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BRIEF ARTICLE

Balanced propofol sedation administered by nonanesthesiologists: The first Italian experience

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Abstract

AIM: To assess the efficacy and safety of a balanced approach using midazolam in combination with propofol, administered by non-anesthesiologists, in a large series of diagnostic colonoscopies.

METHODS: Consecutive patients undergoing diagnostic colonoscopy were sedated with a single dose of midazolam (0.05 mg/kg) and low-dose propofol (starter bolus of 0.5 mg/kg and repeated boluses of 10 to 20 mg). Induction time and deepest level of sedation, adverse and serious adverse events, as well as recovery times, were prospectively assessed. Cecal intubation and adenoma detection rates were also collected.

RESULTS: Overall, 1593 eligible patients were included. The median dose of propofol administered was 70 mg (range: 40-120 mg), and the median dose of midazolam was 2.3 mg (range: 2-4 mg). Median induction time of sedation was 3 min (range: 1-4 min), and median recovery time was 23 min (range: 10-40 min). A moderate level of sedation was achieved in 1561 (98%) patients, whilst a deep sedation occurred in 32 (2%) cases. Transient oxygen desaturation requiring further oxygen supplementation occurred in 8 (0.46%; 95% CI: 0.2%-0.8%) patients. No serious adverse event was observed. Cecal intubation and adenoma detection rates were 93.5% and 23.4% (27.8% for male and 18.5% for female, subjects), respectively.

CONCLUSION: A balanced sedation protocol provided a minimalization of the dose of propofol needed to target a moderate sedation for colonoscopy, resulting in a high safety profile for non-anesthesiologist propofol sedation.

Key words: Colonoscopy; Propofol; Sedation

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INTRODUCTION

Colorectal cancer (CRC) represents a major cause of morbidity and mortality in western countries[1]. Despite the fact that it has been shown to be highly effective in preventing CRC incidence, colonoscopy is usually perceived as an invasive and potentially painful procedure, resulting in a low uptake rate when compared with less invasive options, such as fecal tests or flexible sigmoidoscopy[2-4].

To improve acceptability and tolerability of colonoscopy, different protocols of sedation have been adopted[5]. Such regimens have been mainly restricted to benzodiazepines alone or in combination with opioids, because of the relatively high safety of these substances. Although these drugs result in a substantial improvement of patients' and endoscopists's experiences, some drawbacks have been observed. In particular, due to a relatively long half-life, a slow induction of sedation and a delayed discharging time with significant cost of monitoring have been reported[6]. Moreover, a significant proportion of patients are quite dissatisfied by the suboptimal degree of sedation provided by this protocol, and morbidity and mortality as a result of respiratory depression have also been reported[7,8].

Propofol represents a short-acting sedative agonist of gamma-aminobutyric acid receptor in the central nervous system, and it is mainly used for the induction and maintenance of deep sedation during surgical procedures[9]. Because of its short half-life (2-4 min) and high lipid solubility, propofol has the distinct advantages of a rapid induction of sedation and a fast recovery. When applied to gastrointestinal (GI) endoscopy, patient satisfaction with propofol has been shown to be equivalent or superior to that of benzodiazepines and/or narcotics[7]. Propofol, however, is a respiratory depressant with a narrow therapeutic range and without a reversal agent, resulting in a significant risk of inducing a too deep level of sedation, complicated by hypoventilation, apnea or cardiovascular depression. Moreover, it lacks a reversal agent. For this reason, propofol is largely administered by anesthesiologists or anesthesiologist nurses[10]. When considering the very high number of colonoscopies performed worldwide - 14 million every year in the United States alone[11] - anesthesiologist capacity is, however, likely to be insufficient to assure propofol sedation for this procedure.

It has been recently shown that propofol may be an effective and safe agent when used by non-anesthesiologists to target an adequate level of sedation[12]. A recent systematic review of the literature, including 646 080 cases, provided adequate evidence to the American Gastroenterological Association for them to support propofol administration by non-anesthesiologists (NAP), because of the extraordinary rarity of life-threatening episodes[13]. Most of these series were based on the use of propofol alone, during which NAP targeted a deep level of sedation. To further improve the safety profile, it has been suggested that a substantial reduction of the propofol dose may be achieved by administering this drug in association with other sedative agents, such as midazolam or meperidine[14,15]. This protocol has been defined as balanced propofol sedation (BPS), and, differently from NAP, it targets a moderate level of sedation.

No study has addressed the use of propofol by non-anesthesiologists for colonoscopy in Italy, and very few in Europe[13]. This is largely related to the product label of the drug which allows its administration only by physicians trained in general anesthesia. Due to the lack of an adequate anesthesiologist capacity and the low fee of reimbursement for a colonoscopy in the public system, virtually all the procedures are performed without propofol.

Only a few colonoscopy series have addressed the efficacy and safety of BPS for colonoscopy, most of them including only a few hundred of patients[14,15,17-23]. The purpose of this study was to prospectively assess the safety and the efficacy of endoscopist-administered BPS to target a moderate level of sedation for colonoscopy in a large series of consecutive patients.

MATERIALS AND METHODS

From February 2008 to December 2009, outpatients who presented to our unit for diagnostic colonoscopy were eligible for the study if they were between 18 and 75 years of age, American Society of Anesthesiology (ASA) class Ⅰ or Ⅱ, and capable of providing written informed consent for study participation. Exclusion criteria were inability to provide informed consent, history of allergic reactions or hypersensitivities to midazolam, propofol, eggs, or soybeans, high-risk head and neck anatomy (Mallampati score > 2) that could complicate airway rescue, sleep apnea syndrome, ASA class > Ⅱ.

The use of propofol by non-anesthesiologists in Italy is, at the time being, prevented by the specification in the product label that the use of this drug is exclusively allowed for anesthetists or intensive care unit physicians. For this reason, the administration of propofol within the present study has been performed under a study protocol that was supported by our Institution (Istituto Clinico Humanitas) and approved by the institutional review board. Nine endoscopists participated in this protocol, being authorized to administer propofol.

Patients underwent BPS administered by an endoscopist who was not involved in the endoscopic procedure. The physicians administering sedation were certified in advanced cardiac life support and had also successfully completed an intensively structured training program in propofol administration and laryngeal mask use under an anesthesiologist tutorship. The same anesthesiologist was always on call during the procedure time. Baseline vital signs (heart rate, blood pressure, oxygen saturation) were obtained in all patients before induction of sedation. Endoscopy-dedicated nurses also attended the procedure.

BPS was structured as follows: after a single dose of midazolam (0.05 mg/kg; Hameln pharmaceuticals gmbh, Hameln, Germany), a starter bolus of 0.5 mg/kg

Table 1 Scale for assessing Alertness/Sedation

Responsiveness	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

of propofol (Diprivan, Astra-Zeneca, Stockholm, Sweden) was administered. Repeated boluses of 10 to 20 mg of propofol were then administered on-demand with a 30-60 s interval for the entire duration of the procedure. Propofol bolus frequency and dose were titrated to the patient response, including vital signs and manifestations of restlessness or discomfort. The maximum dose allowed to be administered was 200 mg. Throughout the procedure, all patients received oxygen 2 L/min by nasal cannula. Continuous pulse oximetry, heart rate, electrocardiography, and end-expiratory carbon dioxide were monitored, with blood pressure being assessed at 5-min intervals. Level of sedation was evaluated according to the Scale for assessing Alertness/Sedation (MOAA/S), as reported in Table 1. In detail, deep sedation was defined as MOAA/S 1, moderate as MOAA/S 2-4, and minimal as MOAA/S 5. The following parameters were recorded: patient demographics, procedure indication and duration, midazolam dose, propofol dose, induction time, recovery time, cecal intubation rate, and polyp detection rate. The baseline values and changes in vital signs or oxygen saturation (SpO_2) from the baseline were also recorded. Adverse events were defined as hypoxia (i.e., a reduction in oxygen saturation < 90% for more than 20 s) requiring supplemental oxygen (O_2) by nasal cannula (NC) in excess of 2 L/min; and transient hypotension (< 90 mmHg) or bradycardia (< 60 beats/min) not requiring any active medical treatment. Serious adverse events were defined as hypoxia requiring positive pressure ventilation or laryngeal mask use; hypotension (< 90 mmHg) or bradycardia (< 60 beats/min) requiring medical treatment (i.e., infusion of liquid) other than propofol titration; and any event requiring the administration of a benzodiazepine antagonist (flumazenil). After the procedure, the patients were transported to the recovery room where blood pressure, SpO_2 and heart rate were measured continuously until discharge. Discharge was possible when blood pressure was within 20% of the initial value, SpO_2 > 90%, and the patient was able to drink and walk autonomously. Recovery time was measured from the time the patient entered the recovery area until departure by the recovery room nurse.

RESULTS

During the study period, 1593 eligible patients were included. Of these, 789 (49%) were male, the median age being 60 years (range: 22-75 years). Clinical indication for colonoscopy was evaluation of symptoms in 876 (55%) cases, screening or surveillance of a previous neoplastic lesion in 542 (34%), work-up of a positive fecal test in 96 (6%), and follow up of inflammatory bowel diseases in the remaining 79 (5%) cases.

Baseline mean heart rate and mean blood pressure were 71 ± 13 beats per min and 103 ± 16 mmHg, respectively. BPS was administered to all the patients. The median dose of midazolam was 2.3 mg (range: 2-4 mg), and the median dose of propofol administered was 70 mg (range: 40-120 mg). The median induction time of sedation (i.e., between the initiation of sedation and colonoscope insertion) was 3 min (range: 1-4 min). The deepest level of sedation was moderate in 1561 (98%) patients and deep in the remaining 32 (2%) cases. General anesthesia was not observed in any patient.

There was no serious adverse event related to any of the 1593 patients. The only adverse events observed with BPS were episodes of transient oxygen desaturation requiring O_2 supplementation by NC in excess of 2 L/min in 8 (0.46%; 95% CI: 0.2%-0.8%) patients. No patient required mask ventilation or endotracheal intubation. Although a transient decrease in blood pressure was common (446 patients, 28%), no episodes of sustained hypotension or bradycardia requiring active therapy were observed. No patient required administration of a benzodiazepine antagonist. Median recovery time was 23 min (range: 10-40 min).

The overall cecal intubation rate was 93.5%, corresponding to 1491 complete colonoscopies. Incomplete procedures were due to poor bowel cleaning in 72 (4.5%) patients and sigmoid strictures in 30 (2%) cases. The median procedural time was 11.3 min (range: 9-22 min), consisting of a median intubation time of 4 min (range: 3-9 min) and a median withdrawal time of 6.3 min (range: 4.2-11.9 min). Adenoma detection rate was 23.4% (27.8% for male, and 18.5% for female subjects). No major procedure-related complication occurred.

DISCUSSION

Our study showed that a BSP protocol, based on the co-administration of propofol with benzodiazepine, was a feasible, effective and safe approach for colonoscopy in a large series of consecutive patients. In particular, following a careful and rigid selection of the patients, BSP was successfully administered by non-anesthesiologist endoscopists without requiring anesthesiologist intervention in any of the cases. No BSP-related serious adverse event occurred in the study population, as outlined by the evidence that a midazolam-reversal agent was not needed in any patient. A transient oxygen desaturation was observed in only 0.5% of the study population, and it was treated conservatively in all cases.

The high safety profile of the BSP observed in our study appears to be strictly related to the very low dose

of propofol needed to target a moderate sedation, because of the additional effect of midazolam. Despite the fact that this was a non-randomized study in which a propofol-alone arm was not included, the median dose of propofol shown in the present study, corresponding to 70 mg per patient, appeared to be much lower than the 200-400 mg range described in previous propofol-alone series[16]. A similarly low propofol dose was also reported in previous series in which BSP was adopted[14,15,17-23]. When considering the potential legal implications related to NAP, the ability to minimize the dose of propofol needed appears as an attractive goal for the endoscopists. The very low rate of oxygen desaturation observed in our study may also be related to the systematic adoption of capnography to monitor our patients. It has been suggested that capnography may anticipate the diagnosis of propofol-induced hypoventilation as compared to the simple assessment of oxygen saturation[24].

It could be argued, however, that co-administration of midazolam could reduce the propofol-related advantages. In particular, the slow metabolization of benzodiazepines could result in a prolonged recovery time, reducing the efficiency of an endoscopic turnover system. The median recovery time in our series was consistently lower than 30 min. This value favorably compares with previous accounts of midazolam alone, in which a recovery time as long as 70 min was reported[25]. Such a difference in favor of the BSP regimen is presumably due to the relatively low dose of midazolam administered, the median being 2.1 mg per patient. Moreover, midazolam was administered only at the beginning of the procedure as a bolus, so that the drug started to be metabolized during the procedure itself, lasting on average 11 min.

Quality of colonoscopy procedures in our series appeared to reach the required standards, showing no interference of BSP in the diagnostic or operative procedures. In particular, the adjusted cecal intubation rate of 93.5% in a mixed setting with symptomatic and screening indications is remarkably superior to the 80.7% recently reported in an Italian survey, in which the use of propofol was not reported[26]. Of note, in a similarly designed Italian study, it was observed that the intubation rate in sedation-assisted colonoscopies was superior to that of those performed without sedation[27].

It could be argued that the results of our study were not unexpected; the safety of BSP having already been shown in previous studies. However, most of these series included only 100-200 patients[14,15,17-23], so that a greater confirmation of BSP safety in over 1500 subjects was needed. Moreover, this is the first Italian study in which NAP was applied to colonoscopy, and, more generally, to adults. This would appear to be of major importance when considering that the use of propofol in Italy is prevented by an unequivocal recommendation in the product label stating that only anesthesiologists are allowed to administer such a drug. The safety profile of BSP in our study should call for dedicated studies aiming to ascertain whether such a recommendation is really a protection for the patients and whether it is consistent with literature data or simply represents an obstacle preventing a safe propofol-assisted colonoscopy to most patients. Indeed, in Italy, due to the lack of anesthesiologist capacity, virtually all the colonoscopies are performed without propofol, using at best benzodiazepines and/or narcotics[25].

There are limitations to the present analysis. Our main target was to evaluate BSP efficacy in targeting a moderate level of sedation when administered by non-anesthesiologists, whilst we did not assess the level of satisfaction of patients or endoscopists with our sedation protocol. However, there is enough evidence regarding a higher satisfaction level with propofol as compared to midazolam[16]. Moreover, the short induction time clearly reflects a propofol type of sedation rather than the effect of midazolam. Secondly, we did not compare the propofol/midazolam BSP with other protocols, such as propofol alone or propofol with narcotics with or without midazolam. However, most of the propofol-related toxicity is associated with its narrow therapeutic window, so that it is unlikely that such a high safety profile would be achieved by protocols based on doses of propofol substantially larger than those reached in our experience. Thirdly, we did not blind the discharging nurse regarding the type of sedation, so that we cannot exclude a bias in the computation of the recovery time. Fourthly, we did not assess the alertness level after several hours from discharge, so that we cannot exclude a prolonged effect of midazolam bolus in our series. Fifthly, although our study included over 1500 subjects, we cannot exclude extremely rare events that have been associated with the use of propofol, such as neurologic injuries or even death. However, the lack of severe episodes of respiratory or cardiovascular depression reassures us about the safety of BSP. Moreover, no death has been reported up to now with the use of NAP in colonoscopy; all the cases having been associated with upper GI endoscopy or biliary maneuvers[13]. According to the study protocol, we systematically used a non-anaesthesiologist physician for monitoring propofol administration. It could be argued that this represents a waste of resources, requiring two endoscopists to perform one procedure. However, this simply reflects a prudent choice within the study protocol to prevent eventual litigation for an off-label use of the drug. It has already been shown that appropriately trained nurses may assist the endoscopist in propofol administration and sedation monitoring with a clear saving of resources. Finally, we did not use specific scales of recovery after the completion of the colonoscopy, considering discharge possible on the basis of blood pressure, SpO_2, and the patients' ability to drink and walk autonomously.

In conclusion, we report a large consecutive series showing the efficacy and safety of BSP for colonoscopy, when administered by non-anesthesiologists. When considering the controversy regarding NAP use for GI endoscopy, the very low dose of propofol allowed by the co-administration of midazolam appears to be a rational approach to maximize sedation efficacy and to minimize

propofol toxicity at the same time.

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COMMENTS

Background

Non-anesthesiologists propofol administration (NAP) represents an effective and safe alternative to sedation with benzodiazepines/narcotics for colonoscopy. NAP generally involves the administration of propofol alone to target a deep level of sedation. By associating propofol with other sedative agents, such as midazolam, a moderate level of sedation may be targeted, resulting in a substantial reduction of the propofol dose.

Research frontiers

Despite being validated in small controlled trials, such a balanced propofol sedation has never been tested in a large cohort.

Innovations and breakthroughs

In a large prospective study involving 1593 patients, a balanced propofol sedation consisting of the co-administration of propofol and midazolam resulted in a moderate level of sedation in 98% of colonoscopies. Recovery time also appeared to be favorably short. Such a balanced protocol of sedation appeared to be highly safe, the only serious event being a transient oxygen desaturation requiring further oxygen supplementation in less than 1% of the patients. The median dose of propofol administered was 70 mg, being less than 120 mg in the entire series. The overall cecal intubation and adenoma detection rates were 93.5% and 23.4%, respectively. No major procedure-related complication occurred.

Applications

A balanced administration of propofol by non-anesthesiologists may be safely implemented in dedicated centers.

Peer review

The paper assessed the efficacy and safety of a balanced approach using midazolam in combination with propofol administered by non-anesthesiologists in a large series of diagnostic colonoscopies. It is very interesting.

REFERENCES

1 **Ferlay J**, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007; **18**: 581-592
2 **Winawer SJ**, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF; The National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. *N Engl J Med* 1993; **329**: 1977-1981
3 **Segnan N**, Senore C, Andreoni B, Azzoni A, Bisanti L, Cardelli A, Castiglione G, Crosta C, Ederle A, Fantin A, Ferrari A, Fracchia M, Ferrero F, Gasperoni S, Recchia S, Risio M, Rubeca T, Saracco G, Zappa M. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. *Gastroenterology* 2007; **132**: 2304-2312
4 **Lisi D**, Hassan CC, Crespi M. Participation in colorectal cancer screening with FOBT and colonoscopy: an Italian, multicentre, randomized population study. *Dig Liver Dis* 2010; **42**: 371-376
5 **Cohen LB**, Ladas SD, Vargo JJ, Paspatis GA, Bjorkman DJ, Van der Linden P, Axon AT, Axon AE, Bamias G, Despott E, Dinis-Ribeiro M, Fassoulaki A, Hofmann N, Karagiannis JA, Karamanolis D, Maurer W, O'Connor A, Paraskeva K, Schreiber F, Triantafyllou K, Viazis N, Vlachogiannakos J. Sedation in digestive endoscopy: the Athens international position statements. *Aliment Pharmacol Ther* 2010; **32**: 425-442
6 **Ulmer BJ**, Hansen JJ, Overley CA, Symms MR, Chadalawada V, Liangpunsakul S, Strahl E, Mendel AM, Rex DK. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol* 2003; **1**: 425-432
7 **Huang R**, Eisen GM. Efficacy, safety, and limitations in current practice of sedation and analgesia. *Gastrointest Endosc Clin N Am* 2004; **14**: 269-288
8 **Patel S**, Vargo JJ, Khandwala F, Lopez R, Trolli P, Dumot JA, Conwell DL, Zuccaro G. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. *Am J Gastroenterol* 2005; **100**: 2689-2695
9 **Alkire MT**, Haier RJ. Correlating in vivo anaesthetic effects with ex vivo receptor density data supports a GABAergic mechanism of action for propofol, but not for isoflurane. *Br J Anaesth* 2001; **86**: 618-626
10 **Rex DK**. Review article: moderate sedation for endoscopy: sedation regimens for non-anaesthesiologists. *Aliment Pharmacol Ther* 2006; **24**: 163-171
11 **Seeff LC**, Manninen DL, Dong FB, Chattopadhyay SK, Nadel MR, Tangka FK, Molinari NA. Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? *Gastroenterology* 2004; **127**: 1661-1669
12 **Rex DK**, Heuss LT, Walker JA, Qi R. Trained registered nurses/endoscopy teams can administer propofol safely for endoscopy. *Gastroenterology* 2005; **129**: 1384-1391
13 **Rex DK**, Deenadayalu VP, Eid E, Imperiale TF, Walker JA, Sandhu K, Clarke AC, Hillman LC, Horiuchi A, Cohen LB, Heuss LT, Peter S, Beglinger C, Sinnott JA, Welton T, Rofail M, Subei I, Sleven R, Jordan P, Goff J, Gerstenberger PD, Munnings H, Tagle M, Sipe BW, Wehrmann T, Di Palma JA, Occhipinti KE, Barbi E, Riphaus A, Amann ST, Tohda G, McClellan T, Thueson C, Morse J, Meah N. Endoscopist-directed administration of propofol: a worldwide safety experience. *Gastroenterology* 2009; **137**: 1229-1237
14 **Cohen LB**, Dubovsky AN, Aisenberg J, Miller KM. Propofol for endoscopic sedation: A protocol for safe and effective administration by the gastroenterologist. *Gastrointest Endosc* 2003; **58**: 725-732
15 **Cohen LB**, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc* 2004; **59**: 795-803
16 **Vargo JJ**, Cohen LB, Rex DK, Kwo PY. Position statement: Nonanesthesiologist administration of propofol for GI endoscopy. *Gastroenterology* 2009; **137**: 2161-2167
17 **Reimann FM**, Samson U, Derad I, Fuchs M, Schiefer B, Stange EF. Synergistic sedation with low-dose midazolam and propofol for colonoscopies. *Endoscopy* 2000; **32**: 239-244
18 **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
19 **Bhardwaj G**, Conlon S, Bowles J, Baralt J. Use of midazolam and propofol during colonoscopy: 7 years of experience. *Am J Gastroenterol* 2002; **97**: 495-497
20 **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
21 **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
22 **Sipe BW**, Scheidler M, Baluyut A, Wright B. A prospective safety study of a low-dose propofol sedation protocol for colonoscopy. *Clin Gastroenterol Hepatol* 2007; **5**: 563-566

23 **Mandel JE**, Tanner JW, Lichtenstein GR, Metz DC, Katzka DA, Ginsberg GG, Kochman ML. A randomized, controlled, double-blind trial of patient-controlled sedation with propofol/remifentanil versus midazolam/fentanyl for colonoscopy. *Anesth Analg* 2008; **106**: 434-439
24 **Qadeer MA**, Vargo JJ, Dumot JA, Lopez R, Trolli PA, Stevens T, Parsi MA, Sanaka MR, Zuccaro G. Capnographic monitoring of respiratory activity improves safety of sedation for endoscopic cholangiopancreatography and ultrasonography. *Gastroenterology* 2009; **136**: 1568-1576
25 **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
26 **Radaelli F**, Meucci G, Minoli G. Colonoscopy practice in Italy: a prospective survey on behalf of the Italian Association of Hospital Gastroenterologists. *Dig Liver Dis* 2008; **40**: 897-904
27 **Radaelli F**, Meucci G, Sgroi G, Minoli G. Technical performance of colonoscopy: the key role of sedation/analgesia and other quality indicators. *Am J Gastroenterol* 2008; **103**: 1122-1130

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