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A Prospective, Randomized Comparative Study of Respiratory and Hemodynamic Monitoring during Colonoscopy using Remifentanyl Versus Propofol/Fentanyl

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Abstract

Objective: We hypothesized that remifentanil continuous infusion during colonoscopy in spontaneous respiration may give benefits in terms of quality of sedation and recovery compared to propofol, and that patients' ventilatory drive and consciousness could be accurately evaluated by the continuous measurement of end-tidal CO2 ($EtCO_2$), and of Bispectral Score (BIS) respectively.

Methods: One-hundred and eighty patients scheduled for colonoscopy were randomized in two groups: 76 patients were included in $Group_{control}$ (propofol 0.5 mg/kg bolus plus infusion 1 mg/kg/h) and 78 patients in $Gruop_{remi}$ (0.5 mcg/Kg/1 min bolus plus infusion 0.08 mcg/kg/min, progressively reduced to 0.03 mcg/kg/min). Cardiovascular and respiratory variables were measured before induction and every 3 min throughout the procedure. Sedation level was estimated by BIS and Observer's Assessment of Alertness/Sedation Scale (OAA/S). Respiratory function was evaluated by arterial oxygen saturation (SaO_2) and $EtCO_2$. Recovery from sedation and hospital discharge criteria were assessed by Modified Aldrete Score System (APRS) 30 min after colonoscopy completion.

Results: Remifentanil was effective and well tolerated during colonoscopy. Hemodynamic parameters remained stable throughout the study steps in both groups. In $Group_{remi}$ OAA/S and BIS score were higher ($p<0.001$), and $EtCO_2$ ($p<0.5$) lower that in $Group_{control}$. Recovery time was faster in the $Group_{remi}$ ($p<0.01$).

Conclusions: Our data show that analgosedation with remifentanil allowed to obtain a good quality colonoscopy without respiratory and hemodynamic impairment and with faster recovery than moderate sedation propofol/fentanyl. Moreover, BIS and $EtCO_2$ monitoring proved to be well suited to evaluate the trend variations of patients' sedation level and respiratory drive.

Keywords: Analgosedation; Monitoring; Spontaneous ventilation; End-tidal CO_2; Observer's assessment of alertness/Sedation scale

Introduction

Colonoscopy is one of the most commonly performed outpatient procedures for diagnosis and treatment of gastrointestinal disorders, usually performed under moderate sedation in the ambulatory setting [1]. Colonoscopy in spontaneous ventilation patients may carry a higher risk as opposed to anesthesia inside the operating room [2]. Actually, potential problems that can arise with Non-Operating Room Anesthesia (NORA) are hypothermia, aspiration of gastric content, hypovolemia, airways management difficulties, anaphylaxis, postoperative nausea and vomiting, and procedure related complications [3]. Therefore the use of adequate monitoring tools and of manageable drugs is essential to decrease the complication rate [2]. Moreover since colonoscopy requires a rapid turnover of patients, an anaesthetic agent with rapid onset and offset of action, and convenient titration of anesthetic/analgesic depth would be ideal [2].

Capnometry is widely used in anesthetic practice as non-invasive tool for respiratory monitoring. However a few data are available in literature, on the application of capnometry in non-intubated patients [4]. Although some warnings on the possible inaccuracy of $EtCO_2$ sampling in such condition, due to the risk of mixing of expired gas with ambient air, have been aroused, in the last decades new capnometers specifically designed for $EtCO_2$ measurement in non-intubated patients, were introduced in clinical practice that were found reliable mostly to evaluate the time course of $EtCO_2$ in every single patient [5].

Over the last few years, there has been a growing interest in the use of short acting anaesthetic agents like propofol or remifentanil during endoscopic procedures [5-10].

Propofol(2,6-diisopropyl phenol), since its introduction in the early 80's has been the most common agent used for sedation in spontaneously breathing patients for NORA, due to its rapid onset of action and shorter recovery time compared with traditional sedative regimens and does not have analgesic properties, therefore requiring additional major opioid administration [10-15]. Propofol may have clinically significant advantages compared with conventional sedative-hypnotic agents when used for prolonged or complex therapeutic procedures where deep sedation is the targeted level of sedation. [14]

The use of remifentanil, in endoscopic units might have some advantages because of its deep analgesic effects, rapid onset and offset

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time, rapid titration to the individual patient's requirements, and no intermittent pain during endoscopic procedures [16-17].

The novelty of the present study in our opinion is that we could demonstrate as capnography and BIS, despite considered as optional monitoring, are of surplus value during sedation for colonoscopy. The capnographic monitoring is associated with a reduction of hypoxemia during sedation for endoscopy and early detection of apnea during sedation for colonoscopy. The use of additional BIS monitoring temporally provides an objective measure of sedation during endoscopy.

The aim of this double-blind randomized study was to test the hypothesis that a colonoscopy of good quality in terms of pain relief, patients comfort and discharge times and with less cardio respiratory side effects can be performed using remifentanil as sole agent as compared with the standard protocol propofol-fentanyl. The secondary aim was to test the hypothesis that the different mechanism of action of propofol and remifentanil on patients' ventilator drive and consciousness could be accurately evaluated by the continuous measurement of $EtCO_2$ through a microstream sensor via a nasal cannula and of BiSpecral-Index respectively.

Methods

Ethical approval for this study (Ethical Committee No DS 129) was provided by the Ethical Committee DS of Foggia University Hospitals, Foggia, Italy on 26 March 2012; written informed consent was obtained from all patients. Patients scheduled for total colonoscopy participated in the study. Inclusion criteria were age between 18 and 75 years and physical status I or II according to American Society of Anesthesiologist's classification. Exclusion criteria were: psychiatric/emotional disorders, history of addiction to opiates/sedatives/alcohol, previous adverse reactions to any medication used in the trial and clinically significant cardiovascular or respiratory diseases.

Sedation, analgesia and monitoring were performed by the same anesthesiologist (LM). The endoscopic procedures were performed by two experienced endoscopists (NM and NDV), in a standardized environment using the same type of videoendoscopy equipment (Olympus America CF-2T160L). Patients' data were collected in duplicate by blinded observers (GM, GR), who were unaware of patient randomization groups. Blinding was obtained by providing the study drugs in sealed and coded syringes identified by treatment number and patient's initials.

Study protocol

Patients were randomly allocated to one of two treatment groups by means of a computer-generated table of random number. A researcher not involved in patient care (GCa) assigned participants to their group: patients in $Group_{control}$ received a bolus of midazolam 1 mg iv and fentanyl 0.07 mcg/Kg, followed by propofol 0.5 mg/kg bolus over 30 sec followed by 1 mg/kg/h by continuous infusion; patients in $Group_{remi}$ received a bolus of midazolam 1 mg iv followed by a starting dose of remifentanil 0.5 mcg/Kg/min administered by infusion pump over 30 second plus a continuous infusion of 0.08 mcg/kg/min, progressively reduced to a minimum of 0.03 mcg/kg/min. In case of pain (Visual Analogue Scale VAS score ≥ 50), persistent despite transient suspension of the instrument progression and of any decompression maneuver, in $Group_{control}$ additional boluses of fentanyl 0.06 mcg/Kg were given and in $Group_{remi}$ remifentanil infusion was increased up to a maximum of 0.1 mcg/kg/min until analgesia was reached and then returned to the basal levels.

In all patients oxygen was delivered at a constant flow rate of 4 l/min through the nasal cannula; $EtCO_2$ and Respiratory Rate (RR) were measured using Microstream non dispersive infrared spectroscopy (N85 capnograph/pulse oximeter, Nellcor Puritan Bennet, Pleasanton CA, USA). Standard monitoring by using a multiparametric monitor (Intellivue MP40) included Noninvasive Blood Pressure (NIBP), Heart Rate (HR), Electrocardiogram (ECG) and arterial oxygen saturation by pulse oximetry (SpO_2). Intraoperatively, patient's level of sedation was assessed using the Observed Assessment Alertness/Sedation score (OAA/S) and the Bispecrtal Index (BIS), an electroencephalographic-based method of assessing a patient's level of consciousness. Recovery from sedation and hospital discharge criteria were assessed by means of the Modified Aldrete Score System (APRS) [18-21]. APRS was evaluated every 5 min from removal of the endoscope until hospital discharge. Intraoperative and postoperative pain was assessed by means of 100-points Visual Analogue Scale (VAS). Perioperative side effects, such as pain nausea and vomiting were also recorded.

Throughout the colonoscopy, cardio-respiratory side effects were monitored: in case of inadequate ventilation (defined as $EtCO_2$>55 mmHg, and/or RR<6/min, and/or SpO_2<95%), the study drug was withhold; in case of apnea, manual breathing support was started; hypotension (defined as a decrease in mean BP>30% of the basal preoperative value), was managed with a fluid loading with a plasma expanders infused up to 8 ml/Kg in 15 minutes; bradycardia (defined as a heart rate<50 bpm), was treated with 0.5 mg atropine e.v.

The study drug was withheld on colonoscopy completion. Duration of sedation was calculated as the time from the start of the study drug administration to its discontinuation. Duration of colonoscopy was calculated as the scope-in to scope-out time.

Study steps

Hemodynamic and respiratory variables, OAA/S, BIS, VAS, and APRS, as appropriate, were recorded before drug administration (baseline), and at 1-min intervals for 10 min after induction, at 3 min intervals thereafter until the end of sedation, and 30 minutes after the procedure completion before the patient's discharge from the endoscopic room. For the purposes of present study only data recorded at baseline (T_0), at 3,6 and 9 min after the bolus of Remifentanil or Propofol (T_3, T_6 and T_9 respectively), at the end of colonoscopy (T_{end}), and 30 minutes after procedure before the patient's discharge from the endoscopic room ($T_{post30'}$), were analyzed. Patients in both groups were interviewed by telephone 24 hours after the discharge about their satisfaction and asked if they would like to undergo the same sedation in case of similar procedures in the future.

Endoscopists were also asked about their level of satisfaction according to a scale of 10 points (1 point=dissatisfied; 10 points=more than satisfied).

Statistical analysis

A power analysis was performed to calculate the sample size adequate to detect a 10 percent reduction in mean blood pressure and arterial oxygen saturation during surgery and in postoperative VAS, assuming a power of 90 percent and a significance level of 5 percent (α=0.05). The larger sample size calculated was of 28 patients per group to detect mean blood pressure reduction, and was used for patient enrolment. This number was increased to 30 per group to allow for a predicted drop-out of approximately one-fourth of patients. Data are presented as mean ± Standard Deviations (SD) and 95 percent confidence interval or number (proportion), as appropriate. Statistical analysis was performed by means of one-way Analysis of Variance

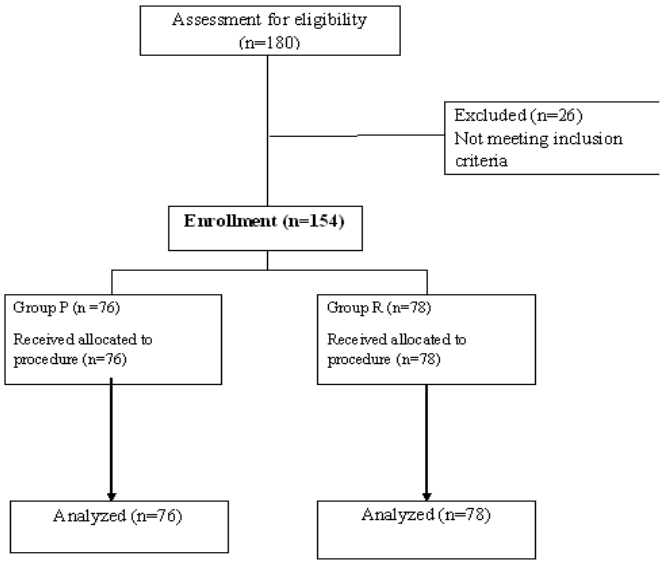

Figure 1: Flow diagram of the progress through the phases of the trial.

Variable	$Group_{control}$(n=76)	$Group_{remi}$(n=78)	
Age, years	53.1 ± 15.8	57.8 ± 15.1	NS
Weight, kg	72 ± 12.9	72.5 ± 14.8	NS
Male-to-female ratio	32/44	42/31	NS*
Procedure time, min	15 ± 2.3	15.4 ± 4.6	NS
Anesthesia time, min	16 ± 2.5	17.7 ± 5.5	NS
mBPbasal, mmHg	93.4 ± 8.1	95.1 ± 16.3	NS
HR basal, b/min	77.2 ± 11.3	76 ± 15	NS
SpO_2 basal, %	97.8 ± 2.2	98.7 ± 1.1	NS
RR basal, b/min	17.5 ± 2.2	16.4 ± 5.7	NS
EtCO2 basal, mmHg	34.1 ± 5.9	36.7 ± 6.1	NS

mBP, blood pressure; HR, heart rate; SpO_2, Oxigen Saturation; RR, respiratory rate; $EtCO_2$, end-tidal CO_2.
Results are expressed as mean ± standard deviation.
Statistical analysis: one-way ANOVA, or *Chi square test as appropriate.
NS: not significant.

Table 1: Demographic patient's characteristics.

Colonoscopy Indications	$Group_{control}$(n=76)	$Group_{remi}$(n=78)	Chi-Square
Polyposiscolorectalcancer	16 (22)	16 (21)	NS
Chronic intestinal infiammation	50 (65)	40 (51)	NS
Hematochezia	10 (13)	22 (28)	NS

Results are expressed as numbers (%) of patients.
Statistical analysis was performed by means of Chi-Square test.
NS, not significant.

Table 2: Colonoscopy indications.

(ANOVA) (patient's demographic characteristics and drug dosages), two-way ANOVA (OAA/S, respiratory and hemodynamic variables), Fisher's exact test (surgical procedures), Chi-square analysis (sex, frequency of excisions). A value of $p<0.05$ was considered statistically significant. All calculations were performed by the use of the software package Statistica 10 [Stat soft Italia srl (2008)].

Results

One-hundred eighty consecutive patients were considered for this study: 26 patients were excluded for not meeting the inclusion criteria, 154 patients were included. Seventy-six patients were included in $Group_{control}$ and seventy-eight patients in $Group_{remi}$. The flow diagram of patient's inclusion is shown in Figure 1. There was no difference between the two groups with as regard to demographics, duration of colonoscopy and anaesthesia (Table 1). Colonoscopy indications for the groups are listed in Table 2. The mean doses of propofol administered were 0.63 ± 0.12 mg/Kg (bolus) and 2.60 ± 0.36 mg/Kg/h (maintenance). The mean doses of remifentanil administered were bolus 36.5 ± 0.12 mcg/kg (bolus) and 88.9 ± 31.7 mcg/kg/min (maintenance).

Patients' comfort

Colonoscopy was completed in every patient without major side-effects. Four patients in $Group_{control}$ (5.3%) and five in $Group_{remi}$ (6.4%) received supplemental analgesia on T_4 or T_5 because they complained for pain (NS). In Figures 2 and 3 OAA/S and BIS are reported. Both scores showed significant intra- and intergroup differences as regards the study drug effects on patients' sedation, as expected. Mean OAA/S and BIS values were significantly lower in $Group_{control}$ than in $Group_{remi}$ ($p<0.001$) in all study steps, indicating a deeper sedation. During remifentanil administration all patients were mildly sedated, gave a lethargic response to verbal commands, and had mild ptosis of the eyes,

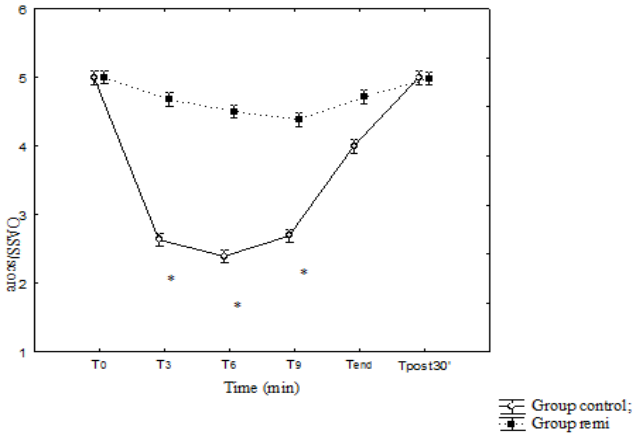

Figure 2: Observer's Assessment of Alertness/Sedation (OAA/S) time course. Two-ways ANOVA: Fischer exact test: *p<0.001 $Group_{control}$ vs. $Group_{remi}$, #p<0.001 vs. $Group_{control}$ at T_0.

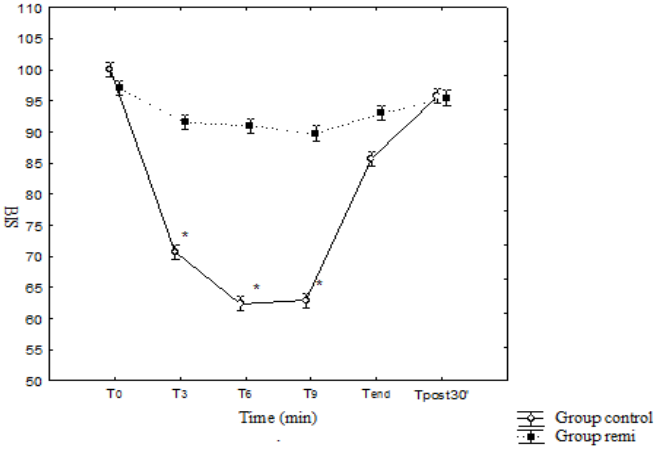

Figure 3: Bispectral Index Score (BIS) time course. Two-ways ANOVA: Fischer exact test: * p<0.001$Group_{control}$vs. $Group_{remi}$; #p<0.001 vs. $Group_{control}$ at T_0.

Variable	$Group_{control}$ (n=76)	$Group_{remi}$ (n=78)	
Drop in O_2 saturation (n)	5	0	P<0.05*
Drop in blood pressure (n)	10	5	P<0.001*
Endoscopist comfort level	8.7 ± 2.1	8.7 ± 2.1	NS
Patient comfort level	8.01 ± 0.43	8.8 ± 1.9	NS

Endoscopist's and patient's comfort level were obtained by means of a 10-points score (see text for explanation). Results are expressed as mean ± standard deviation or numbers as appropriate.
Statistical analysis: one-way ANOVA, or *Chi square test as appropriate.
NS, not significant.

Table 3: Side effects and patients' comfort.

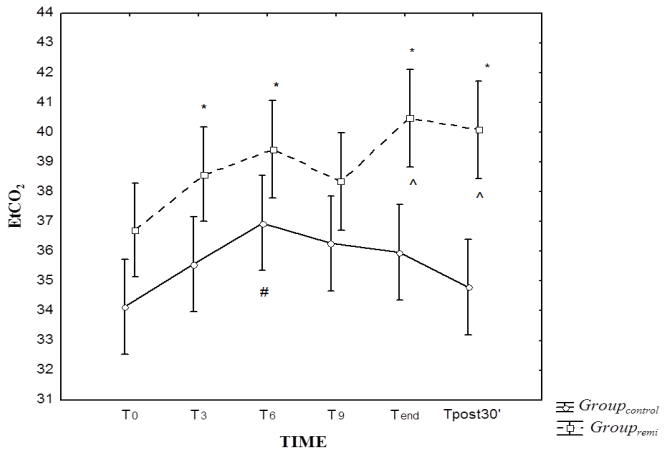

Figure 4: End tidal CO2($EtCO_2$) time course. Two-ways ANOVA: Fischer exact test: *p<0.05 Groupremi vs. Groupcontrol¸ # p<0.05 Groupcontrol vs T0 ; ^p<0.01 Groupremi vs. T^0.

with the BIS value never reaching values <80% and the OAA/S never reaching values <4. Although the target level of sedation in $Group_{control}$ was moderate sedation, 30% of those patients moved to deep sedation during the procedure, with the lowest values of BIS 55% and OAA/S of 2 reached on T_3.

Cardiorespiratory parameters

Mean HR remained stable throughout the study. Bradicardia occurred in five $Group_{remi}$ patients (4%), and in ten patients among $Group_{control}$ (13%; p<0.05) and was counteracted with the administration of 0.5 mg of atropine in all cases. Mean BP remained stable throughout the study in both groups; even if in $Group_{control}$ it was slightly lower than in $Group_{remi}$ though never reaching clinically significant differences.

No patient in $Group_{remi}$ showed de-saturation episodes during the procedure; in five $Group_{control}$ patients (6.6%), episodes of arterial de-saturation with SpO_2 <90% occurred, that were treated with the positioning of an oropharingeal Guedel cannula; in three of them manual ventilation in mask was necessary until SpO_2 returned to baseline values. At the end of the procedure SpO_2 was >95% in every patient and no patient needed supplemental oxygen delivery (Table 3).

In Figure 4, mean $EtCO_2$ time course in the two groups is showed: intra group comparison showed in both group a trend of $EtCO_2$ to increase, though not to clinically relevant values; intergroup comparison showed that in *Group remi* on T_3,T_6, T_{end} and $T_{post30'}$ the $EtCO_2$ value was higher than in $Group_{control}$ (p<0.05).

There was no difference in recovery functions assessed by means of the APRS. At the end of observation period, all patients were transferred to the postsurgical ward. As regards the side effects during the endoscopic procedure, nausea and vomiting were reported in 6 patients among $Group_{control}$ and in 4 patients $Group_{remi}$; abdominal pain was reported only in 4 patients of $Group_{control}$.

Recovery time was faster in the $Group_{remi}$ than in $Group_{control}$ (time 2.6 ± 0.94 minutes, p<0.01 vs. 4.5±1.2 minutes $Group_{remi}$). Mean duration of the procedure was 15 ± 2.33 minutes in $Group_{control}$ and 15 ± 4.8 minutes in $Group_{remi}$.

All patients expressed satisfaction (verbal rating scale score 5) with their intraoperative medication regimen. From the endoscopist's point of view both groups cooperated adequately with no differences between the two study groups.

Discussion

The main results of the present study are that (a) remifentanil infusion at doses as low as 0.05 mcg/Kg allowed to achieve optimal conditions for colonoscopy, without cardio respiratory side effects, as compared with propofol/fentanyl, (b) patients' recovery and discharge times were similar independently from the drug used. Some preliminary considerations about the monitoring equipments used in the present study are required. The American Society of Anesthesiologists (ASA) guidelines on "Sedation and anesthesia in GI endoscopy" approved by the American Society of Gastroenterology Endoscopy (ASGE) established that the physiological monitoring needed for sedation during colonoscopy should include pulse oximetry, electrocardiography, and intermittent blood pressure measurement, while extended monitoring techniques that may provide sensitive measures of patient's ventilatory function (capnography) and level of sedation (BIS), are optional [22].

The originality of the present study in our opinion is that we could demonstrate as capnography and BIS, despite considered as optional monitoring, are of surplus value during sedation for colonoscopy.

The continuous, online recording of capnographic waveform with $EtCO_2$ measurements offer a continuous graphic visualization of patients' respiratory activity and allow to quantify carbon dioxide elimination, therefore reflecting minute ventilation [5]. Despite the direct correlation between $EtCO_2$-$PaCO_2$ may vary under different condition the trend of $EtCO_2$ is considered reliable in mechanically ventilated patients [23,24]. In recent years, growing interest in literature has been aroused on the $EtCO_2$ monitoring during spontaneous breathing, because of the evolution in capnography technologies that were demonstrated sufficiently accurate and of the introduction of portable capnometers appropriate to be used in NORA and for homecare patients [4,23]. However, a few data exists to our knowledge, regarding the use of capnography during moderate sedation for gastrointestinal endoscopy [23,24]. The BIS monitoring allows titrating sedation to the suitable level, without risking an excessive deepening that may induce further respiratory depression [21]. BIS monitoring of sedation uses a complex mathematical evaluation of relevant, descriptive electroencephalographic (EEG) parameters of the frontal cortex corresponding to various levels of sedation. By using a specialized analysis of EEG signals, BIS translates sedation depth into a numeric scale [21]. Besides being an objective, non-operator dependent tool, BIS was demonstrated to be accurate and reliable allowing to detect the level of sedation precociously than by the OAS/S [18,21]. Moreover, BIS do not require the verbal response from the patient that may interfere with procedure [21]. Some limitations exist to the use of BIS and it is not useful to monitor analgesia. Preliminary evidence demonstrated that remifentanil, even at large doses, produced no modification of BIS obtained during a constant propofol

infusion. Significant electromyographic activity may be present in sedated, spontaneously respiring patients, interfering with EEG signal acquisition and contaminating the BIS calculation [25]. As regards the BIS index in our study, a difference between BIS and OAA/S was demonstrated in *Group control* mostly evident from T_3 to T_9 with BIS average value of 62 indicating a moderate sedation while the OAS/S had an average value of 2.5 indicating deep sedation; this data probably in the absence of BIS assessment, would have induced the caregivers to reduce or even withdraw the propofol infusion, that in our case was continued. Therefore, following the kind of assessment used, the anesthetic management could be influenced with the risk of possible effect on the colonoscopy performance and/or on patients' comfort.

According to our hypothesis, the present study results do confirm, in our opinion, the accuracy of $EtCO_2$ monitoring in these patients since we could detect the different behavior on patients' ventilatory drive of the two drugs studied, with the propofol inducing mild hypoventilation, although not clinically relevant at the doses used in $Group_{control}$, as demonstrated by the $EtCO_2 \geq 39$ mmHg throughout the whole procedure, and remifentanil not affecting with patients not showing significant overtime variation in average $EtCO_2$, in $Group_{remi}$.

A combined administration of an opiate and a ipnotic is widely administered during gastrointestinal endoscopy and particularly during colonoscopy, providing excellent sedo-analgesia.

Remifentanil is characterized by a rapid clearance and a highly predictable onset and offset of action and these unique pharmacokinetic properties suggested a possible role for procedures requiring deep but brief analgesic coverage. The most widely used standard association of ipnotic and an opioid generally provides sufficient comfort during colonoscopy. Unfortunately the half life of these drugs extends beyond the time span needed for colonoscopy and this frequently results in prolonged discharge time. For this reason, remifentanil may be well suited for sedo-analgesia during gastrointestinal endoscopy. In literature, Remifentanil during colonoscopy has been used alone or in combination with propofol remifentanil has a short effect-site equilibration time of 1.0 to 1.5 min. This short equilibration time is responsible for the rapid onset of analgesic effects after drug administration, thus facilitating its titration [26-31]. Remifentanil during colonoscopy is usually associated with a faster patient recovery and therefore a rapid discharge time, as compared to synergistic sedation with midazolam and propofol. Furthermore, it doesn't affect patient' safety or satisfaction.

Respiratory depression, is a well-known side-effect of remifentanil as well as of all opioids; when using remifentanil, respiratory depression is observed more frequently with rates of infusion above 0.2 mcg kg^{-1} min and is usually caused by an incremental titration of the drug infusion rate to achieve the desired effect [10,28,29]. In the study of Buvet et al. a comparison between remifentanil and propofol used for Patient-Control Analgesia (PCA) during digestive endoscopic procedure, proved that they were equally effective [17,32]. In this study, patients received remifentanil 0.08 mcg/Kg/min, plus 25 mcg/Kg boli, with refractory period of five minutes; out of 41 patients two cases of desaturation requiring mechanical ventilation were reported.

In a recent study by Manolaraki et al. in patients undergoing colonoscopy, remifentanil infusion (loading dose of 1 mcg/kg over 60s. followed by continuous infusion at an initial rate of 0.05 mcg/kg/min) was found to provide sufficient pain relief with better hemodynamic stability, less respiratory depression, and significantly faster recovery and hospital discharge than moderate sedation with midazolam and pethidine [32,33]. However, Manolaraki although starting with a low infusion rate of remifantanil (0.05 mcg/kg/min), had to frequently change the remifentanil infusion rate to guarantee control of pain and minimize possible adverse events. In the present study, the same choice to titrate the infusion rate of remifentanil rather than administer bolus doses was followed, based on literature data demonstrating that bolus doses given in addition to a continuous infusion of remifentanil may increase the incidence of respiratory side-effects [28,31]. However, in our study we started with a priming dose over 30 sec that probably allowed reaching sufficient analgesia and prevented from the need of frequent infusion rate changes throughout the procedure.

In another recent study by Fanti et al. the aim of the authors was to compare patients and endoscopist satisfaction in terms of effectiveness and safety of remifentanil patient-controlled analgesia (PCA) during colonoscopy with a combination of midazolam and meperidine [32]. Their results suggest that it is not certain whether the one obtained with the continuous infusion of drugs is an optimal sedoanalgesia technique during colonoscopy and whether PCA, whithout background infusion, is a safe and effective remifentanil delivery system [34-36]. Further studies should address the optimization of dosing and lock out setting for remifentanil PCA, leading to an even better safety profile of this technique. In our study, the initial infusion rate was chosen largely on the basis of previous studies which recommend an infusion rate of 0.05-0.2 mcg kg^{-1} min^{-1} while remifentanil is used for Monitored Anesthesia Care (MAC) or postoperative analgesia [10,27,28,30]. We started with a bolus dose infusion of remifentanil 0.5 mcg/kg/min and continued with a relatively low infusion rate of remifentanil, 0.08-0.03 mcg/Kg/min, titrated carefully to patient comfort and to minimize possible adverse events. Bolus doses of remifentanil were administered slowly, in over 60 seconds, to minimize the risk of respiratory depression. In our study, $Group_{remi}$, patients did not experience significant respiratory depression, probably because of the careful titration of remifentanil infusion to patient comfort rather than sedation.

This study presents some limitations: (a) we could not use patient's controlled analgesia or targeted controlled infusion due to the organization of the department, and this would surely have given more strength to the patient's comfort assessment; (b) in both Groups a pre-emptive dose of Midazolam was used, and this could have interacted differently with the study drugs.

In Conclusion, our study has pointed out how good quality sedation can be ensured to patients undergoing colonoscopy using minimal doses of remifentanil, in order to achieve the desired level of sedation, while keeping hemodynamic and respiratory parameters stable. In addition, the BIS monitoring proved to be a useful means to assess objectively the level of sedation desired, and capnography, though less practical than the oxygen saturation alone, was very important for the detection of hypoventilatory accidents.

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