Effect of clonidine on heart rate variability during spinal anesthesia: randomized clinical trial

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Abstract

Introduction:All anesthetic techniques act, in some way, in the Autonomic Nervous System. In spinal anesthesia this effect is well described. The administration of local anesthetics in the subarachnoid space produces sensitive and sympathetic motor block, however, with latencies and variable and independent block levels. Adjuvants administered in association with local anesthetics have the potential to prolong the duration of spinal anesthesia, increasing the incidence of side effects. The recovery of spinal anesthesia is based solely on the return of motor function and does not take into account the recovery of Autonomic Nervous System activity.

Objective:To analyze the autonomic modulation of heart rate in patients undergoing surgical procedures under spinal anesthesia at the moment of recovery of motor function and to compare the autonomic function in patients who received bupivacaine in subarachnoid anesthesia with patients who recover bupivacaine associated with clonidine.

Method:randomized, double-blind clinical trial. The sample consisted initially of 71 patients ASA I to III, submitted to surgery under spinal anesthesia. Patients were divided into 2 groups. Group B received only bupivacaine and group C received bupivacaine with clonidine. The Heart Rate Variability was evaluated during 10 min in three moments: (T1) rest, before the anesthesia; (T2) 20 min after the installation of the anesthetic block, and (T3) at the time of recovery of motor function. Linear methods, frequency domain and non-linear methods in the Chaos domain were used.

Results:The approximate entropy in the clonidine group showed a elevation, which may suggest a protective effect on the cardiovascular system of the addition of clonidine in spinal anesthesia.

Conclusion:The approximate entropy values at the moment of recovery of motor function in patients receiving spinal anesthesia with bupivacaine and clonidine present a reduction when compared to the values obtained at rest. This data suggests that motor and autonomic block recovery occurs at different times when clonidine is used in spinal anesthesia. This data brings a question about the safety of the discharge criteria of the post anesthetic recovery room using only the return of the motor function after spinal anesthesia.

Background

Subarachnoid anesthesia or spinal anesthesia consists in the administration of local anesthetics in the intrathecal space, blocking nerve conduction through the spinal cord of the peripheral nociceptors to the encephalon. It is a relatively easy and inexpensive technique, associated with few complications, and is widely used throughout the world, in the most diverse scenarios [1]. It is well indicated in infraumbilical procedures. In obstetric and traumatological surgeries of lower limbs is the first choice [2].

Local anesthetics have selective affinity for each type of nerve fiber, the so-called differential block. The fibers of the sympathetic nervous system are more sensitive, being blocked by smaller concentrations of local anesthetic, followed by the sensory fibers responsible for the conduction of pain, touch and, finally, motor fibers [3].

Blockade of the efferent fibers of the sympathetic nervous system is responsible for the main complications resulting from spinal anesthesia, and the incidence of bradycardia and hypotension related to the height reached by the blockade. Levels above T4 are strongly associated with these complications. The blocking time is different for each type of nerve fiber, and the sensory blockage reaches two dermatomes above the motor block and the sympathetic block can reach up to six

dermatomes above the sensory. It is assumed that the sympathetic block, to be initiated first, also ceases its effects before the sensory and motor blocks, accepting a similar duration of action of the local anesthetic in all the nerve fibers [2,3].

Over the years, several substances have been added to the arsenal of drugs that can be administered as adjuvants in spinal anesthesia [3]. Clonidine has been highlighted by interacting with local anesthetics, increasing the duration of anesthesia and allowing the reduction of doses [4]. It acts by interrupting the conduction of pain by blocking the fibers C and Aδ, increasing the influx of potassium [5]. However, the ideal dose has not yet been defined in the current literature, using doses of 15 mcg up to 500 mcg via the spinal route [4,5].

The evaluation of heart rate variability (HRV) through electrocardiogram (ECG) or cardiofrequency meter is a validated technique used to evaluate the overall functioning of the autonomic nervous system and its sympathetic and parasympathetic components. Most of the published works use linear methods, however, in the last decade, new methods, based on Chaos Theory have emerged that are proving to be promising and better representing the complexity of the interactions that occur in organic systems. Wagner et al (1998), in an important review, found data indicating that the autonomic control is performed through innumerable complex interactions and not yet fully understood, concluding that the non-linear methods in the domain of chaos can reflect with better trust the biological phenomena, among them the autonomic modulation through of heart rate variability [6].

A search conducted by the authors in PubMed and Scopus found 88 articles that assessed changes in heart rate variability during the installation of subarachnoid anesthesia and its association with perioperative hypotension, the majority using linear methods in frequency or time domain [7-17]. In this same search, only 2 studies described changes in HRV during spinal anesthesia recovery [18,24].

The present study aims to analyze the autonomic modulation of heart rate in patients undergoing surgical procedures under spinal anesthesia at the time of recovery of motor function and to compare the autonomic function in patients who received isobaric bupivacaine in subarachnoid anesthesia with patients who recover isobaric bupivacaine associated with clonidine.

The motor function is evaluated using the modified Bromage scale classified from I to IV, with I complete blockage, II movement of the feet, III elevation of the knees and IV movement of the knee and feet.

Method

This is a double-blind randomized clinical trial, with masking of the patients and researchers involved. The secretion of the allocation was maintained by simple draw with 2 envelopes containing the term clonidine or the term bupivacaine. The study was carried out in a tertiary hospital in the Cariri region, Ceará, in the Northeast of Brazil, whose attendance profile consists mainly of surgical patients of traumatology and orthopedics. The collection was performed between July 1, 2018 and November 1, 2018.

Using a 5% sampling error and a 95% confidence level for type I error, we reached a value of 30 individuals in each group. 71 patients started the study, 7 of which were excluded due to excess artifacts and the sample consisted of the remaining 64 patients, aged 14 to 84 years, with ASA physical status (American Society of Anesthesiology) I, II or III and admitted for orthopedic, lower limb vascular or lower abdominal surgery under spinal anesthesia. The patients were divided into 2 groups named group B (bupivacaine) and group C (bupivacaine + clonidine) Figure 1.

Figure 1*

10 minutes HRV measurements were performed in 3 moments. T1 was considered the measurement at rest; T2 was considered 20 minutes after subarachnoid anesthesia and T3 was the moment of return of motor function in the Post Anesthesia Recovery Room (PACU). The device used to collect the electrocardiographic signal was the POLAR V800® cardiofrequency measurer. After the acquisition of the signal, manual spreadsheet filtering was performed using Excel® and automatic filtering and parameter analysis with KUBIOS 3.0 ® software. Standard monitoring with non-invasive blood pressure, pulse oximetry, cardioscopy and temperature was used in all patients.

All patients received standard monitoring with ECG, pulse oximetry, non-invasive blood pressure, and temperature, which was initiated before the surgical center was prepared, before entering the operating room. The ambient temperature in the preparation was maintained between 22 and 24 °C in the operating room between 18 and 22 °C and in the post-anesthetic recovery room between 22 and 24 °C. Humidity was recorded and ranged from 40 to 60%. Vital signs and anthropometric data were recorded after arrival at the surgical center. All patients had previous rest, as they were hospitalized with a hospital stay ranging from 3 to 25 days. No patient was on energy and fasted for at least 8 hours. Diabetic patients did not use oral hypoglycemic agents. They had the blood glucose measurement performed every 6 hours and the glycemic control was performed with regular insulin. Hypertensive patients used losartan or captopril. Patients taking beta-blocker were excluded from screening.

After the first collection of resting heart rate variability, one of the researchers was in charge of selecting 1 envelope and preparing the syringe with the constant anesthetic solution in the drawn envelope; isobaric bupivacaine 20 mg + clonidine 75 mcg for the group selected with the clonidine term and isobaric bupivacaine 20 mg + distilled water 0.5 ml for the group drawn with the bupivacaine term. All the filled syringes had a volume of 4.5 ml. The anesthesiologist performing the procedure was unaware of the solution to be administered.

All patients received guidance in the infirmary or specialty outpatient clinic regarding the procedures to be performed, as well as orientation on the benefits and possible risks inherent in the procedure. All of them signed the informed consent form and received the information that they could withdraw from the study at any time, without prejudice to the continuity of treatment. The clinical trial was registered in the Brazilian Registry of Clinical Trials (ReBEC) under the number RBR-4Q53D6 and submitted to the Ethics Committee for Research on Human Subjects (CEP) of the Institute of Hospital Management and Health (ISGH). No. 2,447,717 [14].

The primary event analyzed was the return of the HRV parameters to the rest values at the moment of the recovery of the motor function in order to identify if there is concomitance of the recovery of the motor and autonomic functions and to compare the autonomic recovery between the 2 studied groups.

Statistical Analysis

The results were presented in average + standard deviation. The normality of the continuous data was analyzed with the Kolmogorov-Smirnov test obtaining a P value of 0.229571858, demonstrating normal distribution. Fisher's exact test was used to compare the occurrence of hypotension in the 2 groups and a higher incidence of hypotension was observed in the clonidine group with P value equal to 0.0290, considered statistically significant.

The Chi-square test with Yates correction was used to evaluate the sex distribution between the groups, being x2 = 0.005 with 1 degree of freedom and P = 0.9444, showing statistical similarity between the groups. Student t test was used to compare anthropometric and vital signs data between the groups, without statistical difference (Table 1). Two-way ANOVA with repetition was used to compare the means of the 2 groups. The level of significance was 0.05. Student's t-test was used to compare the means of the analyzed parameters between two times within the same group and between the two groups (tables 2 and 3). The ANOVA test identified similarity between the 2 groups in T1 in the various indexes analyzed.

Comparing the approximate entropy of the 2 groups at the hospital discharge moment we found Cohen's effect size d = 0.023029, showing statistically significant difference. In the clonidine group, comparing the approximate entropy of the hospital discharge moment with rest was found Cohen's d = 0.011264. In the Bupivacaine group, comparing the approximate entropy of the high moment with the moment of rest, Cohen's d = 0.033801.

Comparing the Low Frequency/High Frequency(LF/HF) in the clonidine group between the high moments with the rest, Cohen's d = 1.083032 was found, with no statistical difference. Comparing the Bupivacaine group at hospital discharge moments with the resting moment, Cohen's d = 0.099146 was observed. When comparing the 2 groups at the hospital discharge moments, Cohen's d = 1.980402 was identified, also without significant statistical difference.

The discrepancy of results between the two indices may suggest a greater reliability of the non-linear methods when compared to the linear methods for analysis of the complex signal of the HRV of the electrocardiogram, derived from the interaction between several organic systems.

Study protocol

All patients received standard monitoring with electrocardiography, pulse oximetry, noninvasive blood pressure, and temperature, which was initiated before the surgical center was prepared, before entering the operating room. The ambient temperature in the preparation was maintained between 22 and 24 °C in the operating room between 18 and 22 °C and in the post-anesthetic recovery room between 22 and 24 °C. Vital signs and anthropometric data were recorded after arrival at the surgical center.

Patients received 500 ml lactated ringer's solution heated at 38 ° C and were maintained normothermic during the procedure by heated serum and thermal blanket. No patient received

preanesthetic medication.

Measurements of heart rate variability were performed for 10 minutes in 3 moments using a Polar V800 cardiofrequency meter. To evaluate the data collected, Kubios 3.0 software was used and linear methods in frequency domain and non-linear methods in the chaos domain were analyzed, with emphasis on approximate entropy. Samples with more than 5% of artifacts were scorned and excluded from the study.

Result

Regarding the anthropometric data analyzed and vital signs at rest, there was no difference between the groups. The mean age in group B was 41.77 years and in group C was 36.72 years with a p = 0.2127. The average height in groups B and C were 1.67m and 1.68m, respectively. The average weight in group B was 69.31 kg, while in group C it was 71.65 kg. The average resting heart rate in group B was 82.45 bpm and in group C was 79.34 bpm with p = 0.2429 and the resting blood pressure was also in group B of 139.12 mmHg and in group C of 133. mmHg with p = 0.2188 (table 1).

Table 1. Comparison between averages of the clonidine and bupivacaine groups, of the parameters: Age, height, weight, Heart Rate and Systolic Blood Pressure.

Variables	Clonidine	Bupivacaine	p
	Average ± standard deviation	Average ± standard deviation	
Age (years)	36,72±9,80	41,77±21,58	0.2127
(min-max)	(19-50)	(14-88)	
Height (m)	1,68±0,028	1,67±0,083	0.5077
(min-max)	(1,65-1,73)	(1,52-1,86)	
Weight (kg)	71,65±10,34	69,31±12,13	0.3684
(min-max)	(60-90)	(60-90)	
HR (bpm)	79,34±9,98	82,45±12,72	0.2429
(min-max)	(62-98)	(58-120)	
SBP	133±19,56	139,12±23,27	0.2188
mmHg	(110-180)	(106-200)	

m: meterss; kg: kilograms; bpm: beats per minujte; min-max: minimum-maximum; HR: heart rate; SBP: systolic blood pressure.

To analyze the heart rate variability during spinal anesthesia, linear frequency-domain methods were used, using LF (low frequency), HF (high frequency) and LF / HF (low frequency/high frequency); and nonlinear methods in the domain of chaos, sample entropy, approximate entropy, Poincaré plot and DFA (detrended fluctuation analisys).

The ANOVA test analyzing LF / HF found no difference between groups B and C, nor between T1, T2 and T3 times with a p of 0.149668. Student's t test performed to compare the means of the 2 groups in T2 shows a p of 0.2017, also with no statistical difference. In T3 the P between the means was of 0,3288. Comparing the group C at time T3 with T1 was observed a p of 0,1878 and group B at these same moments, a P of 0.7328 is observed, suggesting statistical similarity.

Table 2. Mean and standard deviation of the indices in the frequency domain at the times evaluated in the Bupivacaine and Clonidine groups.

Indexes	Bupivacaine			Clonidine			
	Rest	Spinal anesthesia	Hospital discharge	Rest	Spinal anesthesia	Hospital discharge	P
HF (ms^2)	330,4±594,1	228,37±337,8*	450,75±629,47	410,06±502,76	533,9±494,8*	461±490,7	0,134106
LF (ms^2)	486,75±498,4	491,4±737,9*	641,8±829,9	560,3±321,4	1092,75±1179,8*	1274,6±2000,5	0,001472
LF/HF	3,28±3,211	6±13	3,06±3,6	3,390±3,6	3±2,44	2,42±1,98	0,149668

s^2 – milliseconds, ; HF - high frequency; LF - low frequency; LF/HF - relation between the sympathetic and parasympathetic components of the eart *p<0,05.

Although not statistically significant, there was an increase in LF/HF values after spinal anesthesia in group B from 3.3 to 6 (table 3). HF, which represents the parasympathetic nervous system, presented elevation after spinal anesthesia in the clonidine group and reduction in the bupivacaine group, returning to values close to those of rest at the moment of recovery of motor function. A P of 0.6831 was identified in the clonidine group between T3 and T1 and a P of 0.3378 in the bupivacaine group comparing the same moments. A p = 0.000283 was observed comparing the 2 groups in the T2, with significant increase in the parasympathetic in group C (table 2).

LF values, representative of the sympathetic and parasympathetic nervous systems, with sympathetic predominance, presented progressive elevation in the clonidine group at the 3 T1, T2 and T3 moments. The bupivacaine group presented elevation at time T3 when compared to T1. The Student's t test comparing the clonidine group in T3 with T1 showed a p of 0.0505, not statistically significant and in the bupivacaine group a p of 0.3684, also not significant (table 2).

Figure 2 represents the spectral analysis of one of the patients in the clonidine group throughout the perioperative period of rest at discharge from the PACU, demonstrating a return of autonomic function 30 minutes after the return of motor function.

gure 2 *

Analyzing the non-linear methods in the chaos domain through ANOVA two-ways, no difference was observed between groups, except for the approximate entropy index, where p was 0.048538, with an F of 3.942935 and a critical F of 3.89194, considered statistically significant, but with a value very close to p defined as significant of 0.05. However, when comparing the approximate entropy in the clonidine group at T3 times with T1 using Student's t, the p was 0.0277, with a 95% confidence interval ranging from 8.3220291 to 138.6779709, which is a statistically significant difference. The

bupivacaine group presented a p of 0.1011 between the same times, showing statistical similarity between the high and rest moments (table 3).

The approximate entropy increased in T2 in group C, when compared to T1, but it was reduced in group B. In T3, the approximate entropy in group C, compared with T1 also presented a statistically significant difference, which is not observed in group B (table 3).

Table 3. Comparison between the means of the clonidine and bupivacaine groups, of the parameters: Age, height, weight and HR through student t test.

Indexes	Bupivacaine			Clonidine			p
	Rest	Spinal anesthesia	Hospital discharge	Rest	Spinal anesthesia	Hospital discharge	
Approximate entropy	1187±261,43	1128±178,79*	1119,67±105,36	1224,44±90,8	1255,69±102,36*	1150,9±160,5*	0,048538**
SD1	17,5±13,64	15,57±9,6*	20,73±17,69	19,3±8,04	21,09±13,92*	19,6±14,69	0,47301
SD2	36,24±20,1	30,29±18,76*	40,6±23,18	40,89±12,78	38,64±25,85*	45,61±30,69	0,030464
SD2/SD1	2,39±0,76	2±1	2,398±0,855	2,269±0,577	1,94±0,412	2,15±0,62	0,158489
Sample entropy	1571,6±290	1433,3±280,9*	1506,3±291,5*	1606,5±270,1	1673,7±116,4*	1313,9±288,3*	0,998703
DFAα1	1,22±0,27	1,09±0,22*	1,19±0,29	1.191±0,23	0,97±0,15*	1,12±0,22	0,07404
DFAα2	0,486±0,14	0,56±0,15	0,544±0,19	0,476±0,09	0,63±0,18	0,54±0,17	0,342388
D2	1,197±1,44	0,938±1,39*	1,496±1,65	1,7±1,66	1,48±1,94*	1,7±1,57	0,067991

SD1: standard deviation of the instantaneous variability of beat-to-beat R-R intervals; SD2: standard deviation of long-term R-R intervals; SD2/SD1 represents the ratio of long-term standard deviation to instantaneous standard deviation; DFAα1 is the refined analysis of short-range trends; DFAα2, is the refined analysis of long-range trends; D2: correlation dimension. *p<0,05 **F = 3,942935; critical F =3,89194

The level of sensory blockade was higher in the bupivacaine group, although all punctures were performed in the same L3-L4 interspace and the solution was administered at the same speed in the 2 groups (figure 3). However, no statistically significant difference was observed between the groups by Student t with p = 0.371. The height reached by spinal anesthesia is directly related to the incidence of hypotension and bradycardia [4].

Figure 3 *

Discussion

There are few studies addressing heart rate variability in spinal anesthesia and the vast majority use linear frequency-domain methods. No study evaluating the effect of intrathecal clonidine as an adjunct to spinal anesthesia on HRV has been found. Clonidine, an α2 agonist drug acting at presynaptic receptors at the central and spinal levels, causes bradycardia and hypotension, directly interfering with heart rate variability [1,4,5].

The approximate entropy increased in T2 in group C, when compared to values in T1, but it was reduced in group B, which suggests a protective effect of clonidine. However, comparing group C at time T3 and T1, a statistically significant difference was observed, which may be suggestive of persistence of sympathetic blockade, not observed in the bupivacaine group. The entropy of the sample showed behavior similar to the approximate entropy.

The LF/HF index after spinal anesthesia in group B presented elevation from 3.3 to 6 and in group C a reduction from 3.4 to 3.3, not statistically significant. The HF index in group C at time T2 presented a significant increase, suggesting a predominance of the parasympathetic nervous system. LF showed a slight increase in T2 and a significant increase in T3 in group B. In group C, the LF showed a significant and progressive increase in T2 and T3 times, suggesting an activation of the sympathetic component (Table 3) [13-17].

Elevation in LF/HF values was observed after spinal anesthesia in group B from 3.3 to 6 and in group C a reduction from 3.4 to 3.3. Statistically none of the results is significant, however, Sakata, in a study involving 45 women undergoing cesarean section, concluded that elevation of LF/HF values equal to or greater than 2 times the initial value after postural change is a predictor of a higher incidence of hypotension after spinal anesthesia [19]. The findings of this study may indicate a protective effect of clonidine as an adjunct to spinal anesthesia in the prevention of hypotension after adjustment of drug doses.

The LF/HF ratio acts as an indicator of the sympatovagal balance [20]. After dispersion of the blockade at T3-T4 levels, the LF/HF ratio practically doubled and returned to baseline when the blockade reached T1-T2. In this case, the sympatovagal balance does not seem to have changed, however, the spectral density test reveals a significant reduction in total power that is not obvious in the isolated LF/HF examination as observed in table 3. Although not statistically significant , there was an increase in LF/HF values after spinal anesthesia in group B from 3.3 to 6 (table 3). Hanss et al 2006, in a study involving 100 patients submitted to cesarean section under spinal anesthesia, found that patients with LF/HF values >2.5 presented a higher risk of hypotension than patients with LF/HF values <2.5 [20].

Elevation of HF in group C at time T2 suggests a predominance of the parasympathetic with a possible protective effect of clonidine applied in the subarachnoid space. Introna et al 1995 suggests a reduction of sympathetic activity, represented by LF and elevation of parasympathetic activity after spinal anesthesia with bupivacaine, represented by HF, that was not observed in this study, but was found a reduction in HF in group B at time T2. LF showed a slight increase in T2 and a significant increase in T3 in group B. In group C, LF showed a significant and progressive increase in T2 and T3 times (table 3) [13,18-20].

Some studies use linear HRV methods as predictors of hypotension after spinal anesthesia. However, the hypotension associated with spinal anesthesia is the result of several and complex

interactions, related to the adaptive capacity of the organism to the perioperative stress. There are reports of cardiorespiratory arrest after installation of spinal anesthesia in young patients, without significant comorbidities. The literature suggests that measures of HRV using linear methods in the frequency domain may predict perioperative hypotension. However, linear methods apparently do not reflect the high complexity of the interactions between the various organic systems in the surgical scenario. Nonlinear methods in the domain of chaos seem to be more appropriate [6-11,19,20].

The time series extracted from biological signals in the vast majority of them present complex and chaotic behavior, and it is not possible to characterize their nature with a single method of analysis. In the analysis of heart rate variability in the chaos domain, the association of 2 or 3 methods reveals a more complex and more representative information of natural events (approximate entropy, Poincaré plot, DFA, correlation dimension, etc.). The joint analysis through 2 or more indexes allows to estimate the complex, regular or random behavior of the time series, bringing to light information and variables not evident by traditional methods [13]. Despite this, the importance and clinical applicability of these new methods has not yet been defined. Sassi et al 2015, in an important review on non-linear indices, considers the new techniques promising. However, it suggests caution in the interpretation of the data and believes that the analysis together with the traditional methods is more adequate while new studies do not appear [20].

DFA α1 was reduced after spinal anesthesia in both groups; however, it did not present statistically significant difference in any of the groups when comparing moments T3 with T1. However, there is a statistically significant difference between groups B and C at moment T2 with a p of 0.000922, suggesting a reduction in short-term fractal property in group C, which contrasts with the increase in complexity indicated by the increase in approximate entropy and T2 sample entropy in this group. DFA α2 showed no significant difference between groups with an ANOVA showing a p of 0.342388, but student's t identified a p of 0.000201 in T2 between groups B and C, already demonstrating a longer long-term fractality. in group C, different from that observed with DFA α1. This data may suggest a better adequacy of long-term fractality in the analysis of spinal anesthesia patients compared to short-term fracture.

The approximate entropy increased in T2 in group C, when compared to values in T1, but suffered a reduction in group B, which suggests a protective effect of clonidine, however, comparing group C at moments T3 and T1, it was observed a P of 0.0277, with a 95% confidence interval ranging from 8.3220291 to 138.6779709, which is a statistically significant difference and may be suggestive of persistence of sympathetic blockade, not observed in the bupivacaine group.

Sample entropy showed similar behavior to approximate entropy, with T2 elevation in group C, with difference when compared to T2 of group B, with a p of 0.000202, but with reduction in T3 in clonidine group with p of 0, 000954, not significant when comparing T3 and T1 in group B, but with statistical significance in group C analyzing T3 in relation to T1, corroborating the persistence of persistent sympathetic block in group C after the return of motor function identified by the sample entropy.

The effect of clonidine as adjuvant in spinal anesthesia is not yet fully understood. The doses used range from 15 mcg to 150 mcg and there is still no definition of the optimal dose to be used in spinal anesthesia. Also, the dose of the local anesthetic to be administered when it is associated with

clonidine is not defined in the literature [5]. Some authors suggest the use of doses above 75 mcg in order to obtain a vasoconstrictive effect through α1 receptors, with a lower vasodilator effect triggered by α2 receptors, where clonidine has greater selectivity. The authors advocating this dose argue that they have a lower incidence of perioperative hypotension [5].

Although clonidine is an α2 agonist with α2: α1 selectivity of 1:200, and is responsible for triggering hypotension and bradycardia when used intravenously and on the neuroaxis, analysis of the sample in this study demonstrated greater heart rate stability in the clonidine group. than in the bupivacaine group [Figure 3]. This effect may be due to the α2 action of clonidine, which acts both centrally and on the neuroaxis, inhibiting norepinephrine exocytosis and reducing the action of the sympathetic nervous system, which is primarily responsible for increasing heart rate. major hypotension in the clonidine group, consistent with current literature [1,4]. This fact may have been the result of the absence of adjustment of the doses of local anesthetics, since clonidine potentiates the anesthetic effect, allowing the use of smaller doses of anesthetics. In the study, the same dose of isobaric bupivacaine was used in the 2 groups, and in the clonidine group the adjuvant was added, with consequent increase in anesthetic potency, duration and side effects. There is still no definition in the literature of the optimal dose of clonidine to be administered in the intrathecal space, nor of the dose of local anesthetic when adjuvants are associated in the neuroaxis [5].

The study presents some limitations, considering that the surgical act triggers an individual endocrine metabolic response and variable intensity depending on the surgical aggression. The surgical act itself has the ability to change the heart rate variability, as well as the patient's previous hydration. These factors may influence the final results obtained.

The discharge of PACU after spinal anesthesia is made after the return of the motor function, to the detriment of the other affected neural pathways. Spinal anesthesia provides a sensitive, motor and sympathetic block. This study suggests an extension of sympathetic block in spinal anesthesia, in addition to motor blockade, when clonidine is administered and may indicate a need to review the discharge criteria of the post anesthetic recovery room in patients submitted to surgical procedures under spinal anesthesia, especially when doing use of adjuvants.

At PACU patients are routinely monitored until the return of motor function. They are then discharged and released to the ward where their vital signs are routinely checked every 6 hours. The persistence of sympathetic block after motor recovery and the absence of subsequent continuous monitoring may increase the incidence of adverse events.

Conclusion

The approximate entropy values and entropy of the sample at the time of recovery of motor function in patients receiving spinal anesthesia with isobaric bupivacaine and clonidine presented reduction when compared to values obtained at rest, different from the group that received only bupivacaine. This data suggests that the use of clonidine in spinal anesthesia at a dose of 75 mg prolongs sympathetic blockade beyond motor blockade and may require a longer PACU stay time than is recommended by current criteria, reducing the incidence of postoperative complications.

Abbreviations

HRV: heart rate variability
ECG: electrocardiogram
ASA: American Society of Anesthesiology
PACU: Post Anesthesia Recovery Room
ReBEC: Brazilian Registry of Clinical Trials
CEP: Ethics Committee for Research on Human Subjects
ISGH: Institute of Hospital Management and Health
LF/HF: Low Frequency/High Frequency
LF: Low frequency
HF: High frequency
DFA: detrended fluctuation analisys
D2: correlation dimension
SD: Standard deviation

Declarations

-**Ethics approval and consent to participate**

The clinical trial was registered in the Brazilian Registry of Clinical Trials (ReBEC) under the number RBR-4Q53D6 and submitted and approved to the Ethics Committee for Research on Human Subjects (CEP) of the Institute of Hospital Management and Health (ISGH).
All patients signed the informed consent form and received the information that they could withdraw from the study at any time, without prejudice to the continuity of treatment.
Minors were not involved in the study.

-**Consent for publication**

The authors authorize the publication of this article.

-**Availability of data and material**

The authors make the collected data available for evaluation if requested. Contact must be made by email: hermesmelo@oi.com.br.

-**Competing interests**

The authors declare that there are no conflicts of interest.

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-**Authors' contributions**

Data analysis: LCA, IMPB, VEV, RDR, RRN.

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Figures

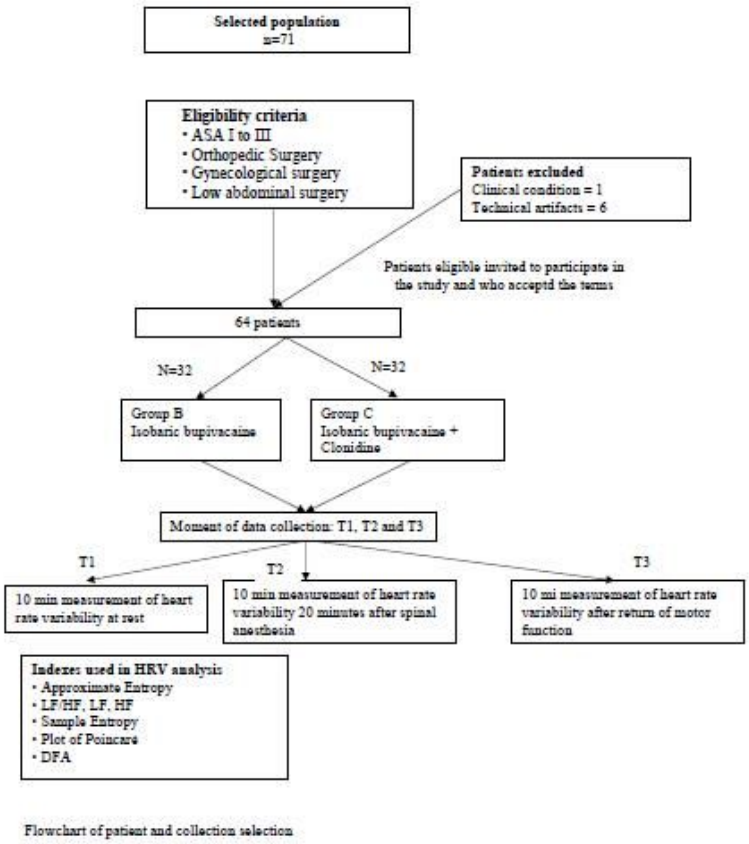

Figure 1

Flowchart representing the patient selection for the study.

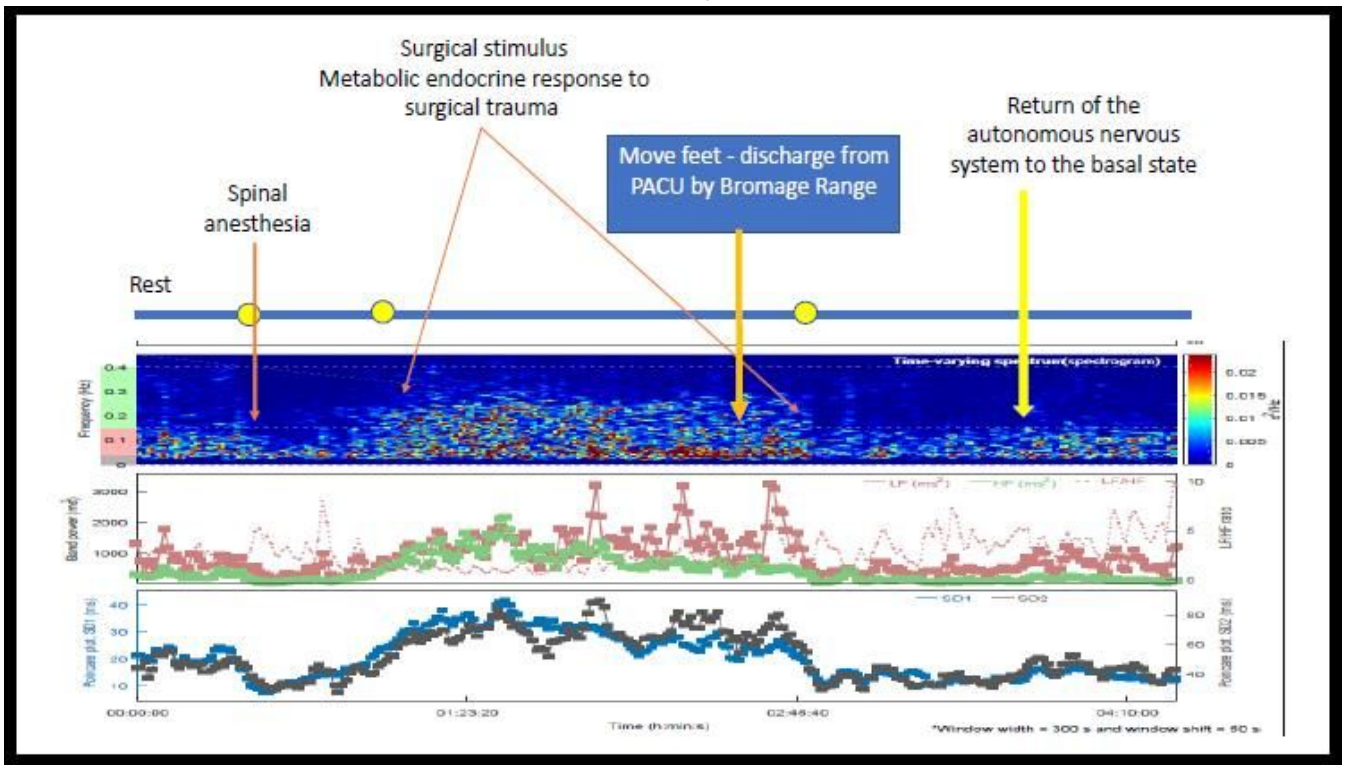

Figure 2

Spectrogram of one of the group C sample patients.

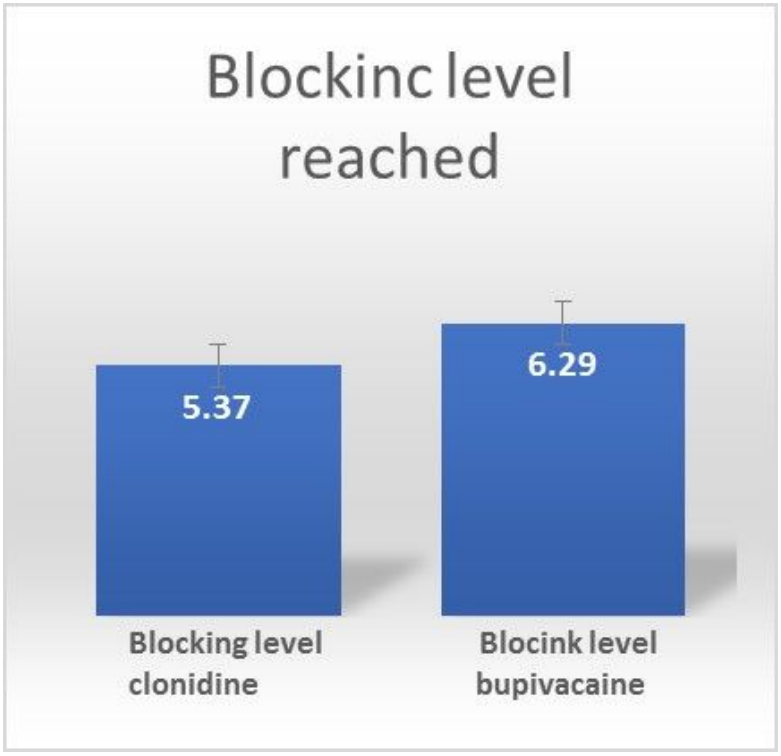

Figure 3

mean height of the sensory block reached in the 2 groups with a p = 0.3710, with no statistical difference.

Supplementary Files

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- CONSORT2010Checklist.doc