Journal of Clinical Monitoring and Computing (2019) 33:107–113
https://doi.org/10.1007/s10877-018-0134-3

ORIGINAL RESEARCH

Computerized tests to evaluate recovery of cognitive function after deep sedation with propofol and remifentanil for colonoscopy

Xavier Borrat[1,2] · Marta Ubre[1] · Raquel Risco[1] · Pedro L. Gambús[1,2,3,5] · Angela Pedroso[4] · Aina Iglesias[2] · Gloria Fernandez-Esparrach[4,5,6] · Àngels Ginés[4,5,6] · Jaume Balust[1] · Graciela Martínez-Palli[1,4]

Received: 30 August 2017 / Accepted: 21 March 2018 / Published online: 27 March 2018

Abstract
The use of sedation for diagnostic procedures including gastrointestinal endoscopy is rapidly growing. Recovery of cognitive function after sedation is important because it would be important for most patients to resume safe, normal life soon after the procedure. Computerized tests have shown being accurate descriptors of cognitive function. The purpose of the present study was to evaluate the time course of cognitive function recovery after sedation with propofol and remifentanil. A prospective observational double blind clinical study conducted in 34 young healthy adults undergoing elective outpatient colonoscopy under sedation with the combination of propofol and remifentanil using a target controlled infusion system. Cognitive function was measured using a validated battery of computerized cognitive tests (Cogstate™, Melbourne, Australia) at different predefined times: prior to starting sedation (Tbaseline), and then 10 min (T10), 40 min (T40) and 120 min (T120) after the end of colonoscopy. Tests included the assessment of psychomotor function, attention, visual memory and working memory. All colonoscopies were completed (median time: 26 min) without significant adverse events. Patients received a median total dose of propofol and remifentanil of 149 mg and 98 µg, respectively. Psychomotor function and attention declined at T10 but were back to baseline values at T40 for all patients. The magnitude of psychomotor task reduction was large (d = 0.81) however 100% of patients were recovered at T40. Memory related tasks were not affected 10 min after ending sedation. Cognitive impairment in attention and psychomotor function after propofol and remifentanil sedation was significant and large and could be easily detected by computerized cognitive tests. Even though, patients were fully recovered 40 min after ending the procedure. From a cognitive recovery point of view, larger studies should be undertaken to propose adequate criteria for discharge after sedation.

Keywords Cognitive recovery · Sedation · Remifentanil · Propofol · Endoscopy

1 Introduction

The number of procedures performed under sedation is rapidly increasing especially with regards to gastrointestinal endoscopy. Benzodiazepines, propofol and/or opioids are the most commonly used drugs [1]. Probably due to the residual

Authorized by Agencia Española de Medicamentos y Productos Sanitarios (MAR-PRO-2010-01).

✉ Xavier Borrat
xborrat@clinic.ub.es

[1] Anesthesiology Department, Hospital Clínic, Villarroel, 170, 08036, Barcelona, Spain

[2] Systems Pharmacology Effect Control & Modeling (SPEC-M) Research Group, Barcelona, Spain

[3] Department of Anesthesia and Perioperative Care, University of California San Francisco (UCSF), San Francisco, CA, USA

[4] Endoscopy Unit, ICMDiM, Hospital Clínic, University of Barcelona, Barcelona, Spain

[5] Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS) , Barcelona, Spain

[6] Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain

effect of sedative drugs, there is a transient impairment of cognitive functions such as memory, attention and executive function during the recovery period.

Several studies demonstrate the effectiveness of propofol as a fast recovery drug compared to other options for sedation in gastrointestinal endoscopy [2–4]. The combination of propofol and remifentanil and their use by means of a target controlled infusion (TCI) system can provide better conditions than propofol alone [5].

Although pain, hemodynamic changes or nausea and vomiting are routinely measured and corrected before discharge, there is a lack of evidence and consensus regarding the duration of recovery period prior to regaining normal cognitive function of the patient. Normal recovery might include aspects such as fast reaction to environment challenges. To include all these different settings, guidelines for discharge of outpatients after sedation tend to be conservative and recommend that the patient must leave the hospital or outpatient clinic under direct supervision of a responsible person [6, 7].

A recent technological advance has been introduced in the clinical setting that allows the evaluation of cognitive functions at the bedside of the patient. CogState™ (Cogstate Ltd, Melbourne VIC 3000 Australia) is a software system that has been designed as a battery of different psychological tests to be presented to patients and it can be done, for instance, in the recovery area using a laptop computer or tablet. It allows specific evaluation and quantification of drug effects on cognitive function [8]. The output of the software is based on the analysis of the speed and accuracy in performing the task to evaluate the cognitive function of each subject. It has been shown that in the recovery phase of sedation the outcome of these tests is worse than baseline values [9].

The objective of the present study is to assess the time course of cognitive recovery using an objective, automated computer auto assessment tests system, Cogstate™, in patients undergoing elective outpatient colonoscopy under deep sedation and spontaneous breathing with the combination of propofol and remifentanil.

2 Methods

Under the approval of the Institutional Review Board of Hospital CLINIC de Barcelona (REF 7784) a prospective observational double blind clinical study was designed. Informed consent was obtained from all individual participants included in the study.

2.1 Patients

2.1.1 Sample size

To determine the study sample size, a pilot study was conducted with 11 patients. Based on those results, for an alpha error set at 0.05, a power of 80% for the attention task (IDN) variable and, assuming a potential loss of 10%, 34 patients were included.

Patients included were older than 50 years old scheduled for a screening colonoscopy to discard colon cancer at the Gastrointestinal Endoscopy Unit of Hospital CLINIC de Barcelona. Patients who refused to participate in the study, those with an ASA physical status III or IV, patients under treatment with drugs affecting the central nervous system, drug addictions or other conditions that prevent or hinder the adequate performance of cognitive tests were not included in the study. The day before colonoscopy, a routine telephone preoperative evaluation was done, ensuring the correct preparation and assessing the eligibility for the study. Those who had no exclusion criteria were invited to participate in the study.

2.2 Anesthetic management

On arrival into the endoscopy room an iv line was placed and routine monitoring including pulse oximetry, electrocardiography and noninvasive arterial blood pressure measurement was started. All patients received supplemental oxygen (3 L/min) via nasal cannula.

Patients received a combination of propofol and remifentanil by means of a TCI system using the pharmacokinetic–pharmacodynamic (PK–PD) model of Schnider et al. for propofol [10] and Minto et al. for remifentanil [11]. Initial target was set at 1.5 µg/mL of propofol and 1.5 ng/mL of remifentanil according to what has been previously described [12]. Three to five minutes was allowed to reach target effect site concentration (as displayed on the infusion device) and adjusted in steps of 0.3 (µg/mL or ng/mL, respectively) to achieve and maintain an adequate level of sedation established as a Ramsay Sedation Score of 4, corresponding to a patient with eyes closed non responsive to normal verbal command but with brisk response to glabellar tap. Targets were maintained until the endoscope probe reached the ileocecal valve. From then on, propofol and remifentanil targets were gradually decreased until complete removal of the colonoscope.

After colonoscopy was completed, patients were transferred to the recovery area, and cognitive measurements using CogState™ were performed at predetermined times. We registered the time when the patient met standard

discharge criteria (Aldrete post-anesthesia discharge score) [13]. After completing T40 evaluation, they were allowed to leave the unit with a responsible adult and they were asked to come back for the T120 evaluation. Patients were not allowed eating or drinking anything that could be stimulant or depressant of central nervous system. After T120 patients definitively left the unit.

2.3 Cognitive evaluation test

CogState™ computerized cognitive tests are especially suited to assess the effects of different drugs on the central nervous system. The tests can be performed by the patient in a short period of time (10 min) and they can be repeated to know the time course of the recovery of cognitive function. Cogstate™ has been designed in a way that there is no learning effect that could alter the meaning of the results. The magnitude of measured cognitive changes enables statistically based decision making regarding cognitive function [8, 14].

Based on work published elsewhere [9] the following tests were chosen: "detection task (DET)", "identification task (IDN)" related both to attention and psychomotor function, "one back learning task (ONB)" and "one card learning (OCL) test" related to integration, processing and retrieval of information.

From DET and IDN tasks speed of reaction expressed as latency mean (LMN) in milliseconds were recorded. From ONB and OCL tasks accuracy expressed as percentage of correct answers were used. Task details are described in Table 1.

The four different tests can be usually done in 10 min. Tests were presented to patients on a laptop screen. First battery of tests was performed on arrival of the patient to the endoscopy unit as training to prevent a learning effect. Thirty minutes after training evaluation, just before starting sedation, a basal evaluation was performed (T baseline). CogState™ battery was again measured at 10 (T10), 40 (T40) and 120 (T120) minutes after colonoscopy was finished. (Fig. 1).

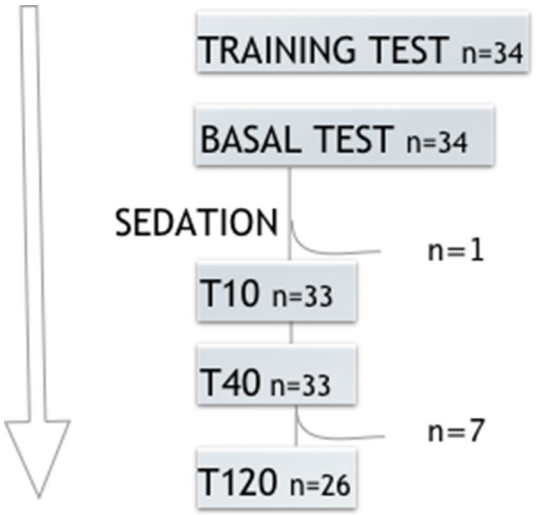

Fig. 1 Flowchart of patients that completed the CogState™ tasks

2.4 Variables

Besides cognitive tests, other variables were also recorded: demographics (age, gender, BMI, ASA physical status), total doses of propofol and remifentanil administered, range of propofol and remifentanil effect-site target concentrations, duration of the procedure (from initial insertion to removal of the colonoscope) which is almost the same as sedation infusion time, and time of anesthetic recovery defined as the time from stopping sedative drugs infusion to the time when the patient meet the standard discharge criteria.

Other variables recorded were those related to the incidence of respiratory side effects such as desaturation (S_pO_2 < 90%), requirements for manually assisted ventilation or need for intubation and mechanical ventilation. Significant hemodynamic changes such as hypotension and bradycardia, defined as a decrease in blood pressure or heart rate lower than 20% from baseline, were recorded. Nausea, vomiting, pain or dizziness were also registered.

Table 1 Description of selected tasks from CogState psychological battery

Detection task (DET): press the button when the card is turned over. The raw result measuring the average speed of reaction of all responses in every test is expressed as latency mean (LMN) in milliseconds
Attention task (IDN): press S if the card on the screen is red and N if not. The result is expressed in speed of reaction. The raw result measuring the average speed of reaction of all responses in every test is expressed as latency mean (LMN) in milliseconds
One back learning task (ONB) related to visual memory: press S if the card on the screen has appeared before. The raw result measuring percentage of correct answers over all cards presented is expressed as accuracy (ACC) in percentage of correct answers (%)
One card learning task (OCL) related to working memory: press S if the card on the screen is the same the prior one. The raw result measuring percentage of correct answers over all cards presented is expressed as accuracy (ACC) in percentage of correct answers (%)

2.5 Statistical analysis

Data are presented as mean ± standard deviation except for those cases were normal distribution could not be assumed where median ± range was used. A *t* test for repeated measures (T paired test) was used to assess the statistical significance of the pairwise comparisons between values at different sessions. Bonferroni correction was used to adjust the significance levels when multiple comparisons are used. Shapiro–Wilk test was used to assess normality of data. When original data were not normally distributed, transformations of the data such as the inverse transformation (for positively skewed) or the arcsine transformation of the square root (negatively skewed) of data were used.

The effect size of observed differences was estimated according to the method proposed by Dunlap et al. [15]. Dunlap method (Eq. 1) is a modified version of "Cohen d" test especially suited for repeated measures calculated from paired *t* test.

$$d = t_c\left[2(1-r)/n\right]^{1/2} \quad (1)$$

where *d* is the so-called Dunlap *d*, t_c is the value of the t statistic for related observations, r is the correlation coefficient and n stands for the size of the sample studied. An effect size in absolute numbers between 0 and 0.2 was considered small, 0.3–0.7 was considered moderate, and 0.8 was considered large [16]. Measuring effect sizes for each difference protected against interpretation of statistically significant but meaningless differences (i.e. Dunlap's $d < 0.2$).

In order to assess individual patient recovery, the Cognitive Change Score (CCS) was calculated for each patient at T10, T40 and T120 expressed as the change from baseline in the speed of performance (LMN) on the IDN task.

$$CCS = \frac{Baseline - Post\,Baseline}{WSD} \quad (2)$$

where Baseline means LMN value in IDN task for subject "i" at baseline test, PostBaseline means LMN in IDN task for subject "i" at the different time points where the test was performed and WSD stands for Within Subject Standard Deviation. A patient with a CCS lower than −1.96 (two standard deviations) in a given test was considered as non-recovered [17]. For all cases, statistically significant differences were considered when $p < 0.05$. All data analyses were performed using SPSS Statistics (SPSS for Windows, Version 19.0. Chicago, SPSS Inc).

Table 2 Demographics and relevant clinical data

Data	n = 34 patients
Gender (M/F), n (%)	20/14 (59/41)
Age, median (range), years	59 (50–69)
BMI, median (range), kg/m^2	26 (21–37)
ASA Class, n (%)	
I	12 (35)
II	22 (65)
Successful procedure, n (%)	34 (100)
Polipectomy and/or biopsy, n (%)	20 (59)
Procedure time, median (range), min	26 (9–65)
Time to discharge, median (range), min (Aldrete post-anesthesia discharge score)	41 (17–96)

Table 3 Sedative drugs dosing details

Propofol		Remifentanil	
Total dose (Mg)	Target Ce (μg/ml)	Total dose (μg)	Target Ce (ng/ml)
149 (85–340)	2.5 (1.2–5)	98 (8.1–306)	1.7 (1–2.3)

Data are expressed in median (range)

Target Ce effect-site target concentration

3 Results

Figure 1 shows the flow diagram of the 34 enrolled patients enrolled and those who finally contributed data for analysis. Demographic data are summarized in Table 2. All 34 patients successfully completed the basal CogState test but only 33 and 26 completed T40 and T120 tests, respectively. Seven patients refused to take the T120 test because they considered themselves fully recovered and did not want to spend more time in the recovery area. No side effects occurred during the study.

The median value duration of the endoscopic procedure was 26 min (range 9–65). Details on anesthetic variables such as dosing and target ranges of propofol and remifentanil are shown in Table 3. The mean and range dose of propofol and remifentanil administered were 149 (85–340) mg and 98 (8.1–2.3) μg, respectively.

3.1 Cognitive recovery results

The results of each test and variable are presented in Table 4 at every time point.

Normality tests indicated a non-normal distribution of data for all variables except accuracy percentage in OCL task. Normality assumption was satisfied after data

Table 4 Changes in cognitive function at different times (data from CogState analysis)

	Session			
	Tbasal (n = 34)	T10 (n = 33)	T40 (n = 33)	T120 (n = 26)
IDN Task LMN (ms), mean ± SD	547 ± 128[a]	620 ± 116	559 ± 86[a]	537 ± 88[a]
DET Task LMN (ms), mean ± SD	414 ± 156[b]	426 ± 92	389 ± 102[b]	363 ± 83[b]
OCL Task Acc (%), mean ± SD	0.64 ± 0.10	0.61 ± 0.08	0.63 ± 0.11	0.64 ± 0.08
ONB Task Acc (%), mean ± SD	0.88 ± 0.14	0.86 ± 0.17	0.88 ± 0.16	0.9 ± 15

IDN Attention task, *LMN* latency mean, *DET* detection task, *OCL* one card learning task, *ACC* accuracy, *ONB* one back learning task

[a,b] $p < 0.001$ and $p < 0.01$ versus T10 session, respectively

transformation with the inverse transformation (for positively skewed data) or the arcsine transformation of the square root of data (for negatively skewed).

When the whole sample of individuals was considered, there was a significant performance decline from baseline at 10 min after the end of sedative drugs infusion for IDN ($p < 0.001$) and DET task ($p < 0.01$), but not for OCL or OCB. Based on these results, it can be said that the effects of sedative drugs affected attention and psychomotor function (IDN or DET tasks) but did not affect memory related tasks (OCL and ONB). Interestingly, mean latency time for IDN test at T40 and T120 was significantly faster than at T10, thus attention task was recovered at T40 and maintained until T120.

The effect size of psychomotor and attention tests, IDN and DET, are shown in Fig. 2. The magnitude of decline of IDN task was large between Tbaseline and T10, estimated as d = 0.81. Since there was a complete recovery of IDN and DET tasks at 40 and 120, the magnitude of decline at these times were close to zero.

When considered for individual patients, at 10 min after stopping sedation only 12 of the 34 patients (36%) showed a CCS higher than − 1.96 in IDN task meaning they were recovered (Fig. 3). All patients were recovered from sedation at 40 min. One patient had nausea and abdominal pain and was the only who could not be recovered at T120. All patients studied were fully recovered from a cognitive function standpoint at the time of clinical discharge (Aldrete Score of 10/10).

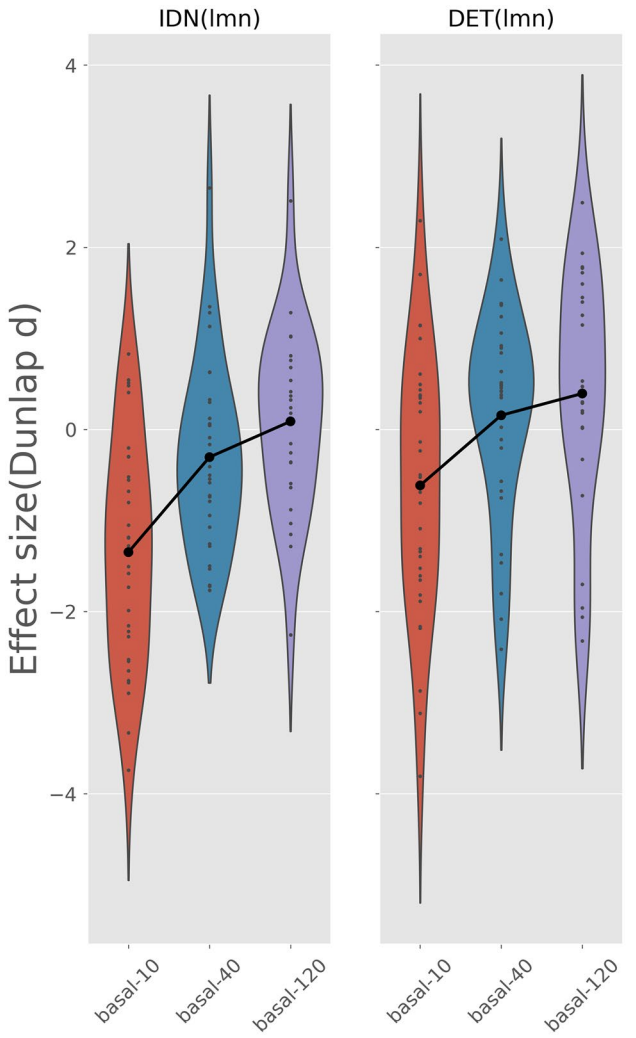

Fig. 2 Violin plot graph of the effect size of the change from Tbasal to T10, T40 and T120 for the IDN and DET tasks measured as lmn (latency mean). X axis represents the differences between basal and each evaluation time. Y axis is the Effect Size. The wider the figure the higher is distribution density at that point. Individual values are represented by the centered dots. Left plot represents the comparison for the IDN test while the DET tasks are shown on the right

4 Discussion

The results in the present study demonstrate that using a computerized method of evaluating cognitive function at the bedside of the patient it has been possible to define that there is a significant decay in cognitive function, specifically attention and psychomotor functions after sedation for colonoscopy. This cognitive decay is recovered in 64% patients 10 min after stop of sedation and completely back to normal in all patients 40 min after propofol and remifentanil infusions were stopped. The seven patients who refused to take the 120 min tests already met the Aldrete discharge criteria and were completely recovered at T40 test.

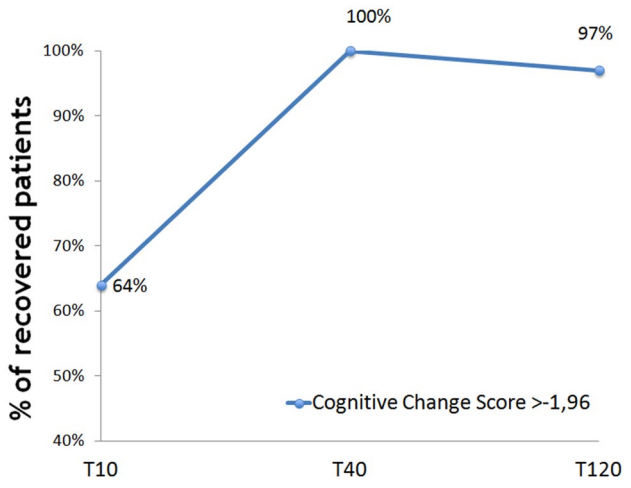

Fig. 3 Individual recovery calculated using Cognitive Change Score (CCS) of IDN task. Data are shown as percentage of patients who were recovered (CCS > − 1.96) at T10, T40 and T120

In terms of magnitude of effect, attention impairment is larger at 10 min after the end of infusion. There was no change in any test related to memory function during the duration of the study. The present study shows that attention tests are more sensitive to detect residual cognitive function impairment than memory function test, a similar finding to what was reported using the so called multiple-choice reaction time as a measure of attention [18].

Sedative effects cannot be isolated from an anxiety component that patients experience when facing a medical procedure probably. This component might be increased by some degree of sleep deprivation the night before of the procedure [19]. We consider these confounding factors as something valuable since it will be the common behavior in most outpatients. In the present study all the colonoscopies were conducted during the morning shift so the effect would be similar for all patients included.

The temporary cognitive impairment due to the residual effect of sedative drugs limits the individual to resume safely normal activities after endoscopy and can involve legal implications [20]. Willey et al. concluded that after meeting Aldrete criteria, 31 patients who underwent different gastrointestinal procedures under sedation with midazolam and meperidine could not be discharged without any responsible adult because their psychomotor function was not recovered [18]. The guidelines for sedation issued by the European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, endorsed by ESA in 2012 [7] and reviewed in 2015, were at least partly based in the previous work and did not include any other study with propofol combined or not with an opioid, which currently is the more common practice [21, 22].

Horiuchi et al. [23] have recently shown in a group of 48 patients undergoing propofol sedation for colonoscopy that cognitive activity measured by number connection test, and psychomotor function measured by use of a driving simulator that both were recovered 1 h after colonoscopy. Other cognitive tests such as Syndrom Kurztest (SKT) [24], number connection test [23, 25] or Mini-Mental State [26] have been widely used to asses cognitive function after sedation for gastrointestinal endoscopy.

There are very few evaluations of cognitive impairment after propofol and remifentanil sedation. Padmadabhan et al. [9] used CogState™ to evaluate cognitive function at the time of discharge after a colonoscopy. Their comparison was between propofol alone and propofol combined with midazolam or fentanyl. They found almost 80% of patients completely recovered at discharge time (51 min median time after stopping sedation) in contrast to full recovery of all patients at 40 min in our study. The higher doses of propofol used (25% more) and the adjuvant drugs (with longer duration of effect as compared to remifentanil) might explain the differences with the present study.

A major concern of measuring recovery and looking for reproducibility in this type of studies is if the patients have equivalent sedative intensity and it could be evaluated. No objective measure of sedative effect was used other than clinical evaluation. However, all sedation was provided by the same team [27], and the doses are comparable to previous studies in this setting. TCI was used because it gives the possibility of an easier and individualized effect titration according to individual patient responses.

Different guidelines for procedural sedation have been recently issued by the American Society of Anesthesiologists (ASA) [6] and the European Society of Anaesthesia (ESA) [7]. Those guidelines usually recommend careful and conservative approaches including a responsible adult taking care of patient and avoiding the performance of tasks requiring concentration. Our preliminary results show that this should not be so strictly required. Given the availability of cognitive evaluation tests through computerized systems it would be interesting to conduct a large scale study including a wider variety of propofol and remifentanil target concentrations. Other factors to consider for such a study could be duration of infusion or potentially affecting covariates such as age and concomitant diseases to definitely assess the dynamics of cognitive function during the recovery process and the potential for using cognitive function evaluation as another aspect to optimal discharge conditions.

To conclude, the significant impairment in attention and psychomotor function quantified after propofol/remifentanil sedation is fully recovered 40 min after the end of the procedure. The availability of computerized systems to test cognitive function at the bedside of the patient opens the possibility to use it as a standard of care in the ambulatory setting.

The results presented might allow rethinking recovery and discharge criteria after sedation and encourage the development of new prospective studies to investigate the effects of different propofol and remifentanil targets and potentially significant covariates on the recovery of cognitive function after sedation and other outpatient anesthetic procedures.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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