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Sedation with midazolam versus midazolam plus meperidine for routine colonoscopy: A prospective, randomized, controlled study

Kolonoskopi işlemi sedasyonunda midazolam ve midazolam/meperidin tedavilerinin kontrollü prospektif randomize karşılaştırılması

Kubilay ÇINAR, Mustafa YAKUT, Ali ÖZDEN

Ankara University, School of Medicine, Department of Gastroenterology, Ankara

Background/aims: *The major goals of analgesia and sedation are to provide pain control and anxiolysis and to facilitate therapeutic and diagnostic interventions. A combination of midazolam and an opioid is usually administered to achieve sedation and analgesia during colonoscopy. However, the value of adding analgesics to sedative agents has not been well evaluated. In this study, we compared the efficacy and safety of midazolam versus midazolam plus meperidine for colonoscopy.* ***Methods:*** *A total of 74 patients admitted for routine colonoscopy to our hospital between September 2008 and March 2009 were eligible for the study. The midazolam group received midazolam (n=34) and the midazolam/meperidine group received midazolam plus meperidine (n=40). Data regarding the procedure times, degree of pain (determined according to the standard visual analog scales and recovery time were collected.* ***Results:*** *There was no significant difference between the two groups with regard to the rate of inadequate bowel preparation. Mean visual analog scales scores were over three points and similar in the two groups. Recovery times (in minutes) were similar in the two groups (28.2 min, SD 5.3 for the midazolam/meperidine sedation group and 28.3 min, SD 5.4 for the midazolam group). The total procedure times were also similar in the two groups (mean 18.64 min, SD 6.7 vs 19.3 min, SD 10.1). There was no statistically significant difference between the two groups regarding the recovery time, procedures times and visual analog scales mean scores.* ***Conclusions:*** *Patient safety, outcomes, and satisfaction are similar in colonoscopy procedures performed under sedation protocols using either midazolam and meperidine or midazolam alone. Although endoscopists favor the use of both medications together, adding meperidine to midazolam before the colonoscopy does not seem to have additive beneficial effect for the patients.*

Key words: Colonoscopy, sedation, midazolam, meperidine

Amaç: *Analjezi ve sedasyon, kolonoskopi işleminde ağrı kontrolünü sağlar ve anksiyolitik etki gösterir. Böylece tanı ve tedavi amaçlı kolonoskopi işleminin yapılması kolaylaşır. Midazolam ve opioid bileşiklerinin kombinasyonu kolonoskopi işleminde sedasyon ve analjezi sağlama amacı ile sıklıkla kullanılır. Bununla beraber kolonoskopi işleminde sedatiflere opioid analjeziklerin eklenmesinin etkisi iyi araştırılmamıştır. Bu çalışmada kolonoskopi işleminde sedasyon ve analjezi sağlama etkisi açısından midazolam ve midazolam/meperidin kombinasyonlarını karşılaştırdık.* ***Yöntem:*** *Hastanemizde Ekim 2008 ile Mart 2009 tarihleri arasında rutin kolonoskopi işlemi yapılan toplam 74 hasta değerlendirildi. Midazolam grubunda 34 hasta ve midazolam/meperidin grubunda 40 hasta vardı. Tüm hastalarda standart görsel analog ölçeklerine göre ağrı derecesi, işlem süresi ve toparlanma zamanları değerlendirildi.* ***Bulgular:*** *İki grup arasında barsak temizliği kalitesi açısından anlamlı fark saptanmadı. Tüm hastalarda ortalama VAS skoru üçün üzerinde olup her iki grupta benzerdi. Toparlanma zamanı meperidin grubunda (28.2 dk, SD 5.3), midazolam/meperidin grubunda 28.3 dk idi. SD 5.4 olup iki grup arasında fark yoktu. Ayrıca her iki grupta toplam işlem süresi benzerdi (ort. 18.64 dk, SD 6.7 vs 19.3 dk, SD 10.1. Her iki grup arasında toparlanma zamanı, ortalama VAS skoru ve işlem süresi açısından istatistiksel fark yoktu.* ***Sonuç:*** *Her iki grupta kolonoskopi işleminin başarısı, işlem güvenirliliği ve hasta memnuniyeti benzerdi. Klinik uygulamada endoskopistlerin çoğunun midazolam ile birlikte opioid analjezik kullanma alışkanlığı olsa da, meperidinin midazolama eklenmesinin ek bir yarar sağladığı gösterilemedi.*

Anahtar kelimeler: Kolonoskopi, sedasyon, midazolam, meperidin

INTRODUCTION

Colonoscopy is the gold standard in identifying lower gastrointestinal pathologies. Achieving and maintaining adequate levels of analgesia and sedation is necessary for a successful colonoscopy.

Address for correspondence: Kubilay ÇINAR
Ankara University, School of Medicine Gastroenterology Section
Cebeci Tip Fakultesi Hastanesi 06100 Dikimevi, Ankara, Turkey
Phone: + 90 312 595 69 00 • Fax: + 90 312 363 62 13
E-mail: cinar@medicine.ankara.edu.tr

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The major goals of analgesia and sedation are to provide pain control and anxiolysis and to facilitate therapeutic and diagnostic interventions. Patients should be calm and cooperative (1).

The form of sedation for gastrointestinal endoscopy that has attracted great interest in recent years is the use of intravenous (i.v.) propofol, either alone or with concomitant benzodiazepines or opioids. The main criteria in assessing the conscious sedation are patient satisfaction and comfort, short duration, amnesia, and above all, patient safety. Well-known properties of midazolam are postprocedural amnesia and tolerability. Meperidine is indicated for the treatment of moderate to severe pain. A combination of midazolam and an opioid is usually used to achieve sedation and analgesia during colonoscopy. However, the value of adding analgesics to sedatives has not been well evaluated. In this study, we compared the efficacy and safety of midazolam versus midazolam plus meperidine for colonoscopy.

MATERIALS AND METHODS

A total of 74 patients admitted for routine colonoscopy to our hospital between September 2008 and March 2009 were eligible for the study. Oral sodium phosphate solution was used in all patients during preparation for colonoscopy. Cecal intubation was performed in all patients. After termination of the procedure, all patients were followed up in the recovery room for 4–6 hours. All patients were randomized into one of the two groups. Every patient undergoing colonoscopy was randomized only once (re-examinations were not included). After randomization, two patients had to be excluded due to failure in cecum intubation.

All study examinations were performed by the same physician. Heart rate, oxygen saturation, and blood pressure (every 5 min) were monitored throughout the examination. In addition to the medication(s), all patients received continuous i.v. saline infusion (100 ml/h). More advanced techniques were not used in our trial because we intended to evaluate the safety of midazolam plus meperidine sedation under routine conditions.

Sedation for colonoscopy was performed in both groups according to the routine practice in the study center, with a total i.v. technique containing midazolam. Sedation in our clinic is always performed by nurses. In the study, both groups received an average dose of 2 mg midazolam (range: 2-5 mg). In the midazolam/meperidine group, a bolus of 25 mg meperidine was added. In case of insufficient sedation, midazolam dose was incremented up to a maximum of 5 mg with additional bolus doses. In case of insufficient analgesia, meperidine dose was increased up to a maximum of 75 mg. In case of oxygen saturation decreasing below 90%, oxygen supplement was provided via nasal cannula (2 L/min).

The main outcome in the study was "safety of sedation", defined by the absence or a clinically not relevant decrease in vital signs under the defined values (heart rate 50 beats per min, oxygen saturation 90%, systolic blood pressure 90 mmHg).

Secondary outcomes included the feasibility and quality of the sedation (procedure times, the degree of pain as determined according to the standard visual analog scales [VAS], and recovery time). The degree of the pain was rated by the endoscopist and an endoscopy nurse on a VAS ranging from 0 to 10 points (Figure 1) (2-4).

Statistics

Mann-Whitney rank-sum test and the Fisher's exact test were used for statistical comparison whenever appropriate, and a value of $p<0.01$ was regarded as significant. Data analyses were performed on a personal computer using the SPSS 15.00 program.

RESULTS

Seventy-four patients were randomized (midazolam/meperidine vs midazolam, n=40 vs n=34, res-

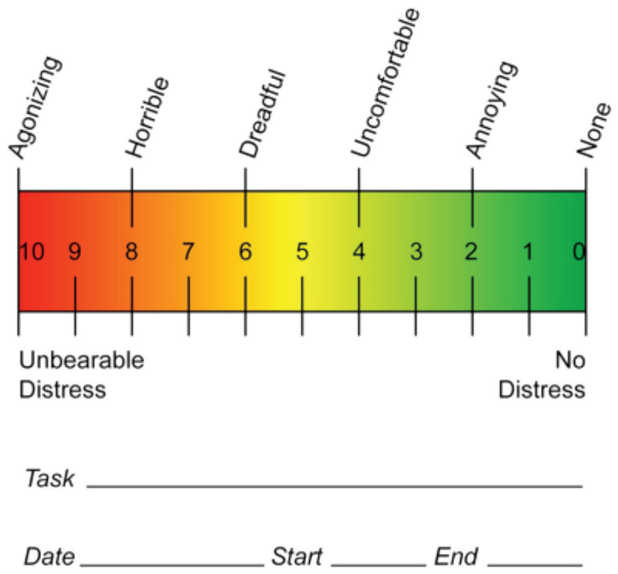

Figure 1. The visual pain scale.

Table 1. Baseline characteristics of patients

Variable	Midazolam group (n=34, 45.9%)	Midazolam/Meperidine group (n=40, 54.1%)	P value
Age (years)	58.9, SD 13.7	49.9, SD 15.8	0.11
Male, n (%)	17 (50%)	14 (35%)	0.240
Alcohol consumption >40 g/day	0	0	
Use of opioid	0	0	
Use of other analgesic medication	4	6	0.165
Baseline oxygen saturation (%)	96.6, SD 1.12	96.7, SD 1.10	0.778
Baseline heart rate (beat per min)	71, SD 8.05	71, SD 7.1	0.902
Baseline systolic pressure (mmHg)	115, SD 15.4	118, SD 15.06	0.332
History of coronary artery disease	2	3	0.782
History of systemic hypertension	7	4	0.202
History of diabetes mellitus	6	7	0.987

pectively) for sedation. There were no significant differences between the two groups with regard to baseline characteristics (Table 1). Sodium phosphate solution was administered via oral route in all patients during the preparation for colonoscopy. There were no significant differences between the two groups with regard to the rate of inadequate bowel preparation (p=0.109).

Data regarding procedure times, the degree of pain (determined according to the standard VAS) and recovery time were collected. A total of 74 patients (43 female [58.1%], 31 male [41.9%], mean age [SD] 54.06 [15.5] years) were studied. Mean VAS scores were over three points and similar in the two groups (p=0.562) (Table 2). Recovery times (in minutes) were similar in the two groups (the mean value for the time until the patient was fully alert after colonoscopy was 28.2 min, SD 5.3 in the midazolam/meperidine sedation group and 28.3 min, SD 5.4 in the midazolam group; p=0.605). Total procedure times were also similar in the two groups (mean 18.64 min, SD 6.7 vs 19.3 min, SD 10.1; p=0.751). There were no statistically significant differences between the two groups regarding the recovery time, procedure times, and VAS mean scores.

A serious decline in oxygen saturation (initial O2 saturation vs lowest O2 saturation during the procedure) was seen in only 1 patient in the midazolam/meperidine group (nasal oxygen supplement with 2 L/min via nasal cannula was provided); however, no potentially harmful drop in the oxygen saturation lower than 90% was observed. An increase in the heart rate was seen in 1 patient in the midazolam/meperidine group and in 1 patient in the midazolam group. The increase in the heart rate was not different between the midazolam/meperidine and the midazolam-alone group. A temporary drop in the heart rate below 50 beats/min did not occur in any patient in either group. A decrease in the systolic and diastolic blood pressure was seen in only 1 patient. No clinically relevant drop in the systolic pressure below 90 was documented in either group. Flumazenil usage was not required in any patient under sedation. Pain at the injection site was not reported in any case. No adverse events such as prolonged psychomotor or cognitive recovery after sedation with midazolam were noted.

DISCUSSION

Colonoscopy is the gold standard in identifying lower gastrointestinal pathologies (5). Colonoscopy is a painful procedure; therefore, conscious sedation is often used. Anxiety and pain cause increased operation time, and a protracted process may lead to higher complication rates. Sedation reduces anxiety and pain. The main end points for sedation during endoscopy are the patient's satisfaction, short duration of the procedure and safety (6).

The form of sedation for gastrointestinal endoscopy that has attracted great interest in recent years is use of i.v. propofol, either alone or together with benzodiazepines or opioids. The quality of sedation is better and recovery time is shorter in patients treated with propofol. However, there are important questions regarding the narrow therapeutic range, and propofol can only be used by anesthetists (7). With respect to the potential side effects of propofol, one should beware of respiratory depression and the risk of hypotension (8, 9).

Table 2. Mean VAS scores

Group	Minor or no pain (VAS 0-3)	Moderate and severe pain (VAS 4-10)
Midazolam group	33	1
Midazolam/Meperidine group	38	2

Sedation with i.v. benzodiazepines is the standard practice for performing endoscopic procedures (10-12). The most common drug used for sedation is midazolam (13). Therefore, midazolam is chosen frequently because of its potent amnestic properties, some anxiolytic effect and a relatively short elimination halftime (e.g., midazolam, t? distribution 30 min, recovery time 15–45 min) compared to other benzodiazepines like diazepam (14, 15). Confusion and amnesia have rarely been reported with midazolam (Vermeeren A., 2004, Residual effects of hypnotics: epidemiology and clinical implications). Midazolam has been used by gastroenterologists for a long time and is considered safe. Therefore, many colonoscopists prefer midazolam for sedation over propofol.

However, the sedative and amnestic effects of benzodiazepines sometimes do not provide adequate patient comfort during colonoscopic procedures. Furthermore, colonoscopy sometimes lasts an hour or more and thus it is not acceptable without adequate sedation. In this situation, opioids are often added, although randomized trials cast doubt on the assumed benefit of this strategy (16,17). Two opioids commonly used are meperidine and fentanyl (18). A combination of midazolam and an opioid is usually used to achieve sedation and analgesia during colonoscopy. However, the value of adding analgesics to sedatives has not been well evaluated (19). There are few studies that have compared the efficacy of midazolam and midazolam plus meperidine. We thus compared in this study the efficacy and safety of midazolam versus midazolam plus meperidine for colonoscopy. In this study, the mean VAS scores were over three points and similar in the two groups (p=0.562) (Table 2). Recovery times (in minutes) were similar in the two groups (the average time until the patient was fully alert after colonoscopy was 28.2 min, SD 5.3 for patients who received midazolam/meperidine sedation and 28.3 min, SD 5.4 in the midazolam group; p=0.605). Total procedure times were similar in the two groups (mean 18.64 min, SD 6.7 vs 19.3 min, SD 10.1; p=0.751). There was no statistically significant difference between the two groups regarding the recovery time, procedures times, and VAS mean scores. There was no significant difference between the two groups with regard to the efficacy of the sedation.

The adverse effects common for all opioids, such as constipation, dry mouth, lightheadedness, muscular twitches, and nausea, have been reported with meperidine (20). Confusion and amnesia have rarely been reported with midazolam (Vermeeren A., 2004, Residual effects of hypnotics: epidemiology and clinical implications). The morbidity and mortality associated with cardiopulmonary complications persist as a significant issue of concern during gastrointestinal endoscopy practice, and guidelines for sedation and analgesia call for continuous monitoring of the patient's hemodynamic and ventilatory status and consciousness. Direct observation is facilitated by electronic devices (pulse oximetry) (21). Monitoring of oxygen saturation (SpO2) and heart rate and systolic blood pressure was performed in all patients during the colonoscopy in this study. In addition to the immediate cardiorespiratory side effects, proven prolonged psychomotor and cognitive recovery may also be seen after sedation with midazolam (22). No adverse events such as a clinically relevant drop in the systolic pressure or prolonged psychomotor and cognitive recovery after sedation with midazolam were noted in our study. We found a decrease in the mean oxygen saturation level in only one patient from the midazolam/meperidine group, but we did not document any significant difference between the two groups regarding the frequency of hypoxemia episodes (fall of the oxygen saturation below 90%). Sedation during colonoscopy was effective and safe in both groups, even in high-risk patients such as the elderly or patients with diabetes mellitus or hypertension. The safety of midazolam in this study may be attributed to the dose of midazolam used in our population, since it was not higher than that recommended in the product information.

Because of the potential risk of apnea in the postprocedural phase, patients should be monitored over an adequate period of time, especially in an outpatient setting. Hence, we followed up all of our patients after the procedure in the endoscopy suite at least for 4 hours. Poser et al. (23) demonstrated the incidence of oxygen desaturation as 24% in the recovery phase, after analyzing the oxygen saturation levels in the post-gastroscopy and postcolonoscopy phases under sedation with midazolam and/or meperidine in 475 patients. The majority of events occurred during the first 10 minutes after completion of the procedure. We did not find any decrease in the mean oxygen saturation level in any of our patients in the recovery phase.

In conclusion, achieving and maintaining adequate levels of analgesia and sedation is necessary for a successful colonoscopy. Patient safety, outcomes, and satisfaction are similar in colonoscopy procedures performed under sedation protocols using either midazolam and meperidine or midazolam alone. Sedation with midazolam or midazolam/meperidine can be administered safely under adequate patient monitoring, even in high-risk patients (the elderly, or patients with systemic hypertension or diabetes mellitus). We demonstrated that adding meperidine to midazolam before the colonoscopy does not seem to have additive beneficial effect for the patients, although many endoscopists favor the use of both medications together.

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