Epidural anesthesia with ropivacaine with or without clonidine and postoperative pain in hemorrhoidectomies[1]

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ABSTRACT

PURPOSE: To determine the safety, pain intensity correlated with age and body mass index (BMI), epidural anesthesia with ropivacaine and clonidine in hemorrhoidectomy.

METHODS: Eighty patients, both genders, 20-70 years old, ASA I or II, for hemorrhoidectomy were randomly divided into two groups: Control (n=38), epidural anesthesia with 14 mL of ropivacaine 0.75 % plus 0.0266 mL/kg of 0.9% saline solution; Experimental (n=42) epidural anesthesia with 14 mL of 0.75% ropivacaine plus 4.0 mcg/kg of clonidine. In preoperative and postoperative period were evaluated: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), pulse oximetry (SpO_2), electrocardiography (ECG), pain intensity (VAS) in four, eight and, 12 hours and analgesic consumption .

RESULTS: The VAS values differed between four, eight and 12 hours in the Experimental Group, where correlation of VAS 12h with age ($p<0.05$) occurred and not with BMI and more patients ($p<0.05$) did not receive analgesics. SBP, DBP, HR changed similarly in both groups at 15, 30 and 45 min. The ECG and SpO_2 remained unchanged.

CONCLUSIONS: Clonidine (4mcg/kg) in epidural anesthesia with ropivacaine 0.75% in hemorrhoidectomy showed safety and greater analgesia within four hours. The pain at 12 hours showed correlation with age and not with body mass index.

Key words: Anesthesia, Epidural. Anesthetics, Local. Clonidine. Hemorrhoidectomy.

Introduction

Pain after hemorrhoidectomy is relevant. For this reason, many patients postpone the surgery, despite the pronounced symptoms of hemorrhoids. Delaying surgery can be harmful, as the disease may progress to more severe forms. The intensity and frequency of postoperative pain may vary among patients and the search for new therapeutic resources for the relief of pain remains a challenge to be met.

In Brazil, the use of techniques of epidural and spinal anesthesia are almost routine in hemorrhoids surgery, together with local anesthetics, with or without the addition of adjuvants. Security, implementation easiness, quality of anesthesia and postoperative analgesia and cost are favorable factors to its use.

Ropivacaine is a local anesthetic of the amide type with anesthetic and analgesic effects of long duration. As occurs with other local anesthetics, it reversibly blocks the impulse propagation through nerve fibers, preventing the entry of sodium ions through the cell membrane.

Adjuvants are the drugs that, added to local anesthetics, enhance or prolong their action. The most commonly used, in descending order, are the opioids (morphine, fentanyl, sulfentanyl, methadone), $\alpha 2$ adrenergic agonists (clonidine and dexmedetomidine), ketamine and neostigmine.

The addition of adjuvants causes a reduction in the dose of local anesthetic and minimizes the hemodynamic and neurological effects[1].

Pharmacologically clonidine (N- (2,6-dichlorophenyl) -4,5 -dihydro- 1H -imidazol- 2-amine) is an $\alpha 2$ adrenergic agonist has affinity with imidazole, due to the presence of an imidazole radical in its molecular structure[2]. Its systemic effects include sedation, hypotension (antihypertensive acting centrally) and bradycardia[3]. It has several applications in anesthesiology, such as premedication, adjunct to anesthesia in ophthalmology and cardiac surgery, postoperative analgesia associated with local anesthetic and sedation and analgesia in pediatric anesthesia.[4]

This study aimed to verify the effect of a dose of 4 mcg/kg of clonidine added to ropivacaine 0.75% for epidural anesthesia for operations on hemorrhoids in following cases: 1 - postoperative analgesia, 2 – pressure and heart rate alterations, 3 - correlation between the doses used, the age and body mass index (BMI).

Methods

After approval by the Ethics Committee of the Federal University of Minas Gerais, (COEP/UFMG - ETIC 001/2008), participated in the study 80 patients of both genders, aged from 20 to 70 years, physical status I or II according to the classification of the American Society of Anesthesiologists (ASA), who were submitted to hemorrhoidectomy under epidural anesthesia (Tables 1 and 2).

TABLE 1 - Characterization of the sample according to the groups, according to the gender.

Gen	Groups				P-value
	Control		Experiment		
	N	%	N	%	
Female	26	68.4	24	57.1	0.417
Male	12	31.6	18	42.9	
Total	**38**	**100.0**	**42**	**100.0**	**-**

Numbers of individuals (n) and p value percentage (%)

TABLE 2 - Sample characterization per groups, according to the mean and standard deviation (in parenthesis) of age, height, weight, BMI and time of surgery.

Groups	Age (Years)	Height (CM)	Weight (Kg)	BMI (Kg/m2)	Time Surgery (min)
Control	46.92 (9.66)	163,87 (11.38)	64.59 (10.43)	23.93 (3.16)	25.92 (6.71)
Experiment	47.45 (5.70)	167.74 (7.89)	67.14 (11.50)	23.84 (5.70)	25.83 (5.70)
P	0.692	-	-	0.427	0.809

BMI = Body Mass Index; in parentheses = standard deviation

Routine preoperative tests were performed by the surgical and anesthetic team plus the complementary tests needed by the patient. As premedication 7.5 of sublingual midazolam was used one hour before the surgery.

In the operating room, venous puncture was performed with 18G or 16G intravenous catheter in a vein in the upper limb and the infusion of Ringer's lactate solution (500 mL) was done. Monitoring consisted of electrocardiogram (ECG), verification of heart rate (HR), pulse oximetry (SpO_2), measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) using an automatic noninvasive method.

Patients were randomized into two groups in a blinded study. In the Control Group, 38 patients underwent epidural anesthesia with 14 mL (104.5 mg) of 0.75% ropivacaine (Cristalia Chemicals and Pharmaceuticals Ltd., Sao Paulo), plus 0.0266 mL/kg of solution 0.9% saline. In the Experimental Group, 42 patients underwent epidural anesthesia with 14 mL (104.5 mg) of 0.75% ropivacaine (Cristalia Chemicals and Pharmaceuticals

Ltd., Sao Paulo) plus 4.0 mcg/kg of clonidine (Cristalia Chemicals and Pharmaceuticals Ltd., Sao Paulo), equivalent to 0.0266 mL/kg of solution. Epidural puncture was performed with 15G Tuohy needle at the L3 - L4 interspace, with the patient seated. The drugs were injected into the epidural space at the speed of 1 mL/s.

The surgical technique used was a semi-closed hemorrhoidectomy Milligan-Morgan. The suture type used was simple running suture with 3-0 catgut chrome wire needled.

In the preoperative and postoperative period were evaluated: systolic and diastolic blood pressure, heart rate, respiratory rate, peripheral O_2 saturation (pulse oximeter) and ECG in leads V5 and D2. Ephedrine was used at a dose of 20 mg when systolic blood pressure fell below 20% of the initial value. After completion of the surgery patients received intravenously 100 mg ketoprofen and dipyrone 1g.

The intensity of postoperative pain was assessed with the aid of a visual analogue scale (VAS) in which 0 (zero) corresponds to no pain and ten (10) to a maximum intensity pain (unbearable). The severity of pain was measured 4h, 8h and 12h after the beginning of anesthesia or between these intervals, as needed, or in addition, if the patient remained hospitalized for any reason. This assessment was performed by a physician who did not know to which group the patient belonged. We calculated the analgesic consumption during the first 12 hours, or more when the patient had to stay in the hospital. The degree of patient satisfaction and postoperative complications were recorded.

To measure the association degree between two metrics the correlation coefficient was used. Test for normality (Shapiro-Wilk) was used in the variables in each group. As the variables were not normally distributed in this study, we used the Spearman correlation coefficient (non-parametric). To the intersection of the variables according to the groups we used the Mann-Whitney test. To the intersection of VAS scores between the moments in each of the groups, the nonparametric Friedman was used. The hypothesis to be tested is that the VAS does not differ between moments. When the p - value is significant (<0.050) this hypothesis is rejected, i.e., there is a difference between the moments.

Results

The values in Tables 1 and 2 show the similarity between the experiment and control groups, the gender distribution of patients, the values of age, height, weight, BMI and duration of surgery.

There was a statistically significant difference in the VAS, between the Control and the Experiment groups, in the moment of 4h. In the moments between 8h and 12h there was no statistically significant difference between groups (Table 3).

TABLE 3 - Results of comparisons of the Visual Analogue Scale (VAS) between times, and control groups in Experiment.

Groups	VAS 4h	VAS 8h	VAS 12h	P
Control	2.53 (2.77)	3.61 (3.63)	2.87 (2.26)	0.139
Experiment	0.69 (1.28)	2.02 (2.03)	2.76 (2.77)	0.000

VAS= Visual Analogue Scale; in parentheses = standard deviation

There was no significant correlation between VAS and age in the control group.

The Experimental Group was found statistically significant in the correlation of VAS 12 h with age (correlation coefficient = -0.407, $p < 0.05$). This coefficient is negative, i.e., as age increases the VAS score decreases and reaches 12 h (Table 4, Figure 1).

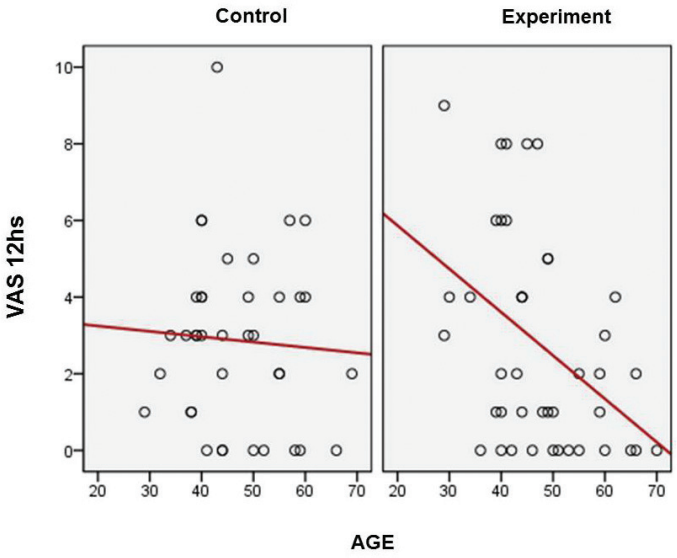

FIGURE 1 - Correlation between age and VAS 12h and control groups in Experiment.

TABLE 4 - Results of comparisons of VAS with age, between moments, in experiment and control groups.

AGE	VAS 4h		VAS 8h		VAS 12h	
	Coefficient OF correlation	P-value	Coefficient OF correlation	P-value	Coefficient OF correlation	P-value
Control	0.220	0.184	0.140	0.401	-0.025	0.881
Experiment	-0.030	0.849	-0,213	0.176	-0,407 *	0.007â§

VAS = visual analog Scale; * significant Coefficient. Spearman Correlation; â§ = (p<0.05)

TABLE 5 - Correlation of VAS with BMI.

BMI	VAS 4h		VAS 8h		VAS 12h	
	Coefficient OF correlation	P-value	Coefficient OF correlation	P-value	Coefficient OF correlation	P-value
Control	-0.009	0.958	-0.046	0.784	-0.162	0.332
Experiment	0.082	0.604	-0.099	0.534	-0.122	0.440

VAS = Visual Analog Scale; BMI = Body Mass Index

There was no correlation of VAS with BMI (Table 5).

There was statistically significant difference ($p<0.05$) only with patients who received no analgesic solution in the Experiment Group, when there are a higher percentage of these individuals. The need to repeat the analgesic solution was also lower in the Experimental Group, however without being statistically significant (Table 6).

TABLE 6 - Number and percentage of individuals who have not received or received analgesic solution by request.

Analgesic Solution	Groups				P-value
	Control		Experiment		
	N	%	N	%	
None	8	21.1	19	45.2	0.041 *
With solution	19	50.0	18	42.9	0.680
Repeated solution	11	28.9	5	11.89	0.105
Total	**38**	**100.0**	**42**	**100.0**	**-**

None = did not receive analgesic solution; With solution = received analgesic solution; Repeated solution = received the analgesic solution more than once; n= number of individuals, % = Percentage of individuals; * = statistically significant difference

There was no statistically significant difference between the moments in the two groups. It can be said that the initial moment differs from all others because of its higher values. No statistically significant difference was noted from 15 min onwards (Table 7).

TABLE 7 - Mean and standard deviation of systolic blood pressure between groups and times.

Groups	Home	15 Min.	30 Min.	45 Min.	P-value
Control	126.79 (15.25)	116.39 (19.28)	119.16 (14.20)	122.18 (12.10)	0.00
Experiment	121.86 (11.58)	114.60 (17.25)	116.52 (11.86)	118.60 (10.38)	0.00

Average = average of the values of the moment; standard Deviation = standard deviation of the values of the time (in parentheses); p-value

There was no statistically significant difference between the moments of the two groups, which differs from the initial moment for all others for presenting higher values. No statistically significant difference from 15 min onwards (Table 8).

TABLE 8 - Mean and standard deviation of diastolic blood pressure between groups and surgery times.

Groups	Home	15 Min.	30 Min.	45 Min.	P-value
Control	77.11 (12.22)	70.16 (15.29)	72.16 (11.22)	74.08 (11.10)	0.00
Experiment	76.14 (11.71)	68.93 (15.10)	70.21 (11.03)	71.67 (11.14)	0.00

Average = average of the values of the moment; standard Deviation = standard deviation of the values of the time (in parentheses); p-value

There was no statistically significant difference between the initial times in the two groups; however a decrease in HR from baseline to the other moments was noted. There was no statistically significant difference between the times of 15, 30 and 45 min within the same group. Statistically significant values were noted in the heart rate, in the times of 15, 30 and 45 min, between the experiment and control groups (Table 9).

TABLE 9 - Mean and standard deviation of Heart Rate between groups and times.

Groups	Home	15 Min.	30 Min.	45 Min.	P-value
Control	77.71 (11.50)	70.74 (11.16)	69.53 (9.11)	69.00 (8.50)	0.00
Experiment	78.00 (10.34)	62.07 (5.89)	60.67 (4.43)	60.69 (3.97)	0.00

Average = average of the values of the moment; standard Deviation = standard deviation of the values of the time (in parentheses); p-value

No significant changes were identified in the electrocardiographic trace and in the values of oxygen saturation in the patients of both groups.

Discussion

Considering that pain, as a postoperative complication, aside from physical suffering, causes organic and functional disorders, it is very important to evaluate the techniques and/or the

anesthetic drugs administered before, during and after the surgery aiming at minimizing its occurrence.

The main factors affecting the intensity and the pain control after a hemorrhoidectomy are: the surgical technique, the material used in surgery, painkillers and anesthetic technique used. The internal anal spasm is considered the biggest factor of the source of that pain[5]. In this study the surgical technique, the material used in surgery and medications used to control postoperative pain were similar in both groups. Considering also that there was no difference between age, gender, BMI, duration of surgery between the two groups, a distinct effect between the two groups could be attributed to clonidine that was used in the Experimental Group.

About the efficacy of clonidine, it is important to state that this drug has clinically significant analgesic properties[6-8], and is advantageous for anesthesiology and it reduces opioid consumption during the perioperative period[8,9] and prolongs the effect of anesthesia performed with epidural lidocaine[10], bupivacaine and[11,12] ropivacaine[13].

Currently, clonidine and dexmedetomidine are $\alpha 2$ - agonists released for spinal cord administration, since they have not shown evidence of neurotoxicity in animal models[14-17]. They can be used in this way for the purpose of analgesic synergism both as local anesthetics with opioids[10,17,18] pre and postoperatively. The intensity of analgesia with this route is correlated with CSF concentrations of the drug, since the degree of sedation is proportional to the serum concentration[19]. Plasma concentration peak was observed at about 30 minutes, and their average time of action was of approximately 13 hours.

In the present work, a clonidine dose of 4.0 mcg/kg associated with 14 mL of ropivacaine in epidural analgesia produced more effective results than saline within 4 hours of application. In other periods, i.e. at 8 and 12 hours, the analgesic difference was not significant. In this regard it should be emphasized that the duration of clonidine analgesia is from 3 to 6 hours, continuous infusion being necessary in case of a long duration analgesia[20,21].

The duration of analgesia is in agreement with the report of Eisenach *et al*.[22,23] which foresees an average analgesia duration of 3 to 5 hours, with doses ranging from 145 to 800 mcg, with the use of epidural clonidine.

Moreover, the number of patients in the Experiment Group who did not receive analgesic solution postoperatively was higher than in the Control Group, with statistically significant difference ($p = 0.041$), demonstrating that the addition of clonidine provided better postoperative analgesia than saline within 4 hours after the surgery. Although there was no statistically significant difference in subsequent periods, the need for repetition of the analgesic solution was higher in the control group individuals.

In hemorrhoidectomy, using sacral epidural anesthesia, clonidine added to a mixture of bupivacaine, lidocaine and epinephrine prolonged the time to analgesic request compared with the technique that used saline (placebo). The bradycardia occurred in seven of 32 patients in the group that used clonidine, but there were no changes in the average blood pressure[24].

In proctologic surgery, including haemorrhoidectomy, clonidine with lidocaine and fentanyl in spinal anesthesia, prolonged the effects of analgesia and decreased pain intensity with minimum adverse effects[24].

Alves and Braz, in a study on the addition of 300 mcg clonidine associated with ropivacaine for epidural anesthesia, showed that there was a decrease in latency but a prolonged duration of analgesia and motor blockade. The study also showed a significant difference between the two groups in the evaluation of VAS in the post-anesthesia recovery room[13]. In the present study, the values of VAS were lower than those obtained by Alves and Braz[13], probably due to the use of a standard dose of ketoprofen and analgesic dipyrone soon after the surgery.

In epidural anesthesia for surgery of the lower abdomen, clonidine and ropivacaine improved postoperative analgesia[13,25].

In a previous study[26] it was found that clonidine, at a dose of 50 mcg, was used to decrease postoperative pain associated with bupivacaine in spinal anesthesia and at a dose of 150 mcg, combined with ropivacaine in epidural anesthesia for hemorrhoidectomy. The addition of 150 mcg clonidine to ropivacaine for epidural anesthesia did not improve the postoperative analgesia. This study concluded that the group of patients who received clonidine in spinal anesthesia showed less pain after the surgery[26].

Tamsen and Gordh were the first to report the use of epidural clonidine in two patients with neurogenic intractable pain[27].

Thus it is clear that the addition of clonidine to local anesthetics, either being subarachnoid or epidural, has analgesic effects.

The dose of 4.0 mcg/kg clonidine, used in this study, is in accordance with the literature. Thus, doses of clonidine, for postoperative epidural analgesia, varied in several studies from 2 to 8 mcg/kg in bolus injection and 0.5 to 40 mcg/h for continuous infusion[28]. Single shot doses ranged from 75 to 800 mcg[29]. In a meta-analysis to assess the efficacy of epidural clonidine, the authors found the use of bolus doses ranging from 75-800 mcg and doses from 1 to 8 mcg/kg when calculated by weight of the patient[30].Doses over 5 mcg/kg present hemodynamic instability[20].

Eisenach *et al*.[22], performing a comparative study of 12 works by several authors, showing the average time of analgesia provided by clonidine as being, 2.7h (mean dose 160 mcg), 6h (at a mean dose of 375 mcg) and 5.1h (mean dose 597 mcg).

Thus, higher doses have no advantages over the duration of postoperative analgesia[22].

Drugs injected into the epidural space have its effects proportional to the doses used. With clonidine the main adverse effects are sedation and hemodynamic changes (hypotension and bradycardia). In this study it was decided to use the addition of 4 mcg/kg of clonidine (0.0266 mL/kg), considered an intermediate dose, at the same volume (14 mL) of 0.75% ropivacaine for epidural anesthesia in the patients of the Experimental Group. Doses used for the Experimental Group ranged from 168 to 368 mcg of clonidine, based on the weight of the patient. Clonidine doses used in this study for epidural anesthesia were approximately the double used in a previous study[26].

When the VAS correlates with age, it is observed that elderly patients had lower pain intensity. Elderly patients have anatomical and physiological changes that influence the epidural anesthesia. An increased sensitivity to local anesthetics can be attributed to the lower number of myelinated dorsal and ventral roots and increased permeability is caused by deterioration of the myelin sheath. A greater longitudinal dispersion of local anesthetics, epidural space, is promoted by the MS and the calcification of the intervertebral foramen and adipose tissue reduction[29,30]. In this study, the use of a standard volume and doses for epidural blocking may have caused higher doses than necessary to age, in the case of elderly patients[31]. Similarly, the use of a standard dose of analgesics (100 mg ketoprofen and dipyrone 1g intravenously) and drugs used in epidural anesthesia (ropivacaine with or without clonidine) may have caused higher doses equivalent to age, leading to a better analgesia (lowest VAS) for older patients as shown in Table 4.

The correlation of VAS with BMI shows no significant difference. Note that obese patients require lower doses of local anesthetic in the epidural and spinal blocks, than non-obese patients, to obtain the same level of anesthesia[32]. One study showed a higher cephalad spread of epidural anesthesia, performed in L3 - 4 with 20 mL of 0.75% bupivacaine in obese patients compared to non-obese[33]. Despite the apparent reduced need for anesthetic dose be justified by lower CSF volume in obese patients[34] its importance in blocking epidural anesthesia is not clear yet[35].

About the safety of clonidine, it should be remembered that this drug produces a reduction in blood pressure by inhibiting sympathetic spinal preganglionic[36,37]. The intensity of hypotension seems to be correlated with the level of epidural injection and the dose of the drug used. Hypotension is most important when clonidine is administered in the thoracic segments to be closer to the sympathetic pre-ganglion neurons[38,39]. In addition, activation of alpha-2 receptors ($\alpha 2$) postsynaptic brainstem and receptor $\alpha 2$ presynaptic peripheral contribute to further reduce blood pressure by reducing sympathetic activity. Likewise, high doses of intrathecal clonidine were more frequently associated with systemic hypotension, probably because they facilitate the dispersion of the drug into the rostral thoracic levels and into the brainstem[40].

Alves and Braz have observed a small proportion of hypotension and similar occurrences when comparing groups that received epidural anesthesia with ropivacaine and ropivacaine with clonidine, but found a higher incidence of bradycardia and sedation, with statistically significant difference in the group that received the addition of clonidine[13].

In the present study the values of SBP and DBP were lower in both groups 15 minutes after the epidural block, so there is no difference between the experimental group and the control period in the period under review. In addition, the HR values at baseline were similar in both groups and showed a decrease statistically significant from baseline for times of 15, 30 and 45 minutes in both groups, with lower values in the Experimental Group.

Sedation provided by premedication was satisfactory for the procedures not requiring the completion of sedation during epidural block and surgery.

Concluding, it is worthwhile to mention that no technical difficulties, need for anesthetic supplementation or change of anesthetic technique or complications occurred during the anesthesia process of both groups at the occasion of the hemorrhoids surgeries undertaken.

Further studies are needed to test new safe doses of clonidine in epidural anesthesia, to assess the comparison of clonidine with other drugs that may be associated with ropivacaine for epidural block, having as objective to test the efficacy and safety of these new drugs and new doses.

Conclusions

The addition of clonidine, at a dose of 4 mcg/kg of body weight in epidural anesthesia with 0.75% ropivacaine for hemorroidectomy showed: 1- Higher analgesic effectiveness in the first four hours, when the VAS was lower than that of the group that did not use clonidine. Moreover, in the clonidine group there was less need for postoperative analgesia; 2- Maintenance of arterial pressure and heart rate were similar to the group that did not use

clonidine; 3- Lower values of VAS at 12 hours, with increasing of age, in patients receiving clonidine associated with ropivacaine were noted; 4 - There was no correlation of VAS with BMI.

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Received: Nov 20, 2013
Review: Jan 21, 2014
Accepted: Feb 19, 2014
Conflict of interest: none
Financial source: Espirito Santo Institute for Sustainable Development

[1]Research performed at University Hospital Cassiano Antonio de Morais (HUCAM), Federal University of Espirito Santo (UFES), Vitoria-ES, Brazil. Part of PhD degree thesis, Postgraduate Program in Ophthalmological Surgical and Applied Sciences, Minas Gerais Federal University (UFMG). Tutor: Renato Santiago Gomez.