Assessment of pain between sedated and unsedated colonoscopy: Double-blind randomized clinical trail

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Background: Colonoscopy plays a vital role for the diagnosis and treatment of colonic diseases but can be associated with anxiety and discomfort or pain. We tested whether unsedated colonoscopy impacts quality indicators and investigated predictors of pain during colonoscopy. Materials and Methods: This randomized controlled trial was performed on candidates for elective colonoscopy at Al Zahra Hospital, Isfahan at 2018–2019. Balanced block randomization was used to allocate 275 cases into two groups. At finally, 124 patients in case and 122 patients in control group enrolled in analysis. Patients in the sedation group received midazolam with/out pethidine before colonoscopy. Pain intensity in rectal examination (PIREX), preprocedural anxiety, pain intensity during colonoscopy, hemodynamics, duration of colonoscopy, polyp detection rate, cecal intubation rate, bloating within 24 h after colonoscopy, and willingness to repeat colonoscopy were assessed and compared between two groups. Results: Compared to the group with sedation, cecal intubation time was shorter and bloating was less frequent (7% vs. 16%, P = 0.02) in the unsedated group. There was no difference between the two groups regarding polyp detection rate, cecal detection rate, and willingness to repeat colonoscopy. Pain during rectal examination was significantly associated with pain during colonoscopy (P < 0.001, 95% confidence interval; 0.5–1.3). Conclusion: The assessment of pain intensity during rectal examination may help to identify patients who can benefit from sedation during colonoscopy. Colonoscopy with sedation does not seem to have a negative impact on colonoscopy quality indicators, and may even reduce cecal intubation time and bloating following procedure.

Key words: Analgesia, colonoscopy, endoscopy, sedation

INTRODUCTION

Colonoscopy is used for diagnostic and therapeutic indications.1] Despite all the new inventions, colonoscopy is still the best way for diagnosing gastrointestinal bleeding and its pivotal role for treating colorectal polyps and cancer screening is proven.2,3] Colonoscopy can reduce mortality of patients with colonic cancer by 50%.4] Colonoscopy is usually operated with sedations. Different medications are used for sedation during colonoscopy including midazolam, pethidine, and propofol,5] with propofol having shorter recovery time.6] However, sedation has some risks and disadvantages such as hypotension, respiratory depression, drug allergy and needs time to recovery.7–11] Furthermore, colonoscopy without sedation can have some important advantages such as reducing load of colorectal cancer screening and it is beneficial to lower the overall cost to patients and health-care facilities.12] Due to the complications of sedation and its extra costs, whether it is acceptable to do colonoscopy without sedation is yet under debate. Also, factors that can predict pain during...
unsedated colonoscopy is not fully investigated which can provide information on candidate for unsedated colonoscopy. Limited studies have examined effects of sedation on quality of colonoscopy. For instance, study by Iqbal et al. showed that sedation does not affect polyp detection rate or complete performance of colonoscopy.\cite{13} Some studies have examined the factors that are related to pain during unsedated colonoscopy and found that nervousness is related to pain during unsedated colonoscopy.\cite{14} We tested whether unsedated colonoscopy impacts quality indicators and investigated predictors of pain during colonoscopy. Therefore, the aim of this study was to determine the effect of sedation in elective colonoscopy on quality indicators, including polyp detection rate, cecal intubation rate, cecal intubation time, rate of complications during unsedated colonoscopy and to compare willingness to colonoscopy with the same manner between sedated and unsedated group, also to assess the factors that are related to pain during unsedated colonoscopy including age, sex, body mass index, pain in rectal exam, previous abdominal surgery, indications for colonoscopy and level of anxiety.

**MATERIALS AND METHODS**

**Participants and study settings**

This randomized controlled trial was performed in the endoscopy unit of AL. Zahra Hospital, Isfahan (Iran) from September 2018 to September 2019. Patients were checked with regards to the inclusion and exclusion criteria by a physician a day before colonoscopy. Eligibility criteria for colonoscopy were, age of above 18 years, indications for elective colonoscopy (e.g., constipation, rectorrhagia, abdominal pain, diarrhea, or screening surveillance for colon cancer), and willingness to participate. Patients with the following conditions were not included in the study: Poor preparation of colon, severe colitis, history of colorectal surgery, hypersensitivity to sedative drugs, cardiovascular or pulmonary instability and colon tumors or colon stenosis that interfere with completion of colonoscopy. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (IR.MUI.MED.REC.1397.247) and registered in the Iranian Registry of Clinical Trials (IRCT20190105042246N1). Informed consent was obtained from all patients after full explanation of the study aims and protocols. Primary outcome was pain relief.

**Sample size**

Determining the sample size according to power 80% and the first type error of 0.05% was determined using the sample size formula equal to 100 people in each group. Sampling was performed sequentially and taking into account the inclusion criteria.

**Randomization**

Eligible patients were enrolled into the study consecutively and were randomized to the sedation and nonsedation group. Balanced block randomization method with quadruple blocks was used for random allocation.\cite{14} The production of blocks was done using Excel software.

**Blindness**

Double-blind study was performed. Participants and the interviewers did not know the type of drug injected.

**Intervention**

Patients consumed 210 g powder of polyethylene glycol in 3 L of water (PIDROLAX, Sepidaj Co, Tehran, Iran) 1 day before colonoscopy, and 140 g powder of polyethylene glycol in 2 L of water at the day of procedure with the time between last dose and colonoscopy set at 2 h. Colonoscopy was done by a Gastroenterologist with experience of more than 10,000 colonoscopies. Midazolam in 2.5-mg increments (Caspian Tamim Co., Tehran, Iran) with or without pethidine 25-mg increments (Caspian Tamim Co., Tehran, Iran) was given in the sedated group 5 min before the procedure. Normal saline was given in the unsedated group as a placebo. In the event of extreme discomfort, experienced frequently during the procedure, sedatives were given also to patients in the unsedated group during the procedure.

**Assessments**

Demographic information including age, sex, body mass index (BMI), reasons of colonoscopy, and history of surgery were taken from patients. Rectal examination was performed before colonoscopy and intensity of pain felt during rectal examination was recorded based on a verbal scale of one to five (PIREX score), where 0 means no pain and 5 means a severe and unbearable pain. Level of patient’s anxiety was recorded 15 min before colonoscopy using a verbal scale from 0 (not at all) to 3 (very much). Quality of bowel preparation was determined using Boston bowel preparation scale and rated from 0 to 9.\cite{15} Colonoscopy quality criteria including polyp detection rate, cecal intubation rate, and cecal intubation time were recorded.\cite{14} Patient’s pain was recorded during colonoscopy, only in unsedated group, using a verbal scale of 0 (no pain) to 4 (severe). Bloating was documented by calling patients until 24 h after colonoscopy. During colonoscopy, patients were monitored for blood pressure and oxygen saturation. Complications including bowel perforation, drug reaction, and bleeding were documented.

**Statistical analysis**

The sample size was calculated based on comparison of two independent proportions \((n = \left[ \frac{Z_{a/2} + Z_{b}}{2 \times \left( P_1 (1 - P_1) + P_2 (1 - P_2) \right)} \right] / \left( P_1 - P_2 \right)^2)\). Data analysis was done using SPSS for windows version 21.0 (IBM SPSS Statistics [IBM Corp, Armonk, NY, USA]). Data distribution was checked for normality.
Continues variables are presented as mean (standard deviation) and were compared between the two groups using Independent sample t-test or Mann–Whitney U-test for ordinal variables. Categorical nominal variables are presented as number (%) and were compared between the two groups using Chi-square test. Ordinal logistic regression was used to determine the associations between pain during colonoscopy and independent variables including age, gender, BMI, preprocedural anxiety, and pain intensity during rectal examination. A $P < 0.05$ was considered significant in all analysis. Known confounding variables including age, sex, BMI, history of abdominal surgery, pain during examination, and individual anxiety were matched in two groups. No missing data were found.

RESULTS

From initially 300 enrolled patients, 246 participants completed the trial in two groups: colonoscopy with sedation ($n = 124$) and colonoscopy without sedation ($n = 122$) [Figure 1]. Patients in the two studied groups were similar regarding their demographic characteristics [Table 1, $P > 0.05$]. There was no significant difference between the two groups regarding history of abdominal pain, or pain in rectal examination and level of anxiety before colonoscopy ($P > 0.05$). Outcomes of the colonoscopy procedure in the two studied groups are presented in Table 2. Mean of cecal intubation time was significantly longer in the sedated group than unsedated group ($P = 0.016$). Bloating was reported more frequently in the sedated group than unsedated ($P = 0.033$). There was no significant difference regarding other variables including polyp detection rate, cecal intubation rate, and willingness to repeat the colonoscopy between sedated and unsedated groups [Table 2]. The association between pain during colonoscopy and independent variables in unsedated group showed significant association between pain during rectal examination and pain during colonoscopy ($P < 0.001$, wald $= 19.4$, 95% confidence interval: 0.5–1.3).

Complications

There was a no colon perforation or bleeding in both groups. Transient hypoxemia due to midazolam was noted in one participant in the sedated group.

DISCUSSION

In our study, there were not any significant differences between sedated group and unsedated group in regard to cecal intubation rate and polyp detection rate as two indicators of quality criteria for colonoscopy.

In study by Aljbreen et al., cecal intubation rate between two group was comparable, though in that study sedated group and unsedated group were not match in terms of male to female ratio and anxiety level.[9] Furthermore, in study by Bannert et al., two groups did not have any statistically significance difference in regards to polyp detection rate.[10] In our study, cecal intubation time in unsedated group was shorter than sedated group and justification of this could be the possibility of changing position in unsedated group that facilities the procedure as study by Zhao et al. proven that changing position of patients to supine can decrease cecal intubation time.[11] In our study, based on multi variant analyzes pain intensity during unsedated colonoscopy didn’t have any correlation with patient’s gender, BMI, anxiety level, and age. Pain in rectal examination was related to pain during colonoscopy in unsedated group. Based on our investigation, this relation was not investigated in previous studies hitherto. Pain during colonoscopy could be due to different anatomic variations and angulation of bowel that can cause looping of colonoscopy or it can be due to lower level of pain threshold. We can determine pain threshold in patients with intra rectal balloon and also, rectal examination can mimic intra rectal balloon and determines pain threshold, hence it can predict severity of pain during colonoscopy maneuvers or insufflation. In the study by Daza et al. same as our study, pain intensity during unsedated colonoscopy did not have any correlation with history of abdominal surgery and age.[12] In study by Holme et al., women’s pain intensity during unsedated colonoscopy was higher. Furthermore, pain during unsedated colonoscopy was related to female gender.[13] However, in these two studies several endoscopists were involved in the research but in our study colonoscopy was performed by one endoscopist and this difference can be due to inter observer variation in their studies or it can be due to lower sample size that

Table 1: Characteristics of the patients in the two studied groups

| Variables                          | Sedation ($n=124$) | No sedation ($n=122$) | $P$   |
|-----------------------------------|--------------------|-----------------------|-------|
| Age (years); mean±SD              | 50.1±12.1          | 49.2±13.6             | 0.43* |
| Male, $n$ (%)                     | 52 (41.9)          | 54 (44.3)             | 0.71† |
| BMI (kg/m²); mean±SD              | 25.2±3.7           | 25.1±3.6              | 0.91‡ |
| History of abdominal surgery, $n$ (%) | 5 (4.0)            | 4 (3.3)               | 0.75† |
| Pain in rectal examination$\dagger$; mean±SD | 1 (1, 2)          | 1 (0, 2)              | 0.060† |
| Anxiety precolonoscopy$\ddagger$; mean±SD | 1 (0, 2)           | 1 (0, 2)              | 0.62† |
| BBSP score; Mean±SD               | 7.8±0.9            | 7.7±0.8               | 0.28† |

$\dagger$Independent sample t-test; $\ddagger$Chi-square test; $\ddagger$Mann–Whitney U-test; $\dagger$No pain (0) to unbearable pain (5); $\ddagger$No anxiety (0) to severe anxiety (4); SD=Standard deviation; BMI=Body mass index; BBSP=Boston Bowel Preparation Scale
was used in our research. In unsedated group bloating after colonoscopy was less than sedated group. One potential interpretation is less insufflation due to the possibility of changing position or reporting pain during colonoscopy in unsedated patients. We did not find statistically significant difference for willingness to repeat colonoscopy with the same manner between sedated and unsedated patients.

Second for insufflation we used air instead of CO$_2$, if we used CO$_2$ insufflation, rate of bloating after procedure in both groups could be different. Moreover, third although in our study lower pain threshold was considered to be the reason of pain during colonoscopy but we did not check the relations between irritable bowel syndrome and pain during colonoscopy.

**CONCLUSION**

Colonoscopy without sedation does not have any significant effect on polyp detection rate and cecal intubation rate but cecal intubation time in unsedated patients was shorter and bloating after procedure in unsedated group was less than sedated group. Furthermore, we acknowledged that
pain during colonoscopy can be predicted with pain during rectal examination.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Rex DK, Schoenfeld PS, Cohen J, Pike IM, Adler DG, Fennerty MB, et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015;81:31-53.
2. Cappell MS, Friedel D. Initial management of acute upper gastrointestinal bleeding: From initial evaluation up to gastrointestinal endoscopy. Med Clin North Am 2008;92:491-509, xi.
3. Lin JS, Piper MA, Perdue LA, Rutter CM, Webber EM, O'Connor E, et al. Screening for colorectal cancer: Updated evidence report and systematic review for the US Preventive services task force. JAMA 2016;315:2576-94.
4. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687-96.
5. Zhang K, Yuan Q, Zhu S, Xu D, An Z. Is unsedated colonoscopy gaining ground over sedated colonoscopy? J Natl Med Assoc 2018;110:143-8.
6. Ferreira AO, Torres J, Barjas E, Nunes J, Glória L, Ferreira R, et al. Non-anesthesiologist administration of propofol sedation for colonoscopy is safe in low risk patients: Results of a noninferiority randomized controlled trial. Endoscopy 2016;48:747-53.
7. Ko CW, Riffle S, Michaels L, Morris C, Holub J, Shapiro JA, et al. Serious complications within 30 days of screening and surveillance colonoscopy are uncommon. Clin Gastroenterol Hepatol 2010;8:166-73.
8. Kim YH, Kim JW, Lee KL, Joo SK, Lee J, Koh SJ, et al. Effect of midazolam on cardiopulmonary function during colonoscopy with conscious sedation. Dig Endosc 2014;26:417-23.
9. Aljebreen AM, Almadi MA, Leung PW. Sedated vs unsedated colonoscopy: A prospective study. World J Gastroenterol 2014;20:5113-8.
10. Umezawa S, Higurashi T, Uchiyama S, Sakai E, Ohkubo H, Endo H, et al. Visual distraction alone for the improvement of colonoscopy-related pain and satisfaction. World J Gastroenterol 2015;21:4707-14.
11. Bannert C, Reinhart K, Dunkler D, Trauner M, Renner F, Knoeflach P, et al. Sedation in screening colonoscopy: Impact on quality indicators and complications. Am J Gastroenterol 2012;107:1837-48.
12. Iqbal N, Ramcharan S, Doughan S, Shaikh I. Colonoscopy without sedation: Patient factors alone are less likely to influence its uptake. Endosc Int Open 2016;4:E334-7.
13. Daza JF, Tan CM, Fielding RJ, Brown A, Farrokhyar F, Yang I. Propofol administration by endoscopists versus anesthesiologists in gastrointestinal endoscopy: A systematic review and meta-analysis of patient safety outcomes. Can J Surg 2018;61:226-36.
14. Morice V. RandoWeb, an online randomization tool for clinical trials. Comput Methods Programs Biomed 2012;107:308-14.
15. Parmar R, Martel M, Rostom A, Barkun AN. Validated Scales for Colon Cleansing: A Systematic Review. Am J Gastroenterol 2016;111:197-204.
16. Zhao S, Yang X, Meng Q, Wang S, Fang J, Qian W, et al. Impact of the supine position versus left horizontal position on colonoscopy insertion: A 2-center, randomized controlled trial. Gastrointest Endosc 2019;89:1193-2010.
17. Holme O, Bretthauer M, de Lange T, Seip B, Huppersz-Hauss G, Haie O, et al. Risk stratification to predict pain during unsedated colonoscopy: Results of a multicenter cohort study. Endoscopy 2013;45:691-6.
18. Ma L, Yan J, Shen J, Sang J, Xu H. Comparison of application value between conventional air insufflation and water infusion in colonoscopy. Int J Clin Exp Pathol 2020;13:2333-41.