found between the sedative requirement and the anxiety scores.*

Conclusion: *Patients with IBS who underwent elective colonoscopy procedures expressed higher pre-procedural anxiety scores, required more propofol consumption, and experienced more disruptive movements compared with controls. On the contrary, the increased propofol consumption was not associated with the increased pre-procedural anxiety scores.*

Keywords: *Colonoscopy, irritable bowel syndrome, sedation, anxiety*

INTRODUCTION

Irritable bowel syndrome (IBS) is associated with abdominal pain, discomfort, altered bowel habits, and change in stool consistency without an organic disorder (1,2). Most patients with IBS have poor quality of life with psychiatric co-morbidities, such as anxiety, depression, and mood disorders (3-5). Moreover, several studies have shown that compared with healthy subjects, patients with IBS have higher anxiety levels (6-8).

Colonoscopy is commonly performed in the differential diagnosis of IBS, and some gastroenterologists believe that patients with IBS remain more uncomfortable or require more sedation and analgesics during colonoscopy (9-11). However, we could not find a prospective study

that investigated the anxiety levels, anesthetic consumption, recovery profiles, complications, and satisfaction in patients with IBS that underwent elective colonoscopy under sedation.

In this study, we aimed to compare the pre-procedural anxiety levels, propofol consumption, recovery profiles, complications, and patient's satisfaction between patients with IBS and controls undergoing ambulatory colonoscopy under sedation.

MATERIALS AND METHODS

This study was performed between May 2013 and August 2015 following ethical approval (Başkent University Institutional Review Board, Project No: KA13/95, May 23,

2013) in a double-blind fashion. Informed consent was obtained from each patient. The anesthesiologist who performed the sedation procedure and collected the data including demographic characteristics, hemodynamic status, complications, procedure times, and drug doses used, and the patients were blinded to the groups. The gastroenterologist evaluated all the patients scheduled for elective colonoscopy for the presence of IBS according to the Rome III criteria (12). Additionally, blood tests and stool analysis were performed to exclude organic diseases in these patients. Patients not belonging to the age group of 18-75 years, American Society of Anesthesiology (ASA) physical status class ≥3, not having a previous history of colonoscopy, anesthesia, or sedation for past 7 days, psychiatric disorders, drug addiction, known allergy to medications used in the study protocol, and inability to provide informed consent were excluded. All patients were informed about the procedure and the protocol, risks and complications of sedoanalgesia via a standard face-to-face interview with the gastroenterologist and anesthesiologist separately.

All patients went through the standard colon preparation protocol the day before colonoscopy. On the day of the procedure, state and trait anxiety levels of the patients were measured by the gastroenterologist using the Spielberger's state-trait anxiety inventory (STAI) and Beck anxiety inventory (BAI) (13,14). Colonoscopies were performed by the same gastroenterologist using the same colonoscope (Fujinon EC-450WL5, Fuji Photo Optical Co. Ltd., Saitama, Japan) in all the patients.

In the gastroenterology unit, after recording demographic data, an intravenous catheter was inserted in the arm, and 0.9% sodium chloride solution was administered intravenously. All patients were continuously monitored for heart rate, systolic blood pressure (SBP), diastolic blood pressures (DBP), heart rate (HR), oxygen saturation (SpO_2), and sedation levels before administration of anesthetic medicines every 2 minutes for the first 10 minutes and every 5 minutes thereafter. Supplemental oxygen (3 L/min) was provided via a facemask throughout the procedure. Sedation levels were monitored using the Ramsay sedation scale (RSS). Recovery and discharge criteria were determined based on the RSS and Modified Post Anesthesia Discharge Scoring System (MPADSS), respectively (15,16). The procedure times were determined as follows:

· induction time=time from first drug administration to the start of procedure,

· cecum intubation time=time from start of procedure until colonoscope insertion into the cecum,

· duration of colonoscopy=time from start of procedure until colonoscope removal,

· recovery time=time from colonoscope removal until the patient reached an RSS of 2,

· discharge time=time from colonoscope removal to achieving MPADSS≥9.

In both groups, patients received a fixed dose of intravenous 0.02 mg/kg midazolam (Midazolam; Zolamid, Defarma, Turkey), 1 µ/kg fentanyl (Talinat, Vem, Turkey), 0.3 mg/kg ketamine (Ketalar, Pfizer, USA), and incremental doses of propofol (Propofol-Lipuro, Braun, Germany) to achieve a RSS of 3-4. Sedation was maintained using 10-20 mg of additional propofol doses at RSS of 3-4 throughout the procedure. Disruptive movements during the procedure were recorded. At the end of the procedure, verbal commands (open your eyes) were repeated at 1-minute intervals until the patient responded. Subsequently, the patients were transported to the post anesthesia care unit (PACU) when the RSSs were 2. In the PACU, the patients were monitored for vital signs, postoperative nausea and vomiting, postoperative pain, and psychological reactions such as hallucination. The patients were discharged upon achieving MPADS≥9. Procedure times and anesthetic consumption were also recorded.

The jaw thrust maneuver was applied when apnea occurred for more than 15 seconds. Mask ventilation was used when SpO_2 fell below 90% and the patient was still apneic. A drop of >20% of the patient's SBP or a drop to a value of <90 mm Hg was defined as hypotension and was treated with an intravenous infusion of 0.9% sodium chloride solution. Hypertension was defined as an increase of >20% of the patient's baseline SBP. A drop in HR to <50 beats/min was defined as bradycardia and was treated using intravenous atropine (atropine sulfate, Galen, Turkey). Any need for jaw thrust or mask ventilation and any other adverse side effects of sedation were recorded.

All patients were asked whether they had experienced unpleasant dreams or hallucinations and to rate their satisfaction with the sedation using the 3-point scale (0=satisfactory; 1=less than satisfactory; and 2=unsatisfactory). They were also questioned regarding their willingness to receive the same sedation protocol if needed in the future at discharge and 24 hours after the procedure (by telephone).

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences 20.0 for Windows (IBM Corp.; Armonk, NY, USA). Normally distributed data, which was confirmed using the Kolmogorov-Smirnov test, was analyzed using Student's t-test; the Chi square test was used for comparison of categorical data. $p < 0.05$ was considered statistically significant. Independent from groups, the Pearson correlation analysis was used to determine the associations between propofol requirement and anxiety scores.

The sample size was calculated based on the propofol consumption of two groups, which was the main endpoint of our study. In a previous trial, we found that the average propofol consumption with midazolam-fentanyl-ketamine based sedation was 70±22.5 mg (17). Assuming a 25% difference of propofol requirement, at least 35 patients were required in each group with an alpha value of 0.05, beta value of 0.95, and an effect size of 87% with a power of 95%. We planned to include 40 patients in each group because we assessed multiple parameters.

RESULTS

In total, 126 potential participants scheduled for elective colonoscopy under sedation were assessed for eligibility. Nineteen of these refused to give informed consent, 27 refused to complete the anxiety inventories; in 4 patients, colonoscopy was aborted because of inadequate bowel preparation. Consequently, 76 patients were included in this study. Indications for colonoscopy were gastrointestinal complaints, including constipation and diarrhea (n=54) and screening for colorectal malignancy (n=17) and anemia (n=5). Patient characteristics were comparable between groups (Table 1). In the IBS group, the mean trait anxiety scores (p=0.015), state anxiety scores (p=0.029), Beck anxiety scores (p=0.018), and the amount of propofol (p=0.024) used were significantly higher compared with the non-IBS group. Procedure times and the amount of midazolam, fentanyl, and ketamine were comparable between the groups (Table 2).

Except the decline in mean SBP at the sixth minute in the IBS group (p=0.026), hemodynamic data including DBP, HR, and SpO_2 were not significantly different between the groups. Bradycardia occurred in one and four patients in the non-IBS and IBS groups, respectively. The incidence of desaturation ($SpO_2 < 90$) and the need for jaw thrust maneuver or mask ventilation were not different between the groups. In the IBS group, the incidence of unintended movements was significantly higher than that in the IBS group (8 vs 2), particularly before cecum intubation (p=0.044). No patient experienced unpleasant dreams or hallucination (Table 3). All patients were satisfied with their sedation protocol and expressed willingness to receive the same sedation protocol again in the future.

Independent from groups, the Pearson correlation analysis showed no association between propofol requirement and the state anxiety scores, trait anxiety scores, and Beck anxiety scores (Figure 1).

Table 1. Endoscopic and histopathologic findings of CD patients

	Non-IBS group (n=39)	IBS group (n=37)
Demographic characteristics (mean±SD or number)		
Age (years)	60.1±10.6	61.1±10.4
BMI (kg/m²)	27.0±3.2	26.8±3.3
Gender (M/F)	19/20	19/18
ASA status (I/II)	11/28	14/23
Educational level		
<High school	7	5
High school	12	14
University	20	18

IBS: irritable bowel syndrome; BMI: body mass index; M: male; F: female; ASA: American Society of Anesthesiologists; SD: standard deviation
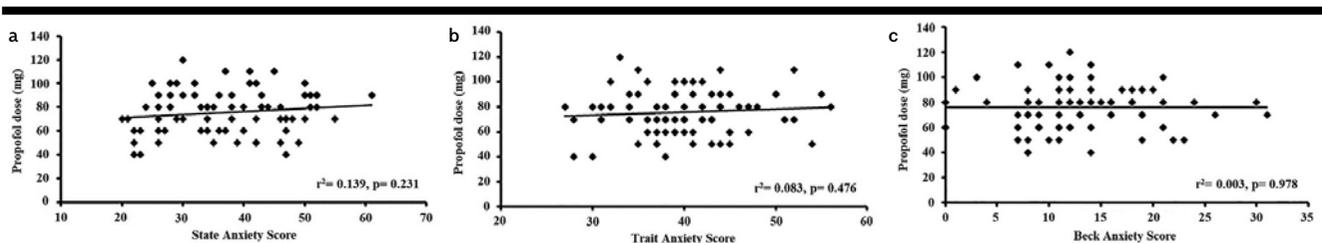

Figure 1. There was no correlation between the propofol requirement and the state, trait, and Beck anxiety scores

Table 2. Anxiety scores, procedure times, and total drug doses used

	Non-IBS group (n=39)	IBS group (n=37)
Anxiety scores (mean±SD/median-IQR)		
STAI-trait anxiety inventory	38.6±6.2/39.0±10.0	42.1±6.0±41.0±7.0 *
STAI-state anxiety inventory	34.8±9.0/34.0±16.0	39.6±9.9/40.0±15.5 **
Beck anxiety inventory	11.2±5.0/11.0±6	14.5±6.9/14±8.5***
Procedure time (minutes) (mean±SD/median-IQR)		
Induction	2.3±0.6/2.1-0.5	2.5±0.7/2.5-1.1
Cecum intubation	5.7±2.4/5.0-3.0	6.0±1.7/6.0-3.0
Duration of colonoscopy	11.7±3.9/10-6.0	11.7±3.2/10.0-6.0
Recovery and discharge times (minutes) (mean±SD/median-IQR)		
Recovery	4.1±1.3/4.0-2.0	4.4±1.5/4.5-2.2
Discharge	14.7±2.7/14.5-3.5	15.5±3.1/15.5-4.2
Total drug doses used (mean±SD/median-IQR)		
Midazolam (mg)	1.5±0.2/1.6-0.5	1.8±2.2/1.5-0.4
Fentanyl (µg)	77.3±11.4/80.0-20.0	75.5±16.8/70.0-15.0
Ketamine (mg)	21.5±2.8/21-6.0	21.2±2.7/21-6.0
Propofol (mg)	71.2±18.9/70.0-20.0	80.5±15.9/80.0-20.0****

Variables are expressed as mean±SD and median with IQR; MPADS≥9, *p=0.015, **p=0.029, ***p= 0.018, ****p=0.024

IBS: irritable bowel syndrome; SD: standard deviation; IQR: inter-quartile range; STAI: state-trait anxiety inventory; MPADS: modified post anesthesia discharge score

Table 3. Complications associated with sedation during and after colonoscopy

	Non-IBS group (n=39)	IBS group (n=37)	p
Bradycardia	1 (2.56%)	4 (10.8%)	0.194
SpO$_2$<90	4 (10.2%)	7 (18.9%)	0.341
Jaw thrust maneuver	4 (10.2%)	7 (18.9%)	0.341
Mask ventilation	0 (0%)	2 (5.4%)	0.234
Disruptive movements	2 (5.12%)	8 (21.6%)*	0.044
Post procedure pain	17 (43.5%)	22 (59.4%)	0.179
Vomiting during colonoscopy	0	0	-
Postoperative vomiting (At discharge/after 24 hours)	0/0	0/0	-
Unpleasant dreaming (At discharge/after 24 hours)	0/0	0/0	-
Hallucinations (At discharge/after 24 hours)	0/0	0/0	-

IBS: irritable bowel syndrome; SpO$_2$: oxygen saturation

DISCUSSION

The present study showed that IBS patients reported greater pre-procedural anxiety scores, required more propofol, and experienced more disruptive movements than the non-IBS patients during colonoscopy under sedation. However, we observed that the increased propofol requirement was not associated with the increased pre-procedural anxiety scores.

Irritable bowel syndrome is a common gastrointestinal disorder characterized by gastrointestinal symptoms, such as abdominal pain, discomfort, altered bowel habits, and stool consistency in the absence of an organic disease as diagnosed by routine physical examination, laboratory tests, and colonoscopy (1). Its prevalence is approximately 10%-20% in the general population (2). Although the etiology is unclear, several studies have shown that psychological, social, and environmental factors are important and that approximately greater than 50%-60% patients with IBS have major psychological problems, including anxiety, depression, somatization, and mood disorders (3-7). A meta-analysis similarly reported that IBS patients had significantly higher anxiety levels than healthy controls (8). Higher anxiety levels in patients with IBS can also be related to their perception of colonoscopy as reported in previous studies (9). Although, a large number of these patients undergo elective colonoscopy to exclude any organic diseases in IBS, to our knowledge, this is the first study

that investigated the pre-procedural anxiety levels, anesthetic requirements, complications, and patient satisfaction in patients with IBS who underwent colonoscopy. Our study revealed that patients with IBS scheduled for elective colonoscopy reported significantly higher pre-procedural anxiety scores than non-IBS patients. These results were consistent with the earlier studies, which reported that anxiety levels of patients with IBS were higher than those in healthy controls (6-8).

The increase in preoperative anxiety level is believed to lead to increased perioperative anesthetic requirement. Nevertheless, previous studies investigating the relationship between pre-procedural anxiety levels and anesthetic requirement revealed conflicting results. Maranets and Kain (18) investigated the association between baseline anxiety and propofol requirement for the induction and maintenance of alfentanil-N_2O-propofol-based general anesthesia in 57 patients who underwent bilateral laparoscopic tubal ligation. It was found that not state anxiety but trait anxiety is associated with intraoperative anesthetic requirement. In 100 patients who underwent total thyroidectomy, Kil et al. (19) reported that patients with high state-trait anxiety scores required more propofol requirement during light to moderate levels of sedation, and that propofol requirement was associated with trait anxiety during deep sedation. Osborn et al. (20) investigated the effects of anxiety on 25 patients who underwent molar extraction under midazolam-fentanyl-propofol based sedation and found that patients with high state and trait anxiety required more propofol, whereas those with high trait anxiety had more intraoperative movements. Hong et al. (21) investigated the effects of baseline anxiety on propofol requirement and recovery profile in 150 patients who underwent oocyte retrieval under conscious sedation with propofol and reported that patients with high anxiety required higher propofol dose and were associated with delayed induction time. In all these studies, there are differences in the anesthetic techniques, drug combinations, anxiety assessment tools, and sedation levels. Moreover, there are also procedural differences that result in different degrees of painful stimulation. Chung et al. (22) investigated the effects of anxiety on sedative requirement in 135 patients undergoing colonoscopy and found that there was no relationship between the level of pre-procedural anxiety and sedative requirement or recovery characteristics. Our findings are consistent with the study of Chung et al. (22), suggesting that there are other possible mechanisms leading to an increase in propofol requirement in IBS patients.

The regulation of the gastrointestinal tract function is under the control of different complex systems. The network, which connects the gastrointestinal tract and the central nervous system, is also known as the brain-gut pathway and connects emotional and cognitive areas in the central nervous system and is thought to be involved in IBS (7,8). Anxiety and/or depression can change the regulatory functions of the autonomic nervous system and neuroendocrine centers, which transfer the message to the enteric nervous system resulting in an alteration in gastrointestinal hormones, mucosal blood flow, and intestinal motility. These changes may influence visceral sensation, intestinal movement, and endocrine function leading to the symptoms in patients with IBS (6,8). It has been documented that increased sensitivity to bowel stretching in patients with IBS leads to an increase in pain experienced during colonoscopy compared with non-İBS patients (10). Therefore, all these features may offer disadvantages in patients with IBS wherein the most unwanted effects are pain, hemodynamic derangement, and vasovagal reactions, possibly because of distension of the colon and stretching of the mesentery during colonoscopy. In this study, vasovagal reactions were observed in 1 and 4 patients in the nonIBS and IBS groups, respectively, which were not significant; fluctuations in hemodynamic parameters were not significantly different among groups, except the decline in mean SBP at the sixth minute in the IBS group. A possible explanation for this decrease is the higher propofol dosage required before cecum intubation in this group. Compared with the non-IBS group, more patients in the IBS group (8 vs 2) required additional rescue dose of propofol immediately before cecum intubation because of disruptive movements in our study. These findings are also consistent with those of authors who pointed out that patients with IBS have increased visceral sensitivity to rectal or colonic distention and decreased threshold for pain (23-26).

In our study, there was no difference between the groups in procedure times, including recovery and discharge, and all the patients in both groups expressed their satisfaction as satisfactory with willingness to receive the same sedation regimen again in the future. Adequate amnesia, analgesia, and sedation provided by an anesthesiologist using a practical scale and midazolam-fentanyl-ketamine-propofol combination might be the reason of high satisfaction scores in both groups.

Our study has several limitations. First, the measures used in anxiety assessments were based on patient's

self-reported subjective scoring systems rather than objective indicators. Therefore, we used both the Spielberger's STAI and Beck anxiety inventories to compare our results with previous studies. Second, the sedation protocol used included a fixed dose of midazolam, fentanyl, and ketamine, and incremental doses of propofol to achieve and maintain adequate sedation during colonoscopy. The variability in either group might be decreased using this combination, and a greater difference might have been detected between the groups if we had used only propofol in the sedation protocol. Third, we used a per body weight dosage for midazolam, fentanyl, and ketamine, which might be unreliable because of inter-individual variability (20).

In conclusion, in adult patients who underwent colonoscopy under sedoanalgesia, the presence of IBS includes problems such as increased pre-procedural anxiety, intra-procedural propofol requirement, and disruptive movements, to both the anesthesiologist and gastroenterologist. However, the increase in propofol consumption is not related to the pre-procedural anxiety scores; however, it is probably caused by other mechanisms specific for IBS.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Başkent University (Project No: KA13/95; Decision Date: May 23, 2013).

Informed Consent: Informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.T., C.A., A.Ç.; Design - B.T., C.A., A.Ç.; Supervision - B.T., C.A., A.Ç.; Resource - B.T., C.A., A.Ç.; Materials - B.T., A.Ç.; Data Collection and/or Processing - B.T., A.Ç.; Analysis and/or Interpretation - B.T., C.A., A.Ç.; Literature Search - B.T., C.A.; Writing - B.T., C.A., A.Ç.; Critical Reviews - B.T., C.A., A.Ç.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This study was supported by Başkent University Research Fund.

REFERENCES

1. Singh P, Agnihotri A, Pathak MK, et al. Psychiatric, somatic and other functional gastrointestinal disorders in patients with irritable bowel syndrome at a tertiary care center. J Neurogastroenterol Motil 2012; 18: 324-31. [CrossRef]

2. Endo Y, Shoji T, Fukudo S. Epidemiology of irritable bowel syndrome. Ann Gastroenterol 2015; 28: 158-9.

3. Mykletun A, Jacka F, Williams L, et al. Prevalence of mood and anxiety disorder in self-reported irritable bowel syndrome (IBS). An epidemiological population based study of women. BMC Gastroenterol 2010; 10: 88. [CrossRef]

4. Hausteiner-Wiehle C, Henningsen P. Irritable bowel syndrome: Relations with functional, mental and somatoform disorders. World J Gastroenterol 2014; 20: 6024-30. [CrossRef]

5. Fukudo S, Kaneko H, Akiho H, et al. Evidence-based clinical practice guidelines for irritable bowel syndrome. J Gastroeneterol 2015; 50: 11-30. [CrossRef]

6. Deechakawan W, Heitkemper MM, Cain KC, et al. Anxiety, depression, and catecholamine levels after self-management intervention in irritable bowel syndrome. Gastroenterol Nurs 2014; 37: 24-32. [CrossRef]

7. Han B. Correlation between gastrointestinal hormones and anxiety-depressive states in irritable bowel syndrome. Exp Ther Med 2013; 6: 715-20. [CrossRef]

8. Fond G, Loundou A, Hamdani N, et al. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci 2014; 264: 651-60. [CrossRef]

9. Denters MJ, Schreuder M, Depla AC, et al. Patients' perception of colonoscopy: patients with inflammatory bowel disease and irritable bowel syndrome experience the largest burden. Eur J Gastroenterol Hepatol 2013; 25: 964-72. [CrossRef]

10. Kim ES, Cheon JH, Park JJ, et al. Colonoscopy as an adjunctive method for the diagnosis of irritable bowel syndrome: focus on pain perception. J Gastroenterol Hepatol 2010; 25: 1232-8 [CrossRef]

11. Lule E, Iddings E, Manandhar L, et al. Utility of Analgesic and Anxiolytic Medication Dose during Colonoscopy in Identifying Patients with Irritable Bowel Syndrome. ISRN Gastroenterol 2012; 2012: 969015. [CrossRef]

12. Rome Foundation. Guidelines--Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders. J Gastrointestin Liver Dis 2006; 15: 307-12.

13. Manual for the State-Trait Anxiety Inventory (Form Y). Palo Alto, CA: Consulting Psychologists Press, 1983.

14. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56: 893-7. [CrossRef]

15. Ramsay MA, Savege TM, Simpson BR, et al. Controlled sedation with alphaxalone-alphadolone. BMJ 1974; 2: 656-9. [CrossRef]

16. Chung F, Chan V, Ong D. A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Monit 1995; 7: 89-91. [CrossRef]

17. Tuncali B, Ozvardar Pekcan Y, Celebi A, et al. Addition of low dose ketamine to midazolam-fentanyl-propofol based sedation for colonoscopy. J Clin Anesth 2015; 27; 301-6. [CrossRef]

18. Maranets I, Kain ZN. Preoperative Anxiety and Intraoperative Anesthetic Requirements. Anesth Analg 1999; 89: 1346-51. [CrossRef]

19. Kil HK, Kim WO, Chung WY, et al. Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia. Br J Anaesth 2012; 108: 119-25. [CrossRef]

20. Osborn TM, Sandler NA. The Effects of Preoperative Anxiety on Intravenous Sedation. Anesth Prog 2004; 51: 46-51.

21. Hong JY, Jee YS, Luthardt FW. Comparison of conscious sedation for oocyte retrieval between low-anxiety and high-anxiety patients. J Clin Anesth 2005; 17: 549-53. [CrossRef]

22. Chung KC, Juang SE, Lee KC, et al. The effect of pre-procedure anxiety on sedative requirements for sedation during colonoscopy. Anaesthesia 2013; 68: 253-9. [CrossRef]

23. Kanazawa M, Hongo M, Fukudo S. Visceral hypersensitivity in irritable bowel syndrome. J Gastroenterol Hepatol 2011; 26: 119-21. [CrossRef]

24. Zhou Q, Verne GN. New insights into visceral hypersensitivity – clinical implications in IBS. Nat Rev Gastroenterol Hepatol 2011; 8: 349-55. [CrossRef]

25. Keszthelyi D, Troost FJ, Jonkers DM, et al. Visceral hypersensitivity in irritable bowel syndrome: evidence for involvement of serotonin metabolism - a preliminary study. Neurogastroenterol Motil 2015; 27: 1127-37. [CrossRef]

26. Lee YC, Wang HP, Chiu HM, et al. Factors determining post-colonoscopy abdominal pain: prospective study of screening colonoscopy in 1000 subjects. J Gastroenterol Hepatol 2006; 21: 1575-80. [CrossRef]