Clonidine in Cineangiocardiography: Sedative Effects on Blood Pressure and Heart Rate

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Objective: To evaluate the effects of clonidine on heart rate (HR), and blood pressure (BP) as well as its sedative effect on patients submitted to a cineangiocardiography.

Methods: A randomized, controlled, double blind, prospective clinical trial was conducted on 62 patients submitted to an elective cineangiocardiography. The patients were divided in two groups: the clonidine group, that were administered a 0.8 μg/kg dose of this drug and the control group, that were administered a 0.9% saline solution. Sedation was evaluated based on the Ramsay Scale and the administration of a 0.04 mg/kg dose of meperidine that was given to the patients who were agitated or anxious during the procedure. The invasive BP, HR and sedation score based on the Ramsay Scale were analyzed every 5 minutes and four different intervals were considered for the assessment: I1- start of the test; I2- 5 minutes after the start of the test; I3- median time of the test and I4- end of the test.

Results: The clonidine group presented better BP and HR stability and sedation efficacy while the control group presented a higher intake of meperidine ($p<0.05$). In the statistical analysis, the inference of the continuous variables was calculated using the Student's t-test or Mann-Whitney test and the χ^2 or Fisher Exact Probability test was used for the categorical variables.

Conclusion: This study demonstrated that clonidine was an efficient means to control BP and HR and provided a conscious sedation for patients submitted to a cineangiocardiography.

Key words: Clonidine, sedation, cineangiocardiography, anesthesia.

The increased incidence of coronary artery disease has accelerated the development of diagnostic and therapeutic protocols, and the coronary angiography is one of the most important tests to define therapeutic decisions[1].

During a coronary angiography, patients are anxious and under emotional stress. This can unleash sympathetic responses leading to tachycardia and hypertension that could be dangerous for a patient suspected of having heart failure[1].

The use of drugs to control sympathetic responses and stabilize the cardiovascular system appears to be beneficial and clonidine has pharmacological characteristics that justify a study in this population[2-8].

The autonomic response of patients suspected of having heart disease is already controlled with beta-blockers whose efficacy is well known[8]. Studies on alfa$_2$-adrenoceptor agonists such as clonidine are ongoing, however, very few studies have been published regarding their use in invasive procedures[5,8].

Studies in reference to sedation for coronary angiography procedures are especially limited and information on the use of alfa$_2$-adrenoceptor agonists during this test is inadequate[2-8]. Therefore, the objective of this study was to evaluate the effects of clonidine on heart rate (HR) and blood pressure (BP) as well as its sedative effect on patients submitted to a coronary angiography.

Methods

After approval by the Research Ethics Committee and the informed consent forms were signed, a randomized, controlled, double blind, prospective clinical trial was conducted.

Before signing the informed consent form the patients were briefed on the hospital's routines and the objectives of this study. They were also informed that clonidine could be used and its possible benefits during the test would be evaluated.

Sixty-two patients from both genders between the ages of 18 and 80 were admitted to the study and were submitted to an elective coronary angiography. All the patients had previously undergone a myocardial scintigraphy or stress test which was positive for ischemia.

Exclusion criteria included patients with unstable angina, a body mass index greater than 35, altered sensory function that would hinder evaluation and a history of allergies to the drugs to be used.

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The parameters used in this study were blood pressure (BP), heart rate (HR) and sedation score in accordance with the Ramsay scale[9] (Tab. 1).

The patients were monitored in the hemodynamic laboratory with a pulse oximeter (Criticare 504DX), a continuous six-lead electrocardiograph and invasive blood pressure measurement through the femoral or brachial artery depending on the approach used in the test (Polígrafo SP12 - TEB™).

All patients had fasted for at least eight hours and did not receive any type of ansiolytic medication.

A number 20 catheter was introduced into the cephalic vein of the left upper limb and a standard infusion of 10 ml/kg/h of 0.9% saline solution was administered.

The patients were randomly divided into two groups using a raffle with sealed envelops and the computer program PEPI (Computer Programs for Epidemiologists by J.H. Abramson and Paul M. Gahlinger. Version 4.04x). The syringes containing the drug were prepared by a researcher that would not evaluate the patients. The clonidine group was administered 0.8 μg/kg of clonidine diluted in 5 ml of distilled water intravenously and the control group received 5 ml of 0.9% saline solution, both with standard syringes.

A femoral artery puncture was chosen for the patients admitted to the hospital and a brachial artery dissection for the out-patients. Afterwards, the patients were monitored with a pulse oximeter and a continuous electrocardiogram and the evaluation was started. HR, BP and sedation were evaluated by the vein injection and every five minutes up until the end of the procedure.

The length of the test varied from 15 to 90 minutes depending on the patient and technical difficulty. Consequently, the creation of an evaluation at specific intervals was required to correct this aspect. Therefore, four intervals were chosen to evaluate the patients' BP, HR and sedation scores: Interval 1 (I1) - the control interval before the intravenous injection; Interval 2 (I2) - five minutes after the drug was injected; Interval 3 (I3) - median time of the test, this was chosen since it occurred halfway through the procedure and Interval 4 (I4) - end of the test.

The complications evaluated were bradycardia and hypotension.

For ethical reasons, 0.04 mg/kg of meperidine was used as a sedative for the patients who remained agitated or anxious ten minutes after the start of the test. The use of this drug was one of the parameters to test the sedative efficacy of clonidine.

After the test was completed the patients were kept under observation for a period of one to four hours with the possibility of an extended hospital stay if the seriousness of the pathology warranted it or if a femoral artery approach had been used as this requires a longer period of imobilization through complete bed rest.

The patients who had the test via the femoral vein were released from the hospital roughly 24 hours after the procedure, as long as the coronary angiography diagnosis permitted it.

The out-patients, who had the brachial artery dissection approach, could be released from the hospital as long as there were no complications during the procedure or there were no severe coronary lesions that justified their admission. These patients were also informed to return to the hospital in the case of any complications.

The results of the continuous variables were presented as mean and median values and the categorical variables as percentages. Inference was calculated using the Student's t-test or the Mann-Whitney test for the continuous variables and the χ^2 or Fisher Exact Probability Test for the categorical variables. An α of 5% was adopted (Type I error).

Results

Gender, age, weight, height and body mass index were similar for the study groups. (Tab. 2).

The six month study was conducted between July and December, 2004.

Variations in HR and BP for the clonidine group patients were lower than the control group patients (Fig. 1).

Statistical analysis of HR between the groups for each interval confirmed that the control group had higher values for I4 than the clonidine group ($p<0.05$), however the other intervals presented no significant differences. Statistical analysis of the differences between the intervals for each group revealed I1=I2=I3=I4 for the clonidine group and I4>(I1=I3)>I2 for the control group (Fig. 1).

Comparison of systolic blood pressure (SBP) between the groups for each interval demonstrated that I1 was similar for both groups; however the control group values for the other three intervals were statistically higher ($p<0.05$) than the clonidine group. Statistical analysis of the differences between the intervals for each group revealed I1>(I2=I3=I4) for the clonidine group and I1>(I2=I3)>I4 for the control group (Fig. 1).

Analysis of diastolic blood pressure (DBP) differences between the groups for each interval revealed that I1 was similar for both groups; however the control group values for I2, I3 and I4 were higher than the clonidine group ($p<0.05$). The differences between the intervals for each group revealed I1>(I2=I3=I4) for the clonidine group and I3>(I1=I2)>I4 for the control group (Fig. 1).

1. Patient anxious, agitated or impatient
2. Patient cooperative, oriented and calm
3. Patient only responds to verbal commands
4. Patient that demonstrates a brisk response to the glabella tap test or auditory stimulus
5. Patient that demonstrates a sluggish response to the glabella tap test or auditory Stimulus
6. Patient that does not respond to the glabella tap or auditory stimulus

Table 1 - Ramsay Scale[9]

In regard to sedative effect, twelve patients in the control group required meperidine versus four patients in the clonidine group ($p<0.05$) (Fig. 2). The sedation scores between the two groups did not present a significant statistical difference (Fig. 3).

In relation to study intervals, the average test time was 25.73 ± 10.45 minutes. Interval 3 which was the median test time was 15.20 ± 10.94 minutes.

No patient presented hypotension that required treatment and only two of the clonidine patients required treatment for bradycardia with atropine 0.01 mg/kg however, no statistical significance was found.

Only three of the patients submitted to this study, one an outpatient, were kept in the hospital due to the severity of the coronary lesions.

Discussion

Clonidine proved to be an effective drug to control BP and HR with a slight sedative effect that is desirable in the hemodynamic laboratory.

The sample size was calculated using the following parameters: error α of 5%, power of 80%, a mean difference between the groups of 16 mmHg for systolic blood pressure, a standard deviation of 20.22 mmHg for the control group and 22.58 mmHg for the test group. Using these parameters a minimum sample size of 30 patients for each group was obtained.

Invasive BP monitoring using the femoral or brachial vein is routine for coronary angiography and is the most dependable method to evaluate blood pressure.

The Ramsay scale was used to evaluate sedation since it has been widely used by various authors and in several anesthesiology and intensive care studies and has proven to be a reliable method to evaluate sedation[9-11].

Since the average test time was 25.73 ± 10.45 minutes, four punctual evaluations during this timeframe were sufficient to consider the majority of the variations that occurred.

The 0.8 μg/kg clonidine dose is lower than that used in medical literature (usually higher than 1μg/kg). Some authors defend that doses, such as the one used in this study, are effective to control of BP and HR[12,13].

In relation to bradycardia and hypotension, that would be the most common complications associated with clonidine, no

	Age* (years old)	Weight* (kg)	Length* (m)	Body Surface* (m^2)	Sex M/F(n)
Clonidine (0.8 μg/kg)	61.07±11.07	67.10±12.09	1.63±7.68	25.01±3.59	17/14
Control (0.9% Saline Solution)	59.50±10.68	67.13±10.72	1.65±9.17	24.4±3.40	18/13
	p>0.50	p>0.10	p>0.50	p>0.10	p>0.50

*There were no significant differences among groups. *Values expressed in averages ± standard deviation*

Table 2 - Antropometrics Data and Gender Distribuition in the Groups

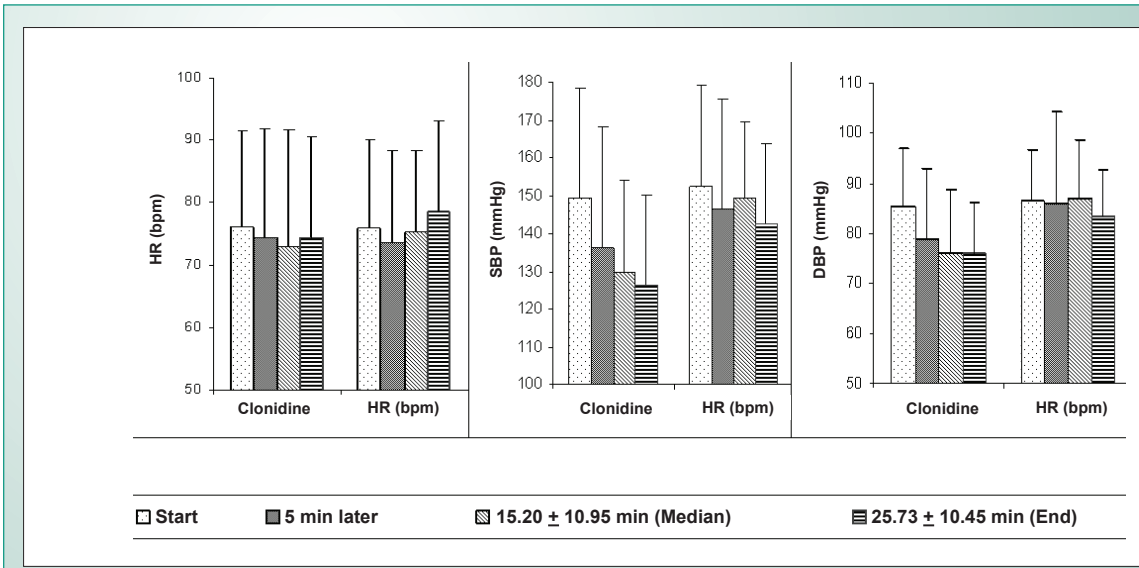

Fig. 1 - *Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) (Averages and Standard Deviations)*

patient presented hypotension and only two patients presented bradycardia, however, without statistical significance.

In relation to HR and BP behavior, variations in the averages and standard deviations for the clonidine group were lower (Fig. 1). Likewise, both systolic and diastolic blood pressures presented a progressive reduction in the clonidine group while the values for the control group remained at higher levels with greater variations between the intervals.

It was important to have a control interval (I1) since it validated the similarity of the groups before the interference of the researcher. All the parameters evaluated were similar between the two groups, without any significant statistical difference (p>0.05).

I2 led us to believe that the intravenous administration of clonidine would have an immediate effect. Comparison of the two groups during this interval revealed a significant statistical difference for blood pressure (p<0.05) (Fig. 1).

I3 presented a statistical difference for BP between the two groups (p<0.05). The clonidine group had lower HR values, however without any statistical significance (p>0.05) (Fig. 1)

I4 presented statistical differences (p<0.05) between the groups for both BP and HR (Fig. 1).

A point that should be emphasized is the importance of the reduced oxygen consumption by the myocardium in patients with coronary artery disease. As the heart rate and blood pressure levels increase in these patients, the harder the heart must work and the higher the risk of ischemia[1].

Obviously as long as the HR and BP values remain within the physiological limits this is important, since if there was hypotension the ischemia risk could occur. Since no patient in this group presented hypotension it is assumed that the clonidine dose used was satisfactory.

Some authors refer to the potential of alfa$_2$-adrenoceptor agonists, such as clonidine, to reduce cardiovascular morbidity[14,15]. This point is still controversial and requires more studies with reliable methods and a larger number of patients to reach more concrete conclusions.

There is no consensus in medical literature regarding the sedation of patients in the hemodynamic laboratory, however, some authors have related that patient cooperation during the exam is essential and question whether sedation would diminish patient responsiveness and jeopardize the procedure[16].

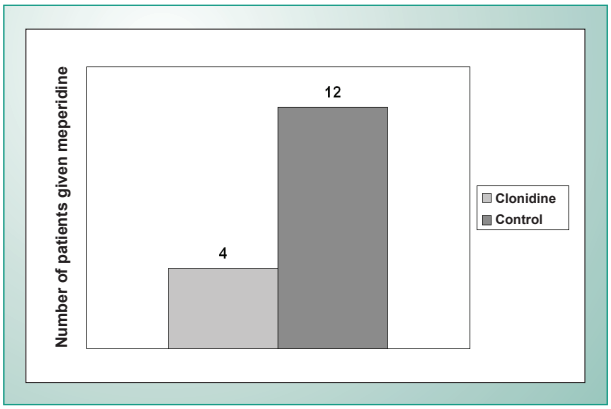

Fig. 2 - *Meperidine Administered During Sedation*

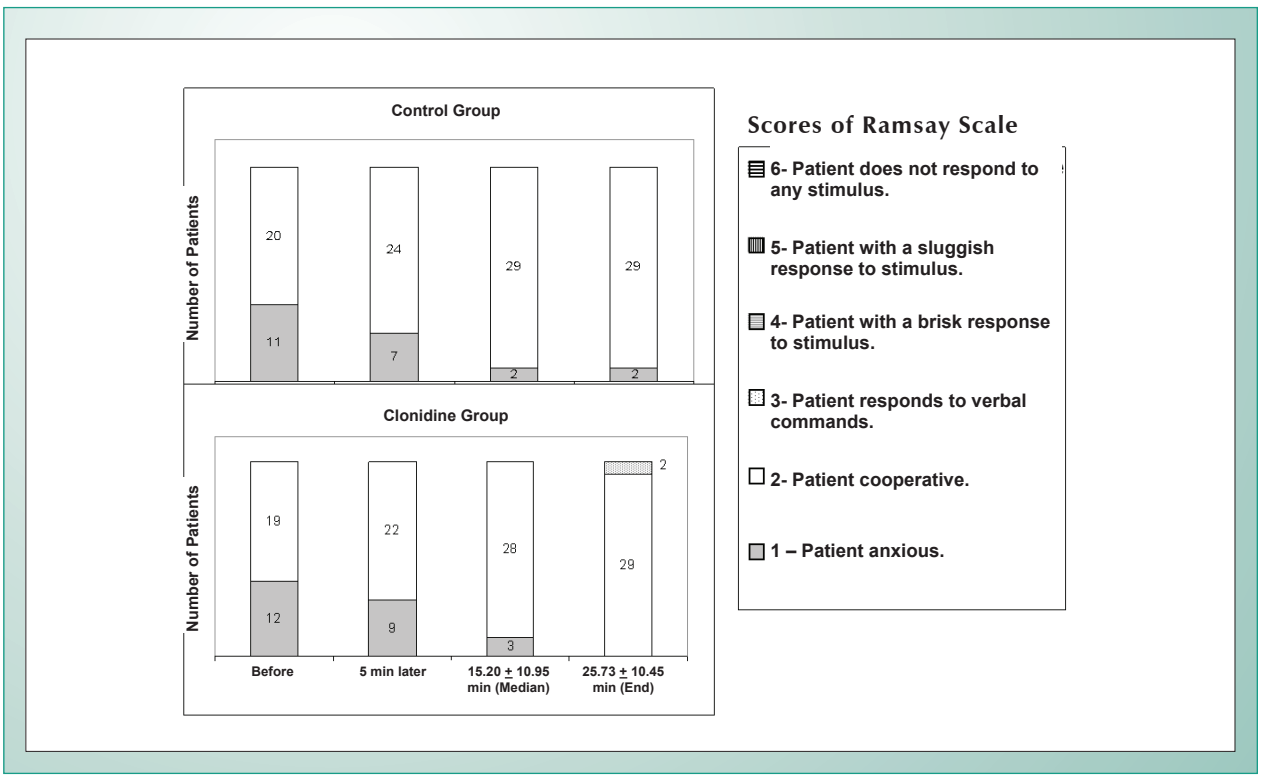

Fig. 3 - *Sedation Scores According to the Ramsay Scale*

This aspect could be contested by the conscious sedation technique. Conscious sedation is defined as the pharmacological state of conscious depression that enables the maintenance of protective reflexes. Even though the patient is sedated, she is alert enough to respond correctly to physical stimulation or verbal orders. During conscious sedation the patient is able to maintain a patent airway without help or stimulation[16,17].

The sedative effect of clonidine is directly related to the dosage. The site of action is the *locus ceruleus*, a small neuron nucleus located in the upper part of the brain stem. This effect has been described by various authors and it is important to emphasize that the sedative effect is not a consequence of hypotension or any cardiovascular effect[12,18].

For ethical reasons a sedation option was required for the patients that remained anxious during the procedure and because of this meperidine was selected. This drug is widely used for sedation in various procedures and was also an evaluation parameter for sedation effectiveness[19,20].

It could be said that the use of meperidine hindered the sedation evaluation in the patients; however it was only used for 38% (12 patients) of the control group and 12% (4 patients) of the clonidine group (Fig. 2). For sure this was the reason why there was no significant statistical difference between Ramsay scale scores of the two groups (Fig. 3). However, considering only the anxious patients that used meperidine, the control group presents a difference ($p < 0.05$) in relation to the clonidine group.

Without a doubt, lowering the anxiety levels had an influence on the progressive reduction of the parameters evaluated. This was observed with the control group, but the clonidine group presented a more intense and progressive reduction than the control group. This suggests that the drug had an influence on the cardiovascular and sedative data, since the sedative effect started later than the cardiovascular effects (Figs. 1 and 3).

This dissociation between the sedative and cardiovascular effect of clonidine has already been documented. However, the studies relate that the effects of clonidine begin roughly 10 to 15 minutes after injection in the vein. In this study we found evidence that within 5 minutes it had influenced at least BP.

In Brazil there are very few studies regarding sedation for coronary angiography procedures. It is our hope that this study will help to increase the methodological information available and improve the care for patients with coronary risk.

From a practical view point, we have raised the issue of improving medical care for patients who are submitted to a coronary angiography. Currently there is absolutely no consensus as to whether or not these patients should be sedated[16]. In this study we have demonstrated the benefits of controlling BP and HR and that the procedure was not technically jeopardized, since even though the patients were sedated they remained cooperative.

In the future we plan to compare clonidine with benzodiazepines, which have been documented in medical literature for this procedure; however no comparisons have yet been made[16].

The scope of this study did not include the evaluation of coronary angiography morbidity and mortality rates associated with sedation. We evaluated the complications associated with the use of clonidine during this procedure which were hypotension and bradycardia; however no statistical significance was found.

Therefore, this study demonstrated that for patients submitted to a coronary angiography, clonidine is an efficient means to control BP and HR and offers a conscious sedation that is desirable for this type of procedure.

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References

1. Chassot PG, Delabays A, Spahn DR. Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery. Br J Anaesth 2002; 89(5):747-59.
2. Ambrose C, Sale S, Howells R, et al. Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability. Br J Anaesth 2000; 84(6): 794-6.
3. Ellis JE, Drijvers G, Pedlow S, et al. Premedication with oral and transdermical clonidine provides safe and efficacious postoperative sympatholisys. Anesth Analg 1994; 79: 1133-40.
4. Stevens RD, Burri H, Tramèr MR. Pharmacologic Myocardial Protection in Patients Undergoing Noncardiac Surgery: A Quantitative Systematic Review. Anesth Analg 2003, 97(3): 623-33.
5. Talke P. Pharmacodynamics of alpha2-adrenoceptor agonists. In: Alpha2-adrenoceptor agonists in Anaesthesia and Intensive Care. Baillieres Clin Anaesthesiol 2000; 14(2),271-83.
6. Taittonen MT, Kirvella OA, Aantaa R, Kanto J. Cardiovascular and metabolic responses to clonidine and midazolam premedication. Euro J Anest 1997; 14(2): 190-6.
7. Taittonen MT, Kirvella OA, Aantaa R, Kanto J. The effect of clonidine or midazolam premedication on perioperative responses during ketamine anesthesia. Anest Analg 1998; 87(1): 161-7.
8. Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. Am J Med 2003; 114(9): 742-52.
9. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974; 2: 656-9.
10. De Jonghe B, Cook D, Appere-De-Vecchi C, et al. Using and understanding sedation scoring systems: a systematic review. Intensive Care Med 2000; 26(3):275-85.
11. Watson BD, Kane-Gill SL. Sedation assessment in critically ill adults: 2001-2004 update. Ann Pharmacother 2004; 38(11): 1898-906.
12. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidina infusion in humans; Br J Anaesth 2001; 86(1): 5-11.
13. Bergendahl HTG, Eksborg S, Lönnqvist PA. Low-dose intravenous clonidine in children: plasma concentrations and haemodinamic response. Acta

Anaesthesiol Scand 1997; 41(3):381-4.

14. Nishina K, Mikawa K, Uesugi T, et al. Efficacy of clonidine for prevention of perioperative miocardical ischemia: A critical appraisal and meta-analysis of the literature. Anesthesiology 2002; 96(2): 323-9.

15. Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. Am J Med 2003; 114(9): 742-52.

16. Baris S, Karakaya D, Aykent R, Kirdar K, Sagkan O, Tur A. Comparison of midazolam with or without fentanyl for conscious sedation and hemodynamics in coronary angiography. Can J Cardiol 2001; 17(3): 277-81.

17. Hall SC. Practical solutions for difficult problems I – Pediatric anesthesia outside the operation room. Anesthesiology Clinics of North America 1996; 14(2): 385-405.

18. Stermer E, Gaitini L, Yudashkin M, et al. Patient-controlled analgesia for conscious sedation during colonoscopy: a randomized controlled study. Gastrointestinal Endoscopy 2000; 51(3):278-81.

19. Marriott P, Laasch H-U, Wilbraham L, et al. Conscious sedation for endoscopic and non-endoscopic interventional gastrointestinal procedures: meeting patients' expectations, missing the standard. Clin Radiol 2004; 59(2):180-5.

20. Quintin L, Ghignone M. Risk associated with perioperative use of alpha2-adrenoceptor agonists. In: Alpha2-adrenoceptor agonists in anaesthesia and Intensive Care. Balières Clin Anaesthesiol 2000; 14(2): 349-68.