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Remifentanil vs. propofol controlled infusion for sedation of patients undergoing gastrointestinal endoscopic procedures: A clinical randomized controlled clinical trial☆

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ABSTRACT

Background: Target controlled infusion (TCI) for the administration of anesthesia may provide a safe alternative for managing the discomfort of patients undergoing gastrointestinal endoscopic procedures. However, the most appropriate drug available for TCI is yet to be established. The objective of this trial was to compare remifentanil vs. propofol in TCI for sedating patients during GI endoscopy.

Materials and methods: Sixty-nine patients requiring GI endoscopies were randomly distributed to receive remifentanil ($n = 30$) or propofol ($n = 39$) TCI at the effect site (e). The primary outcome was patient's satisfaction. Secondary outcomes included the gastroenterologist satisfaction, comparison of the percentage of adverse events between the two groups (occurrence of arrhythmias, major respiratory depression, bradycardia, hypotension, pain, nausea or vomiting and absence of amnesia), and the level of awareness. Retrospective registration number is NCT01746641 at Clinicaltrias.gov.

Results: The mean (range) of patient satisfaction with remifentanil vs propofol was 1 (1–2) and 2 (1–4), respectively (Chi^2, $p < 0.001$). Pain during the procedure was found to differ between remifentanil and propofol (mean 2 vs. 1, Chi^2, $p = 0.042$), nausea or vomiting (4 vs. 0, Chi^2, $p = 0.01$), and absence of amnesia (29 vs. 10, Chi^2, $p < 0.001$), respectively. No statistically significant differences were found between the two groups.

Conclusion: Propofol in TCI seems to be an adequate agent for sedation of patients undergoing GI endoscopic procedures, with less adverse effects and higher patient satisfaction.

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Most likely, the combination of these two drugs may be synergistic and further reduce any adverse effects.

Remifentanilo versus propofol con infusión controlada a objetivo en sitio efecto para la sedación de pacientes durante procedimientos endoscópicos gastrointestinales: ensayo clínico controlado aleatorizado

Palabras clave:
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Anestésicos intravenosos
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RESUMEN

Contexto: La administración de sedación con sistemas de infusión controlada a objetivo (TCI) podría ofrecer una alternativa segura para el manejo del malestar de los pacientes llevados a procedimientos endoscópicos gastrointestinales. Sin embargo, no se conoce qué medicamento de los disponibles para TCI es el más apropiado. El objetivo del estudio fue comparar remifentanilo y propofol en TCI para la sedación de pacientes durante procedimientos endoscópicos gastrointestinales.

Materiales y métodos: Sesenta y nueve pacientes que requerían un procedimiento endoscópico gastrointestinal fueron asignados aleatoriamente a recibir una TCI en sitio efecto (TCIe) de remifentanilo (n = 30) o propofol (n = 39). El desenlace primario fue la satisfacción del paciente. Los desenlaces secundarios incluyeron la satisfacción del gastroenterólogo, se compararon las proporciones de eventos adversos entre los 2 grupos (ocurrencia de arritmias cardiacas, depresión respiratoria leve, depresión respiratoria mayor, bradicardia, hipotensión, dolor, náuseas o vómitos, y ausencia de amnesia) y el nivel de consciencia. Número de registro retrospectivo: NCT01746641 en Clinicaltrias.gov.

Resultados: Las medianas (rango) de satisfacción del paciente entre remifentanilo y propofol fueron 1 (1-2) y 2 (1-4), respectivamente (2, $p < 0,001$). Se encontraron diferencias en la ocurrencia de dolor durante el procedimiento (mediana 2 vs. 1, 2, $p = 0,042$), náuseas o vómito (4 vs. 0, 2, $p = 0,01$), y ausencia de amnesia (29 vs. 10, 2, $p < 0,001$) entre remifentanilo y propofol, respectivamente. Para las otras variables estudiadas no se encontraron diferencias estadísticamente significativas entre los grupos.

Conclusión: El propofol en TCIe parece ser un medicamento adecuado para la sedación de pacientes durante procedimientos endoscópicos gastrointestinales, y presentó menores efectos adversos y mayor satisfacción del paciente. Es probable que con la sinergia de estos 2 medicamentos se pudiera lograr disminuir aún más los efectos adversos.

Introduction

Target-controlled infusion (TCI) systems can control the concentration in the plasma or at the site of drug effect. Since their introduction into clinical practice in 1996[1] various pharmacokinetic models have been developed to simulate the expected concentration of these agents in humans.[2–4] The starting point was programming of the Marsh & Schnider[5–7] models for propofol, followed by the Shafer & Scott[8] models for fentanyl, and lastly the Minto model for remifentanil.[9] Several authors felt that the models should be adapted to a few sub-groups of patients, i.e. obese patients, with important differences in the distribution of body compartments.[8,10]

Medical practice usually demands doing procedures that may cause pain or anxiety. Sedation for clinical procedures reduces any procedure-associated discomfort, fear and potential unpleasant memories, and facilitates the performance of the procedure.[11] In GI endoscopies some studies report using patient controlled sedation/analgesia (PCA) with midazolam, fentanyl, propofol and remifentanil that have evaluated the patient's satisfaction, the level of sedation in accordance with scales like Ramsay's and frequency of adverse events.[12,13]TCI models are often used for administering general anesthesia.[14–17] However, only few cases have reported their use to provide analgesia and/or sedation for airway endoscopic procedures; as far as we know, there have been no reports on TCI used for GI endoscopic procedures.[18–22] Of particular interest is the use of TCI models in situations in which spontaneous ventilation should be allowed and in patients with a critical health status. A study using remifentanil TCI for sedation during flexible fiberoptic bronchoscopy in critical patients suggests that this is a safe and effective sedation technique for this type of patients.[23] Another study compared bi-spectral index (BIS) monitor guided propofol TCI against manual infusion for dental procedures and found that the TCI infusion is useful and safe in patients with intellectual disability.[24] Furthermore, several studies have evaluated the use of TIC for awake fiberoptic intubation.[22,25–27]

Target controlled infusion (TCI) systems may offer a safe approach for managing discomfort in patients undergoing GI endoscopic procedures. However, the most appropriate agent

available for TCI is yet to be determined. The purpose of the study was to compare remifentanil vs. propofol in TCI for sedating patients undergoing GI endoscopic procedures.

Materials and methods

Design

Randomized controlled clinical trial. A parallel and superiority design was used to compare remifentanil vs. propofol TCI administration for sedation of patients undergoing GI endoscopic procedures. Retrospective registration number is NCT01746641.

Patients

Gastroenterology patients were selected for the trial. The inclusion criteria were: patients scheduled for elective upper, lower or combined GI endoscopy at the San José Hospital, Bogotá, between January and June, 2010; age between 18 and 70 years old: American Society of Anesthesia classification of physical status (ASA-PS) between 1 and 3; written submission of informed consent exclusion criteria were. Patients with difficult airway, chronic pain, chronic opioid or benzodiazepines users (≥3 months), history of allergy to any of the study drugs or to eggs, psychoactive drug users, smokers (≥5 cigarettes per week in the last 3 months), and patients with a BMI ≥ 30.

Interventions

Distribution and randomization

Patients were included consecutively in accordance with the selection criteria. During the planning phase of the study, a numbered list was developed for simple randomization to the two types of sedation studied using the Microsoft Excel 2010 RAND command. The hospital pharmacy that provided the study drugs was aware of the list, but both the researchers and assisting staff involved in the evaluation of the selection criteria and the administration of the sedation (anesthetist) were blinded. The anesthesiologist responsible for administering the sedation once the patient was admitted to the trial and the pharmacy delivered the medication was informed about the intervention. Both the patient and the researcher collecting the information were blind to the agent.

Sedation procedure

Monitoring was standard for all patients with continuous electrocardiography (DII), pulse oximetry and non-invasive blood pressure monitoring every 3 min. A venous access was established with an 18-gauge catheter and supplementary oxygen was provided through a nasal tube at 3 L/min.

Patients were assigned to one of the following interventions: propofol or remifentanil sedation. Both propofol and remifentanil were administered using TCIe according to Marsh[6] & Minto[9] models, respectively. Depending on the model, several patient variables were considered including gender, weight, and size. All patients received topical anesthesia (lidocaine 2% gel for lower GI procedures and lidocaine 10% in spray for upper GI procedures). The infusions were started at rates of 1 mcg/mL for propofol and 1 ng/mL for remifentanil. The propofol and remifentanil doses were reduced by 0.5 mcg/mL and 0.5 ng/mL, respectively, depending on the occurrence of bradypnea (FR ≤ 8), apnea, desaturation (SO_2 ≤ 90%), hypotension and bradycardia as appropriate. Otherwise, the doses were titrated in accordance with the occurrence of hypertension (MBP > 80 mmHg) and tachycardia (FC > 90).

Outcomes

The primary outcome was patient's satisfaction measured with an analog scale of 1–4 for excellent, good, fair and poor, respectively. Secondary outcomes included the gastroenterologist satisfaction (analog scale), adverse events (occurrence of cardiac arrhythmia, mild respiratory depression, major respiratory depression, bradycardia, hypotension, pain, nausea or vomiting and absence of amnesia), and the level of awareness.

Clinical records

An anesthesiologist who recorded the patient's ID information, gender, age, weight, American Society of Anesthesiology Physical Score (ASA-PS), indication for endoscopy (diagnostic, therapeutic or mixed), and type of endoscopic procedure (high, low or mixed) supervised the sedation procedure. An independent assessor recorded the basal values for heart rate (HR), respiratory rate (RR), oxygen saturation (SO_2), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) and the minute-by-minute level of awareness was recorded using the Ramsay scale.[28] The minimum and maximum doses of remifentanil or propofol TCIe were recorded during the sedation procedure, the duration of endoscopy and the post-sedation recovery using the Aldrete scale.

The occurrence of minor respiratory depression (apnea ≥ 15 s) was defined as mild if responded to verbal stimulation and severe when ventilation was required. Bradycardia was recorded when the heart rate was ≤40 beats per minute for patients receiving remifentanil and ≤50 beats per minute for patients receiving propofol.[29] Hypotension was defined as a mean blood pressure ≤55 mmHg or a 30% drop in the mean blood pressure vs. the baseline.

Ethical considerations

The Research Committee of the Fundación Universitaria de Ciencias de la Salud and the Ethics Committee on Human Research of the San José Hospital approved the protocol on November 9, 2009 (Minutes No. 197) and December 4, 2009 (Minutes No. 19), respectively. During the implementation of the trial, the researchers followed the Declaration of Helsinki for experimentation in humans.

Sample size and analysis of the data

This clinical trial was designed following a 1–1 distribution ratio. 50 patients were included in each arm of the trial for a 95% probability of finding a statistically significant difference with regard to patient satisfaction (excellent) (primary objective) with a two-tailed level of significance of 0.05, assuming that the difference in response to treatment

was 25%. However, the sample size was not achieved because a remifentanil-triggered severe event (severe respiratory depression) led to termination of the trial. With the new sample size the power of the trial to detect equal differences for the primary objective was recalculated at 80%.

Stata 12 statistical software was used to analyze the data. The remifentanil and propofol doses were described with measures of central trend and scatter. Pearson's Chi square test was used to assess the differences between the drugs in terms of level of sedation, percentage of adverse events (occurrence of arrhythmias, mild respiratory depression, major respiratory depression, bradycardia, hypotension, pain, nausea or vomiting, and absence of amnesia), the level of awareness and, patient and gastroenterologist level of satisfaction. Statistically significant differences were established at $p \leq 0.05$.

Results

The study was terminated in June 2010 with patient number 69, due to the occurrence of severe respiratory depression in the last patient randomized to the remifentanil group. 30 patients in total were assigned to the remifentanil group and 39 to propofol and the data were analyzed in accordance with this distribution. The patients' characteristics are shown in Table 1. No data were lost in the follow-up of patients included in the trial.

The mean (range) patient satisfaction score for remifentanil and propofol were 2 (1–4) and 1 (1–2), respectively (Chi^2, $p < 0.001$). In terms of gastroenterologist's satisfaction, the means (range) were 1 (1–3) and 1 (1–4), respectively ($p = 0.218$). The mean (range) pain scores for the remifentanil and propofol groups were 1 (0–6) and 2 (0–9), respectively ($p = 0.042$).

Table 2 shows the results of the categorical variables test for percentage differences. 1 patient developed arrhythmia (2.56%) in the propofol group and none in the remifentanil group ($p = 0.377$). There was mild respiratory depression in 5 (12.82%) patients in the propofol group and 3 (10%) in the remifentanil group ($p = 0.716$); major respiratory depression occurred in only 1 (3.33%) patient in the remifentanil group ($p = 0.250$). No episodes of bradycardia were recorded among the patients, regardless of the group. There were 2 (5.13%) cases of hypotension with propofol and none with remifentanil ($p = 0.208$). Nausea and/or vomiting occurred in 4 (13.33%) patients in the remifentanil group and none in the propofol ($p = 0.018$) group. No amnesia was present in 10 (25.64%) patients in the propofol group and 29 (96.67%) patients in the remifentanil group ($p < 0.001$).

Table 1 – Patient characteristics.

Characteristic	Propofol ($n = 39$)	Remifentanil ($n = 30$)
Male, No. (%)	12 (52)	11 (48)
Age, mean (SD)	53 (16)	52 (16)
Weight, mean (SD)	65 (11)	65 (13)
ASA-PS		
1	21 (54)	16 (53)
2	16 (41)	11 (37)
3	2 (5)	3 (10)
Indication for endoscopy		
Diagnostic	16 (41)	13 (43)
Therapeutic	1 (3)	6 (20)
Mixed	22 (56)	11 (37)
Type of endoscopy		
Upper	17 (44)	14 (47)
Lower	18 (46)	16 (53)
Mixed	4 (10)	0

SD: standard deviation.
ASA-PS: American Society of Anesthesiology Physical Status.

Remifentanil TCIe doses ranged between 1 ng/mL and 4.5 ng/mL with a mean (range) of minimum dose of 2 (1–2) ng/mL and a maximum of 3 (2.2–4.5) ng/mL. Propofol TCIe doses varied between 1.5 mcg/mL and 5 mcg/mL. The Ramsay means (range) for remifentanil and propofol were 2 (1–6) and 3 (1–4) (Chi^2, $p = 0.01$), respectively.

Discussion

The technique for administering IV anesthetic agents to reach a target at effect site has been used as the basis for total intravenous anesthesia. However, it is not described in the literature as a technique for analgesia and/or sedation in endoscopic procedures. Procedures outside the OR are increasingly frequent and are performed with the participation of the anesthesiologist, in some cases to provide sedation, as is the case with MRI and dental procedures and in others to administer general anesthesia.

Table 2 – Differences in the percentage of adverse effects between propofol and remifentanil (categorical variables).

Adverse effects	Test statistics (Z)	Difference SE × 10^2	95 CI % for percentage difference × 10^2
Arrhythmia	0.88	2.53	−2.39; 7.52
Minor respiratory Depression	0.36	7.65	−12.19; 17.83
Major respiratory Depression	−1.15	3.27	−9.75; 3.09
Bradycardia	–	0	0; 0
Hypotension	1.26	3.53	−1.79; 12.05
Nausea or vomiting	−2.35*	6.20	−0.25; −1.16

SE: standard error.
Shows up when the statistics could not be calculated for the test.
* $p \leq 0.05$.

Sedation is also used for endoscopic diagnostic and therapeutic procedures of the airway and the GI tract. As far as we know, this is the first study reporting the use of remifentanil and propofol with a target controlled infusion model at the effect site for sedation of patients undergoing gastrointestinal endoscopic procedures.

The studies with TCI models for sedation procedures have been done with a view to compare the conditions provided by either propofol or remifentanil for airway endoscopic procedures, intubation and post-intubation and no differences have been found between the two drugs.[25]

Once again, the two drugs in the TCI modality were compared in a clinical trial for intubation with fibrobronchoscopy. Remifentanil provided better intubation conditions and is considered a safe drug for TCI in this particular procedure.[22] In contrast with previous trials, our study resulted in higher satisfaction with propofol and one adverse event with remifentanil – chest wall stiffness – requiring non-invasive mechanical ventilation, and the researcher was forced to terminate the trial. This limitation required us to recalculate the trial for a new sample size, obtaining an 80% value. Another limitation was the inability to blind the anesthetist; however, the person responsible for collecting the information, a gastroenterology intern, was blinded.

Remifentanil is an analgesic and a sedative used for maintaining general anesthesia and sedation in the ICU.[30,31] Propofol's positive characteristics are reflected in outcomes such as nausea, vomiting, amnesia and patient satisfaction. It is somewhat surprising that remifentanil is no better than propofol in terms of pain during the procedure. Probably the amnesic effect of propofol has an impact on any pain episodes during the endoscopy. The propofol group did not exhibit any adverse hemodynamic effects, notwithstanding the fact that one of its effects is a reduction in cardiac output and blood pressure.[32] The absence of propofol deleterious effects could be due to the low dose administered, which could give us an idea of the optimal level to be administered for these procedures. In contrast, even at low doses of remifentanil, there were some manifestations such as rash, urine retention, nausea and vomiting.[33]

The fact that patient recruitment had to be terminated explains the imbalance between the groups. However, there were some similarities in the characteristics of the patients in both groups, as shown in Table 1.

Conclusions

Propofol TCI delivery seems to be an adequate agent for sedating patients undergoing gastrointestinal endoscopic procedures; it exhibited less adverse effects and higher patient satisfaction. Remifentanil may cause severe undesirable adverse effects requiring emergency expert intervention. Probably the synergistic action of these two drugs may further attenuate any adverse effects.

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Conflict of interest

The authors have no conflicts of interest to declare.

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