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Clonidine as a pre-anesthetic agent for flexible bronchoscopy

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Summary Several drugs have been employed for sedation during flexible fiberoptic bronchoscopy (FOB). Clonidine attenuates stress-induced sympathoadrenal responses and has sedative properties. We investigate the effects of clonidine premedication on hemodynamic and comfort parameters of patients submitted to FOB under airway topical anesthesia only. Patients received placebo ($n=22$; men = 16; median age = 50.5 years) or intravenous clonidine (3 μg/kg; $n=20$; men = 15; median age = 46.0 years) 15 min before FOB. Blood pressure (BP), heart rate (HR), plasma norepinephrine (nor) and cortisol levels were measured before, during, and 1 h after FOB. Comfort was assessed by the examiner and by the patients using a visual numerical scale (0–10). The placebo group showed significant increases in systolic BP, HR, and nor levels during FOB (SBP = 125 mmHg × 145 mmHg; HR = 74 bpm × 85 bpm; nor = 316.2 pg/dl × 483.1 pg/dl), whereas clonidine group did not display such changes. Clonidine group showed a lower frequency of cardiac arrhythmias than the placebo group during and after FOB (supraventricular = 39% × 50%; ventricular = 22% × 40%). Levels of comfort were high and comparable in both groups. We concluded that although clonidine led to a somewhat better hemodynamic profile, it did not contribute to better comfort in this setting.

Introduction

Different agents have been employed for premedication and sedation during flexible fiberoptic bronchoscopy (FOB), depending on the personal preferences of individual operators.[1,2] Most bronchoscopists use sedative drugs before FOB in order to reduce stress and improve comfort and cooperation. Among a wide list of sedative drugs, opioids and benzodiazepines, alone or in combination, are those most frequently chosen. However, the necessity of any sedation for FOB has been questioned due to potential complications with the routine use of these drugs.[3,4] In addition, FOB is a brief procedure generally performed on an outpatient basis, and the use of sedation may prolong hospital stay and increase costs related to the exam.

Clonidine is a centrally acting α_2-agonist that attenuates stress-induced sympathoadrenal responses, promotes intra-operative hemodynamic stability, and reduces anesthetic requirements during surgical procedures.[5,6] Clonidine itself has slight sedative properties.[7] It has been shown that the use of clonidine as pre-medication attenuates the hemodynamic responses induced by flexible and

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rigid bronchoscopy.[8,9] However, the usefulness of clonidine in patients submitted to FOB without any sedation has not been investigated.

The objective of this randomized, double-blind, placebo-controlled study was to investigate the effects of clonidine pre-medication on hemodynamic, hormonal, and comfort parameters of patients submitted to FOB under airway topical anesthesia only.

Methods

Patients

Forty-two patients undergoing routine diagnostic FOB were evaluated. The indications for FOB included lung masses (38%), pulmonary infections (31%), interstitial lung diseases (19%), and others (12%). Patients with a history of recent myocardial infarction, or who had used drugs with cardiovascular actions, like calcium channel antagonists or beta-blockers, during the previous week were not studied. Patients who had been on steroids during the past month were also excluded. The research protocol was approved by the Institution Ethics Committee, and written consent was obtained from each patient immediately before the procedure.

Procedure

Patients were admitted to the bronchoscopy suite and, after installation of a venous access and monitoring devices, received a verbal explanation and were tranquilized about the procedure to be performed. They were then allowed to rest for 30 min in a quiet atmosphere, and randomized to receive a previously coded intravenous preparation containing placebo or clonidine (3 μg/kg, not exceeding a total of 300 μg, a generous gift of Cristalia Laboratories). Drug or placebo in proportional volumes was diluted in 50 ml of saline and administered over a period of 15 min. Next, all patients received topical anesthesia by the administration of puffs of 4% lidocaine spray to the oropharynx, and 2% lidocaine jelly to the nostrils. At this point, supplemental oxygen was introduced routinely via a nasal catheter. Additional anesthesia was performed as the bronchoscope progressed into the airways by instillation of 2% lidocaine aliquots through its work channel, according to individual patient's requirements.

The same physician performed all examinations by the trans-nasal route, with the patients in the supine position, using an Olympus BF P 30 bronchoscope (Olympus®, Tokyo). The physician and nursing staff were blinded about the allocation of patients to one of the two groups. All exams were performed at the same time in the morning, between 8:00 and 10:00 AM.

Measurements

Data collection was performed at three different points: (i) immediately before drug or placebo application (*baseline conditions*), (ii) at the beginning of airway endoscopic examination, just after lidocaine administration had been concluded (*intra-procedure conditions*), and (iii) 1 h after the procedure ended (*post-procedure conditions*). Monitoring during FOB included continuous EKG by a holter system (DMS®, São Paulo), pulse oximetry (Dixtal-2515®, São Paulo) and blood pressure measurements. Blood samples were obtained at each point, and kept frozen for later measurements of plasma cortisol and nor-epinephrine levels according to a previously published methodology.[10,11]

Patient comfort was assessed at the end of bronchoscopy by the examining physician, employing a visual numerical scale ranging from 0 to 10, the high limit representing the best degree of tolerance. This assessment was called *objective evaluation*. The subjects were also asked to express their comfort during FOB employing a similar scale 1 h after the end of the procedure. This assessment was called *subjective evaluation*.

Statistics

Results are expressed as medians and ranges of variation. Comparisons of basal features and frequency of cardiac arrhythmia between groups were performed using the chi-square test.[12] Comparisons of hemodynamic, biochemical and comfort results for the two groups were performed using the Mann–Whitney test. Intra-group comparisons for data obtained at the three different points were performed using Friedman's test followed by Dunn's post hoc test when indicated. A P-value < 0.05 was accepted as statistically significant.

Results

There were no statistically significant differences between the two groups in terms of age, sex, type of procedure, requirements of topical anesthesia, and duration of the FOB (Table 1).

Table 1 Patient's characteristics.

	Placebo group ($n = 22$)	Clonidine group ($n = 20$)
Male/Female	16/6	15/5
Age (years)	50.5 (33–70)	46.0 (18–71)
FOB duration (min)	25.0 (10–40)	25.0 (15–45)
Instilled lidocaine (mg)	180.0 (100–220)	175.0 (120–200)
Procedures (Times performed)		
Broncoalveolar lavage	16 (53.3%)	16 (59.3%)
Bronchial aspiration	5 (16.7%)	4 (14.8%)
Bronchial brushing	3 (10.0%)	2 (7.4%)
Endobronchial biopsies	2 (6.7%)	2 (7.4%)
Transbronchial biopsies	3 (10.0%)	3 (11.1%)
Bronchial inspection only	1 (3.3%)	0 (0%)

Clonidine administration was well tolerated, and only two patients showed hypotension, characterized by a decrease in systolic blood pressure higher than 30% at the post-procedure point. No patient required fluid replacement due to these episodes. Two patients in the clonidine group fell asleep during the post-procedure period.

The placebo group exhibited statistically significant elevations in heart rate and systolic blood pressure during FOB (Table 2), which were not observed in the clonidine group. Post-procedure systolic blood pressure and heart rate were significantly lower than intra-procedure values in both groups. The post-procedure diastolic blood pressure was also significantly lower than the intra-procedure values in the placebo group. In addition, the clonidine group displayed a significant decrease of both systolic and diastolic blood post-procedure pressures in comparison to baseline values. Comparisons of hemodynamic results between groups did not reach statistical significance at any time.

A substantial number of subjects in both groups showed ventricular and supra-ventricular extra-systolic beats before FOB (Table 3). The frequency of these cardiac arrhythmias did not differ significantly between groups under baseline conditions or during the intra/post-procedure period. The frequency of arrhythmias tended to be lower in the clonidine group during and after FOB. No ST segment changes were observed in any patient at any time.

Plasma cortisol levels did not change significantly over time in the placebo group, but the clonidine group displayed post-procedure values significantly lower than baseline (Table 2). A significant increase in plasma nor-epinephrine levels was observed in the placebo group during the intra-procedure period, but not in the clonidine group. The clonidine group also showed significantly lower levels of nor-epinephrine during the post-procedure period in comparison to baseline and intra-procedure points.

The median objective and subjective comfort scores were similar and elevated for both groups (Fig. 1). There was also a high degree of agreement between the two types of scores.

Discussion

The purpose of sedation in FOB is to improve patient comfort for what may be an unpleasant procedure.[1,2] Sedation may also make the procedure easier to perform for the bronchoscopist, and the patient more willing to accept a possible repeated procedure. Some placebo-controlled studies have found a beneficial effect of diazepinic sedation during FOB, and the "BTS Guidelines to Diagnostic Flexible Bronchoscopy" recommend to offer sedation to all patients, when there is no contraindication.[2,13,14] However, the necessity for any sedation for FOB has been questioned, and surveys have shown that some medical centers still perform the exam with airway topical anesthesia only.[3,4,15,16] Arguments against routine sedation include concerns about patient safety, particularly regarding COPD and hypoxemic subjects. The administration of sedative drugs also requires medical and nursing staff with specific training, and adequate facilities for resuscitation and prolonged monitoring.

Clonidine is a drug known for more than 30 years that has been increasingly used as a pre-anesthetic agent, mainly due to its anti-sympathoadrenal actions.[5,6] Its use is associated with better intra-operative hemodynamics and a lower incidence of perioperative myocardial ischemic episodes during major surgeries.[17] Clonidine has also analgesic and hypnotic properties[7] and has been reported to be a

Table 2 Haemodynamic profile, pulse oximetry and biochemical measurements.

		Baseline	Intra-procedure	Post-procedure
Systolic blood pressure (mmHg)	Placebo group ($n=22$)	125 (90–160)	145* (100–180)	120^{+} (90–180)
	Clonidine group ($n=20$)	125 (100–180)	110 (100–190)	110*, $^{+}$ (90–150)
Diastolic blood pressure (mmHg)	Placebo group ($n=22$)	80 (60–110)	85 (60–120)	80^{+} (50–114)
	Clonidine group ($n=20$)	80 (70–100)	80 (60–90)	70* (50–90)
Heart rate (beats/min)	Placebo group ($n=22$)	74 (50–101)	85* (58–111)	74^{+} (52–100)
	Clonidine group ($n=20$)	73.5 (50–109)	80.5 (45–120)	72.5^{+} (46–100)
SaO_2 (%)	Placebo group ($n=22$)	96 (93–99)	96 (90–98)	96 (92–99)
	Clonidine group ($n=20$)	96 (92–99)	96 (92–99)	96 (91–99)
Nor-epinephrine (pg/ml)	Placebo group ($n=13$)	316.2 (132–1177)	483.1* (180–1538)	320.5 (103–1539)
	Clonidine group ($n=10$)	309.1 (136–667)	321.2 (165–667)	302.4*, $^{+}$ (103–544)
Cortisol (mg/dl)	Placebo group ($n=22$)	11.0 (2.9–31.2)	10.8 (4.9–24.0)	9.8 (4.9–24.4)
	Clonidine group ($n=20$)	12.4 (3.1–23.4)	9.9 (2.4–25.2)	9.2* (3.3–17.4)

*$P<0.05$ in comparison to baseline conditions by Dunn's test.
$^{+}P<0.05$ in comparison to intra-procedure conditions by Dunn's test.

Table 3 Frequency of arrhythmias.

	Baseline		Intra-procedure and post-procedure	
	Placebo group ($n=20$)	Clonidine group ($n=18$)	Placebo group ($n=20$)	Clonidine group ($n=18$)
Ventricular ectopic beats	5 (25%)	4 (22%)	8 (40%)	4 (22%)
Supraventricular ectopic beats	4 (20%)	5 (28%)	10 (50%)	7 (39%)
Supraventricular tachycardia	0	1 (6%)	0	1 (6%)

successful substitute for sedation in short surgical procedures performed under local anesthesia such as ophthalmologic operations.[18]

Previous work has shown that the pre-operative use of clonidine could blunt reflex tachycardia and hypertensive responses secondary to endo-tracheal intubation.[19,20] In addition, in two studies investigating the effects of clonidine premedication on hemodynamic responses to rigid and fiberoptic bronchoscopy, the oral use of 300 μg of clonidine 90 min before microlaryngoscopy and bronchoscopy led to smaller increases in arterial blood pressure and to a lower incidence of ventricular arrhythmias and evidence of myocardial ischemia than placebo.[9] Clonidine-related side effects were not observed, and the time to extubation from the end of sedative infusion and to discharge from the recovery room did not differ between groups.

Another study compared the effects of oral clonidine at doses of 150 and 300 μg with placebo given 90 min before FOB.[8] The patients were also sedated with intravenous meperidine and midazolam. It was found that 150 μg of oral clonidine was well tolerated, and attenuated the blood pressure

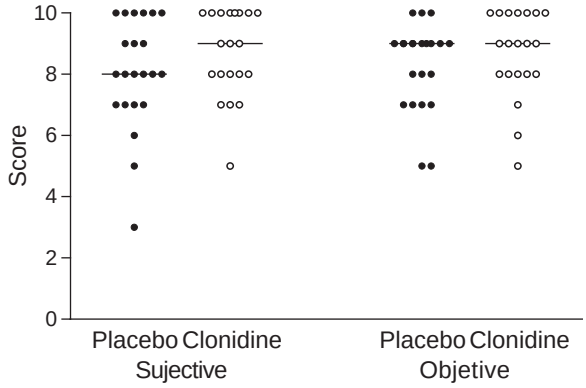

Figure 1 Objective and subjective comfort scores for patients treated with placebo or clonidine. Horizontal lines represent median values.

and heart rate increases observed during the procedure in the placebo group. The use of 300 μg, however, was associated with longer awakening times and expressive hypotension episodes in 75% of the subjects.

The present study investigated the potential utility of clonidine as pre-medication for FOB performed with topical anesthesia only. We hypothesized that, due to its anti-stress and anxiolytic properties, the drug could be an alternative to conventional sedative agents in this setting. The groups of patients were comparable, with no difference in gender composition, age, duration, or type of procedure performed between them.

We made an option to employ IV clonidine in order to reduce the time between medicine administration and FOB beginning. A waiting time of 90 min after oral clonidine intake would cause operational difficulties in routine ambulatory bronchoscopies. Although a higher frequency of complications could be expected with the IV preparation, we did not observe expressive side effects or substantial hypotensive episodes related to treatment.

We observed wide variation in the hemodynamic results obtained for both groups at all points of the study. Most probably due to this, the comparisons between groups did not reach statistical significance at any time. The results would have probably been different if we had performed statistical analysis employing the highest values of blood pressure and heart rate obtained by continuous monitoring during the procedures instead of measurements recorded at pre-fixed time points.[8,9] Nevertheless, analysis of the intra-group comparisons revealed that the events were distinct in each group. The placebo group displayed significant elevation of intra-procedure systolic blood pressure and heart rate compared to baseline. Such changes were not observed in the clonidine group. In addition, the effect of clonidine was protracted, since the post-procedure systolic blood pressure values were significantly lower than those obtained at baseline and during the procedure. As expected, the plasma nor-epinephrine levels accompanied the systolic blood pressure changes in both groups.

Cardiac arrhytmias are a frequent finding during FOB. A classical study described an incidence of 32% and 20%, respectively, for supra-ventricular and ventricular disorders during the procedure.[21] In the present study, we found an even higher frequency of supra- and ventricular ectopic beats. Although there were no statistically significant differences in the frequency of cardiac arrhythmias between groups before, during or after FOB, we could observe a favorable trend with the use of clonidine. The incidence of supra-ventricular and ventricular ectopic beats during and after the procedure was lower in the clonidine group than in the placebo group. Therefore, the present results indicate that pre-medication with clonidine in patients submitted to FOB under no sedation slightly contributed to a better hemodynamic profile.

Plasma cortisol levels have been traditionally employed as a measurement of the stress-induced response to surgical proceedings. Significant increases in cortisol have been described during FOB performed under topical anesthesia.[22] These increases were higher in patients who reported more discomfort during the procedure. The cortisol elevations were abolished by the administration of diazepam just before examination.[22] The present study did not find significant differences in plasma cortisol levels between groups at any time. Cortisol levels tended to drop over the different sampling times in both groups. Clonidine use led to a significant decrease in post-procedure plasma cortisol in comparison to baseline levels. These results show that the hormonal stress response associated with FOB performed with no sedation was of little amount, and that clonidine use had only a minimal influence on it. However, as all bronchoscopies were performed early in the day, our results may have been influenced by the physiological fall of cortisol levels observed over the morning.

Patients of both groups were asked to express their degree of comfort during FOB using a visual numerical scale at the end of the observation period. Both groups reported high median scores of comfort during examination. There was also agreement between patients' subjective evaluation and objective scores given by the examiner at the end

of the procedure. It is also interesting to note that both groups required the same amount of instilled lidocaine for anesthesia and that the results related to comfort agreed, in general, with the plasma cortisol findings. Therefore, the data clearly show that FOB performed without sedation, and under adequate topical anesthesia, can be well tolerated by the patients. Although previous papers have reported similar results, we believe that the initial conversation about the proceedings to be done and the half-hour rest period in a quiet atmosphere must have significantly reduced early psychological tension and stress among our patients.[3,23–25] It has already been shown that a high degree of anxiety before bronchoscopy is correlated with poor tolerance to the exam.[14] In addition, since most of the people attended at our University Hospital are from the low-income population, we may not completely exclude the potential influence of social and cultural factors on patients' answers. It is worth also to emphasize that, all exams were performed by the same highly skilled and experienced physician. Whatever the explanations may be, since FOB was so well tolerated by the placebo group, the administration of clonidine did not add any advantage regarding patient comfort.

In conclusion, the use of IV clonidine as premedication for FOB was well tolerated, and contributed to a somewhat better hemodynamic profile during and after examination. Fiberoptic bronchoscopy performed without sedation, under airway anesthesia only, was well accepted by the patients, and the use of clonidine did not add to comfort in such circumstances. We believe that the present results do not support the routine use of clonidine as a pre-anesthetic drug before FOB.

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