JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2016, 67, 4, 617-624
www.jpp.krakow.pl

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INFLUENCE OF PREMEDICATION WITH ALPRAZOLAM ON THE OCCURENCE OF OBSTRUCTIVE APNEAS. A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY

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Postoperative development or worsening of obstructive sleep apnea is a potential complication of anesthesia. The objective of this study was to study the effects of a premedication with alprazolam on the occurrence of apneas during the immediate postoperative period. Fifty ASA 1 – 2 patients undergoing a colonoscopy were recruited. Patients with a history of obstructive sleep apnea (OSA) were excluded. Recruited patients were randomly assigned to one of two groups: in Group A, they received 0.5 mg of alprazolam orally one hour before the procedure; and in Group C, they received placebo. Anesthesia technique was identical in both groups. Patients were monitored during the first two postoperative hours to establish their AHI (apnea hypopnea index, the number of apneas and hypopneas per hour). Nine patients were excluded (4 in group A and 5 in group C) due to technical problems or refusal. Interestingly, premedication by alprazolam did not change intra-operative propofol requirements. During the first two postoperative hours, the AHI was significantly higher in group A than in group C (Group A: 20.33 ± 10.97 h^{-1}, C: 9.63 ± 4.67 h^{-1}). These apneas did not induce significant arterial oxygen desaturation, or mandibular instability. Our study demonstrates that a premedication with 0.5 mg of alprazolam doesn't modify intra-operative anesthetic requirements during colonoscopy, but is associated with a higher rate of obstructive apneas during at least three and a half hours after ingestion. No severe side effects were observed in our non-obese population. Our results must be confirmed on a larger scale.

Key words: *alprazolam, obstructive, sleep apnea, postoperative complications, hypopnea, anesthesia, perioperative period*

INTRODUCTION

Obstructive apnea is defined as an interruption of the airway flow during a minimum of ten seconds (1). Hypopnea is defined as a limitation of this airway flow during the same period (1). The apnea hypopnea index (AHI) corresponds to the number of apnea and hypopnea per hour. The obstructive sleep apnea (OSA) syndrome is characterized by the repetitive occurrence of apneas or hypopneas during sleep. OSA is defined as mild when the AHI ranges between 5 and 15 events per hour, moderate when it ranges between 15 and 30 events per hour, or severe when AHI is higher than 30 events per hour) (2). Obstructive sleep apnea is an independent risk factor for perioperative complications (2). Danger for the patient is particularly high when it occurs on the ward, outside the post-anesthesia care unit, or worse, after hospital discharge (3, 4). The incidence of obstructive apneas increases with the perioperative administration of several medications such as opioids, sedative agents, or neuromuscular blocking agents (5).

In clinical practice, anesthesiologists are aware of the risk of apnea associated with the administration of opioids or muscle relaxants (6). Although frequently omitted, premedication is a possible cause of obstructive apneas (7). Anxiolytic premedication has been common practice in many centers (8). Benzodiazepines have long been used for this purpose (9), and alprazolam is one of the numerous benzodiazepines that are commonly used in that indication (10). In some countries, such as Belgium, alprazolam is still widely used, including for outpatients. Dahmani *et al*. have already demonstrated that premedication with clonidine may have a better risk/benefit ratio (11), as do dexmedetomidine (12). However, the effects of alprazolam on the occurrence of postoperative apnea, or the effects of those apneas on arterial oxygen saturation have never been assessed. Our primary hypothesis was that alprazolam could jeopardize the upper airway stability, and therefore favor the occurrence of obstructive apneas during the immediate postoperative period. To distinguish the effect of alprazolam from OSA pathophysiology, patients with a known or suspected history of OSA were excluded from this study.

MATERIALS AND METHODS

This study has obtained the approval of our Institutional Ethics Committee (Ethical Committee of Liege University Hospitals, Liege, Belgium, Chairperson: Prof Maurice Lamy, Ref: 2007-110). EudraCT registered this study with the reference number: 2007-002429-66. Informed consent was obtained from all individual participants included in the study.

Patients

Fifty patients scheduled for day-care colonoscopy were recruited (*Fig. 1*). Exclusion criteria were patient's refusal, patients with known obstructive sleep apnea (OSA) syndrome, and/or an ASA class ≥ 3. Patients in the first group (Group A) received an oral premedication, consisting in 0.5 mg of alprazolam one hour before colonoscopy. Patients in the second group (group C) received placebo. The placebo was an inactive comparator indistinguishable from the alprazolam tablet.

Experimental procedures

A researcher who did not participate in managing anesthesia and data recording prepared the randomization schedule using a computer-generated sequence. During the preoperative visit, a second investigator recorded patient age, weight, height, neck circumference and airway difficult score (ADS), which is the score for difficult intubation and ventilation used in our hospital (13). This second investigator was blinded to between-group patient repartition.

In the endoscopy suit, patients were equipped with standard monitoring, including electrocardiogram, non-invasive blood pressure, capnography, and a peripheral saturation in oxygen (SpO_2) sensor (Datex-Ohmeda, GE Healthcare, Fairfield, USA). A Bispectral Index® (BIS, Covidien, St. Ingbert, Germany) electrode was also placed on the forehead of all patients. An 18G IV line was inserted, and a Hartmann's solution (Baxter SA, Lessines, Belgium) was infused (rate: 200 ml h^{-1}). Patients were also equipped with an oxygen face mask (Mallinckrodt, Covidien, St. Ingbert, Germany), and the oxygen flow rate was 10 L min^{-1}. This corresponds to the standard in our Institution.

During induction of anesthesia, patients received a single intravenous bolus of ketamine (0.5 mg Kg^{-1}). After that, a continuous infusion of propofol was adjusted to maintain a BIS value between 70 and 80. This range was determined by a pre-test on five patients (unpublished data). From a clinical point of view, sedation was targeted at a deep level, so that patients were not responsive throughout the procedure. The respiratory rate was measured using a capnograph, whose sampling line was inserted into the oxygen face mask. Throughout the procedure, spontaneous ventilation was maintained in all patients.

After colonoscopy, patients were admitted to the post-anesthesia care unit (PACU) for two hours. They were monitored using a portable monitoring device (Somnolter®, Nomics SA, 4031 Angleur, BELGIUM, www.nomics.be). This device is validated as a portable device for diagnosing OSA (14-16). It consists in a SpO_2 sensor, and two piezoelectric sensors placed on the face of the patient. Those sensors measure mandibular movement. This mandibular movement (JAWAC: JAW

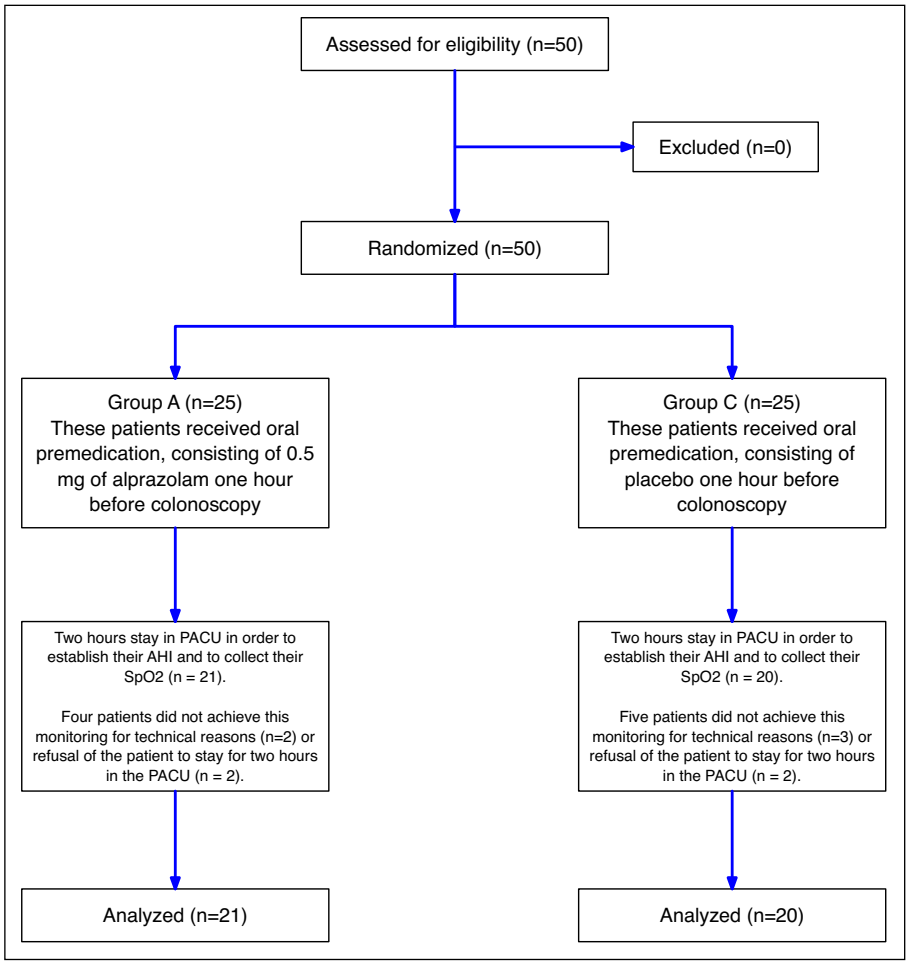

Fig. 1. CONSORT flow chart (PACU, post-anesthesia care unit; AHI, apnea hypopnea index).

ACtivity) correlates with the esophageal pressure during obstructive sleep apnea (14-16). The Somnolter® provides an estimate of mandibular stability, expressed in percent. One hundred percent corresponds to a fully closed mouth, and 0% to the largest mouth opening for a given patient. No calibration of the device is needed. The software can distinguish obstructive apneas from other mandibular movements such as speaking. In the post-anesthesia care unit, no oxygen was administered.

Somnolter®-recorded SpO_2 and AHI were analyzed offline, and the analyzing investigator was blind to group assignment.

Analgesics consumption in the post-anesthesia care unit was also recorded. Any administration of paracetamol, ketorolac or butylhyoscine bromure was also recorded.

The Lickert psychometric scale (17, 18) was used to estimate patient satisfaction and anxiety (*Table 1*). The anxiety level was assessed at three different time points: 1) before colonoscopy by the anesthesiologist in charge of providing anesthesia, 2) upon arrival in the PACU and 3) at PACU discharge by the anesthesiologist responsible for post-anesthesia care. Both practitioners were blind to group repartition. The overall patient satisfaction regarding the whole procedure was evaluated upon patient discharge from the post-anesthesia care unit.

Statistical analysis

Data were compiled into a computer file and compared between groups. The normality of data distribution was evaluated using a Shapiro-Wilk test. Proportions were analyzed using Fisher's exact tests, and normally distributed data were compared between groups using two-tailed unpaired t-tests. Data that did not show a normal distribution were assessed using Mann-Withney U tests, or Friedman tests as appropriate. A two-tailed P value < 0.05 was considered as statistically significant. Data were analysed using XLSTAT for Mac® (version 2015.5.01,

Table 1. Psychometric Lickert's scale used to appreciate anxiety and satisfaction of the patient. See text for explanations.

	1 point	**2 points**	**3 points**	**4 points**
Anxiety and sedation score	Drowsy	Awake but not anxious	Awake and anxious	Very anxious and uncomfortable
Patient satisfaction on the whole procedure	Satisfied, but next time, he/she would rather be premedicated more lightly	Satisfied, he/she would like the same premedication next time	Satisfied, but next time, he/she would rather be premedicated more deeply	Unsatisfied, he/she was too anxious and would rather be premedicated more deeply next time

Table 2. Demographic, operating room and post-anesthesia care unit data. Reported values are means (S.D.), unless otherwise indicated.

	Group A (n = 21)	Group C (n = 20)	Statistics	P
Age	55.1 (13)	49.7 (11.6)	$t_{(39)} = 1.4$	0.17
Male/female (n)	5/16	11/9		0.03
BMI in Kg m^{-2}	24.9 (4)	24 (3.1)	$t_{(39)} = 0.7$	0.47
Neck circumference in cm	36.5 (3.2)	36.9(3.9)	$t_{(39)} = 0.4$	0.7
Airway Difficult Score (ADS) [median (IQR)]	6 (8 – 5)	6 (9 – 5)	U = 187.5, Z = –0.6	0.34
Ketamine in mg	27.9 (5.6)	31.5 (7.3)	$t_{(39)} = 1.8$	0.08
Ketamine in mg kg^{-1}	0.4 (0.1)	0.4 (0.1)	$t_{(39)} = 2$	0.15
Propofol consumption in mg	236.4 (65.1)	291.4 (117.8)	$t_{(39)} = 1.8$	0.08
Propofol consumption in mg kg^{-1}	3.5 (1.2)	4.4 (2.4)	$t_{(39)} = 2$	0.16
Analgesic consumption in PACU	None	None	N/A	N/A
Anxiety upon arrival in the operating room [median (IQR)]	2 (1 – 3)	3 (2 – 4)	U = 106.5 Z = –2.7	0.01
Anxiety upon arrival in PACU [median (IQR)]	2 (1 – 2)	2 (1 – 3)	U = 189 Z = –0.5	0.34
Overall patient's satisfaction [median (IQR)]	2 (2 – 2)	2 (1 – 2)	U = 231 Z = –0.5	0.34

BMI, body mass index; IQR, interquartile range; PACU, post-anesthesia care unit.

Addinsoft SARL®, Paris, France) and MedCalc® (version 15.11.0 MedCalc Software bvba®, Ostend, Belgium).

RESULTS

Nine patients were excluded from the study (4 in group A and 5 in group C). Reasons for exclusion were related to technical problems or refusal of the patient to stay for two hours in the post-anesthesia care unit. Post hoc power calculation revealed a study power of 78% at detecting a clinically relevant 40% between-group difference in the incidence of apnea during the first two postoperative hours, at a 0.05 a threshold.

Patient characteristics: age, body mass index (BMI), neck circumference, intubation and ventilation score were similar in the two groups, except for the gender ratio (*Table 2*). There were significantly more women in Group A than in Group C. There was no statistically significant between-group difference regarding administered ketamine or propofol amounts. BIS values were comparable between the two groups (mean BIS (S.D.) was 74.52 (1.75) in Group A, and 74.95 (1.67) in Group C, Mann-Whitney U = 179, P = 0.417). No laryngeal device had to be inserted during colonoscopy. No patient requested the administration of analgesic medications in the post-anesthesia care unit (*Table 2*). No additional oxygen was necessary in the PACU.

During the two hour stay in the post-anesthesia care unit, the number of apneas and hypopneas was significantly higher in Group A than in Group C: median AHI (IQR) was 17.5 (11.45 – 30.29) in Group A, and 9.25 (7.32 – 10.74) in Group C, Mann-Whitney U = 74, Z = –3.55, P = 0.0007) (*Fig. 2*). Subdividing the two hours spent in the PACU in four 30-minute periods allowed demonstrating that the difference in the absolute number of apneas and hypopneas episodes became statistically significant between groups after 30 minutes (*Table 3*, *Figs. 3* and *4*). Within-group comparisons did not reveal any significant change in the AHI across the 30-minute time points.

Peripheral oxygen saturation was similar in both groups at all times (*Table 4*). Similarly, in the post-anesthesia care unit, there was no difference in mandibular stability between the two groups (*Table 4*).

Patients premedicated with alprazolam were significantly less anxious upon arrival in the operating room than patients who received placebo (P = 0.01). On the opposite, anxiety was similar in the two groups upon arrival in the post-anesthesia care unit (P = 0.34). The overall patient satisfaction concerning the whole procedure did also not differ between groups (P = 0.34) (*Table 2*).

DISCUSSION

The main result of the present study is that administration of 0.5 mg of alprazolam one hour before colonoscopy significantly increases the number of apneas and hypopneas at least during two hours after the completion of the procedure. However, this increase is not associated with more frequent arterial oxygen desaturation episodes. It is worth to point out that our population was not at risk of such events. None of the patients were obese nor had a history of OSA. Administrating the same alprazolam premedication in patients with an increased risk of obstructive apnea could lead to different results (19). Propofol and ketamine were used to provide respectively anesthesia and anti-nociception. This allowed avoiding opioid administration that could influence the occurrence of postoperative apneic events (6, 20-22). Another reason for not observing desaturations can be related to the increased genioglossus activity associated with the administration of ketamine (23). However, this property is observed for much higher doses of ketamine (60 and 125 mg Kg^{-1}) (23). Finally, ketamine could have some actions on delta- and mu-opiod receptors, but without any influence on airway patency (24, 25). Zirlik *et al*. have demonstrated that melatonin and omentin seem to be involved in pathogenesis of OSA (26).

Of note, the incidence of apneas and hypopneas tended to increase with time in the PACU. However, this increase did not reach the significance level. Hence, the risk of apnea and hypopnea in alprazolam-premedicated patients more than probably persists after PACU discharge, when patients are no longer monitored.

Other studies have investigated the perioperative effects of an alprazolam premedication. Contrarily to our study, they were not

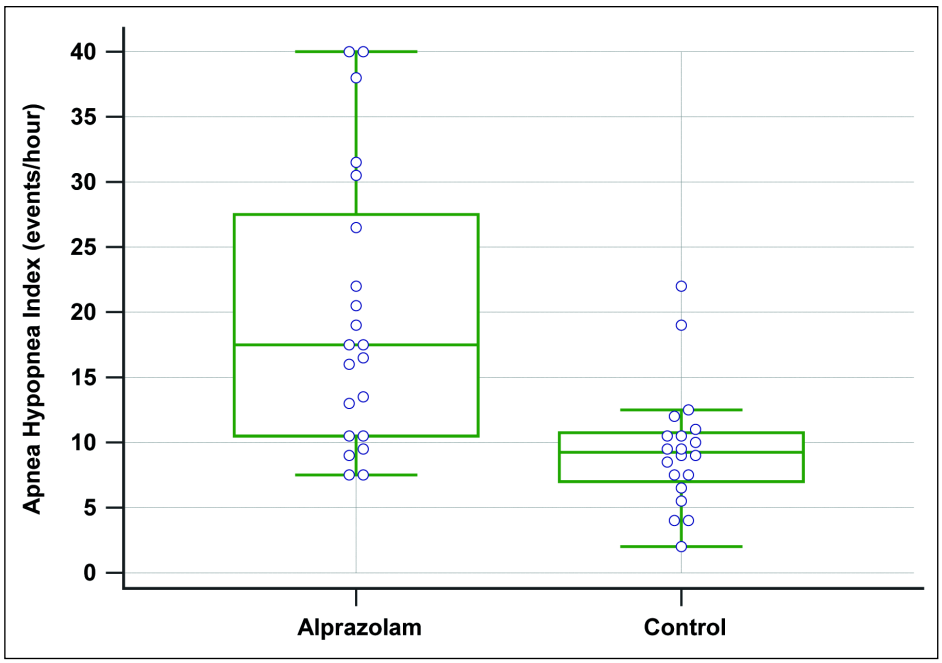

Fig. 2. Between-groups difference in AHI values during the first two hours after colonoscopy. Boxplots represent median, IQR, maximum, and minimum values.
AHI, apnea hypopnea index (events/hour); IQR, interquartile range.

Table 3. Incidence of apnea and hypopnea in the post-anesthesia care unit. Data are means (S.D.).

	Group A (n = 21)	Group C (n = 20)	Statistics
Total number of apneas and hypopneas observed during 2 hours [median (IQR)]	35 (21 – 53)	18.5 (14.5 – 21.25)	U = 75 Z = –3.5 P = 0.0008
AHI over the 2 hours [median (IQR)]	17.5 (11.45 – 30.29)	9.25 (7.32 – 10.74)	U = 74 Z = –3.5 P = 0.0007
Number of apneas and hypopneas during first 30 minutes [median (IQR)]	12 (5.5 – 18)	8 (5 – 17)	Friedmans test: F = 3.20; P = 0.09
Number of apneas and hypopneas observed minutes 30 – 60 [median (IQR)]	14 (6 – 29.5)	6 (4 – 11)	Friedmans test: F = 8.88; P = 0.008
Number of apneas and hypopneas observed during minutes 60 – 90 [median (IQR)]	14 (9.5 – 29)	7 (2 – 12)	Friedmans test: F = 7.31; P = 0.014
Number of apneas and hypopneas observed during minutes 90 – 120 [median (IQR)]	22 (10 – 30.5)	11 (4 – 16)	Friedmans test: F = 5.21; P = 0.035

AHI, apnea/hypopnea index; IQR, interquartile range.

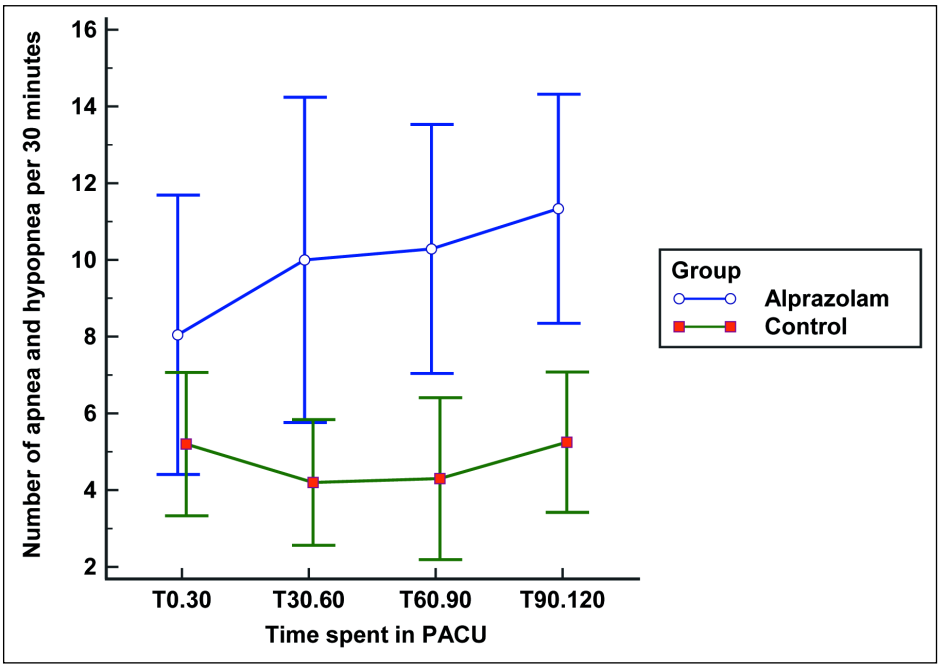

Fig. 3. Between-groups difference in the number of apnea and hypopnea per period of 30 minutes during the first two postoperative hours. Data are expressed as mean (S.D).
T0.30 - first thirty minutes spent in PACU; T30.60 - period between 30 and 60 minutes spent in PACU; T60.90 - period between 60 and 90 minutes spent in PACU: T90.120 - period between 90 and 120 minutes spent in PACU; PACU, post-anesthesia care unit.

necessarily designed to address the problem of postoperative apnea incidence and were not necessarily rid of the influence of opioids or muscle relaxants (10, 12, 21, 27-30). None of these studies have studied the influence of alprazolam on the occurrence of postoperative apneas. This point was the objective of our study.

Gentil *et al.* studied the effects of a premedication by midazolam in an OSA patient population (70). They demonstrated that midazolam did not increase the number of apneas in the OSA group. Similarly to our results, they did not evidence any significant difference in the incidence of peripheral oxygen desaturation. Of note, however, this study was performed in only seven OSA patients.

Aside apnea/hypopnea findings, our study demonstrates that alprazolam is effective at reducing patient anxiety before colonoscopy. This is in line with the results of previous studies (29-31). On the opposite, alprazolam administration did not alter the anxiety level in the PACU, nor the overall patient satisfaction. This is in accordance with the recent study of Maurice-Szamburski *et al.* (28, 32). Interestingly, the premedication by alprazolam did not modify propofol requirements to achieve the BIS target during colonoscopy.

Our study shows that alprazolam administration increases the risk of obstructive apneas. Although our patient population was not obese or suffering from OSA, this should prompt cautiousness when administering an alprazolam premedication to them. Those patients are particularly sensitive to drug-induced apneas, all the more if they do not have or use a CPAP (4, 19, 33, 34). According to Pawlik *et al.*, clonidine could be an alternative in such a high-

Table 4. Peripheral saturation in oxygen (SpO_2, %) and mandibular stability (%) during the perioperative period.

	Group A (n = 21)	Group C (n = 20)	Statistics
SpO_2 before induction of anesthesia [median (IQR)]	96 (94.7 – 98)	96 (95 – 97)	U = 204 Z = 0.16 P = 0.87
Maximal SpO_2 in PACU [median (IQR)]	98 (97.8 – 99.3)	99 (98 – 99.5)	U = 183 Z = 0.07 P = 0.95
Minimal SpO_2 in PACU [median (IQR)]	91 (90 – 93)	91.5 (90 – 95)	U = 207.5 Z = 0.07 P = 0.95
Mean SpO_2 in PACU [median (IQR)]	95.17 (95.17 – 95.17)	94.28 (92.46 – 95.98)	U = 175.5 Z = 0.97 P = 0.33
Number of events when SpO2 drop below 94% in PACU [median (IQR)]	4 (1 – 19.75)	5 (0 – 18.5)	U = 197 Z = 0.34 P = 0.73
Maximal MO in PACU [mean (S.D.)]	95.88 (48)	90.78 (12.4)	$t_{(39)} = 0.47$ P = 0.99
Minimal MO in PACU [mean (S.D.)]	57.1 (28.3)	61.32 (32.8)	$t_{(39)} = 0.44$ P = 0.78
Mean MO in PACU [mean (S.D.)]	72.19 (22.4)	78.65 (16.7)	$t_{(39)} = 1.05$ P = 0.89

IQR, interquartile range; PACU, post-anesthesia care unit; NS, not significant; MO, mouth opening

risk population (35). Hence, the choice of such premedication should be weighed carefully, and should ideally be assessed in a specifically dedicated study enrolling such patients (36, 37).

Readers should keep in mind that OSA is also correlated with oxidative stress and thrombotic events that represent also a risk of postoperative complications (38, 39). Recently, Sharman *et al*. have demonstrated that repeated obstructions of the airway do not lead to cardiovascular dysfunction in healthy individuals (40). Hypoxemia could play a role in the development of postoperative complications (41, 42).

This study has limitations. First, one may argue that a polysomnography is not performed in each patient before colonoscopy to exclude OSA. However, the risk of OSA can also be assessed using a clinical score, such as the DES-OSA score (43). None of the fifty patients included has a score higher than 5. This result indicates a very low probability of OSA. Second, our study was performed on a small number of patients. Our study is slightly underpowered. Thus our study can indicate an estimation, but a larger scale study is required for definitive conclusions (44). Third, the level of anxiety was assessed using a 4-point Lickert scale, as it was the standard practice in our institution at the time of completion of the study. However, this option is debatable and other scales, such as a verbal patient self-rating numeric scale, could have been more sensitive.

In conclusion, our study demonstrates that alprazolam significantly increases the risk of postoperative apnea for at least three and a half hours after administration. In a non-obese OSA-free patient population, the increase in the number of apneas does not result in an increased incidence of peripheral oxygen desaturation. Although reducing preoperative anxiety, it does not alter postoperative anxiety. It does not modify the anesthetic requirement during colonoscopy. The preoperative administration of alprazolam is questionable and must be confirmed on a larger scale.

Preliminary data for this study were presented as a poster and/or oral presentation at: The First World Congress of Chest-ACCP (American College of Chest Physicians), Madrid, March 2014 and The Annual Congress of the American Society of Anesthesiologist, New Orleans, October 2014.

Acknowledgements: The authors want to acknowledge Sandrine REMY, Murielle KIRSCH, Gaetane HICK, Pol HANS, and Laurent CAMBRON as participating investigators.

Conflict of interests: None declared.

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Received: June 19, 2016
Accepted: September 5, 2016

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