Original Article

Do we use too much Propofol for Sedation in Colonoscopy? An Observational Study with Sedline Monitor

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ABSTRACT

Objectives: Propofol and midazolam are popular sedatives in colonoscopy. Our aim was to measure depth of sedation with propofol-fentanyl and midazolam-fentanyl in patients undergoing colonoscopy using a blinded electroencephalogram (EEG)-based SEDLine monitor.
Design: Non-randomized, prospective, observational
Setting: Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey
Subjects: One hundred and eight adult volunteers with American Society of Anesthesiologist (ASA) class I-II-III, aged 18 – 80 years, and undergoing colonoscopy with propofol-fentanyl (Group P) or midazolam-fentanyl (Group M) -based sedation
Interventions: Demographic variables, depth of sedation and recovery times were recorded.
Main outcome measures: Depth of sedation was measured and recorded with an EEG-based SEDLine monitor. Patient State Index (PSI) values at colonoscope insertion, removal, and at return of verbal responsiveness after colonoscope withdrawal were documented.
Results: Patients in group P were younger ($p < 0.0001$) and had lower ASA scores ($p = 0.02$) than group M patients. Group P patients experienced significantly deeper degrees of sedation at all times and longer sedation and recovery times ($p < 0.0001$ and $p = 0.01$). Group P patients were more deeply sedated and had lower PSI values at the 5th minute ($p < 0.0001$) and lower PSI scores after recovery ($p < 0.0001$). Group M had more comorbidity but more stable PSI values. Their sedation levels were also closer to normal.
Conclusion: Clinical signs for sedation showed that propofol was over-used. The titration of propofol using a processed-EEG monitor, such as SEDLine, can improve sedation procedures by reducing time spent in states of deep sedation/general anesthesia while maintaining the clinical advantages of propofol.

KEY WORDS: depth of sedation, electroencephalography (EEG)-based monitor, midazolam, propofol

INTRODUCTION

Colonoscopy is a diagnostic and therapeutic procedure that causes discomfort and pain. Maintenance of amnesia with sedation is advised during the procedure in order to minimize these complaints, as well as patient anxiety, especially in cancer patients who require multiple procedures[1]. Sedoanalgesia is also performed in order to increase tolerance on the part of the patients who require close attention and careful monitoring in order to avoid the risk of complications[2]. Sedative agents may affect patient satisfaction, safety and ease of procedure, and thus also endoscopist satisfaction. Propofol is a well-known drug frequently used during induction and maintenance of anesthesia in adult and pediatric patients and with no analgesic properties. It is preferred during colonoscopy for the maintenance of conscious sedation. In subhypnotic doses, it results in sedation and amnesia[3,4]. Studies have evaluated the effects and efficacy of many drugs, including propofol. Wide use of propofol sedation has been crucial in improving patient tolerance. Patient compliance has also improved, thus permitting extensive screening. The efficiency of endoscopy units has also increased due to early

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and lucid recovery, in turn making early discharge possible. While similar studies have investigated depth of sedation using other monitors, few have investigated depth of sedation in patients undergoing colonoscopy using a SEDLine monitor (SedlineInc., San Diego, CA, USA)[5,6]. The purpose of this study was to calculate depth of sedation in an objective manner by means of an electroencephalography (EEG)-based SEDLine monitor.

SUBJECTS AND METHODS

Local ethical committee approval was granted for the enrollment of patients undergoing outpatient colonoscopy over a 6-month period. This non-randomized prospective study was performed in the colonoscopy unit in Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey. Patients undergoing colonoscopy and receiving either propofol-fentanyl based sedation (Group P) or midazolam-fentanyl sedation (Group M) were included. The recruitment period lasted approximately 6 months (2014 – 2015), and 108 adults (58 males, 50 females) were finally enrolled. An approved signed informed consent form was received from all patients prior to the start of the operation. Patients aged 18 - 80 years, American Society of Anesthesiologists (ASA) scale I to III, and undergoing colonoscopy for various reasons and receiving sedation during the operation were included. No acute intoxication or chronic alcoholism was present in any patient, and all patients were referred from outpatient clinics. Depth of sedation was monitored using a SEDLine EEG (Masimo Corp., Irvine, CA, USA)-based monitor, a device that measures and displays the patient state index (PSI), a recognized and validated indicator of depth of sedation. PSI scores of 0 – 25 indicate deep general anesthesia, 25 – 50 indicates general anesthesia/deep sedation, and 50 – 100 indicate mild to moderate sedation[7,8]. Patients were not allocated to groups P or M on a random basis. We prefer to use midazolam-based sedation for comorbid patients, and propofol for others in our routine clinical approach. The use of sedatives is based on various factors, including age (propofol-based sedation is recommended for younger patients) and comorbidity. In this study, the anesthesiologist added fentanyl to sedatives for analgesia, and sedative drugs were administered by an experienced anesthesiologist. The level of sedation was examined using the Richmond Agitation-Sedation Scale. It was attempted to keep all the patients at the same level. No other sedatives or analgesic medications were administered. All patients received supplemental oxygen via nasal cannulae. Intravenous propofol, typically at 0.5-2 mg kg^{-1}, and fentanyl at 1 μg kg^{-1} were started simultaneously in group P. Further propofol boluses were administered in the light of the patient's reaction to the ongoing stimulation. In group M, midazolam was administered at 0.03 - 0.1 mg kg^{-1} and fentanyl at 1 μg kg^{-1}. Following routine procedure under normal conditions, the anesthesiologist administers any extra doses of the sedative drugs required according to the patient's needs. Meanwhile, it is desirable that the patient's spontaneous breathing should be maintained, so respiratory rate and pulse oximetry are monitored. The sedation administrator was blinded to the depth of sedation indicators, and the SEDline monitor was concealed for the anesthesiologist. PSI scores were recorded at the 5th minute after drug administration, with colonoscope insertion, and when the patient started to respond to instructions after colonoscope removal. The numbers of patients at different depths of sedation (PSI scores of 0–25, 25–50 and 50–100) were accessed from the computer database.

Statistical Analysis

Descriptive statistics were used to analyze demographic data. Central tendencies were expressed by the use of mean (parametric data) and median values (non-parametric data). Normality of distribution was analyzed using the Kolmogorov–Smirnov test. Parametric data (mean SEDLine score) were analyzed using Student's unpaired t-test. Frequency data (gender distribution in groups) were compared using Pearson's Chi-square test. Intergroup comparison of non-parametric data (patient ASA status distribution) was performed using the Mann–Whitney U test.

RESULTS

One hundred and eight patients were enrolled in this study, 49 receiving propofol-fentanyl (Group P) and 59 patients receiving midazolam-fentanyl (Group M). There were meaningful statistically significant differences between the two groups in terms of demographic variables (mean age and ASA score). ASA scores of Group P patients were lower than those of Group M patients ($p = 0.02$) (Table 1), while mean baseline and recovery PSI values differed (60.8 ± 9.9 and 77 ± 10.2) ($p < 0.0001$). PSI scores at time of scope insertion (5th min) were significantly lower in Group P in comparison to Group M (53.9 ± 9.7 vs 69.5 ± 9.8 respectively) ($p < 0.0001$). Similarly, PSI scores at the end of the procedure, when patients were once again responsive to verbal commands, were significantly lower in Group P in comparison to Group M (60.8 ± 9.9 vs 77 ± 10.2 respectively) ($p < 0.0001$). PSI values associated with general anesthesia/deep sedation were significantly prolonged in Group P (PSI scores of 0 – 50) in comparison to Group M ($p < 0.0001$) (Table 2). Similarly, analysis showed a significant difference in the number of patients with PSI values below 25, an

Table 1: Comparison of demographic and clinical variables in terms of sedation protocols during colonoscopy under SEDline monitoring

Variables	Group P (n = 49)	Group M (n = 59)	p-value
Age (years) (mean±SD)	44.1 ± 8.9	66.7 ± 7	<0.0001*
Gender (male/female)	25/24	33/26	0.3
Weight (kg) (mean±SD)	75.7 ± 15.1	73.4 ± 12.2	0.3
Height (cm) (mean±SD)	167 ± 9	164 ± 7	0.1
Body mass index (kg/m^2) (mean±SD)	26.8 ± 4	26.9 ± 4.1	0.9
ASA scores (I/II/III)	36/12/1/0	23/33/3/0	0.02*
Comorbidities	13 (26.5%)	32 (54.2%)	0.004*
Sedation time (min) (mean±SD)	17.2 ± 4.6	13 ± 6.1	<0.0001*
Recovery time (min) (mean±SD)	13.8 ± 14.6	8.4 ± 5.3	0.01*

Group P: patients who received the propofol-fentanyl protocol; Group M: patients who received the midazolam-fentanyl protocol; *: statistically significant; SD:standard deviation; ASA: American Society of Anesthesiologist

indicator of deep general anesthesia [2 patients in Group P vs 0 patients in Group M (p <0.0001)] (Table 2). Patients in Group M who had more comorbidity had more stable PSI values. Their sedation levels were also closer to normal values. Patients were transferred to the recovery room once hemodynamic stability and verbal responsiveness had been confirmed.

Table 2: Comparison of depth of sedation using SEDline monitoring between the groups in terms of sedation protocols

PSI level	Group P (n = 49)	Group M (n = 59)	p-value
5th min PSI n (%)			<0.0001*
0-25	2 (4.1)	0 (0)	
25-50	16 (32.7)	3 (5.1)	
50-75	29 (59.2)	26 (44.1)	
75-100	2 (4.1)	30 (50.8)	
5th min PSI (mean±SD)	53.9 ± 9.7	69.5 ± 9.8	<0.0001*
Post recovery PSI (mean±SD)	60.8 ± 9.9	77 ± 10.2	<0.0001*

Group P: patients who received the propofol-fentanyl protocol; Group M: patients who received the midazolam-fentanyl protocol; *: statistically significant; SD: standard deviation; PSI: patient state index

DISCUSSION

The aim of this study was to monitor depth of sedation with a blinded anesthetist during a procedure that we perform many times every day. Following routine procedure under normal conditions, the anesthesiologist administers any extra doses of sedative drugs required according to the patient's needs. Meanwhile, it is desirable that the patient's spontaneous breathing should be maintained, so respiratory rate and pulse oximetry are monitored. In our study, patients were sedated and monitored in a routine manner, and by applying this approach we recorded the degree of sedation depth. Our findings showed that propofol was used more than clinically required.

The anesthetist should aim to limit unnecessary deep anesthesia while still preserving suitable conditions. One recent large study demonstrated a significant increase in the risk of pulmonary aspiration with propofol-based sedation in patients undergoing colonoscopy[4]. When we used the clinical signs for sedation in this study, it emerged that propofol was used considerably more than necessary. The use of propofol also enhances both patient's satisfaction and compliance. However, one of the difficulties involved in propofol sedation concerns titration for the appropriate sedation depth. The majority of anesthetists employ end points including loss of verbal contact or eyelash reflex to assist with administration. However, these are not entirely reliable, and also entail a risk of over-sedation and even, on rare occasions, cardiorespiratory arrest[9]. Additionally, even experienced administrators may not have a full understanding of the pharmacokinetic and pharmacodynamic variations deriving from individual patient variability[10,11]. The use of a validated EEG-based monitor to guide sedation will facilitate titration. New, appropriately powered clinical trials are now needed to investigate this. Cerebral function monitors are safer and more efficient in general anesthesia, and are also used for guiding conscious sedation for various procedures[12]. Bispectral Index (BIS) values exhibit good correlation with sedation levels, and previous studies have validated the role of BIS as an objective technique for monitoring sedation[13,14]. BIS monitoring is commonly employed in a range of surgical and endoscopic procedures. Research has confirmed that propofol dosages can be lowered and recovery accelerated with the use of BIS in endoscopic retrograde cholangio-pancreatography (ERCP)[15]. Previous researches have also described the benefits of BIS monitoring in submucosal dissection or ERCP, and a significant difference in propofol doses or levels of satisfaction on the part of both endoscopists and patients have also been reported[15,16]. Studies performed using BIS monitors[17,18] have also reported that the PSI can be used to assist the administration of intravenous and inhaled anesthetics to optimize drug delivery to meet the needs of the individual patient, thus facilitating an earlier recovery from anesthesia. Pierce *et al*[19] suggested that using the PSI for propofol administration significantly lowered maintenance dosage requirements and resulted in earlier recovery times, with no increase in side-effects. The PSI monitor displayed PSI values during the operation of the electrocautery unit better than the BIS monitor. Baseline PSI values in this study were significantly lower in group P compared to group M. Propofol provides a wide range of sedation, from conscious to deep and to general anesthesia, but

is also difficult to regulate. However, midazolam has a limited capacity to induce deep sedation at recommended dosages. These sedatives also exhibit pharmacokinetic differences, resulting in a shorter wake-up time using propofol despite deeper degrees of sedation. Recovery times were also measured. Only 5.1% of the total time was spent in a state of general anesthesia/deep sedation in group M, compared to 32.7% with propofol sedation. Based on the current dosing strategies, while propofol can provide greater patient satisfaction, there is nevertheless a genuine and not uncommon risk of over-sedation[20,21]. Unfortunately, in clinical practice, greater doses than necessary may be administered to provide adequate depth of sedation, due to pharmacokinetic and pharmacodynamic variations deriving from individual subject variability. This in turn results in consequences such as an increased risk of aspiration pneumonia[2]. A higher incidence of aspiration has been observed in patients undergoing colonoscopy with propofol-based sedation[3]. One suggested mechanism involved is the greater probability of passive regurgitation and aspiration in patients sedated with propofol. The risk of aspiration and the total level of propofol consumed can be reduced by titrating propofol administration to a lighter depth of sedation. An additional outcome is that patients may probably wake up earlier and be discharged sooner. This may also help in reduction of cost. Another highly significant factor is that deeper levels of sedation will also result in a greater risk of hypotension. Patients frequently become hypovolemic following bowel preparation, with an attendant increase in the risk of intraprocedural hypotension[22].

Propofol-based sedation produces significantly deeper sedation in subjects undergoing colonoscopy compared to other forms of intravenous conscious sedation. Our study findings explicitly reveal this using objective measurements. The doses of midazolam and fentanyl employed in group M produced mild sedation, while the amount of propofol employed in group P elicited a level of sedation compatible with general anesthesia. Cohen *et al* performed all procedures using a lower dose of propofol and reported a high degree of patient satisfaction[23]. Anesthetists generally administer higher doses of propofol, leading to a deeper degree of sedation. However, this can exacerbate the risks of aspiration and hypotension, in turn resulting in a lower level of patient satisfaction. An increased depth of sedation may also cause complications such as colonic perforation[24]. As detailed in the results, the propofol dose in this study was within the range of general anesthesia. Better titration may therefore be possible with the use of a cerebral function monitor. Dissatisfaction reported by gastroenterologists represents another limitation[11]. However, the use of a validated EEG-based monitor may be of assistance to anesthetists in administering appropriate depths of sedation.

There are some limitations to this study. First, the propofol and midazolam groups were not randomized. We also did not collect data regarding patient satisfaction in order to compare the clinical applicability of the two materials investigated. However, this was not one of the aims of the study.

CONCLUSION

The use of clinical signs for sedation in this study showed that propofol was used considerably in excess of requirements. In the literature, midazolam has been associated with delayed discharge and decreased patient satisfaction. Propofol provides better patient satisfaction, although overdose is more common. Propofol titration with a processed-EEG monitor, such as the SEDLine device, can improve sedation procedures by reducing length of deep sedation/general anesthesia while preserving the known clinical advantages posed by propofol. EEG-based monitoring can result in more objective, uncomplicated and tolerable sedation. Lighter titrations of sedative drugs may also result in improved patient care, such as reducing the risks of aspiration and hypotension, and lower levels of delayed discharge.

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